UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC ADVISORY COMMITTEE

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MEETING

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MONDAY, JANUARY 13, 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, PhD	Voting Consultant
DEAN FOLLMAN, PhD	Voting Consultant
DEBORAH GRADY, M.D., M.P.H.	Member
LAWRENCE HUNSICKER, M.D.	Voting Consultant
J. CHARLES JENNETTE, M.D.	Voting Consultant
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, PhD	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 (Non-Voting) Industry Representative
KAREN M. TEMPLETON-SOMERS,PhD.	Acting Executive Secretary

FDA REPRESENTATIVES:

JOHN HILL, PhD
JAMES KAISER, M.D.
MARC WALTON, M.D., PhD
KAREN WEISS, M.D.

SPONSOR REPRESENTATIVES:

MARK A. GOLDBERG, M.D.
ALISON LAWTON
BARRY M. BRENNER, M.D.
ROBERT J. DESNICK, M.D., PhD
DOMINIQUE P. GERMAIN, M.D., PhD
RICHARD MOSCICKI, M.D.
HELMUT G. RENNKE, M.D.
DONALD B. RUBIN, PhD
PK TANDON, PhD

PUBLIC SPEAKERS:

RICARDO D. BORREGO, M.D.
ROSCOE O. BRADY, M.D.
JEAN-PIERRE GRUNFELD, M.D.
HAYA (JACQUI) HOWELLS
DEBRA JOHNSON
JACK JOHNSON
TRACY MYATT
ABBEY S. MEYERS
GERALD I. WALTER
DAVID G. WARNOCK, M.D.

I-N-D-E-X

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

(8:00 a.m.)

CHAIRMAN AOKI: Good morning. I am Thomas Aoki, the Acting Chairman of this Committee, the Endocrinologic and Metabolic Advisory Committee.

The topic for this morning is Fabrazyme, a product of the Genzyme Corporation. Before we launch into that presentation, I would like the members of the Committee, starting to my left, to identify themselves to allow the other members of the Committee and the audience to know who they are.

DR. ZERBE: I am Bob Zerbe. I am the CEO for QUATRx Pharmaceuticals, and I am the Industry Representative.

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

DR. FOLLMAN: I'm Dean Follman, statistician on the Committee, and I work at the National Institutes of Allergy and Infectious Diseases.

DR. BARISONI: Laura Barisoni,

renopathology.

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

DR. FLEMING: Thomas Fleming, University of Washington.

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

MS. KNOWLES; Kathy Knowles, Health Information Network, Seattle, Washington, Consumer Representative today.

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

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

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, Acting Executive Secretary for the Committee.

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 Hospital.

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

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

DR. SCHNEIDER: Jerry Schneider, University of California-San Diego.

DR. GRADY: Deborah Grady, the University of California-San Francisco.

DR. KAISER: Jim Kaiser, medical reviewer, FDA.

DR. WALTON: Marc Walton, FDA.

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 interests in firms regulated by the Center for

Drug 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 U.S.C. 208(b)(3) for his consulting for his appearance for the sponsor on unrelated matters. He receives between $10,001 and $50,000 a year. The limited waiver allows Dr. Jonas to participate fully 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 12-A-30 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 a Saloman Smith Barney managed account.

In the event that the discussions involve any other products or firms not already in 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 the exclusion will be noted for the record.

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

CHAIRMAN AOKI: Thank you. Without further ado, I would like to ask Dr. John Hill to make a brief introduction.

DR. HILL: Thank you all for being in attendance today. We are here to discuss Genzyme's BLA application for Fabrazyme, recombinant human alpha galactosidase for the treatment of Fabry's disease.

I am John Hill, Chairman for the CBER Review Committee for this BLA submission, presenting a brief overview of the CMC portion of Genzyme's application.

CBER received Genzyme's application on June 23, 2000. Since CBER received this BLA

application, a review process encompassing extensive interactions between CBER and Genzyme has taken place. CBER reviews have raised numerous comments during the course of this BLA review. These comments have been communicated to Genzyme in several complete response letters.

The first complete response letter in December 2000 from CBER to Genzyme acknowledged the findings presented were robust but, because of histological effects, may not be uniform. Antibody formation was widespread and might lead to diminution of long term effects.

There is concern whether a prediction of long term efficacy was sound and whether there would be a favorable risk/benefit balance with chronic administration. These concerns led to the need for additional data to be submitted.

Genzyme responded to CBER's comments by submitting additional information with a complete response in April 2001. CBER's review of this information culminated in the second complete response letter in October 2001, which acknowledged that the

additional information had alleviated some concerns regarding the breadth of the cell types affected by the treatment, and again highlighted the need for an adequate verification study under accelerated approval and the importance of demonstrating that Genzyme's proposal plan was feasible to successfully conduct.

Genzyme's response to these requests were completed in May 2002, and included longer term histology data and partial data supporting plans for historically controlled study.

CBER's review of this information was completed in June 2002, at which time a third CR letter was issued which highlighted the need for the complete data and analysis supporting the historical control proposal.

Genzyme's response to these requests were completed in October 2002, supplying CBER with the complete historical dataset and analyses and additional longer term histological data.

The review of this information is the subject of the current review cycle, and includes the information submitted by Genzyme in the last part of

2002, including a revised proposal for analyzing the historical dataset.

There have been -- There have, in fact, been discussions, requests and responses between CBER and Genzyme on a more frequent basis than reflected in just these official regulatory milestones. I guess, to summarize, this interactive review process is still ongoing.

I would now like to summarize the biochemical features of the drug substance. Fabrazyme is a recombinant human alpha galactosidase expressed in the continuous Chinese hamster ovary or CHO cell line. Alpha galactosidase exists as a homodimer comprised of two approximately 50-kilodalton subunits.

The amino acid sequence for the recombinant enzyme is identical to the sequence for the endogenous enzyme. Finally, there are three N-linked glycosylation sites.

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

I would now like to summarize the properties of the drug product. Each vial of drug product is filled with 7.4 mils of a mannitol, phosphate buffer containing 5 milligrams per mil alpha galactosidase. The drug product is supplied as a lyophilized powder in a single use vial.

The lyophilized product is reconstituted with water for injection to final concentration of 5 milligrams per mil prior to use. There are no outstanding review issues concerning the drug product.

Finally, I would like to acknowledge the members of the CBER review team and thank them for their thorough reviews. That completes my presentation.

CHAIRMAN AOKI: Thank you, Dr. Hill. I now would like to start the sponsor presentation, starting with the introduction by Alison Lawton, Senior Vice President, Regulatory Affairs and Quality Systems.

MS. LAWTON: Can everybody hear me here?

Okay, good morning. My name is Alison Lawton, and I am Senior Vice President for Regulatory

Affairs at Genzyme Corporation. I would like to start this morning by providing a brief introduction and an overview of our presentation.

So after my brief introduction, Dr. Mark Goldberg will talk about Fabry's disease and the Fabrazyme clinical development program. Dr. Rennke will then talk about the rationale for the renal pathology endpoint. Dr. Goldberg will then return to the podium to talk about the safety and the Phase IV clinical program for Fabrazyme, and then Dr. Rubin will discuss the statistical methods for setting clinical benefit in our Phase IV program.

Finally, I will return to the podium to leave you with some thoughts for consideration in addressing the FDA questions today.

As well as the speakers with us today, we have a number of leading experts in their fields with us who are available to answer questions from the Committee, and their names and areas of expertise are shown on this slide.

Just to provide you a brief overview of the regulatory history for Fabrazyme: Fabrazyme has

orphan designation and, in fact, at Genzyme it is what we like to term ultra orphan where there is less than 5,000 patients in the U.S. compared to the cutoff of 200,000 patients for a standard orphan drug.

It has fast-track status, and the BLA was filed in June of 2000, as you previously heard. The BLA was filed under accelerated approval based on many discussions with the FDA and the agreement on assessing a surrogate endpoint in the pivotal clinical trial.

At the time the BLA was filed, it was given a priority review. Fabrazyme is approved in 26 different countries currently around the world, including the European Union where it was approved in August of 2001.

The proposed indications of Fabrazyme is as long term enzyme replacement therapy for patients with a confirmed diagnosis of Fabry disease, but very specifically, Fabrazyme treats the underlying pathology of Fabry disease by significantly clearing GL-3 to normal or near normal levels from the vascular endothelium of the kidney, heart, and skin.

We have two key objectives during our presentation to the Committee this morning. One of those objectives is to outline for you how we currently meet the requirements for accelerated approval, and this is the various aspects of accelerated approval just shown here, and we will cover each one of those during our presentation.

The second key objective of our presentation this morning is to actually address what we consider to be five key issues. Although you have four questions in front of you with many subparts to them, we believe there's really five key issues that we will address during our presentation.

Now I would like to hand over to Dr. Mark Goldberg.

DR. GOLDBERG: Good morning. I would like to first give you a brief overview of Fabry disease, and then I will describe to your our clinical development program, and not only what we did but why we chose to do it.

Fabry disease is a rare, legal, X-linked inborn error of metabolism for which currently only

palliative therapy is available. It is due to a mutation in the gene which encodes the enzyme alpha galactosidase-A. This results in a markedly deficient enzyme activity, which in turn leads to some accumulation of neutral glycosphingolipids, in particular globotriaosylceramide, which I will abbreviate GL-3.

The GL-3 accumulates in multiple cell types, and ultimately culminates in end organ impairment. Now when one carefully correlates the clinical manifestations of the disease with the underlying pathology, it becomes clear that the vascular pathology plays a critical role in many of the most devastating manifestations of the disease.

Specifically it is the abnormal accumulations of GL-3 in the lysosomes of the vascular endothelial cells that leads to this ultimate end organ damage, and I will discuss, along with Dr. Rennke, in more detail this pathophysiology during the presentation.

I think it is worth noting that the clinical pathological correlation in Fabry disease has

certain similarities to other diseases such as hypercholesterolemia and diabetes. In all three of these diseases, significant pathological abnormalities are seen for many years, and they continue to progress until there is such significant underlying pathology that the end organs ultimately begin to fail.

Additionally, like in treatment of hypercholesterolemia and in diabetes, in treatment of Fabry disease with the effective therapies one can see dramatic reductions in pathological markers in a relatively short period of time, but it takes much longer periods of observation to demonstrate improvement in end organ damage.

I would now like to focus specifically on the clinical pathological correlations in Fabry disease. It is very informative to focus on certain subsets of the Fabry population.

The first subset that I would like to talk about are the classical phenotype. These patients have virtually no residual enzyme activity. Pathologically, their endothelium cells have very extensive accumulations with GL-3.

Clinically, they often present in childhood with severe pain, this both in the form of acroparesthesias and pain crises which are episodic. Interestingly, over time these decrease and in some instances completely resolve in a subset of these patients.

Now as I mentioned before, the ultimate end organ damage occurs later in life. It usually begins in the fourth and fifth decades, although there is some heterogeneity. Renal failure is the most common reproducible devastating feature of the disease. In fact, prior to dialysis or transplantation, patients generally die a renal death in their early forties.

The vascular component of this disease is expressed in the CNS where transient ischemic attacks and strokes occur. In addition, there is a significant cardiac component, the vascular component resulting in angina, myocardial infarctions. Arrhythmias are very common, and there is also a hypertrophic cardiomyopathy associated with this disease.

Now there is a second subset of the Fabry population, the so called cardiac variance. Because of the mutations that these patients have, they have a small amount of residual enzyme activity. When one looks pathologically, one sees minimal endothelial cell accumulations in their cells.

They have a much milder clinical course. They present much later in life with cardiac disease, with much less of a vascular component and more of the hypertrophic cardiomyopathy. They very rarely develop renal insufficiency, and occasionally may have some proteinuria.

Now a third subset of the Fabry population that at times has been underappreciated are the female heterozygotes. These patients -- In a recent study by K. MacDermot, it was shown that they have significant symptoms. However, very rarely does one see significant end organ damage such as renal insufficiency. In this study, two percent of the patients had renal failure.

It is very interesting when one looks at the pathology in these specific patients. When renal

failure occurs, on biopsies one sees endothelial cell involvement in the kidney.

In patients -- and Dr. Rennke will discuss this in more detail, but in the majority of the patients female heterozygotes who do not have any renal dysfunction, pathologically their endothelial cells have minimal, if any, accumulations of GL-3, though they have significant epithelial cell accumulations.

This is most likely due to the fact that, remember, this is an X-linked disorder and, because of the stochastic nature of X inactivation or lionization, there may be a significant variability from patient to patient.

So to summarize what I have said so far with respect to the clinical pathological correlation, the most severely affected, the classically hemizygote males, have marked epithelial cell involvement and also very extensive endothelial involvement. The mildly symptomatic and occasionally asymptomatic patients have epithelial cell involvement but have minimal to no endothelial cell involvement.

The idea of enzyme replacement therapy with Fabrazyme is as follows. Fabrazyme is a recombinant form of human alpha galactosidase A, and it is given to replace the deficient enzyme. It is given intravenously. It is taken up in large part by a manno-6 phosphate receptors and trafficks appropriately to the lysosomes where it can then degrade the abnormal accumulations of glycosphingolipid.

This concept of enzyme replacement therapy for lysosomal storage of disease has proven effective in the treatment of Gaucher's disease where a recombinant form of beta glucocerebrosidase has been available on the market, Cerazyme, for a number of years.

So what we will show you today is that, with Fabrazyme therapy, we will take patients with very extensive both epithelial and endothelial cell accumulations, and we will convert that pathology, as shown here, by dramatic reductions and statistically significant reductions in endothelial cell involvement, and some improvement in epithelial cell

involvement, to convert the pathology to a much milder or even resemble that of asymptomatic patients.

Now I would like to turn to our clinical development program. This is a summary of all the studies that are either completed or ongoing. I will focus primarily on our Phase I-II and our Phase III study and its extension.

Worldwide, when one takes into account the clinical trials, the compassionate use and commercial use of Fabrazyme, over 350 patients have been treated. This represents well over 4,000 infusions, and the longest patients have been on therapy for over three years.

Our Phase I-II trial assessed not only safety but, very importantly, dose ranging and the impact of dose on pharmacodynamics. We looked at several different dosing regiments, but I'd like you to focus on three of them: 0.3, 1.0, and 3.0 mg/kg every two weeks for a total of five doses.

We saw evidence of biological activity at all three of these dose levels. However, we saw the strong suggestion of a dose response when we focused

on the reduction of plasma GL-3, a reflection of intracellular enzyme activity.

At both 1.0 and 3.0 mg/kg, most of the patients had a reduction to normal and, in many instances, undetectable levels of GL-3 after one dose, and the plasma GL-3 levels remained at that low level for the remainder of the study. At 0.3 mg/kg there is a much more modest and graded reduction in GL-3 over time.

At 3.0 mg/kg we saw a much greater incidence of infusion associated reactions than we did at 1.0 mg/kg. Therefore, we felt that 1.0 mg/kg provided the optimal balance between safety and efficacy, and this is the dose that we have used going forward in our pivotal trial.

Our Phase III trial was a randomized, double blind, placebo controlled trial. It was a multi-center trial conducted at eight sites in four countries in the United States and Europe. A total of 58 patients were enrolled and randomized. Twenty-nine were randomized to Fabrazyme at 1.0 mg/kg every two weeks, and 29 were randomized to placebo.

It was a 20-week study, and at the completion of the study patients were eligible to roll over into an open-label extension trial in which they would be followed for an additional 54 months. This provides a total duration of exposure and follow-up of these patients to five years, for which we are committed to following these patients.

It is important to appreciate that all 58 patients chose to roll over into the open-label extension trial.

Now, obviously, the primary endpoint selection for this trial was of critical importance. It's something that we gave great thought to, and I would like to walk you through our thinking as we arrived at our primary endpoint.

As I mentioned, pain is often the presenting feature of this disease. So we thought about using pain as a primary endpoint. However, it is subjective. It is episodic, and as I mentioned to you, it occasionally spontaneously wanes over time.

Unfortunately, there is no validated pain instruments in Fabry disease, and very importantly,

when we looked at the statistical power that would be required to do an appropriate trial, we felt that this wold require a very large trial, particularly for the relatively small size of this patient group.

We next looked at considering the cardiac or cerebrovascular events as a primary endpoint. Here the problem was determination of the sample size and study duration. This is not feasible, because for these types of events the literature poorly documents the event rate.

Additionally, remember, this is an X-linked disease. So it is primarily male hemizygotes who are affected the most severely, and diseases such as hypercholesteremia and hypertension, which are common in these males, represent common concomitant conditions that would confound our analyses.

We thought hard about renal function, because again this is the most common devastating end organ that is damaged in this disease, and the damage is felt to be irreversible. So the goal would be to prevent end organ damage from occurring.

Now as I mentioned, renal function remains

normal for many years, and then, we know from the literature, it begins to decline over a few years. We realized that demonstrating a significant difference from placebo would require several years and a very large trial, given the -- and this would be problematic again, given the relatively small size of this patient population. I will return, however, to this area when I discuss our Phase 4 program.

Now the FDA has anticipated such problems, and it has put in place an accelerated approval mechanism, and this was put in place so that one can develop a clinical development program, and it can proceed based upon a mutually agreed upon surrogate endpoint reasonably likely to predict clinical benefit.

We, therefore, had extensive discussions with outside consultants and with FDA, and we arrived upon a mutually agreed surrogate endpoint that we all felt was reasonably likely to predict clinical benefit, and that endpoint was the reduction of GL-3 inclusions in the renal capillary endothelium to essentially normal levels at 20 weeks.

We focused on the kidney, again because this is the organ that is most reproducibly damaged by this disease. We focused on the endothelial cells for the reasons that I discussed before. This has many aspects of a vascular disease.

We made very clear that we would not just reduce the levels, but actually reduce them to essentially normal levels. If this was going to show clinical benefit, these vessels needed to appear essentially normal.

This was assessed morphologically by light microscopy by three independent renal pathologists. They were blinded to pre- and post-biopsy sampling. A very extensive and rigorous scoring system was put in place, which is summarized here, with a zero score being essentially normal vessels, and a score of three would represent vessels that had very significant inclusions still in them.

We looked at a number of secondary endpoint. We wanted to make sure that this was not an isolated finding to the kidney endothelial cells. So a secondary endpoint was the composite score of the

accumulation in the capillary endothelium not only of the kidney but also of the heart and the skin.

We wanted to complement our morphologic assessment with a biochemical assessment, and we looked at a composite score of reduction in urinary sediment GL-3 and kidney tissue GL-3.

A third secondary endpoint was focusing on pain, using the McGill Pain Questionnaire. The only comment I will make here is that at the end of 20 weeks in the double-blind study, the Fabrazyme patients showed a statistically significant decrease in pain compared to baseline. However, there were similar decreases in the placebo group, and there was not a statistically significant difference between groups.

We explored a number of additional endpoints. Obviously, we wanted to look at renal function carefully. So we followed serial serum creatinines, glomerular filtration rates, proteinuria, and plasma GL-3.

Now I would like to review with you our efficacy data. With respect to demographics, the two

groups were comparable. It is important to note that the mean age for this study was 30 years.

This is our primary endpoint. None of the placebo patients, zero out of 29, achieved the primary endpoint of a zero score. Twenty out of 29, or 69 percent of the patients who received Fabrazyme, achieved a zero score. This was a highly statistically significant result with a P value of less than 0.001.

Importantly, it was also a very robust result that, when one looked at a number of different covariates, this finding was independent of study site, of renal pathologist, of age, as well as a number of additional covariates.

Additionally, this finding was confirmed in the open label extension trial. So when these placebo patients were rolled over into the open label extension and a third biopsy was performed six months into that open label extension, you can see that 24 out of 24, 100 percent of the placebo patients who had biopsies, achieved a zero score. And importantly, the original Fabrazyme group -- they had a sustained

clearance. In fact, 23 out of 25 biopsies, or 92 percent, had a zero score at six months into the extension trial.

As I mentioned, our secondary endpoint -- one of our secondary endpoints was a composite reduction not only in the kidney capillary endothelial cells but also in the skin and the heart. For each of these types of endothelial cells independently, there was a significant reduction from baseline to week 20, and the composite showed again a marked reduction, and this was highly statistically significantly different from the placebo group where there was no change, again the P value of less than 0.001.

Skin biopsies, because they are not nearly as invasive as heart and kidney biopsies, could be done much more frequently. So throughout the extension trial here, at six months intervals for the first 18 months we did skin biopsies, and then yearly thereafter.

This shows you that the same result in the skin that we saw in the kidney and the same confirmation, that when the placebo patients roll over

into open label extension, they achieve zero scores and, very importantly, this is sustained now out into 30 months of the extension trial, representing three years of follow-up on these patients.

Now FDA has raised some questions about the five patients here who had zero scores at one time and then no longer had zero scores. We do have follow-up biopsies subsequently on four of these five patients, and they have zero scores at this time.

Now we focused initially on the capillary endothelial cells of the kidney, because FDA specifically asked us to focus on a specific cell type that was reasonably likely to predict clinical benefit. But appropriately, they then later wanted to make sure this was not an isolated finding within the kidney, and asked us to look at a number of different cell types as well.

So with the same renal pathologists and with those biopsies in hand, we looked in the glomerulus. We looked at glomerular endothelial cells, the mesangial cells. We looked at large vessel endothelial cells and interstitial cells, which play a

critical role in fibrosis.

In biopsies taken six months into the open label extension, you can see, for all of these cell types the vast, vast majority, in many instances approaching or actually at 100 percent of the biopsies, achieved a zero score. So this clearly demonstrates this was not an isolated finding. It was a much more robust finding, encompassing many cell types.

Now, however, to be fair, not all cell types clear at the same rate, and here we are looking at a number of the different epithelial cell types. This is the only slide I will show you where, instead of showing you zero scores, I'm showing you a reduction in score; and even here in the epithelial cells, they are slower to clear. But we did see marked reductions in the distal convoluted tubules, in the collecting ducts, in the smooth muscle cells. The podocytes are the hardest cells to clear.

Dr. Rennke will show you some examples of this and discuss the clinical relevance or lack thereof of these findings during his presentation.

Now, remember, we wanted to complement the morphologic assessments with a biochemical assessment. So this is the prospectively designed endpoint, secondary endpoint, looking for the decrease in the ranked sum score of GL-3 accumulation in the urinary sediment and the kidney tissue. Once again, this was achieved with a highly statistically significant finding, a P value of 0.003.

Plasma GL-3 levels -- again, a reflection of intracellular enzyme activity. We saw here that, with Fabrazyme therapy, patients very rapidly had median plasma GL-3 levels, went down well into the normal range, in most instances to undetectable levels, and remained so for the duration of follow-up.

In the open label extension trial the placebo patients also had a similar decrease that remained at the same low level for the remainder of follow-up.

It is important to note that the plasma GL-3 is an interesting marker in that it is a dynamic marker based on both preclinical studies and also in anecdotal experience in patients who missed a dose, we

see that plasma GL-3 levels start to rise in a relatively short period of time, in the order of weeks. So it is an interesting way of following patients long term perhaps.

I now want to turn our attention to our assessments of renal function. We assessed inulin clearance, and here I am showing you baseline and 12 months into the extension study for the placebo group and for the Fabrazyme group. As you can see, over this approximately 18 month period of time in each group, there was not a significant change over time in inulin clearance.

We had a large number of serum creatinine measurements over time. These patients started with serum creatinine measures well within the normal range. The means were 0.8 and 0.9, and these remained well within the normal range for the duration of follow-up, now 24 months into the extension or up to 30 months approximately of exposure to Fabrazyme in the original Fabrazyme treated group.

We looked at urinary protein excretion, and specifically we focused on urinary protein to

urinary creatinine ratios. We were very pleased to note -- and what I am showing you here are data from the 30 patients for whom we have values across this long period of time, over approximately 30 months.

We were very pleased to see that the median urinary protein to creatinine ratio was quite stable over time. When we looked into this a little bit further, it was very interesting that, if you looked at the changes in urinary excretion -- urinary protein excretion over time as a function of baseline urinary protein to creatinine ratio, those patients that had a low ratio at baseline in many instances had a decrease in urinary proteinuria.

This is perhaps reminiscent of the improvement in microalbuminuria that is seen i patients who have the effective ACE inhibitor therapy for diabetic nephropathy.

Because the pathologic changes are so critically important in the study, I would now like to turn the floor over to Dr. Helmut Rennke, who is Professor of Pathology at Harvard Medical School and head of the renal pathology lab at Brigham and Women's

Hospital, who will actually walk us through and show us examples of this pathology and its importance.

DR. RENNKE: Thank you. Next slide, please.

It is our premise that, as a result of ongoing ischemic damage due to the vascular accumulation of GL-3, Fabry patients develop progressive secondary renal pathology, and this is over time. This pathology is characterized by focal and segmental and eventually global glomerulosclerosis, tubular atrophy, extensive interstitial scarring, and eventually these changes lead to progressive end stage renal disease.

The clearance of vascular GL-3 is our premise. We prevent this permanent damage through improvement of the circulation. Next slide.

I would like to show you some examples of a pre- and post treatment, but before I do that, I would like to emphasize that these changes are all progressive. If you take an early and a relatively young patient, you will find that most glomeruli in these patients are preserved in terms of sclerosis.

The tubules are intact, and so is the interstitial.

It is, however, the microvascular that already shows the accumulation of GL-3. With time, this particular patient, an older patient, shows extensive glomerulosclerosis, extensive tubular atrophy as well, as well interstitial fibrosis. So these processes are all progressive with time. Next slide.

I am showing you now the comparison between pre- and post treatment examples. What you have here highlighted are the endothelial cells and the peritubular capillaries with the red arrows. They all show extensive accumulation of GL-3. Post-treatment, you see that this material completely disappears form the interstitial capillaries in these patients, and you saw already the quantitative data that Dr. Goldberg presented to you.

This is not unique to this particular cell type, as you know. We chose one particular cell type at the advice of FDA. But this is also seen in other cell types, not only endothelial cells in the glomerulus but the mesangial cells, the interstitial

cells which have important hormonal functions, the arterial and arteriolar endothelium, the smooth muscle of these vessels, distal tubular epithelial cells and, to some extent, of course, significantly less, the podocytes. I will come to that at the end. Next slide, please.

Here you have an example of high power under oil magnification of a glomeruli. Again highlighted by the red arrows are the endothelial cells, and you can see post-treatment there is complete disappearance from the glomerular endothelial cell, as I showed you before, for the interstitial endothelium as well as from the mesangial cells, here as highlighted by the yellow arrows. Prominent GL-3 accumulation in the mesangial cells and disappearance of this material in the post-treatment biopsies. Next slide.

Similar, the effects on the interstitial cells, as mentioned before, highlighted here again by the arrows. Prominent aggregates of the lysosomes, disappearance in the post-treatment period. Next slide.

The glomerular podocytes is a slightly different story. Even though we saw some significant change in some of the cases, the accumulation of this material was maintained in the majority of the post-treatment biopsies. We think that this is not as relevant as it appears morphologically, especially since, if you consider the early age patients that do have already significant accumulation in the podocytes, these patients very rarely have significant clinical manifestation.

In particular, the proteinuria occurs much, much later in the course of the disease, and therefore, we think that the podocyte or the epithelials in the glomerulus is much better protected from this accumulation. Next slide.

Here is an example that was published independently some years ago of a patient -- of a person that was considered as a potential kidney donor, and this patient was eventually studied by biopsy. They showed, even though the patient was completely asymptomatic -- this was a woman, by the way, retrospectively, of course, a heterozygote --

there was extensive infiltration by the GL-3 in the podocytes. However, this patient did not manifest significant renal -- and her renal function was entirely normal.

There are other studies in the literature of small groups of patients or isolated case reports in which the same phenomenon has occurred, namely presence of significant epithelial cell accumulation of GL-3 in heterozygotes with a cardiac variant, if you want, in some cases, in which there was minimal or no clinical manifestation, and certainly no end stage renal disease in these patients with the residual enzyme. Next slide.

I summarize this by comparing the classic Fabry patients to patients that have some residual enzyme, namely the female heterozygote, as previously shown, or the cardiac variant. What these two subgroups have in common is they do have residual enzyme activity, but they have no or minimal endothelial involvement, and these patients in general do not develop renal symptomatology or end stage renal disease.

In contrast, classic Fabry patients do not have residual enzyme activity. They have, of course, significant endothelial involvement and progressive renal disease. All three groups, however, have significant podocyte and tubule accumulation. Yet in the groups with minimal endothelial involvement, there is no progressive renal disease.

So from these observations from the literature, we conclude that the female heterozygotes and the cardiac variants, since they have residual activity, they have no significant endothelial GL-3 accumulation and, hence, the disease overall is much more benign, and certainly end stage renal disease occurs very, very seldom.

Dr. Goldberg.

DR. GOLDBERG: I would now like to review the safety profile for Fabrazyme.

There are only two types of related adverse events that occur to a statistically significant greater degree in the Fabrazyme treated patients compared to placebo, and these were fevers and chills or rigors.

These were part of a symptom complex of infusion associated reactions. These were mild to moderate in severity. They were generally transient in nature, and they were managed conservatively, usually with antipyretics such as acetaminophen and antihistamines.

Importantly, the number of patients experiencing infusion associated reactions has decreased over time, and it is worth noting that these infusion associated reactions usually follow seroconversion with IgG antibodies.

I show you on this slide examples of what I just said on the previous slide. On the x axis is visit number. What I am showing you here is the placebo population from our double blind, Phase 3 study. So you can see, during the placebo period, shown in green here, the patients haven't seroconverted.

They roll over to open label therapy at this point, and you can see subsequently there is an increase in the percentage -- This is a cumulative percentage of patients who seroconvert, and you can

see over the first several visits the vast majority seroconvert, and then it stabilizes out.

On the heels of this IgG seroconversion there is an increase in the frequency of fevers and chills or rigors, and this subsequently decreases over time to very low levels and remains so.

Now I do want to talk a little bit about the IgG seroconversion. It is quite important. Fifty-two out of the 58 patients developed IgG antibodies. The median time to seroconversion was six weeks. The median time to peak titer was just under three months. Then subsequently, over half of the patients have had declines in their antibody titers.

Very importantly, over the past year we have seen patients continue to have declines in those titers, and in fact, seven patients have tolerized. By tolerized, our definition of that is that there is no detectable antibody to Fabrazyme on two consecutive radioimmunoprecipitation assays. Also, importantly, there is no evidence of immune complex disease clinically, pathologically, or by laboratory testing.

Now a critically important question, one

which is being addressed to the panel today, is does this IgG seroconversion impact efficacy? I would now like to show you, based on several independent lines of evidence, that this does not impact efficacy.

First of all, if one looks at the double blind trial and we look at the ability to achieve a zero score based on whether a patient seroconverted or not, there is no significant difference in the ability to achieve a zero score. In fact, the P-value is 1.00.

Very importantly, we see sustained clearance from tissue and plasma GL-3 now up to three years. In fact, we have just very recent data that we haven't even submitted to FDA yet that shows that at 30 months into the extension trial, so three years of follow-up, the skin biopsies continue to show zero scores.

Also, I would point out that one should think about the plasma GL-3. I mentioned before a very dynamic mark in that, if you miss one or two doses, your plasma GL-3 levels begin to rise. Yet even though patients seroconverted very early in the

course of treatment, we have data out over a year showing that plasma GL-3 levels remained at undetectable levels.

Then additionally, renal function has remained stable in the vast majority of the patients during the follow-up.

Now the FDA on page 32 of their briefing document does focus on three patients who had high peak antibody titers early on in the study and had a decrease in the area under the curve of Fabrazyme concentration.

We have data that we would be happy to share with you which demonstrates that these aren't the only patients with these titers and that patients with very similar titers had actually an increase in the area under the curve, and we think that this change in the area under the curve over time is a biological variable that is independent of titer. However, most importantly, this reduction in AUC in these three patients that have been highlighted does not impact efficacy, again following these patients out for three years.

So you can see skin biopsies at 24 months, here at 18 months. The last biopsies are all zero. These patients also all achieved a zero score in the kidney capillary endothelium. Their renal function has remained stable as well, again indicating that IgG seroconversion does not impact efficacy.

Now we did look at hypersensitivity reactions, particularly when patients had certain symptoms such as pruritus or urticaria. In so doing, we identified two patients who, by an *in vitro* assay, were IgE positive. Both of these patients have been successfully rechallenged without significant adverse events.

Three patients were identified who had positive skin tests. Two of these patients have been rechallenged, one without any problem whatsoever, and the other had similar problems to what they had initially. This was primarily pruritus or urticaria and mild bronchospasm, and we are still working with those physicians for this patient to try to successfully rechallenge the patient. One patient is still awaiting rechallenge.

So in summary, less than 1.4 percent of the patients who have been exposed to Fabrazyme have had either IgE seroconversion or skin test positivity, and most importantly, no patient has experienced signs consistent with anaphylaxis.

Now with respect to serious adverse events, in our randomized double blind placebo controlled Phase 3 trial ten serious adverse events were reported, five in the placebo group, five in the Fabrazyme group.

None of these serious adverse events were reported by the investigators to be related to therapy. In fact, the most common serious adverse event was related to the biopsies of the kidney and the heart that were performed.

There has only been one death reported that was possibly related to Fabrazyme, and in that instance it is important to note that this patient had known severe heart disease prior to receiving the Fabrazyme, had a history of arrhythmias, in fact had a pacemaker implanted, and died at home ten days after Infusion Number 29.

So to summarize safety, the most common adverse events were primarily fevers and chills associated with these infusion reactions. They were generally mild to moderate in severity. They were usually managed conservatively, and they decreased over time.

Although the majority of patients developed IgG antibodies, this did not impact efficacy. No patient experienced signs of anaphylaxis, and the long term use of Fabrazyme is well tolerated.

Now when Ms. Lawton talked in the introduction about the accelerated approval mechanism and what is required of it, one of the requirements is that it is incumbent upon the sponsor to undertake Phase 4 trials that verify and confirm the clinical benefit.

Genzyme takes this commitment very seriously. I would now like to describe for you our Phase 4 program.

First, you will recall, our Phase 3 patients had a mean age of 30 years. Most of them had

normal -- did not have clinical manifestations of the disease, though it had very significant underlying pathology. Our goal there was to prevent further pathological accumulations and avoid, for example, renal damage.

In order to assess changes in clinical function over a shorter period of time -- and I'm still talking about several years -- we focused on an older patient population for our Phase 4 studies, and the average age of this patient population is in the mid-forties.

These patients have begun to manifest some clinical decline. Our goal here is to halt the pathologic accumulations and, in fact, reverse them and slow or stop the rate of further decline, clinical decline.

So let me review the design of that Phase 4 study. This is a multi-national, multi-center, randomized, double-blind, placebo controlled trial. Our sample size estimates led us to conclude we would need 70 patients enrolled in this trial.

These patients would have mild to moderate

renal insufficiency. There is a two to one randomization scheme with two patients receiving Fabrazyme for every one patient who receives placebo.

Based on our initial calculations as well as two interim analyses, we estimate that this study will take approximately three years to complete.

Now we wanted to focus primarily on preserving renal function and build upon our Phase 3 study. However, our investigators were very concerned that a patient could have progression of cardiac disease or CNS disease and still potentially be on placebo.

This led us to have as our primary endpoint a composite endpoint. It was event driven where, when patients had very clearly predefined progression of renal, cardiac or CNS disease, an event would be declared, and the patients would roll over onto active therapy with Fabrazyme.

Remember now, we are studying a subset, a small subset of an already small patient population. So to conduct this study, we have utilized 34 sites around the world. We have screened over 235 patients,

and again many of these patients failed screening, because they didn't meet the requirements of that mild to moderate renal insufficiency. They either had -- They were too mild or too severe.

Nonetheless, we identified, randomized and infused 76 patients, and we, therefore, oversubscribed this trial.

Now once the trial began, there were several design issues that were raised. The most important of these related to the ethics and the feasibility of completing a long term placebo controlled trial in a post-marketing setting with an endpoint of irreversible organ damage.

In order to address these concerns, Genzyme has proposed to the FDA a three-point program to modify this Phase 4 program and to expand it. The first step is to develop a Fabry Disease natural history database.

One could then utilize that database and look at the appropriate subset of patients to compare to our Phase 3 population. These are the patients with a mean age of 30. They have significant

pathologic accumulations but not yet the end organ damage leading to clinical manifestations of disease.

We are going to be following these patients for a total of five years. So it would be very nice to compare their outcomes to those from the natural history database.

Also, to address the concerns of the ethics and the feasibility in the post-marketing setting, we proposed initially to convert this Phase 4 trial to a single arm, active treatment trial, and compare patients to the appropriate historical controls from this database.

First let me update you on the status of our natural history study data collection. It is complete. Twenty-seven sites from around the world were utilized. We collected data on 447 unique patients.

The data were collected by an independent contract research organization with expertise in epidemiological studies. They used prospectively designed care report forms, and although -- It is important to appreciate that, although the data is

historical, it is fairly contemporary in that 71 percent of the serum creatinine measurements occurred after February of 1996.

Now as I mentioned, once we had this historical database in place, one thing that we could do is compare it to the rate of, for example, renal progression for the patients who are currently in our Phase 3 trial and its extension.

Here is a preliminary analysis that we did using matched historical controls, 57 matched historical controls this database, and comparing them to patients in our Phase 3 extension study. We used as an endpoint a 33 percent or greater increase in serum creatinine during a two-year period.

Five percent of our Phase 3 patients met this criteria for renal progression, whereas 11 percent of the matched historical controls met this criterion. This shows a marked reduction. However, it is not yet statistically significant. We expect that, with further follow-up, this will also reach statistical significance.

Now our Phase 4 program has evolved. As I

described to you, we initially proposed a randomized -- and we have conducted and well underway and fully enrolled a randomized, double-blind, placebo controlled, Phase 4 trial. Because of the ethics and feasibility concerns that were raised, we initially proposed to convert this to a single arm, open label treatment versus a historical control.

The reason for this proposal was that it has the advantages that it allows all patients to be treated, and it obviates the feasibility and ethical concerns. However, the FDA had concerns about this. They are well delineated in their briefing document, and I'm sure we will have a healthy discussion of these today.

These concerns focused on the comparability of the groups and the comprehensiveness of the data. We appreciate these concerns. They are understandable, and in order to address these concerns, we began a collaboration with Dr. Don Rubin, who is the professor -- he is the Loeb Professor of Statistics and Chairman of the Department of Statistics at Harvard University.

Dr. Rubin has extensive expertise in matching algorithms for historical controlled trials, particularly propensity scoring matching algorithms. He also has great expertise in imputing data. Together with Dr. Rubin, we have most recently proposed to the FDA not a traditional historical controlled trial, rather a randomized, blinded, placebo controlled trial that we have underway now, but modifying and supplementing it with carefully matched historical control data.

We believe this addresses the FDA concerns. However, we also appreciate that there is advantages and disadvantages of our original proposal and our current proposal, and we certainly welcome what I hope will be a healthy and vigorous discussion during the course of the day on these different proposals. However, we feel that when one factors in all the variables, the most appropriate approach would be this most recent approach that we have developed with Dr. Rubin, and I will now turn the floor over to Dr. Rubin to discuss this in more detail.

DR. RUBIN: Thank you, Mark.

The objective of this redesigned Phase 4 study is to modify the Phase 4 study from a randomized, double blind, placebo controlled design to a blinded, two-control group design. The first control group will be the placebo controls from the Phase 4 double-blind study. The second control group will be an appropriately matched subgroup from the historical study.

The objective will still be to compare renal rates of the Fabrazyme treated patients with the appropriate untreated controls from both control groups. Next slide, please.

Now there are three stages in the proposed analyses that we are going to be doing. The first stage is propensity score matching to select the historical control group. Propensity scores are a powerful technique that can be used to select historical controls who match the randomized group, thereby eliminating or minimizing bias between the two groups with respect to the variables, the covariates that were included to estimate the propensity score.

Of great importance, this design of an

observational study parallels the design of a randomized experiment, because we are blinded to the outcome data. The only criteria that have been used is balancing the baseline covariates.

The covariates that are being used in this study, the matching covariates, are two sets. These will be matched more closely on the other set, but they are basically gender, age, baseline serum creatinine, etcetera.

We also used matching methods that accounted for the missing data. That's of some importance, because in the historical dataset some of these variables are sometimes missing, as well as they are sometimes missing in the randomized experiment as well.

The end result will be a subset of historical patients as comparable as possible to the set of the randomized patients, as comparable as possible with respect to these covariates and the patterns of missing data. Next slide, please.

Propensity score matching has been around for about two decades, even though it is becoming

especially popular in recent years. This display shows just some fairly recent publications in medical journals that utilized propensity scores to matched, treated, and control groups. Next slide, please.

The propensity score is defined this way: It is defined to be the conditional probability of receiving a treatment given pre-treatment characteristics. So it is one number.

The probability is estimated probability that gets attached to each patient, both in the randomized group and the historical control group, that gives the probability, the estimated probability, that that person would be in the randomized group versus the control group. It is just an indicator variable as a function of all these baseline covariates, and they can be extended to include the missing data indicators.

Now the principal theorem of propensity score -- that's this theorem that Paul Rosenbaum and I did in this paper in 1983 -- is the following: That if you take a group of treated and control patients that are matched relative to their propensity scores -

- so they have matching propensity scores -- the differences between the two groups, on average, cannot be due to the observed covariates. This will become clear in the next transparency, I believe.

What this transparency shows are the propensity scores, the values of propensity scores -- this axis is propensity scores -- for the randomized patients, the 69 randomized patients that were available at the time that this analysis was done in November and the propensity scores for the 85 chosen historical controls.

That is, of the full database of historical controls, there are 85 who had propensity scores sort of within the range of the randomized patients. Of these randomized patients, about two-thirds of them are treated with Fabrazyme. About one-third are placebo controls. So one-third of these guys up here -- Randomly, one-third of them are going to be placebo controls. Next slide, please.

What these vertical lines display is what happens when you sub-classify, like standardize, on the propensity scores. Just like age standardization

except there is only one covariate that is being used, which is this propensity score, takes the place of age.

The claim of this principal theorem is that, within each group -- because within this group they have about the same propensity score, within this group they have about the same propensity score, etcetera -- that within this group, even though they only have been matched on the propensity score, they will have the same distribution approximately of all the variables going into the estimation of the propensity score.

So, for example, within this group they will have about the same age, randomized controls and historical controls about the same average age. They will have the same average baseline serum creatinine. There will be the same proportion male, etcetera, etcetera.

The same thing is true within this subclass, same thing here, same thing here. This proposed balance in covariates is also very easily checked, and in the documents we did very carefully

check it, and it works to balance the full set of covariates that went into the estimation of propensity score. Next slide.

The second stage of our analysis plan for Phase 4 is to multiply impute the missing data. Remember, there are two control groups, the historical controls who never had access to the treatment and placebo controls while on placebo in the current Phase 4 study. But both have missing serum creatinine data.

The imputation of the missing serum creatinine data for the two control groups will utilize data from the other. That is, the two groups have complementary patterns of missing data.

The Phase 4 placebo group, prior to open label -- so prior to when the drug became open label -- provides uniform short term measurements, because in fact, in the randomized experiment monthly serum creatinine measurements are taken.

The historical control group doesn't necessarily have uniform short term measurements, but it does provide longer term data, often greater than two years. So look at the long term progression of

serum creatinine. That will become clear in the next transparency.

This transparency displays the pattern of missing data among the 85 chosen controls. Each row represents one of the chosen controls. This is the baseline, baseline serum creatinine, which is available for all historical controls, and each dot represents a measurement for that person of serum creatinine.

So some people are incredibly dense with measurements; other people less dense, but they go far out. They go out beyond four years, which gives good evidence on what the long term progression will be. I want to emphasize at this point, although this is the real pattern of missing data, and so this really gives the true pattern of when measurements are taken or not, I have still not seen any outcome data, and I won't see any outcome data until certain decisions are made well into the future.

Now to get a feeling for how this works with the placebo controls -- next slide, please -- these vertical lines are aligned at each month. So in

the sense then that, if a historical control had the same frequency of measurements as a placebo control, there would be a dot at each one of these vertical lines. But you will notice that this is for the full three years of study, and many of these patients had data far beyond the three years, and also far beyond the point at which a patient who is in the randomized control may go open label for which the data will be missing. This will become clear in the next transparency.

Most imputation -- Well, before the blind is broken, an acceptable model for disease progression will be defined, for example, linear quadratic and one over creatinine versus time. We will see later why we suspect there will not be much sensitivity to the particular model chosen, even if there is sensitivity to the coefficients in that model.

Each set of multiple imputations will create one complete dataset. I want to emphasize that multiple imputation, although proposed quite a while ago, is now becoming quite standard, taking that we are dealing with missing data. For example, it is now

available in SAS. Next transparency, please.

These are hypothetical data, because they show outcome measurements, outcome measurements of serum creatinine, for a particular historical control patient. So this is data that's just created to illustrate the idea.

The vertical lines, again, are the monthly measurements that would be taken if this person were a random placebo control. The pink dotes display actual data, and they show the actual data for this historical control patient of the progression of serum creatinine.

The white dots are the created multiple imputations at each of the times that this person would have been measured, had he been a randomized placebo control. So there are -- At each point in time, there are five dots that are vertically shown which display the uncertainty in creating the imputations. There is less uncertainty right here, because we have a measurement the previous month. Less uncertainty there, because we have measurements, and they get more variable and then less variable and

continue out like that.

So there is an envelope of possible values that cover the range of possible real values for this historical control patient. In contrast, if you are a placebo control, you have measurements every month until you go open label. So you have measurements on placebo until you are on treatment, and then the measurements that you would have had, had you remained on placebo, are missing, and they are imputed. Again, there is more variability as you go farther out in time.

Go back to the previous slide just for a second. But because of these measurements far out in time for the historical controls, we have a good understanding of what this progression is like. We have a good trend. So -- next slide -- it is not nearly as difficult to do this as if we had no data from the historical controls.

So these patterns of missing data are complementary. This is not purely extrapolation. We have data of how to do this. Next transparency, please.

The stage 3 of the analysis plan is to compare the randomized treated patients to the control groups. At the end of the second stage, there will be complete datasets for both control groups, the matched historical control of 85 patients and the placebo control group of 25 patients.

When the study is completed, the renal events rates between the treated, the Fabrazyme treated patients, and both control groups will be compared; for example, using time to event analyses within propensity score subclasses, because within propensity score subclasses they have the same distribution of these baseline covariates that we have been able to match on. Next slide, please.

So in conclusion, the use of matching algorithms eliminates/minimizes potential sources of bias from the historical controls, due to all the coavariates that we used to estimate the propensity score.

The use of placebo controls retains the benefits of the randomized, controlled trial. It is very important that we are retaining the placebo

controls. It is also important doing the matching that we are blinded to outcomes.

Multiple imputation allows both sources of controls to characterize disease progression in the absence of treatment, and these datasets with their missing data patterns are complementary.

The randomized trial supplemented with historical control data, which is our plan, is a powerful method of verifying clinical benefit in a rare disease when the randomized trial really must go open label.

MS. LAWTON: I'd like to just finish our presentation this morning, just spend a few minutes just summarizing some points we would like you to consider during your discussions on the questions that the FDA have put to you this morning.

As I mentioned earlier, you have four questions with many subparts, but I am actually going to cover five key topic areas that I think the FDA have asked you to discuss, and go through each one of those individually.

So the first area for discussion is you

are being asked to consider the clinical outcome measures and the results seen from the Phase 3 clinical trial.

I think the first thing to remember which we believe is very important is that the Phase 3 clinical trial, the double blind, placebo trial, actually conclusively demonstrated the agreed upon primary endpoint.

More specifically, I think, neither Genzyme nor the FDA -- I think we agreed up front that we would not expect to see statistically significant improvements in pain or renal function, given the design of the Phase 3 clinical trial.

Objective clinical measures such as renal function certainly require long term data. It certainly requires much longer term data than the five months duration of the Phase 3 clinical trial. In particular, our natural history data at the moment would suggest that it actually requires greater than three years to see a difference in renal function.

We do have encouraging trends, as Dr. Goldberg talked about, that patients who have been

receiving Fabrazyme for up to 30 months actually show a slowing in the progression of their renal disease compared to an untreated matched historical control group.

Finally, I want to comment that we actually have over 24 different case series that have been presented as abstracts on patients who have actually shown clinical improvements in a number of different parameters, including renal, cardiac, and CNS outcomes, but we have really -- For the sake of time this morning and because of the anecdotal nature of those reports, we have chosen not to present them, but we do have all of that information with us, if anybody on the Committee would be interested to see that information.

The second point which we think you have been asked to consider is the histological endpoint and the clearance of GL-3 from the renal capillary endothelium to essentially normal levels.

I think both Dr. Goldberg as well as Dr. Rennke very nicely described for you earlier on how considerable endothelium cell involvement is

correlated closely with marked symptomology in Fabry patients, and in particular, as you reduce the endothelial cell involvement, we see a more mild symptomatic form of Fabry disease.

What we have demonstrated with Fabrazyme is we have certainly reduced, if not back to normal levels, the endothelial cell involvement. So at the very least we have shifted patients from a marked symptomatic phenotype to a more mild phenotype of the disease.

Specifically, we have shown this in the Phase 3 clinical trial with highly statistically significant results which were very robust. I would like to just comment that we have also repeated -- we have also conducted an additional clinical study in Japan as a Japanese bridging study, and all of this data has actually been confirmed in that second study in japan.

Finally, I think very importantly, in follow-up to a question from the FDA, we looked at many other critical cell types involved in the Fabry pathology, and we have shown clearance or significant

reduction of GL-3 in those other critical cell types.

The third point for you to consider is the potential impact of antibodies on the long term efficacy of Fabrazyme. I think that Dr. Goldberg, again, showed you, and we have certainly demonstrated, that we've seen sustained efficacy in patients, regardless of whether they have seroconverted.

In particular, we have shown this by sustained clearance of GL-3, both in the tissue and in the plasma. Very importantly, we have also shown stable renal function in these patients. This data is from both the Phase 3 clinical study as well as the long term follow-up in the Phase 3 extension study.

Importantly, we have seen the majority of patients who have seroconverted -- we've seen their titers reduce over time. Actually, we have seen a number of patients tolerize.

We recognize that managing this is an important part of treatment of Fabry patients with Fabrazyme, and indeed in our proposed labeling submitted to the FDA, we do have some details on how we would continue to monitor this.

The fourth point as far as the discussion, the FDA have asked for your advice on what to consider in looking at the verification of clinical outcomes.

One of the things -- If you consider that Fabry disease is a genetic disease where the patients are missing an enzyme, Fabrazyme provides that missing enzyme in a recombinant form. We have shown that Fabrazyme gets to the cells involved in the underlying pathology of the disease, and we have shown that that enzyme in those cells reduces the substrate to normal levels.

So it could be argued that, based on that, our clinical endpoint in our Phase 3 trial is actually tantamount to a clinical endpoint. If that is the case, then verification studies wouldn't be required.

In fact, in the FDA's own guidance they do talk about accelerated approval regulations would only be used when it is essential to determine effects on survival or irreversible morbidity. However, I do want to comment that our strategy -- Genzyme's strategy, and in discussion with the FDA and in agreement, has been the accelerated approval

mechanism.

So we have continued to pursue our commitments for the Phase 4 study. As you heard earlier, we have fully enrolled in that Phase 4 study. So assuming that indeed a Phase 4 study is required to confirm the clinical outcomes, we think there are some important points for you to consider when you discuss this aspect.

First of all, it is obviously important to take into account that we have a very small patient population of Fabry patients. Renal outcomes actually require very large numbers of patients and long term follow-up.

As we have mentioned to you, our current Phase 4 study is fully enrolled and ongoing and, therefore, meets the requirements of accelerated approval. But most importantly, the proposed modifications that Dr. Rubin spoke about, we believe, really provide an opportunity for maximum flexibility, optimal feasibility of a post approval setting -- in a post approval while ensuring that still have adequate for our Phase 4 study.

We believe that these details can actually be finalized in the post approval setting.

The fifth point, really, for you to think about during the discussions with regards to the verification of the clinical outcomes is the natural history database and the data that we have collected on the natural history of Fabry patients.

I think in FDA's questions they certainly talk about one of our proposals, and you heard earlier that one of our proposals was to convert our current placebo controlled trial into a historical controlled trial. I think it is important just to remind you that that is not our current proposal.

The proposal that Dr. Rubin spoke to you about, we believe, is actually a preferred method at this point. That is really supplementing the current placebo controlled trial by using matched historical data. We think this is a reasonable method for verifying the clinical benefit in this rare disease population.

We believe the proposed statistical methods that Dr. Rubin spoke about eliminate bias and,

certainly, it uses all the available data that we have to us, both from the historical database as well as the placebo control, the placebo patients.

Importantly, we believe it addresses the FDA concerns regarding the historical dataset and the use of that dataset. But, obviously importantly, it will allow all patients to have access to treatment for their serious or life threatening disease.

What I would like to now do is just very briefly go through -- In my introduction, I touched on the different aspects of accelerated approval. I would like to now just show you why Fabrazyme currently meets the requirements for each one of those aspects for accelerated approval.

Fabry disease is clearly a progressive and fatal disease. Current therapies for Fabry are palliative and, in fact, we have shown that Fabrazyme would indeed provide meaningful therapeutic benefit over these current palliative therapies.

Approval under accelerated approval regulations require adequate and well controlled clinical trials. We certainly have a multi-center,

placebo controlled Phase 3 clinical trial. We have confirmed the data from this trial with a cross-over in the extension phase of the study as well as with an additional study conduced in Japan.

As far as the use of a surrogate endpoint, I think we have demonstrated to you that the pathophysiology involved in Fabry disease really supports that, if you clear GL-3 from the capillary endothelium to normal levels, that that is indeed predictive of clinical benefit.

Finally, the last point of accelerated approval regulations is that post marketing studies would usually be underway at the time of approval. As we have already mentioned, we have a Phase 4 study fully enrolled and ongoing. We do have some proposals for how we can modify this, and we believe that those modifications can be conducted and finalized in the post approval setting.

So in conclusion, currently there is no treatment for preventing or slowing the progressive vascular damage and the results in end organ destruction of Fabry disease. Fabrazyme meets the

requirements, all of the requirements, for accelerated approval, and therefore, can be approved at this time.

Most importantly, if it is approved at this time, Fabry patients can be allowed access to Fabrazyme, and we can stop the progressive deterioration in these patients due to their Fabry disease.

So with that, I would like to -- That is the end of our presentation and, obviously, we would be happy to take questions from the Committee.

CHAIRMAN AOKI: Thank you, Dr. Lawton. Are there any questions from the Committee? Dr. Hunsicker?

DR. HUNSICKER: I have one question for Dr. Goldberg and three questions interrelated for Dr. Rubin.

To Dr. Goldberg, my question is: What is your anticipation of the impact of Fabrazyme treatment on the heart disease that is still present, for instance, in the patients who have the heterozygous form of the disease or the cardiac variant who does not have capillary deposits but still have,

presumably, myocardial deposits?

I realize this is something of an extrapolation, but I couldn't extract out of the data whether there was a substantial reduction of the deposits in the myocytes which are also involved.

DR. GOLDBERG: Sure. That is a very important question. First, with respect to the capillary endothelial cells of the heart, we did see very significant reductions.

Cardiac myocytes were much slower to change. We have not seen -- Very similar to the podocytes, these long lived cells, we have not seen as dramatic a reduction as we have with the endothelial cells.

Nonetheless, we -- and I think it is also important to appreciate for the cardiac disease, there is really a vascular component and a hypertrophic component which occurs much later in life. That said, we do have anecdotal data that we would be happy to share with you. This comes mainly from the commercial experience in Europe where, in fact, they have seen in a number of series and case reports decrease in

hypertrophy and improvement in function.

Actually, I believe that Dr. Grunfeld is here today, and I know that he has published an example of this, and he may be showing that. We have some slides that we would be happy to share with you as well, if the Committee would like. And Dr. Moscicki has those data.

DR. HUNSICKER: I leave to the Chairman the question of whether we do that now or later.

CHAIRMAN AOKI: Sure. Why don't we have it.

DR. MOSCICKI: As mentioned before, if I could go ahead and have the slides, we focused our presentation on rigorous analytic data of our own primary data for you to consider initially. But I think it is useful to look at the real world experience that is being reported by investigators over the past year in Europe and in Australia.

Now again, this data has not been reviewed by either us or by FDA, but it has been reported at major scientific meetings, and some of it has been published.

In the first three slides, you can actually see the fairly large number of these. There are 24 that have come out in this past year. Rather than take up your time with trying to go through these individually, if you will go on, I will try to quickly summarize many of these experiences.

Dr. Grunfeld is here, I understand. So he will cover the first. But on this slide you will see that, in fact, there are a number of case series in which patients also had abnormal renal function in a substantial number of these cases at baseline, and after one year of therapy in each of these, this abnormal renal function as well as the normal renal function has remained stable without further progression.

In fact, in the bottom you can see that the proteinuria has also been stable in those cases, and one young patient who was 17 and had proteinuria less than a gram for 24 hours, in fact, had a very marked improvement in that proteinuria. Next slide.

In this slide you can actually see that there is also a number of case reports. The first on

there is very interesting in that the proteinuria actually resolved in a patient who had been treated the longest, four years, had been initially participating in the Phase 1-2 trial, and a baseline creatinine clearance had improved.

Let me skip forward. This is more recent data on renal stabilization, and again I think it makes the same point that I made before. So let me skip forward to the cardiac, which was the emphasis of your question.

In this case there have been a number of case series from France, Dr. Guffon, and a number in Germany, Dr. Breunig, in which there have been a reduction in cardiac mass measured after one year of therapy with Fabrazyme.

For example, in the first case the mean cardiac mass was reduced from 159 grams to 127. In five out of five patients with Dr. Breunig there was a reduction in the posterior wall thickness by a mean of 2.2 millimeters, and in one of these patients there was a normalization of the baseline hypertrophy and diastolic dysfunction.

If you go to the next slide, here is more recent data from the German group which is very carefully measuring posterior wall thickness in their patients, and now with eight patients you can see that there is a reasonably consistent decrease that is beginning to occur in these patients in their posterior wall thickness. Next.

Here are some additional changes from many other case reports, also substantiating very similar kinds of changes. For example, Spinelli with another four patients has also shown a reduction in left ventricular mass.

I will jump down to Grek and Germain, who -- Dr. Germain is here today as well -- who describe seven patients with a conduction defect, which is not uncommon in patients with Fabry disease, a shortened PR interval.

They were able to demonstrate that that shortened PR interval is associated with a reduced -- the shortened PR interval was associated with an increased in GL-3 in the cardiac tissue, which improved after reduction in GL-3.

Waldec emphasized one of these cases, which I will show you in the next slide, which nicely illustrates this in which you can see a progressive increase in the shortened PR interval. A normal PR interval, I'll remind you, starts around 140 milliseconds. This then increased steadily at the same time that the ejection fraction in cardiac function increased and was associated with a reduction of GL-3 on the cardiac biopsy.

There are additional data on the next slide regarding CNS outcomes as well. For example, from France Dr. Guffon followed 11 patients over one year of therapy. Among these, five had reported a history of strokes or TIAs. Many of these were multiple and had occurred within the past year.

During the year of therapy and subsequently, there have been no further CNS events. This is interesting, because again CNS manifestations are specifically cerebrovascular in their nature, and one, of course, cannot biopsy the brain in order to look at the vessels. So such clinical data may be of use to the panel in considerations. I'll stop there.

DR. HUNSICKER: If I could put the other questions to Dr. Rubin, and I'll preface this by saying that the plan that you put up there is only roughly introduced in the stuff that we got from Genzyme and not at all -- and the FDA hasn't had a chance to respond to it. So that we are all coming into this a little bit cold.

As a consequence, I am not going to be able to be quite as precise as I'd like to be in putting the question. But with respect to the propensity scores, one of the questions that I had about the earlier proposal is that, when you have patients who come into a study as opposed to patients who first qualified based on your history, you realize that you get the people as they first qualified, that on average they are going to be earlier in the disease than they would be if they had dropped in sort of randomly.

Now you are correct for this with the -- in the propensity score for the creatinine difference. My question is: What is your estimate of whether the duration of disease difference, if you will, will be

corrected for? Are we actually going to get people who are properly matched up as to when we are starting to follow them?

DR. RUBIN: As you noted there, we chose the point in time for each historical control that gave characteristics closest to one of the randomized patients with respect to baseline creatinine and the other measurements.

So they will look similar with respect to those covariates at baseline.

DR. HUNSICKER: So in essence, you didn't necessarily take the patients when they first qualified, the historic patients when they first qualified, but rather when they qualified and actually looked as though they had gotten as far as one of the other patients?

DR. RUBIN: Exactly. We have a slide on that, but I don't think it's necessarily worth putting it up. So each historical control -- actually, there were several versions of each historical control, defined by which of the measurements will be considered the baseline.

The constraint was that that baseline had to allow him into the randomized trial, if he had been allowed in, and moreover, you had to have at least one measurement after that baseline. Corresponding to the requirement in the randomized trial, you have to be willing to at least stay for one more measurement.

So among each version of a historical control, we found the closest matching randomized person, and then used that matching randomized person to establish the baseline date -- used that version. And as a result of that, I think that, in fact, many of the historical controls were eliminated as not having a close baseline match.

So in this document -- in the report that was submitted, those details are there. But there were 85 chosen controls, but there were 90 controls who matched, and there were 117 historical controls who had exclusion criteria to be allowed into the randomized experiment, but of those 117, we reduced it first to 90 as not having a good match for the baseline value, and then reduced it to 85, because they didn't have propensity scores that were within

the range.

So I think we have done about as good a job as can be done to adjust for that.

DR. HUNSICKER: The second question deals with the -- or the second pair of questions deals with the issue of estimates of rates of progression. One of the major concerns that one has with the historical controls is not anything that you can correct for statistically.

It is that the world is different today from what it was and, as you well know, blood pressure control is better. Dr. Brenner is assured that we are now using agents that blockade the RA system much more consistently.

Now this will impact the estimates of the rates of progression from the historic to the modern. The method that you proposed is now going to use those longer term data to fill in effectively the data that are missing from the randomized trial, because the trial would be rolled over earlier.

DR. RUBIN: Right.

DR. HUNSICKER: To what extent will those

estimates of slope that might be more rapid historically than they are presently in the whole cohort be corrected by the data that we have from the current study? In other words, will in fact that be pulled down.

The question that is related to that is: When you get to the end of the study, what fraction of the originally planned observation time -- When you get to the point of conversion, when the study goes open, if things go that direction, what fraction of the total exposure time will have been completed in the randomized still double blind trial? So how much of the information are you, in fact, going to have to fill in from the historic control?

DR. RUBIN: Right. Those are both excellent questions. Because we will be building a common model for these slopes, not necessarily linear but just to talk about it simply, slopes using both the placebo controls while they are on placebo combined with the historical controls, you will get estimates of progression that are really informed by the randomized half of the -- randomized third of the

historical controlled trial. They get to fill in each other.

The long term results from the historical controls are used really to nail down the extrapolation. So we know what the progression is like. But the levels don't have to be the same between the historical controls and the placebo group. So we still do allow for some biases between the historical control group and placebo control group and the randomized.

It's not perfect, because the historical control group -- but what else are you going to do? I mean, we are really taking into account of everything that we can, I think, by this method.

DR. HUNSICKER: And the fraction of the exposure?

DR. RUBIN: Pardon?

DR. HUNSICKER: The fraction of the exposure, let me turn over to someone else who knows more about that, but I will say that, when you look at those plots, you may get the impression that there is a lot of missing data. We don't know what the

proportions will be in the randomized group, but there is a big difference between -- technically as well as intuitively, between fraction of missing data, fraction of data that is missing, and fraction of information that is missing.

An analogy would be I decide to measure -- Every time you come in, I am going to measure your height, and you go to the doctor, you measure your height. Well, if you measure it every month, it may vary a little bit, but you pretty much know what's going on. Even if half the height measurements are missing, it doesn't mean half the information about height is missing.

To the extent that we get stable progression of serum creatinine, for example, in the placebo controls and in the historical controls, the missing information will be much less than the missing data. But address the missing data proportions.

CHAIRMAN AOKI: I am going to have to ask you to hold. We have a series of questions from other.

DR. HUNSICKER: He's answering the

question about the duration.

DR. GOLDBERG: If we were to change now, we would have an average of 14 months follow-up of the patients who are in the placebo controlled trial.

I should also mention, we have ACE inhibitor data from the historical controlled trial.

CHAIRMAN AOKI: Thank you. Dr. Jennette.

DR. JENNETTE: Several questions for Dr. Rennke concerning the surrogate marker, the endpoint, primary endpoint.

The zero score, in fact, is not zero. It is referred to as essentially normal, but it is not completely normal in that, as I recall, a percentage of the most severely affected capillaries could be disregarded, and there could be a few lesions in some endothelial cells. You might make that statement a little more precise.

In any event, the point is that, if zero is the score, you can't go any lower. In fact, some of the patients with the zero score had some lesions. So especially in the follow-up of these patients, if you continue to assess the pathology, how are you

going to be able to determine if, in fact, they are getting even better than essentially normal and/or approaching normal?

DR. RENNKE: As you know, the light microscopy iteration of these inclusions is not perfect. The lysosomes sometimes can be confused by other inclusions that may not necessarily be GL-3 inclusions. This is what makes it so difficult in the proximal tubule, for example, where we didn't even attempt to try to characterize it, because of the frequency of lysosomes in those particular epithelial cells.

Coming back to the endothelial cells, when you see an isolated dot in one capillary, that is basically trace or not completely distinguishable as an inclusion and, therefore, an occasional capillary occurs. I don't have the exact criteria in front of me, but you are essentially right, that some endothelial cells had a single isolated inclusion that was considered as within the zero group. That is correct.

DR. JENNETTE: An unrelated question to

that. But with respect to the sensitization of the patients and the development of circulating IgG antibodies, in some of the follow-up biopsies after patients had developed IgG antibodies, was immunohistology performed to see if there is immune complex disease welling up?

DR. RENNKE: Yes, indeed. That study was done in Mass. General by Colvin and Collins. Both immunofluorescence and electron microscopy were performed, and in no case was there evidence of immune complex disease in the glomeruli.

DR. JENNETTE: And one final question, which is maybe more conceptual. But even if endothelial inclusions are the best surrogate or the best marker for likelihood of an improved outcome, isn't it still possible that that is really not the site of the major injury that, in fact, leads to the major deterioration of renal function and function in other organs? Could the podocyte accumulation or the mesangial accumulation really be more important pathogenetically, even if the endothelial cell inclusions are the best marker for outcome that you

can measure?

DR. RENNKE: I agree that every cell is affected by this condition, and obviously, every cell contributes probably to organ injury. However, the naturally occurring findings in the hemizygotes and in the cardiac variance suggest that, for example, the podocyte by itself is not that relevant, because these patients very seldom -- First of all, they don't present with a nephrotic symptom, which is what you would expect if the podocyte was really functionally damaged to a significant extent.

I am not saying that there is no damage, but clinically it has relatively little relevance, given the information that we have on this. There is no question in my mind that the presence of GL-3 in great amounts in the podocytes does something, but from the current information that we have, it does not lead to significant proteinuria. Fabry disease is not known to be a nephrotic state.

Number two, in those patients that have significant epithelial involvement, they do not -- and not endothelial involvement -- they do not manifest

significant injury from the glomerular point of view.

Yes, to summarize, there is a contribution, but we think the contribution is less than the vascular contribution.

DR. GOLDBERG: Can I briefly just clarify one point.

CHAIRMAN AOKI: Very briefly.

DR. GOLDBERG: The mesangial cells actually did clear as efficiently as the endothelial cells, and we also did a sensitivity analysis that -- you are right. It said five percent of the vessels could be outliers. We were taking into account that not all capillaries are necessarily profused. But as you can see in this slide, we did a sensitivity analysis where we said what if you required 96, 97, 98, even 99 percent of the cells to have a zero score in order to be counted, instead of 95 percent.

You still see a highly statistically significant difference.

CHAIRMAN AOKI: Dr. Sampson?

DR. SAMPSON: I would like to follow up on Dr. Hunsicker's question. In the current Phase 4

study, I understand you are looking at time to event as the response. So it is a hard question to answer.

If it were to be run to completion as planned, what is the current expected completion date of that?

DR. GOLDBERG: The last patient would be enrolled in January/February of 2004 with the analyses, locking the database and the study report -- it would go to FDA about August of 2004, and they would have until early 2005 to assess it.

MS. LAWTON; Just to clarify that, it won't be the last patient enrolled. It would be the last patient out in January '04.

DR. SAMPSON: And if that study, say, were terminated, just hypothetically, June 30th of this year, what would be the loss in power? Is there some sort of calculation on that vis a vis the original power planned for that study?

DR. TANDON: The power of the study was based on 14 renal events. So far we have 7 renal events, and we think --

DR. SAMPSON: Could you repeat that,

please, one more time?

DR. TANDON: The power was based on 14 renal events, and so far as of last week we had only seven renal events. Our assumptions -- I can show you the slide.

At the outset we put together -- This is blinded. I just wanted to reinforce here that we predicted based on interim analyses which was performed October 17 that we were expecting about five or six renal events, and we were able to calculate the duration of the total duration of the study. At that time we had only six renal events, and we predicted the total duration is about 35 months, which will be January of next year, as Dr. Goldberg said, that the study will be complete in August.

So probably, we believe that if we stop the study now or, say, in June, this will be an underpowered study.

DR. SAMPSON: If you were to -- I don't know if you have done this, but if you were to project the event rate for, say, another six months, and then look at the difference that you powered the study at

originally, what would be the power at that point? Do you have any idea?

DR. TANDON: If the events are all in the, say, for example -- We have not broken the blind, and I think what you are asking us: If you do an unblinded interim analysis, what will be the power of the study.

We believe that, if all the events were in the placebo group and none in the Fabrazyme group, then you have a power to conclude the efficacy. But I think that's extremely, you know -- You are talking all the events in the placebo group and no events in the Fabrazyme group.

DR. SAMPSON: Thank you.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: Yes. I have a couple of questions of clarification first.

You talked about renal events in this study. Isn't it a composite endpoint that includes stroke, TIA and so on?

DR. GOLDBERG: For the Phase 4 study, it is, but we have had discussions with the FDA. The

endpoint would be reached when there is 14 renal events. But the endpoint is a composite endpoint. That is correct.

DR. FOLLMAN: So even if you have seven strokes, you would be waiting for 14 renal events. And so you would have 21 events?

DR. GOLDBERG: Yes. I can tell you that right now there have been a total of 13 events. Seven of them have been renal events. Four of them have been cardiac events and two CNS events.

It is also important to appreciate -- and this is one of our secondary analyses -- the cardiac and CNS events, just about all of them, occurred within the first three months of the study, in fact some of them within the first few days. Very likely, these patients had vessels that were just about to occlude in which Fabrazyme really didn't have a role.

So in discussions, you know, we really wanted to focus on the renal events. We agreed that, while it is a composite endpoint, it would be 14 renal events that would determine the duration.

DR. FOLLMAN: Okay. The second question

of clarification is, I guess, directed toward Dr. Rubin.

I wasn't clear where creating a control group of 110 patients, which would be 25 of the Phase 4 controls and 85 historically randomized controls or if we are just taking the 25 Phase 4 controls and imputing creatinine data for them for the remainder of follow-up. That will be missed once the study becomes open label.

So is it a control group of 25 or 110?

DR. RUBIN: Well, the current view is that the control group --

CHAIRMAN AOKI: Could you raise the mike up a little bit?

DR. RUBIN: Okay. The current view is that the control group will consist of all 110 possible controls, both the placebo controls and the historical controls, but the analysis can still reflect that there are differences between those two groups. So that's where the ambiguity arose. So that when you have two control groups, there are indicator variables that can be interactions built in to

distinguish between the two controls.

DR. FOLLMAN: I would feel more comfortable with analysis that just took the 25 controls in the Phase 4 study and imputed data for them, because, you know, they are balanced and so on. They have been randomized, and you are just, in some sense, trying to accommodate a small fraction of the study that will be ruined once the study -- once it becomes open label. But if you bring in the 85 control group, so now you have 85 historical controls and now you have a sample of 110 in the control group, it is really basically an historical control study, and the randomized trial has mostly gone away.

So you know, I wasn't clear why the decision was made to bring in this much larger control group, especially if the study had been properly designed in power, and we are really just talking about imputing a bit of missing data toward the end of the study.

DR. RUBIN: I'm sympathetic with that comment, and it was ambiguous about how to treat the control group because of that. So maintaining the

distinction between the randomized placebo controls is, obviously, important. If there were any appearance of a substantial difference, I would agree with you -- a substantial difference between the randomized and the historical controls.

DR. FOLLMAN: I just feel more comfortable if we just stuck to the 25, no matter what.

Then finally, there is another way of approaching inference, I guess, with this Phase 4 study imputation that you are proposing. You could, for example, have the company give you 1001 datasets instead of a single dataset, where the thousand would be where the treatment and control labels are scrambled up.

If your method of imputation in calculating whether the treatment really works correctly or not, for those 1000 scrambled up datasets you should reject in all about five percent of the time. And if you don't do that, we just have to trust that what you are doing is going to work out and make sense.

You know, it sounds reasonable. You have

arguments. We can go back and forth on that, but it seems like there would be an advantage of sort of including this 1000 scrambled datasets to try and properly calibrate your procedure.

DR. RUBIN: I have no problem with that. In fact, I have often written papers about how you can do a Fisher test to handle noncompliance, for example. This is like that. There's some things, an imputation you want to do under no model and you want to make sure that you still get as close as you can to randomization based inferences.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: I have a two-part question, but before that just a comment on an important question that Larry had asked.

If there is, in fact, a difference in the time frame in which your historical control group is accrued and your experimental treatment group is accrued, and if during that time there is a difference in supportive ancillary care that, in fact, influences renal or cardiac or neurologic outcomes, there will be a confounding here that will compromise the

interpretation of the results, and adjustments for baseline covariates won't correct for that confounding.

Unless one has specific information on how those groups differ in terms of that ancillary care, one is not able to make that correction.

My question really relates to a very powerful statement made on slide 95. That statement was that normalization of GL-3 in the capillary endothelium is predictive of clinical benefit.

That's a strong statement. That's clearly a very critical issue as we look at the validity of a surrogate here. One of the best ways of actually getting evidence about that might be from the randomized clinical trials that are targeted to try to achieve that biologic effect as well as clinical outcome information.

We've heard that we have the Phase 3 trial, although we understand that there was a five-month follow-up which was argued to be inadequate to provide adequate power to see clinical benefit. At least it would have been interesting to see some kinds

of clinical trends in the data, and we saw the glomerular filtration rate data that was quite inclusive, but there were eight other measures, as I understand, that were presented.

I would like to know from the sponsor if the summary that I have gleaned from the FDA report essentially is that for the neuropathy impairment score there was a slight trend favoring placebo; for the neuropathy symptoms and change score there was no difference in change from baseline. The total symptom score, there was no change.

The SF-36 had identical end of treatment scores. The physiologic assessment of Fabry disease showed no difference between the groups. The symptom free days showed small trends favoring treatment. The episode free days had no difference, and the mean pain score showed very nice differences in both groups that were not different between the groups.

Is this, in fact, an accurate summary? You didn't show us any of these data, and are there further insights beyond this that you would like to show us about these clinical endpoints?

DR. GOLDBERG: Well, for the double blind portion, this limited five-month period, those are indeed accurate. Your statements are accurate. Remember, those were exploratory endpoints.

You know, this disease -- I would view it much more like treating hypercholesteremia. You are not going to see the long term benefit. It's going to take a long time to see the long term benefits on end organ damage. We didn't expect to see changes in pain. Certainly, we followed these things.

Indeed, with respect to some of the neurological assessments, Professor Max Hills has presented data not comparing the two groups but longer term follow-up out to 24 months. He has seen significant differences from baseline in things like vibratory threshold, heat sensation, ability to test to see differences in -- detect differences in heat sensation, and also in orthostatic stress changes that are improved to a statistically significant degree from baseline. But, no, the study was never designed or intended to show clinical benefit during that double blind period, and those points that were

explored were just that, just exploratory information.

DR. FLEMING; Well, understandably, it wasn't designed to be powered to prove differences in these endpoints, but by its design it was intended to explore and, at least when it was designed, because they were identified measures, I assume it was anticipated that it was possible to show differences. And not seeing trends and, in fact, in cases seeing trends in the wrong direction, doesn't at least serve as a reinforcing basis to have greater confidence in the surrogate.

We have seen -- You presented some anecdotal cases and, interesting, the anecdotal cases would seem to suggest maybe you could see differences in shorter periods of time. At least, though, putting aside then that clinical trial, what we would typically look for are substantial datasets that would allow us to explore the correlation between this marker or changes in this marker and clinical endpoints.

I will point out, even if we have that, we only have a correlate, and a correlate does not a

surrogate make. But at least getting your foot in the door here is a correlate, and I'm struggling to see where are substantial databases that we would have that would follow not anecdotal cases but substantial, carefully selected databases that would follow in time and really establish that normalization of GL-3 is a correlate.

If we can change it, change it in a sustained fashion, because this is a chronic setting, then we can have confidence that there was a correlation between such a change in clinical benefit.

Is there such a database?

DR. GOLDBERG: Again, if you are talking about clinical trends, the trends in the renal function, I think, over a long periods of time are what we would be most comfortable with, and we both -- I think it's fair to say that, you know, we've seen now for 36 months stabilization in these patients, the vast majority of these patients, and we would expect the --

DR. FLEMING: Can you show us these data again, the data that shows for the entire cohort --

DR. GOLDBERG: We showed you the mean -- in the primary presentation, the mean changes.

DR. FLEMING: Could we see again how, for an entire cohort, we see a correlation between changes in the GL-3 --

DR. GOLDBERG: Again, what I'm saying is it's stabilization in renal function is what one would expect. The goal here is to prevent deterioration. And so we see stabilization over periods of time.

DR. FLEMING; Well, what I would like to be seeing, presumably, is something to the effect that in a cohort where we see normalization of GL-3 for an extended period of time against a cohort in which that is not achieved, that there is, in fact, an association between that and meaningful clinical outcomes.

DR. GOLDBERG: Sure. But again, in the double blind study, the 29 patients, essentially all -- not all, but the vast majority of patients did achieve a zero score in those endothelial outcomes, and here you are seeing that in both groups, now out to, you know, up to 30 months of treatment, 24 months

into the extension period, renal function is well within the normal range and has remained so. Same thing with the inulin clearance data we have.

Serum creatinine data is certainly much more extensive. I think this is supported by the stabilization of proteinuria over the long period of time as well. These are things that in similar diseases one might expect to see progressions in proteinuria, for example, and indeed we saw some improvements.

DR. TANDON: Dr. Fleming, I want to correct one thing there, that we saw some trends in some secondary and tertiary endpoints, and tertiary endpoints symptom free days and episode free days. That was prospectively defined in the protocol, and the trends which we have seen, those are meaningful trends. They will never reach statistical significance.

As you can see on this slide that we are talking a number of days pain medication taken, for example, placebo on average of 65 days versus 58 days here, and number of symptom free days. I think you

want to say intention to treat? No?

DR. FLEMING: But when you are looking at the neuropathy impairment scores, weren't those slight trends now in favor of placebo? I mean, basically, in the aggregate, aren't we looking at very slight trends with a lot of measures, a few in favor of placebo, a few in favor of intervention?

DR. TANDON: One thing I just want to point out. This episode free days and symptom free days has been used quite a bit in asthma trials, and you clearly can show that in the Fabrazyme group there are more episode free days compared to placebo group, and they did not reach statistical significance. We know that, because of the high variability here.

We never expected that to be significant. There is a trend emerging, but these are trends which, we believe, are meaningful, but they are not statistically significant, because you need almost 200 patients to do this kind of trial.

CHAIRMAN AOKI: Okay, last question, Dr. Woolf.

DR. WOOLF: In the supplementary data

there was a cessation of cerebrovascular events. There were no more TIAs or strokes. These are macrovascular events. The surrogate is microvascular marker. I am struggling to understand the pathogenesis of that observation.

DR. GOLDBERG: In this instance, I think there is maybe an analogy that can be made to, say, sickle cell disease where you get -- in the intima of these large vessels, you get -- from the small capillaries, you have these abnormal vessels. They are inflamed. You get fibrosis and scarring, narrowing of the vessel, the larger vessels, leading to the ultimate strokes and TIAs.

That, I think, is a similar mechanism that has been seen in, for example, diseases like sickle cell.

DR. WOOLF: But the time frame was virtually immediate. It would suggest that scarring wouldn't be reversible in that time period.

DR. GOLDBERG: I'm sorry. Say that again.

DR. WOOLF: The time frame for the cessation of the cerebrovascular events was immediate.

It happened within days.

DR. GOLDBERG: Now you are talking about the data that Dr. Moscicki showed, which was clinical experience from patients in France treated on ATU, and I believe, you know, they have followed those patients out for a year, and they've seen -- Their data are that they haven't seen anymore strokes in that patient population. They were more advanced patients, presumably.

DR. HUNSICKER: Dr. Aoki, could I ask for one thing, either now or later?

CHAIRMAN AOKI: Dr. Grady. I think that's the last question.

DR. GRADY: You know, we have been talking about this statistical issues surrounding this historical control, but I would really like to be clear about the data.

Am I correct in understanding that the historical control group -- were those patients ever examined or interviewed or surveyed, or is this entirely based on medical record extraction?

The second question is: Don't you have

more variables that could be used in propensity score analysis rather than the five or so you have used? I mean things like presence of hypertension, presence of diabetes and various treatments and so on. It seems like a limited set of covariates.

DR. GOLDBERG: The patients were not examined. This was an IRB approved study, medical record. Informed consent was obtained, and medical records were reviewed, and we presented to you, I think -- and Dr. Rubin, if you would allow him to discuss it further. But this was one approach of the covariates that could be used.

Certainly, we could explore using additional covariates or other covariates very easily.

CHAIRMAN AOKI: Okay. We will now take a ten-minute break, meeting back here at 10:15.

(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: I would like to start so we can be semi on schedule. Could you take your seats as quickly as possible so that we can begin again.

Okay. Our next speaker is Dr. James Kaiser, the Medical Reviewer for CBER. Dr. Kaiser.

DR. KAISER: Members of the Advisory Committee and consultants, thank you for your attention. I am Jim Kaiser, the clinical reviewer for this BLA from CBER's Division of Clinical Trials.

The primary purpose of my presentation is to outline the information that Genzyme has developed to support a marketing application for their recombinant human alpha galactosidase for Fabry disease. As part of this presentation, I will discuss Genzyme's plan to redesign a trial whose objective is to verify that agalsidase beta confers a clinical benefit.

Throughout this presentation, I will refer to Genzyme's product as agalsidase beta. This is the name given by USAN, the United States Adopted Names Council.

Agalsidase beta is proposed for use as a long term enzyme replacement. The proposed dose is 1 mg/kg intravenously every other week. Genzyme has requested approval for agalsidase beta under an

accelerated approval framework.

This slide gives the order of topics that I will be discussing today. First I will present a brief overview of Fabry disease.

Fabry disease is caused by an X-linked deficiency of the activity of alpha-Galactosidase. It affects males predominantly. It is thought that accumulation of the enzyme substrate, alternatively called GL-3 or GB-3, results in the clinical manifestations of the disease.

This accumulation may occur in many different cell types throughout the body, vascular endothelium, perithelial, and smooth muscle cells of the vasculature, histiocytic and reticular cells of connective tissue, epithelial cells of the cornea, glomeruli, and tubules of the kidney, muscle fibers of the heart, and ganglion cells of the autonomic nervous system.

Early manifestations of the disease include pain, burning and tingling in the arms and legs, vascular skin lesions called angiokeratomas, decreased sweating or hypohidrosis, and corneal and

lenticular opacities. Morbidity and mortality are due to complications in the kidney, heart, and brain, renal failure, arrhythmias and myocardial infarction and strokes.

There is no approved treatment in the United States. Patients are treated for the manifestations of the disease.

Fabry disease meets criteria for designation as an orphan disease population. There are estimated to be several thousand males with the disease in the United States.

Genzyme's agalsidase beta has been granted orphan designation for the treatment of Fabry's disease. However, it is important to note that the standards of evidence to gain marketing approval for products with orphan designation are no different from those used for non-orphan designated products.

This is an overview of the major trials conducted by Genzyme. In addition, there are special access protocols involving a few subjects in the United States and other countries and post-marketing experience from Europe. The trials marked in yellow

have provided bioactivity data, those in white safety data only.

My discussion of Genzyme's clinical results will focus on the principal trials conducted by Genzyme. The first trial conducted in humans was FB9702. This was a trial of 15 males with Fabry disease. Subjects were sequentially divided into groups of three receiving one of five regimens in an open label fashion, 0.3, 1.0 or 3.0 mg/kg every 14 days, or 1.0 or 3.0 mg/kg every 48 hours. Subjects were not randomized.

Biopsy samples of liver, heart, kidney and skin were examined by a pathologist specialized to the organ in question, blinded to sample sequence. The degree and extent of glycolipid inclusions were graded on a scale from zero to three, normal, mild, moderate, and severe, based on an overall judgment of light microscopic appearance of the slide. Pharmacokinetics and safety were also assessed.

The results of FB9702 are briefly summarized as follows. Routine stains for the liver didn't work, so that these data were uninformative.

However, electron microscopy showed reductions in GL-3 in some cell types, sinusoidal endothelium and Kupffer cells and, variably, in hepatocytes.

For skin, heart and kidney where paired samples existed, capillary endothelium showed reductions in score. For each organ, cells other than capillary endothelium, podocytes, myocytes, perineurium did not show as robust a reduction response.

Most subjects had total GL-3 determinations for skin and liver, and most showed reductions. Fewer subjects had GL-3 determinations for kidney and heart. Four of the five available paired kidney biopsies showed reductions. Results in the heart were quite variable. Plasma GL-3 levels fell in all groups.

Terminal half-life of agalsidase beta was about one to one and a half hours. Higher doses yielded higher than proportionate increases in area under the curve and Cmax. There was no clinical effect observed on multiple physiological and imaging tests in this short trial.

In terms of safety, no deaths occurred. Two serious adverse events occurred in this trial. One subject experienced a serious infusion associated reaction that required cessation of treatment and medical treatment. Pulmonary emboli occurred in a subject who was otherwise at risk.

Four subjects experienced nonserious infusion reactions that resulted in slowing or stopping of the infusion or medical treatment or both. The rest of the safety record was unremarkable.

In conclusion, there was a reduction in histological and total GL-3, no clinical benefit in this short study, and some infusion reactions.

I will now discuss AGAL-002, Genzyme's only completed controlled trial of agalsidase beta. This trial was the principal source of data to gain marketing approval.

AGAL-002 was a double blind trial of 58 subjects with Fabry disease randomized one to one to placebo infusion or infusion of agalsidase beta, 1 mg/kg every other week.

The original duration of the trial was to

be six months. It was shortened to five. The objectives of the trial were to show activity and safety. Subjects were to be at least 16 years old with clinical features of Fabry disease in plasma or leukocyte alpha galactosidase activity set within limits. They were not to have advanced renal disease.

They were also not to have other clinically significant organic disease unless attributable to Fabry disease.

Baseline and end of trial biopsies were performed as the main outcome evaluations. Clinical laboratories were collected, and antibody determinations made.

The primary endpoint was originally proposed as a composite of kidney, skin and heart capillary endothelium. However, after consultation with CBER the endpoint was changed to reflect capillary pathology in one organ, the kidney.

Genzyme established procedures for evaluation of biopsy slide quality and subsequent transport in a blinded fashion to a panel of three kidney pathologists. Pathologists attended a training

session in which they were familiarized with the contents of a training manual providing the criteria for coding slides.

Each of the three kidney pathologists received blinded samples and rendered a severity score from zero to three, evaluating the amount of substrate deposition in the capillary endothelium cells. This initial procedure was conducted prior to CBER concurrence.

In consultation with CBER, to provide a quantitative and consistent method for scoring, Genzyme developed and implemented a rereading of slides that, on initial reading, were zero or one. This procedure involved quantifying the amount of substrate inclusions using a zero, trace, one, two, and three score individually in each capillary on a slide.

The criterion for a zero score was that the capillary cross-section was devoid of any substrate; trace, that only one small inclusion was visible. An algorithm was employed to assign an overall slide score of zero to three based on the

portion of capillaries in a given slide with various scores, after disregarding the worst five percent of capillaries.

A slide score of zero indicated that all capillaries had scores of only zero or trace and that more than 50 percent were zero. This was designed to differentiate biopsies where near normalization of the capillaries had occurred from those that, even if reduced in deposition, were not essentially nearly normal in appearance.

It should be borne in mind, however, that since up to just less than half of the capillary cross-sections could still have trace amount of substrate, and the slide sections were quite thin compared to the surface area of a capillary endothelial cell, it is possible that, even with a slide score of zero, all endothelial cells could still have a speck or two of substrate somewhere within them.

Consequently, we refer to the endpoint as assessing near normalization, not complete clearance of the substrate.

The endpoint analysis was a comparison of the number of subjects per group with a score of zero. The secondary endpoints of AGAL-002 were pain as assessed on the McGill short form Pain Questionnaire; a composite score of kidney, heart and skin capillary endothelium GL-3, histologically determined; and total GL-3 in urine and kidney tissue.

The trial contained numerous physiological, imaging and questionnaire type endpoints that will be discussed later.

The major protocol changes that occurred after the initiation of the trial have been mentioned: Recrafting of the primary endpoint, a rereading of the lowest scoring renal slides; and shortening the trial to five months. These changes were made before unblinding of data.

Eight sites enrolled subjects. By far the largest site enrollment was at Mt. Sinai.

Treatment assignment errors occurred. The four-subject treatment misassignment occurred when the contractor preparing study kits did not apply the proper markings to the outside of the kits prior to

sending them to the study site.

The study site assigned kits to patients in an unbiased manner, but not using the random code number intended by the central randomization list. We regard these patients as having been randomly assigned to treatment groups, albeit not by the prospective centralized randomization list.

The treatment errors for the two subjects at another site occurred due to a misunderstanding of treatment misassignment within different departments at Genzyme that led to an attempt to correct a presumed kit use error that had not occurred, and resulted in two patients having treatment switched on the fourth infusion and maintained for the remaining doses, the majority of the trial.

There was no evidence that the treatment misassignments were done knowingly or that the blind was broken. The primary study analysis reviewed by FDA includes these subjects in the groups according to the treatment received, not the central randomization list assignment.

Finally, adherence to trial drug infusion

and dose amount was excellent. Demographs and baseline characteristics were well balanced. The reason blood type is mentioned is that alpha-Galactosidase catabolizes blood group B specific glycolipids. Persons who are blood group B or AB may be more severely affected due to additional accumulation of these glycolipids.

The numbers of females was small, predictably. The distribution of white and non-white was similar. I'm sorry. The distribution -- There was about 90 percent white in both groups. I misspoke.

This slide shows baseline and end of trial primary endpoint results, kidney capillary endothelium scores. The column denoting biopsy scores is on the left. Columns are organized by baseline score, then end of trial score for each treatment group.

Baseline slide scores were reasonably well balanced, but there was a dramatic difference in the number of zero and non-zero scores at the end of the trial, five months, favoring the Agalsidase beta group. The P-value is on the chi-squared test for

numbers of zero or non-zero scores.

Thus, this study solidly demonstrated a treatment effect on the capillary substrate accumulation. The patient biopsy score, marked with an asterisk, is an attributed worst score for a biopsy that was not obtained.

Several important supportive analyses conducted by Genzyme are shown here. All pathologists gave the Agalsidase beta treated group many more zero scores. Six of eight sites showed more zero than non-zero scores at the end of the trial. The other two sites did not contribute to the effect but had small subject numbers from which conclusions cannot be drawn.

There is no affect of age. There were two few non-white and women to render any conclusions regarding differential bioactivity in these populations.

Manipulation of the method for counting capillary scores in individual slides did not alter the predominance of zero scores in Agalsidase beta over placebo.

CBER examined the distribution of change from baseline scores as a function of baseline plasma or renal GL-3. There was no notable pattern of change scores.

In summary, the activity of Agalsidase beta on the reduction of renal interstitial capillary GL-3, the primary endpoint, was robustly shown in this trial.

I will discuss two secondary endpoints now, pain and a combination of heart, skin and kidney histology.

Results of the McGill Pain Questionnaire showed no treatment associated differences. Both groups showed a marked decrease in pain score during the course of the study.

The secondary outcome, composite score on renal, skin and heart capillary endothelium, contains kidney results that have been shown before. This table shows results on heart, upper rows of table, and skin, lower rows of table, only. These results were based on an overall judgment of the slides and not a quantitative method such as the one used in the

primary endpoint.

The results are expressed as numbers of subjects with zero scores. Columns represent baseline and end of trial scores in the placebo an Agalsidase beta groups. Baseline scores were comparable between the two groups.

The great majority of Agalsidase treated but not placebo treated subjects had end of trial zero scores for both organs' capillary endothelium. The P-value for the chi-squared test on the number of zero scores at the end of the trial was less than .001 for both organs.

These results show clear consistency with renal interstitial capillary endothelium.

I will discuss briefly the results of additional secondary and other endpoints, antibody and pharmacokinetic data.

Urinary GL-3 data were inconclusive. Urine for GL-3 was determined on a subset of subjects, as samples from two sites were not evaluable. In addition, the median change for placebo during the trial was considerably positive, a median 43 percent

increase, which is unexpected.

The reliability of the result for the kidney is greater. Agalsidase beta treatment resulted in a 34 percent median reduction in total GL-3 compared to a six percent median reduction in the placebo group. The P-value for the difference in change between treatment groups was 0.003, using the Cochran-Mantel-Haenszel test.

Renal function results are very important to Genzyme's clinical aims. Neither GFR nor serum creatinine showed any treatment effect. However, it is important to note that the subjects in this trial had normal baseline renal function and that placebo subjects retained normal function to the end of the trial.

No other laboratory or clinical findings showed a treatment effect. These included various physiological tests and symptom assessments.

In terms of antibody, nearly all of the subjects receiving Agalsidase beta, 24 of 29, developed an IgG titer against it at some point during the trial. The earliest time to development of an IgG

antibody to Agalsidase was month one, the latest month five, the end of the trial.

There was no evidence that development of antibody affected the achievement of a zero score in this relatively brief trial.

Pharmacokinetics was analyzed in only 11 treated subjects. The pharmacokinetic response following repeated dosing fell into three basic patterns of the area under the curve. A few patients had no change in AUC during the study. A few patients had pharmacokinetic values change at mid-study relative to first infusion and return to initial values at the end of the study.

There were three patients whose pharmacokinetic values declined and remained lowered at the end of the study. AUC and maximal concentration were reduced to about one-quarter of the initial values. These latter three subjects were those with the highest antibody titers, greater than 12,800 at visit 11. The development of antibodies did not alter the terminal elimination half-life.

I will now discuss the safety record of

this trial. There were no deaths in this trial, and serious adverse events did not show a concerning pattern. Infusion associated events were the chief concern.

Sixteen of 29 agalsidase treated patients and no placebo treated subjects had infusion reactions. Suspected hypersensitivity reactions occurred in 12 of the 16 subjects with infusion reactions at the fourth infusion or later. Symptoms in some subjects included chest tightness and shortness of breath, itchiness, flushing, wheezing, and hypotension, as well as the more common shaking, chills, and fever.

These infusion reactions occurred in some subjects, despite the institution of steroids in addition to the routine pre-infusion medications. With pre-treatment, the events were mostly of mild to moderate severity, but infusion rate adjustments and medications were instituted in most cases.

With treatment, infusion reactions resolved. All subjects completed their trial regimen of infusions. Most, but not all, subjects with

suspected hypersensitivity reactions had serum IgG to agalsidase consistent with the overall seroconversion rate.

Although IgE was not tested for every reaction, serum IgE was not found in the great majority of subjects at the last infusion tested, indicating that serum IgE was not required for infusion reactions.

The presence or absence of leukocyte alpha galactosidase activity or protein did not correlate with the presence of an infusion reaction. There remains no way to predict who will get infusion reactions.

Other nonserious adverse events showed no concerning pattern. Pain and Fabry pain occurred slightly more in treated subjects but not much more in terms of the severe events. The database was searched for events correlated with the development of antibody antigen complexes, but these were not found in greater abundance in the treated group.

In conclusion regarding AGAL-002, AGAL-002 was the largest controlled experience of agalsidase

beta to date. Primary endpoint of this trial showed robust effect on renal endothelium histology.

There were no differences between the groups on clinical efficacy outcomes. Infusion reactions were common and sometimes severe. Antibody reactivity was common.

Next I will discuss results from the extension trial, AGAL-005. This trial has the most long term data available.

AGAL-005 is the extension to AGAL-002. In it, all the subjects from the control trial were enrolled and treated with agalsidase beta at the proposed dose.

The most important procedures performed in the trial are biopsies. At six months subjects received skin, kidney and heart biopsies. Beyond that, only skin biopsies are a protocol requirement.

The principal effect measurement is kidney histology GL-3. Serum and urine labs, antibodies, clinical status, and safety are determined.

The primary outcome of the open label extension is kidney interstitial capillary endothelial

GL-3 as determined histologically. This table shows results of kidney interstitial, superficial skin, and heart capillary endothelium at six months of the extension.

Totals reflect the availability of biopsies and not the full complement of subjects. However, the majority of subjects are represented. These results show that the majority of subjects newly switched to agalsidase beta had a score of zero at six months for each organ's capillary endothelium. Subjects maintained on agalsidase beta six months beyond the initial five months of the control trial also had scores of zero.

CBER sent an Initial Complete Review Letter in December 2000 describing the FDA's assessment of the information submitted at that time. In the Letter FDA acknowledged that agalsidase beta had shown an effect on endothelial cells.

FDA raised a concern over the ability of the surrogate to predict clinical benefit. Renal function was not affected during the study, and it would be possible that years of treatment would be

needed before benefits would be seen.

Histologic findings were not uniform across all cell types. Certain cell types in the kidney, skin and heart did not show reductions in accumulation.

Infusion reaction information was limited. Some reactions were severe. There was a concern raised over the possibility of an increase in frequency or severity with duration of use. The data had provided an insufficient basis upon which to predict an individual's susceptibility to the occurrence of an infusion reaction.

The development of antibodies was widespread, with the potential for a diminution of effect possibly prior to any clinical effect. The six month data from the extension study did not alleviate the concern over long term use.

As Genzyme had requested accelerated approval regulations be used, a clinical benefit verification study was necessary, and FDA had concerns regarding the plans for this study. FDA expressed concerns over the adequacy of powering of the study

and the feasibility to complete the trial in a post-marketing circumstance.

After receiving this Letter, discussions between FDA and Genzyme occurred, resulting in a complete response from Genzyme in April 2001. As has been noted in the introductory presentation, there was a series of interactions, submissions and reviews during this BLA. The remaining portion of this presentation will discuss the information received not only in the April 2001 submission but also in subsequent submissions through the latter part of 2002.

The original three pathologists who performed analyses in AGAL-002 performed analyses of additional cell types in renal biopsies from baseline, end of AGAL-002 and at six months of AGAL-005. The quantitative reading of slides was not performed. Rather, an overall judgment was made of severity of the inclusions of GL-3.

This table is a partial summary of additional renal cell types analyzed. Patient score at the end of the control trial for these subjects is

not shown on this slide. However, for the cell types shown, no placebo and the great majority of agalsidase beta treated subjects had shown reductions in scores to zero at the end of the controlled trial.

This table shows numbers of subjects with zero scores at six months of AGAL-005 for the subset of subjects with non-zero baseline scores at the start of 002.

The columns designate placebo crossovers to agalsidase beta and agalsidase beta continuers -- continuers and crossovers. For the four cell types shown, the majority of subjects had a score of zero at either six months of treatment, placebo crossovers, or 11 months, agalsidase beta continuers. Results were not quite as dramatic with certain other renal cell types.

Podocytes and mesangial cell matrix showed no notable effect of treatment. For noncapillary smooth muscle cells, the minority of subjects experienced a score of zero even after six months of the extension. However, the majority of subjects experienced some reduction in score while treated with

agalsidase beta.

For distal convoluted tubule and collecting ducts, at six months of the extension between one-half and two-thirds of subjects with non-zero scores at baseline had some decrease in score from baseline.

In conclusion, many renal cell types, but not all, showed notable reductions in histologically determined GL-3. Six-month results were also submitted for skin perineurium. There was no effect of agalsidase beta on the perineurium of the skin at six months of the extension.

The most long term histology data are available from the skin biopsies. Results are available for the majority of subjects at 18 months of the extension, which is equivalent to 18 months of treatment for the subjects who crossed over form placebo, and 23 months of treatment for agalsidase beta continuers.

In data not shown on this slide, the great majority of agalsidase treated but almost no placebo subjects had zero scores for their superficial and

deep vessel capillary endothelium after five months of the controlled trial.

This table shows the numbers of subjects with scores of zero, 18 months. Skin superficial capillaries are in the top row. Deep vessel capillaries are in the bottom row. The majority of placebo subjects experienced a reduction to zero, and the majority of agalsidase continuers kept their zero scores.

The results shown in the table revealed a possible concern over attenuation of the response to agalsidase beta. For superficial vessel endothelial cells at month 18, there were five subjects who experienced an increase in score from zero to non-zero compared to an earlier biopsy.

For deep vessel endothelial cells, there were six agalsidase continuers who experienced an increase in score from zero to non-zero. Genzyme submitted additional data to address the observation in superficial capillary endothelium at 18 months.

This slide shows 30-month results for four of the five subjects with increases in scores at 18

months, showing that the increases were temporary. Each row is a subject. These are the 18-month results that seem to show an increase, and these are the 30-month results.

We understand that Genzyme has 30-month results on other subjects. These will be useful for FDA to review. The score marked with an asterisk is really a 24-month score, and n.d. means not done. Month 30 deep vessel capillary evaluations were not available.

This slide briefly encapsulates the rest of the important clinical results. There were no changes in GFR or serum creatinine during the 18 months of the extension trial. Once again, it should be noted that the subjects started with normal renal function, and the time to deterioration of renal function is unknown.

Three subjects had remarkable rises in serum creatinine. The reasons for these deteriorations are not clear. Genzyme has postulated a possible connection with prominent glomerular sclerosis at baseline.

Urinary GL-3 data were based on a subset of subjects with a large amount of variability, making quantitative interpretation difficult. Plasma GL-3 fell in the subjects who crossed over from placebo from a mean of 15 nanograms per microliter at entry to the extension trial to 0.6 at 12 months.

In continuers it started at 2.3 upon entry and was at 1.4 nanograms per microliter at 12 months of extension, which is 17 months total of agalsidase exposure.

The great majority of subjects exposed to agalsidase beta developed antibodies. Of the subjects who crossed over from placebo, 25 of 28 seroconverted. Of the initially agalsidase patients, most had antibodies at the start of the extension study. Three more seroconverted by month 18 of the extension. So that at the 18-month visit, 26 of 28 evaluated agalsidase continuers were seropositive.

The summary of safety I will present contains data submitted to FDA up to infusion 42 of the extension trial. The death reported in this trial occurred in a 43-year-old man, a crossover from

placebo, who suffered a cardiac arrest with dysrhythmia 400 days after starting treatment with agalsidase beta. He had a history of cardiac disease.

Serious adverse events could be grouped into biopsy related, miscellaneous, infusional, and cardiac/neurological. Infusional and cardiac/neurological events deserve special comment.

Five infusion related serious adverse events have been reported from this trial to 18 months, and an additional one at 29 months. Cardiac/neurological events did not constitute a strong pattern of concern, as these events can occur naturally in Fabry disease, and there was no strong apparent link to enzyme administration.

Among the non-serious adverse events, infusional events were common, occurring in 34 of 58 subjects in the extension trial in the first six months. Infusion related events decreased somewhat with time but were still present during the last six months of the 18-month observation period of the extension trial.

In the period from about 18 to 24 months

after initiation of treatment, subjects on agal in AGAL-002, four subjects had infusion associated nausea, and two subjects each had the following events: Rigors, hypertension, and vomiting.

The incidence of a testing for IgE as a causative agent in infusion reactions has diminished over time. Three subjects have been withdrawn from treatment after suggestive symptoms for the presence of IgE to agalsidase beta. One of these was withdrawn after more than 18 months of treatment.

There is no pattern of increased incidence of adverse events with increased time on agalsidase beta. There is no pattern of other toxicities in the extension experience.

Biopsy data in placebo crossovers confirmed the short term results from AGAL-002. Multiple cell types, but not all, show striking decreases in substrate deposition. Despite widespread antibody development, histological effects, GFR, and serum creatinine appear to be stable.

The skin capillary endothelium data suggests a largely stable reduction in deposition

through one and a half to two and a half years. Infusion reactions wane in frequency, do not disappear with time.

AGAL-007 was a trial conducted in Japan, not under FDA regulatory purview. In it, 13 males with Fabry disease were treated for five months, and the same endpoints were studied as in AGAL-002.

Histological endpoints were determined, including the additional cell types presented as well as renal outcomes and various clinical data. Endothelial cells in the kidney showed reductions to zero in nearly all cases. The pattern of reductions of histologically determined GL-3 was consistent with that seen in AGAL-002.

Skin results were also consistent with those for AGAL-002. Only one subject had paired heart biopsy data. There was no change in renal function or in sweating or abdominal pain. Eleven of 13 subjects seroconverted.

Safety information is available from various open label trials conducted by Genzyme and some post-marketing experience. The following brief

discussion of additional safety events is based on a summary of safety provided by Genzyme in April of 2002.

AGAL-006, the extension to the dose finding trial, is an open label trial using the proposed dose and frequency of dosing. AGAL-007 is the open label Japanese trial briefly summarized before. AGAL-008 is an ongoing, blinded clinical trial of subjects who have moderately advanced renal disease.

The exact numbers of treated subjects in the AGAL-008 trial are not known, as it is still blinded.

Five deaths have -- In addition, there are some -- I'm sorry. Five deaths have been reported in this additional database. Causes of death were cardiac arrest, ventricular tachycardia, ischemic colitis, and stroke as well as sepsis.

Most of the deaths were consistent with vasculopathy and possibly with the natural course of Fabry disease. Three of these occurred at or within six weeks of the start of treatment. As two of these

three events were blinded, the evidence implicating treatment is weak, but is cause for being watchful.

I should have mentioned that this slide does include some other experience beyond these trials, other clinical trial or treatment experience that Genzyme has collected.

Detailed information was not available for every serious adverse event. Possibly cardiac/neurologic serious adverse events occurred in 12 subjects in this database. Six of these subjects are on blinded treatment.

There were three infusion related serious adverse events, all with hypersensitivity-like symptoms. Other serious adverse events did not fit a particular pattern. Nonserious adverse event information from AGAL-007 were generally consistent with that from AGAL-002 and 005.

In summary, the largest single group of events were possibly vascular, cardiac and neurologic events. Some of these events occurred shortly after treatment. However, because of the lack of a control group, the predisposition of patients with Fabry's

disease to vascular events and the documented history of cardiac and neurological events in some of the subjects, there is not a strong safety concern at this time.

Infusion related events were consistent with those in the clinical trial data presented earlier, and merit continued concern.

In summary, histology results are robust, not isolated, but not uniform. They appear to be stable to antibody formation. There has been no treatment effect observed on clinical efficacy assessments, including pain or on renal function.

Antibody development has been nearly universal. Severe infusion reactions may occur. There is no predictive factor known at this time for who will get these reactions. IgE development occurs, and there has been some diminution in the frequency of infusion reactions.

Related to IgE development, there have been five protocol mandated withdrawals from clinical trials due to hypersensitivity-like symptoms with the detection of IgE. Genzyme has related to you the

readministration of product to some of these subjects, but the risk of recurrent IgE mediated hypersensitivity reactions is still present.

I am now going to shift the focus of my presentation to the requirements for accelerated approval and to Genzyme's current proposed means to address certain requirements of the regulations.

The Code of Federal Regulations states the scope of an accelerated approval. Accelerated approval applies to biologic products studied for safety and effectiveness in treatment serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.

In accelerated approval, the FDA may grant marketing approval on the basis of: Adequate and well controlled clinical trials; establishing an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit.

Approval carries the requirement to study the product further to verify and describe its

clinical benefit. This often would be accomplished by trials completed post-approval but which would usually be already underway at the time the accelerated approval were granted.

Such studies must also be adequate and well controlled and should be carried out with due diligence.

Note that the establishment of the validity of the surrogate is not required. Rather, it is the verification of the expected clinical efficacy that is the goal of the verification study.

Under accelerated approval regulations, the FDA may withdraw approval if the verification study fails to verify clinical benefit or the applicant fails to perform the required study with due diligence.

As I have mentioned previously, AGAL-008 is ongoing. It is proposed as the verification trial for accelerated approval. The trial is designed to enroll subjects with Fabry disease who have moderate renal impairment as determined by a serum creatinine between 1.2 and 3.0 or estimated GFR less than 80 mls

per minute.

Subjects are treated until they reach an endpoint event. The endpoints of the trial are the first occurrence of: An increase in serum creatinine by 33 percent from baseline or the need for dialysis for 40 days or more; or myocardial infarction, new symptomatic arrhythmia, unstable angina, new or worsening heart failure; or new stroke or TIA, transient ischemic attack.

The event rate is expected to be driven by renal events, primarily by the increase in serum creatinine by 33 percent. This study is well progressed and, under the initial plan for powering of the study, is expected to complete in approximately one year from now.

Genzyme now proposes to convert this trial into an open label trial in which each subject continues for there years. Importantly, the control for this revised trial will be the event rate calculated from a sample of patients not in clinical trials but in the community, a natural historical database.

The next few slides will discuss the issues and analysis concerning the historical database.

The collection of historical data was conducted under protocol AGAL-014. Sites were asked to enroll, and consent was obtained from patients. This meant that data from patients now deceased were excluded.

Data were collected by review of the sites' medical records and concentrated on renal, cardiac, and neurologic outcomes. No new actively acquired data were obtained. Since Genzyme has decided to focus the clinical trial endpoint on renal events, it is the analysis of these events with which FDA has been concerned. Demographics and characteristics were also collected.

Importantly, Genzyme established a procedure for the subsetting of the entire dataset into a qualified set that they proposed corresponded to the subjects in the ongoing clinical trial, AGAL-008. For each patient, Genzyme determined if there was a date at which the patient would have qualified

as a subject for AGAL-008.

The patient's data beginning at that date would be included in the qualified dataset. Data for the qualified dataset would stop if the patient received agalsidase in a clinical trial or had a renal, cardiac or neurologic adverse event. The qualified data will often not include all collected creatinine values for each patient.

This slide summarizes aspects of the data collection and review process leading to the qualified dataset. Genzyme identified 51 sites for potential participation, of which 27 did participate. These 27 sites identified all Fabry patients seen at the site previously, and attempted to contact the patient.

A partial review of the screening logs indicated that approximately 58 percent of identified patients at these sites consent to have their charts reviewed. The complete study had 447 patients with their charts reviewed. Of these, 103 patients formed the qualified dataset of patients.

Very recently, Genzyme submitted the final report for the AGAL-014 data collection. Genzyme has

added one patient to the qualified database. Many analyses have been done on the 103 patient set, and these are presented here.

The inclusion of this one additional patient has no significant impact on the conclusions stated here.

This slide shows the reasons that patients in the overall database did not provide data for the qualified dataset. The largest group of patients who did not qualify, 186, failed to qualify due to having a normal creatinine or creatinine clearance.

Among the qualifiers there were 115 who met the age, alpha galactosidase, and serum creatinine criteria, 447 total minus 332, but 12 of these 115 had an event that would exclude them.

This limited number of patients who fit into the qualified dataset highlights the nonprospective nature of the collection of medical information on these patients, many of whom, one might predict, at some point in their lives would qualify for AGAL-008.

This slide shows comparative demographic

and baseline characteristics of the qualified population and a subset of the subjects enrolled in the verification trial. I should note that this table compares the full 104 patient dataset from the historical database, and that data on the entire subject population from the verification trial are not available.

Note that the ages and estimated GFRs of the populations are somewhat different. The GFRs shown here is estimated and not independent of serum creatinine. Data on blood type for the subjects in the verification trial have not been provided. So comparisons are not possible. Many patients in the qualified historical dataset do not have blood type recorded.

The following slide shows important characteristics of the data in the qualified dataset. The number of observations is limited in many cases. Among the 103 qualified patients, 18 patients had only one creatinine value, and 22 patients had only two creatinine values. Sixty-three patients had three or more values.

The median period of follow-up in the qualified dataset is 1.4 years. This means that half of the patients have data over a time period that is less than half as long as the observation period of the proposed trial. Forty-one patients have data for one month or less.

In the next few slides examples of patients will be shown to illustrate the time course patterns of the data. Examples are solely limited to be from the minority of patients with more extensive numbers of data values.

Note that the creatinine data are plotted on a logarithmic scale. This is to assist in consideration of an analytic method proposed by Genzyme, which will be discussed shortly.

This patient is an example with data over a reasonable period of time where the data appear to be linear on a logarithmic scale.

The majority of cases had data for which it is difficult to draw a line. This is an example of one such case.

In some cases there appear to be more

biphasic time courses to the creatinine data with time. There are ample data in this case to observe that the change in rate of progression seemed to occur at just over three years after meeting qualification criteria for the qualified dataset, and to estimate what the rate of creatinine increase was over the first three years.

The interpretation of some patients' data is more uncertain. While this patient is still among the minority with a substantial number of data points, these points are not uniform in time. This patient appeared to have largely stable renal function for more than two years and then was absent from follow-up for over two years.

When they did return to the clinical site, there had been a substantial increase in creatinine. However, when that increase began is unknown. The straight line shown in this figure is only one possible time course. The increase could have occurred later. The true history of this patient cannot be known from the data in hand.

Genzyme proposes to use the historical

data to derive an estimate of the proportion of subjects with renal progressions to provide a comparison to a revised design of study AGAL-008.

The revised, open label study will have a new primary endpoint. The outcome measure will be the percentage of patients with renal progression, defined as a 50 percent or greater rise in creatinine within three years of starting agalsidase treatment.

The historical dataset would be evaluated to derive an estimate of the proportion -- or percentage of patients showing a 50 percent or greater rise in creatinine within three years of the qualification date. The AGAL-008 study data would be analyzed by comparing the observed rate of renal progression to the historical estimate.

At this point I will digress a little to discuss another use of the data and analysis that has been proposed by Genzyme.

Genzyme has proposed to use the historical data as a comparator to the renal function data obtained during the extension trial. It should be repeated that the subjects form that trial had normal

baseline renal function.

Defining criteria to identify a time point for putative comparability of the agalsidase treated patients and historical patients when neither have clinically apparent renal involvement appears impossible to do with any exactness. Thus, FDA regards the historical database as infeasible to be used with any confidence as a comparator for these patients.

This slide lists some important issues in the use of historical data. These topics will be addressed in the next slides.

Comparability between the two patient populations is an important requirement. With regard to patient ascertainment, the factors that led patients to present to centers spontaneously versus responding to active recruitment are unknown. It is possible that patients with milder disease will be enriched in active recruitment processes.

The patient choice selection process for enrollment into the historical protocol and a clinical trial may be different. As was noted earlier, about

60 percent of patients agreed to participate. Also as noted earlier, about one-half of the sites agreed to participate in the historical data collection protocol.

Thus, it may be that only a minority of the known Fabry patients are included in the historical database, and the factors that brought these patients to be included are difficult to assess.

The distribution of important demographics and disease specific factors may be different. In addition, our knowledge of the patient characteristics that are important predictors of natural course may be incomplete in some important manner.

While this problem of incomplete knowledge about the disease is true for the situation of randomized studies as well, it is especially important for non-randomized studies.

In randomized studies the randomization process is relied upon to provide balance between groups for unknown and unmeasured characteristics. Non-randomized studies are unable to rely upon this and need to assess balance between groups explicitly

for all important factors.

In order to address these issues and promote comparability, Genzyme has applied the eligibility criteria of Study AGAL-008 to the historical dataset to narrow down to a qualified dataset. Genzyme proposes that this qualified dataset will be sufficiently comparable in natural history.

Factors external to patient characteristics may have an influence upon the course of the disease. If these differ between the two populations, then the disease history of the two populations will not be comparable.

For example, medical management may change over time. This might, in some cases, include disease specific treatments. It may also be changes in the management of disease symptoms, possibly with apparent changes in severity of disease manifestations.

The method used to analyze the historical data should provide estimates of the outcomes that are accurate and unbiased. The estimate of the outcome from the historical database is used as the control comparator for the actively treated population.

Modeling may or may not be used as part of the analytic method.

If a model is used, there is a question of the adequacy of the factors included in the model which may importantly affect or predict the disease natural course. Again, if a model is used, the validity of the model's assumptions is critical to accurate outcome estimates.

A historical dataset that is robust to analysis can provide important strength to the ultimate historical comparison. The issue of robustness does not derive from just the dataset or analytic method. It is an issue of the dataset in conjunction with the selected method of analysis.

One concept of a robust dataset is that similar outcome estimates are obtained from similar datasets. Some dataset factors that may affect the robustness of the analysis include: The number of patients in the dataset; the extent of data on each patient; and the distribution of the data throughout the clinical course.

The frequency of observation may be

nonuniform and nonrandom and may overestimate disease progression, if patients are more prone to return to the site when adverse changes are occurring.

I will now present an examination of an analysis method previously proposed by Genzyme as an illustration of the importance of some of these concerns.

Genzyme's previously proposed method is based on the modeling of creatinine rise over time. IT assumes that the rise of log creatinine is linear with time. Genzyme would apply the method to calculate a slope of creatinine rise for each of the 103 patients.

The method employs an empirical Bayes element that permits a slope to be calculated for patients with only one or more data values. Genzyme would then determine the proportion of patient slopes that predict at least a 50 percent rise in creatinine within three years.

The adequacy of the model can be examined in certain areas. The model assumes linearity in the rise of log creatinine. However, as seen in the

sample patient data shown earlier, not all, and perhaps not most, patient data exhibit a clear linearity of the rise of log creatinine.

When models with non-linear elements were examined, it was seen that a model permitting some curvature of the time course -- for example, a quadratic fit -- more closely modeled the data. Therefore, the linearity assumption of this method is uncertain.

This assumption is particularly important in this modeling method with this dataset. There are a substantial number of patients with only one data value. However, this method employs an empirical base feature which permits attribution of a slope to patient data with only one data point. The accuracy of this attribution is uncertain, and may be untestable. An estimate of 32 percent was obtained with the proposed method.

This slide shows another way that was considered to examine the adequacy of the previously proposed modeling. The creatinine data are transformed by use of a logarithm function to create

data values treated as if linear over time.

If, instead, the inverse of creatinine transform of the data was used and then applied to the linear modeling method, a notably different estimate of the progression rate is obtained, 23 percent. This does not permit a determination of which method is more true, but does illustrate that the model is very sensitive to initial assumptions.

The robustness of the method to portions of the data was examined. Genzyme had previously submitted an analysis of the first 43 patients in the dataset selected only by an arbitrary cutoff date to allow initial analysis by a preselected calendar date.

Consequently, the entire dataset can be viewed as comprising two parts created by a data unrelated arbitrary division. The analysis of the first part of the data with 43 patients yielded an estimate of a 40 percent progression rate, while the remainder of the full dataset, 60 patients, yields an estimate of just 27 percent. These are substantially different.

This illustrates that the dataset analysis

is marked sensitive to exactly which patients are included. What the analytic result might be, if there were another 50 patients to include, is unknown.

In another assessment of the robustness of the dataset to this analysis, it can be recognized that the dataset includes data of creatinine rises well beyond the progression criterion of a 50 percent rise. These data would not be included in the analysis of the Study 008 patients.

In a well filled historical dataset, these would be superfluous, as the data would be frequent enough to permit calculation of a rate of rise stable to the elimination of the extreme creatinine data.

An analysis was performed using data for qualifiers up to a doubling of their creatinines. This analysis discarded only a small proportion of the data. Eighty-seven percent were retained.

This analysis resulted in a dramatic decrease in the projected event rate, down to 21 percent, compared to 32 percent for the entire dataset. Again, this suggests this analytic method applied to this dataset did not provide robust

estimates of progression rate to use as a control comparison.

An alternative was considered that might provide a useful comparison. An empirical assessment would be free of modeling assumptions. One could examine the dataset for all patients with approximately three years of data, equivalent to the proposed primary endpoint time point, and calculate the fraction who show renal progression.

Using this method, a 41 percent progression rate is obtained from the qualified dataset. Unfortunately, the present dataset includes only 17 patients with the requisite three years of data. So the 41 percent progression rate is not reliable.

Conclusions about Genzyme's prior proposal are that the method is dependent upon the validity of the assumptions and sensitive to changes in the model. The validity of the assumptions is uncertain and may be difficult to test.

The empirical method may have an advantage in being assumption free, but the present dataset is

too limited to provide a precise estimate of renal progression rate.

Recently Genzyme has submitted a new proposed method to analyze the historical database for use as the historical control comparator to the revised study AGAL-008. There has been insufficient time since FDA receipt of this to permit complete review and discussion of this proposal between FDA and Genzyme, so that only preliminary comments can be offered by FDA today.

Since you have heard this proposal in more detail earlier this morning, we will only briefly summarize the approach in this presentation and offer some comments as to topics that we feel will need further clarification and exploration in evaluating this proposal.

This slide briefly touches upon the main points of the proposal. The same historical dataset will be used as in the prior proposal. Thus, any concerns that may exist regarding that historical dataset will carry over to this new proposal.

The new method begins by forming a subset

of the qualified subset of the historical data that Genzyme proposes will be better matched to the patients in AGAL-008. This is done using a technique called propensity scores which are a composite score of certain specified coavariates.

The selection of covariates and completeness of the covariate information are, therefore, important elements of this method. Genzyme recognizes that this subset subset will have certain gaps in the record of creatinine values due to the sparseness of the historical dataset.

Therefore, the monthly creatinine values from the placebo patients in the existing AGAL-008 design will be used as a source of information to fill in the blanks. There will be a prediction model devised, which is unspecified at present, that will be used in this imputation process of the AGAL-008 placebo data into the propensity score subset of the historical dataset.

When that is completed, the propensity score subset will be a less sparse dataset, comprising in some presently unknown manner a mixture of the

historical data and values imputed with an influence from the AGAL-008 placebo data.

Lastly, this filled in dataset will use an outcome measure, also not specified at present, to calculate a predicted outcome event rate or some other outcome characterization. This prediction will be compared to the actual observed outcome in the study AGAL-008 enzyme treated patients.

As mentioned, FDA is able to offer only preliminary comments today, due to the recency of receiving this proposal. However, we have identified at least some of the issues that we feel will require further information and discussion.

First, the selection of covariates is central to the propensity score method. Whether the best set of covariates has been identified is an important question to consider. Are there other factors or patient characteristics that are known to be predictive of renal disease progression? Are we confident that our knowledge of the disease is adequate to define all the important factors?

Then there is the fact that some patients

in the historical dataset do not have all covariate information available. How extensive is this, and how well justified is the method's approach to handling these missing data?

The propensity score matching method, as we understand it at this point, is a 1:1 historical to Agal patient matching, but does not necessarily ensure that all Agal patients have at least one match. This requires further evaluation and assessment of what the consequences of this apparent potential imbalance may be.

The prediction model, which is central to the imputation process is unspecified at this point. AS we learned in the evaluation of the prior proposal, evaluation of the model is critical. This model may or may not be suitable for this purpose with this dataset. FDA is unable to evaluate this critical step without further information on this model.

Last, the outcome measure is presently unspecified, and thus, how it will be calculated from the filled in historical dataset is unclear. FDA is also unable to evaluate the appropriateness of this

critical calculation without further information.

Therefore, at this time FDA is unable to provide a comprehensive assessment of the method. Further information is needed from Genzyme for discussions and evaluation to proceed.

We will be asking for your comments and advice regarding how best to focus future efforts later today. Thank you for your attention.

CHAIRMAN AOKI: At this time, we will take the most pressing questions that you would like to address to this FDA presentation by Dr. Kaiser. Dr. Hunsicker.

DR. HUNSICKER: First, I should like to congratulate the FDA for what I think is an absolutely superb statistical analysis that I received, and I really was very impressed by that, and I thank you for it. I also want to thank Genzyme for having provided a very good presentation, and I think Dr. Rubin's contribution is good.

There is a major issue here that I wanted to talk about last time, but maybe it's just as well to talk about it this moment, and I was going to quote

form the regulation, but I buried it right here. That deals with the definition of a surrogate. I'll read it over here.

It says that a surrogate is based almost -- Well, okay -- on the -- I wish I could get the quotation. It was either treatment, epidemiologic, pathophysiologic or other data or information about outcomes that are other than life, survival, or permanent morbidity.

In the whole issue that we are dealing with here today, we have really no evidence about the impact of any of the treatments on outcomes, whether they be life threatening or non-life threatening. So it is going to really rest on the first part.

Now it has been underlined for me. Thank you very much. It's going to rest upon the first part, which is the -- No, that's not the part I was going to say -- whether there is epidemiologic evidence, treatment evidence -- it's up at the top there -- epidemiologic, therapeutic or pathophysiologic or other evidence that makes the surrogate a likely surrogate.

The nature of the situation that we have here is that all of the patients seem to have the findings of the deposits in the endothelium with the exception of the cardiac variant and the patient that was described who was a candidate -- a female who was a candidate for donation.

Therefore, there isn't very much basis for an epidemiologic assessment of the relationship of the surrogate to outcome. They all have it, and people have whatever results they have.

Similarly, there isn't any prior therapeutic information that clarifies this. So the entire argument for this surrogate rests on a pathophysiologic assumption, which in large measure is defended only by the data on the cardiac variant and on that patient, the female who had the deposits.

Now we come to this knowing that the FDA has approved the performance of the trial 02 based on the clearance of the deposits from the endothelium and of the interstitial -- no, the capillaries, the interstitial capillaries of the kidney.

I have a couple of questions, some

primarily directed to the FDA. The question is what was the series of logic that led to the acceptance of this particular surrogate as a surrogate, which is hanging on this very thin thread of rationale right now? Not that it's wrong. I think the rationale is perfectly reasonable, but there are hundreds of other possible rationales for progression. And what is the impact on the -- what do I want to say? -- the process that we have here of the fact that this surrogate was accepted by the FDA?

I say this, coming from the point of view that there is absolutely no question in my mind that the outcome is positive of the study for the issue that was put. It clears the stuff from the endothelium. There is no question about that.

DR. KAISER: I hear your question. I am going to defer the answer to my supervisor.

DR. WALTON: Dr. Aoki, if I may, I would like to answer the question.

CHAIRMAN AOKI: Yes. Thank you.

DR. WALTON: From the FDA's perspective, the pathway that we got to this surrogate was that

there were initial discussions with Genzyme, and their perspective they wish to pursue employing a surrogate endpoint, and consideration of what kinds of things might constitute a reasonable surrogate.

Initial discussions talked about taking one of the biochemical or histological observations and demonstrating a lessening of the abnormality. The agency felt unable to have much confidence in any particular modest, perhaps quantitative, lessening of an abnormality from some baseline, perhaps to a 40 percent lessening or 50 percent lessening or a 70 percent lessening.

Amongst the considerations is: Is there a threshold effect where the residual abnormality is still adequate to lead to the clinical impairments? We were unable to conclude that we could rule that out, and Genzyme was unable to provide us with any information with regard to that.

That led to the further discussions between Genzyme and the FDA. In their early initial study, they noted that on the vessel -- that one of the reasons they really believed in this product was

the belief that many of the clinical impairments are derived from the vascular injury. So that much of the clinical impairment can be viewed as a vascular based disease.

On their examination of the slides, they felt they were seeing that the capillaries were becoming what they felt were clear of deposition. That appeared to provide the -- much more than the quantitative but rather a qualitative change. That is, a restoration of those vessels to an appearance of normality.

Thus, it was on the basis of the belief that the vascular injury was the etiology of much of the clinical impairment, and that they would have the ability with their product to produce a near normalization of those vessels that they focused upon the surrogate.

I would like to note that the FDA has not in any sense absolutely accepted this as a clearly adequate surrogate. This really is an important question. That is amongst the questions for discussion of the Committee this afternoon, and we

very much wish to hear your opinions on whether or not this is an appropriate surrogate under the framework of accelerated approval.

There was an understanding between Genzyme and the FDA that this, on the face of it, had much to speak for it and would be a worthy surrogate to examine and consider further.

DR. HUNSICKER: Could you explicitly comment on the regulatory impact of the fact that Genzyme has proceeded to do this study on the assumption that this would be accepted as a surrogate, or at least appears to have done that? Was there an understanding that this would be accepted as a surrogate?

DR. WALTON: I think that the -- As Dr. Kaiser noted, this study was conducted and it was initiated and much of it was conducted prior to there being any agreement between the agency and the company on what exact endpoint to use.

So in fact, that was why there was a, late in the study, revision of the endpoint. So Genzyme was not under the impression that they had absolutely

accepted surrogate, even while they were conducting the study.

As far as the later goes, I think Genzyme has been aware of the agency's viewpoint that we are very impressed with the results of this surrogate. We find the rationale for the surrogate to be very reasonable and to be very appropriate for consideration under accelerated approval, but that no permanent -- no definitive decision has been made until we had gone through our complete regulatory review process, of which this Advisory Committee is a portion.

CHAIRMAN AOKI: Dr. Grady?

DR. GRADY: Could I just be clear that -- I mean, were you telling us that a large consideration in choosing this surrogate was that there was already a demonstrated major impact on it, and that's partly what made it a reasonable surrogate?

DR. WALTON: Not what made it a reasonable surrogate. However, it was in the FB9702, their Phase 1 study -- that was an open label study in which they gained their first experience with the product in

people -- that they made the observation. They had kidney biopsies in that study as well, and it was in that study that they began to get a sense of what this product might be capable of.

So it was with high expectations that they would succeed on the endpoint selected that they did select it. That is, in many ways, not incomparable to clinical studies that do Phase 2 studies prior to Phase 3 studies, and so there is experience with the endpoint prior to selecting the definitive clinical endpoint. But there was not any review of data from the AGAL-002 study prior to selecting the endpoint.

Those data remained unknown to either Genzyme or the FDA during -- throughout our discussions.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: My comments were going to be on the same two issues. I am still -- I am convinced that this is, to a certain extent, circular reasoning where initially this appeared to be a change that would occur with the drug, irrespective of whether it correlated with an improvement in clinical

outcome, and the selection of the endpoint was not because there was any evidence that it correlated with clinical outcome, but rather that there was evidence that it would be something that would correlate with drug administration.

Now having said that, that doesn't mean that it still couldn't be an outstanding surrogate for clinical outcome, but I am just concerned that it was selected with no evidence at all that it would correlate with clinical outcome but only with treatment administration.

DR. WALTON: I think you are quite correct in that there was no evidence that it did correlate in a strict sense. There was the literature evidence of the cardiac variance of the heterozygote women that are rather coarse and really don't provide a fine, quantitative correlation. But I would note that the regulations do not -- on accelerated approval do not -- do not object to that sort of approach -- that is, not having the direct evidence of correlation that the -- The regulations talk about an effect on a surrogate, that based on the epidemiologic,

therapeutic -- whatever that may be -- pathophysiologic or other evidence is regarded as reasonably likely to predict clinical benefit.

It may be any or all of those types of evidence that are involved in creating the belief, the opinion, of reasonably likely to predict. The source of evidence can be broad ranging. It is the totality of the strength of the evidence that we will be -- regarding the reasonableness of the likeliness to predict that we will ultimately be asking you about this afternoon.

DR. JENNETTE: Just one follow-up. With respect to the surrogate again, there are no observations yet that show that the absence of the inclusions in the endothelial cells improve outcome, to the extent we have been able to follow it, but there is also evidence that this is in the face of very substantial change in the surrogate.

Is there concern that now with this study no evidence for clinical improvement has surfaced, even though there are very dramatic changes in the surrogate? I certainly agree with that.

DR. WALTON: I think that we have highlighted to you very clearly, and you clearly are drawing upon that, that in the clinical studies to date we do not have evidence of a treatment related difference in clinical outcomes, and we certainly do have dramatic differences in the histologic outcome.

I think this speaks to the FDA's wariness initially of being supportive of perhaps a 50 percent decrease in the amount of substrate accumulation, and is that adequate to predict or do we have the potential for a threshold effect?

It might well be that there are very nonlinear relationships between the amounts of inclusion and the clinical impact, and it was out of those concerns that we felt uncomfortable with the percentage decreases, but rather than near normalization was perhaps a stronger piece of evidence.

The degree to which that is an adequate piece of evidence, as I said, is what we are looking to hear.

CHAIRMAN AOKI: Dr. Weiss?

DR. WEISS: To follow up to some extent as well, and I hope we can get into some of that discussion, that potentially could be a factor of the types of patients that were enrolled in the 002 trial. As you recall, they all began, both placebo and treated patients, with normal renal function, and at the end of the controlled portion of the trial they both remained with normal renal function.

That is one of the reasons why the specific verification study 008 is really targeted with people with somewhat more advanced renal disease, to begin with, with the idea, to some extent, it's who you are selecting for the study and whether or not, during the course of any trial, you are going to be able to see the events of interest.

That goes to a real fundamental issue as well with accelerated approval, verification studies. In some settings, the verification studies are just a continuation of the ongoing clinical trial. That's been the experience in the setting of HIV/AIDS, for instance, where it is the same populations, and a surrogate is looked at early but within the same

population, and then the trial is continued to look at the more relevant clinical outcomes.

In other settings -- and this is one case -- the verification study is proposed to be in a different population, and that goes to the issues of being able to show, to some extent -- the question is really does that particular surrogate correlate with the outcome. You are talking about a different population where you are going to be looking potentially at the clinical outcomes.

CHAIRMAN AOKI: I think -- One last question. Dr. Woolf?

DR. WOOLF: A point for clarification from the FDA. If you have a mutually agreed upon surrogate in advance, does that obligate the FDA to accept the orphan drug pending verification of a suitable clinical trial?

DR. WEISS: One of the issues that, I think, was outlined in the presentation is that, while we all thought this was a potential surrogate that might be reasonable, there were enough questions based on the initial information submitted to the FDA -- It

was pointed out, I think, by Dr. Fleming, for instance, that some of the clinical outcomes and the pain outcomes, for instance, and the renal function data did not show anything in that trial. It was nothing that we hadn't initially thought that was going to happen. There was no evidence of any other outcomes.

The concern about the isolation of the renal histology is a question about whether or not it was isolated cell type. And then probably also, very importantly, what came out in that controlled portion of the trial and part of the extension trial was the fact that all patients developed a seroconversion and had infusion reactions, and did the presence of antibody then somehow impact the ability to give this product long term and to get benefit long term. Longer term outcomes would be where you would more than likely see the clinical outcomes.

So as usual, clinical trial results, when analyzed, highlighted not concerns about the findings. I think we were all pretty clear that the findings on the particular cell type highlighted were quite

striking, but it raised concerns about other aspects of this particular population. It raised new concerns that we felt were absolutely critical to address.

DR. WOOLF: So a surrogate is only a surrogate, subject to the findings in the trial? It's not an absolute?

DR. WEISS: It has to also be viewed in the context of all the data that come out from the trial.

CHAIRMAN AOKI: Thank you. At this point, we will now turn to the public hearing, and I would like to start with --

DR. FLEMING: Could we just -- There are more questions on this very issue, but would you like to take them this afternoon?

CHAIRMAN AOKI: Yes, we are planning to address those questions.

DR. FLEMING: I want to discuss this issue at some depth.

CHAIRMAN AOKI: You will have ample opportunity.

I would like to ask the speakers to limit

their comments to three to five minutes, because there are a fairly large number of individuals who would like to speak. I would like to start with Roscoe Brady, M.D. And please come to the podium.

DR. BRADY: Thank you. I am Roscoe Brady from the National Institutes of Health. I must announce that I am a consultant to the Genzyme Corporation, but I have not conducted a clinical trial with the Genzyme related to Fabry disease nor any other clinical trial in the past 12 years.

Many of you may know me best for the work that we did with Genzyme developing a very successful therapy for patients with Type I Gaucher disease. This was approved in 1991, and during the past 12 years many, many patients with this disorder have benefitted immensely from the opportunity to receive this medication.

I would like to go back one brief moment to the history of some of this development. Back in 1965 when we learned the enzyme defect Gaucher disease in 1966, when we learned it in Niemann-Pick disease, we began to think about what the problem was in Fabry

disease, and in 1966 we predicted that it was due to missing galactosidase required to split the terminal galactose from the GB-3, and in 1967 we were able to verify this prediction.

At the same time, we began to think about what might happen to patients if we were able to supply them with the missing enzyme, and we began some studies along that time with purification of single lipid hydrolase from the human placental tissue.

The first one that we got available was the alpha galactosidase, and we began to investigate this in two patients with classic Fabry disease. We were not able to do kidney or other organ biopsies at that time, but what we showed was something which you have seen again today.

Following the infusion of this enzyme, there is a rapid reduction, clearance of the GB-3 from the blood, from the circulation. Then over a period of three or four days, it gradually reaccumulated.

This was shown in two patients, and with this information we were then permitted to do kidney biopsies before and after infusing subsequent

quantities of the enzyme.

We tried this twice, and both of these trials ran into severe technical difficulties, which I shan't go into at this point. So we were on hold for many, many years until the present time when larger quantities of enzyme became available through recombinant production or through gene activation procedure, about which you will hear tomorrow.

We have carried out a number of studies with these gene activation product, three of which I want to touch on briefly. One is with an animal model of Fabry disease in which the clearance of the entire accumulated GB-3 from the liver is affected, and the spleen. There is also 85 percent clearance from the heart, and about a 50 percent clearance following injection of this enzyme from the kidney.

We also carried about a Phase 1 safety and dose response trial with this product, and followed this with a Phase 2 clinical efficacy trial, about which you will hear tomorrow.

Let me state simply that the quality of life of all the recipients in the Phase 2 trial has

been greatly improved. I think at this point, based on some of the evidence that you have had today and some of the evidence that you may hear tomorrow, that these patients certainly deserve the opportunity to receive this enzyme at the present time.

It is my fervent hope that this will be approved by the FDA. Thank you.

CHAIRMAN AOKI: Abbey Meyers.

MS. MEYERS: I am Abbey Meyers. I am President of the National Organization for Rare Disorders, and we are the orphan drug folks. We are the patient groups that have passed the Orphan Drug Act and have worked very hard to make sure that it produces the kinds of enzyme replacement therapies that we are talking about today.

I want to say that we have gotten substantial donations from both companies, both TKT and Genzyme, particularly for our Roscoe Brady Research Fellowship program, and we have awarded two-year fellowships to many, many scientists because of that.

We hope that in that way we will produce

more researchers in this field, because he is -- Roscoe Brady is the world's expert on lysosomal storage diseases.

I want to explain to you the Orphan Drug Act and how the drugs today and tomorrow are going to be implicated. It doesn't matter if there are ten companies developing an enzyme, specific enzyme for a specific disease. The one that gets approval first is the one that gets seven years exclusivity.

If one company gets approved and another company gets approved five minutes later, it cannot get on the market for seven years. So understanding that the question of which drug gets approved first is extremely important.

We have always encouraged companies to make a voluntary agreement up front to share exclusivity, and this has worked in many, many cases. In some cases, it hasn't, and I have personally asked both companies to agree to share exclusivity, and yet there doesn't seem to be any movement, although I understand that TKT released a statement on Friday saying that they are willing to share exclusivity.

Coming from the point of view of the patient groups, and we have spoken to many Fabry's patients, what they want ideally is for both to get on the market. The reason is they are afraid, if they build up an immunity to one of these drugs and there is only one available here in the United States for seven years, what are they going to do?

Knowing that there are very few patients, and yet for these clinical trials they are enrolled with either one company or the other, their products, it means that if one company is approved, the other half of the patients are going to have to stop taking the drug that they are doing well on and switch to another one.

So it would be absolutely humane to get both of them on the market, because people are going to suffer if they are unable to do that. But I saw on the list of questions that there is no question to this Advisory Committee about whether you would advise the FDA to approve or not approve these drugs. It is missing out of all of these questions.

They are wonderful questions, and I can't

wait to hear your discussion and what you say, but you are not being asked to recommend approval. And that's it. Thank you.

CHAIRMAN AOKI: Next, Dr. Warnock.

DR. WARNOCK: Good afternoon. It is my pleasure to be here. I am David Warnock. I am the Director of the Nephrology Program at the University of Alabama in Birmingham. I am the President-Elect of the National Kidney Foundation.

I am an investigator in the AGAL-008 study that you have heard of, and I am here this afternoon in my role as a clinical nephrologist in the patients that I treat with Fabry's disease. I have approximately six patients I have seen, three of whom who have moderate to severe renal impairment. Two of those, in fact, are enrolled in the protocol.

Fabry's disease at this point, you are quite familiar with. The point that I would like to emphasize in my brief remarks is, in fact, this is a multi-systemic disease. The kidneys are affected. The heart and the brain, of course, are the important target organs.

The analogy I would like to present to you is between Fabry's disease and diabetes. Both are, if you will, a metabolic syndrome. Both have neuropathic pain. Both have multi-system involvement. Both are marked with proteinuria and renal impairment.

We know from the published experience that transplantation, in fact, will correct the renal problem. However, the patients are left with the underlying metabolic defect. The vascular/cardiac and neurologic involvement continues.

This is a description of the outcomes of patients who have diabetes in the ESRD dataset, patients who are not diabetics and, as you can see, patients with Fabry's disease who have end-stage renal disease. Even though they are not as severe in their progression as diabetics, clearly are worse than the non-diabetic controls.

The future directions that we are very excited about is the fact that enzyme replacement therapy can occur with objective endpoints. Of course, adjuvant therapy -- Dr. Hunsicker touched upon this -- all of us treating proteinuric renal diseases

use: Converting enzyme inhibitors, ARBs, everything we have.

The analogy I would make and leave with you is how could we possibly treat diabetic nephropathy, even though we would use the adjunct therapy, without having the proper replacement therapy. We desperately need to have effective replacement therapy in our armamentarium, and I thank you for your attention.

CHAIRMAN AOKI: Next is Dr. Grunfeld.

DR. GRUNFELD: Thank you very much. I am a nephrologist working in the Hopital Necker in Paris. I have no financial link with Genzyme, but my travel expenses are covered by Genzyme.

I have longstanding interest in Fabry's disease. In 1970 with Marie Kubler and others, we have seen some Fabry families in Paris, including three carrier females with no urinary abnormality. On the renal biopsy of two of them, we found typical Fabry deposits in the lysosome of podocytes. Minimal and patchy lesions were present in the renal vessels.

To my knowledge, none of them progressed

to clinical kidney disease. With that thought, that podocytes lesions were not evident in the progression of renal involvement, renal progression is mainly due to progressive occlusions of intrarenal vessels by glycolipid deposits leading to ischemic nephropathy.

This view was, in some way, confirmed by the following unique observation. In September 1966 we performed a kidney transplantation in a young woman with primary chronic glomerulonephritis. he donor was her mother, who was healthy.

On the first an earlier renal biopsy of the transplant, glomerular lesions typical of Fabry's disease were found, involving mainly exclusively podocytes. Vessels were completely normal, and these lesions remained unchanged on successive renal biopsy of the transplant.

To understand this surprising observation, we investigated the mother (the donor) and the daughter (the recipient) in 1973, and it was clear that the donor's mother was heterozygous for Fabry's disease, 50 percent alpha galactosidase activity on leukocytes and skin fibroblasts. The activity was

normal in the daughter, the recipient.

The transplant underwent chronic rejection over a 20-year period. A second successful kidney transplantation was performed a few years ago in the daughter. The mother was presently 83 years old has a single kidney containing probably similar podocyte lesion, and she has no urinary abnormality and normal renal function.

The second case I would like to recall deals with a male patient with Fabry's disease who has been followed up in our clinic for many years. He developed renal failure, and Fabrazyme administration was started two years ago when he was 36.

Estimated creatinine clearance at that time was 39 milliliter per minute with a serum creatinine of approximately 245 micromole per liter. The loss of creatinine clearance was 6.4 milliliter per minute per year before Fabrazyme administration, and this is the average loss of creatinine clearance in our male patients with Fabry's disease, and this loss dropped dramatically to 2.2 milliliter per minute per year during the two years of Fabrazyme

administration.

If the rate of progression of renal failure were constant during the whole course, this man would have been in end-stage renal failure within five years before Fabrazyme administration, and with Fabrazyme administration within 15 years.

Fabry's disease includes also cardiovascular complication, and this man developed left ventricular hypertrophy before Fabrazyme administration. During -- Before treatment you see that the left ventricular mass increased from high value 150 grams per square meter to 200 grams per square meter, and during -- Again, during Fabrazyme administration left ventricular hypertrophy regressed significantly during this two-year period.

This case shows that enzyme replacement therapy is able to show the progression -- to slow the progression, excuse me -- to slow the progression of established renal disease in some patients with Fabry disease. It can also reverse left ventricular hypertrophy.

This is confirmed in the series of eight

patients treated with Fabrazyme by Nathalie Guffon in Lyons, France, where you see the left ventricular mass decrease from 159 to 127 after 18 or 24 months of treatment. Thank you very much.

CHAIRMAN AOKI: The next speaker is Jack Johnson.

MR. JOHNSON: FDA, Committee members and guests, my name is Jack Johnson. I am a Fabry patient, founder and President of the Fabry Support and Information Group. FSIG has received unrestricted grants from both Genzyme and Transkaryotic Therapies, as well as support from the public.

With help from family, I started FSIG in '96. Our membership has grown to over 900, with over 650 affected members in 30-plus countries. After communicating and meeting hundreds of patients, I am very aware of their concerns and wishes. I am here to represent the thousands of patients that these proceedings will impact.

As you know, Fabry is a horrible, progressive, chronic, fatal disease. It directly affects thousands in the U.S. and impacts many

thousands more. It causes suffering few can understand or appreciate and prematurely steals our lives.

You will hear others speak of the toll the disease takes on life and, hopefully, you will better understand our urgent need for hope.

Enzyme replacement therapy represents the only drugs available to treat Fabry disease. Fabrazyme and Replagal have been under FDA review for over two years and, while waiting, we know of at least 17 patients that have died. Based on FSIG membership, U.S. population numbers and the estimated prevalence of Fabry, patient deaths during this time could be from 100 to over 200. Enough have suffered and died without hope of treatment.

We have waited long enough. Access to treatment is needed now, and it must be for all affected patients, regardless of sex or age. Fabry has great variation in presentation, and recent research shows females carry a larger than previously recognized burden of disease.

No matter what the books say, females

suffer and die from this disease, and the effects on this group, on this previously overlooked group, are no less tragic.

Patients demand safe and effective treatment. There is clear evidence that patients benefit from both drugs. Patients respond to treatment with variability, just as they are affected by Fabry, as the response to treatment of some is nothing less than miraculous. Others report little change in how they feel, but their disease progression is being halted.

Some have experienced complications. Fortunately for most, these have been successfully managed. For those few remaining, access to treatment choice could be a matter of life and death.

It is clear, patients want to have choice. They have expressed their desire for both Fabrazyme and Replagal to be approved for the treatment of Fabry disease. With variation in response to therapy, some patients may receive greater benefit from one drug than the other.

The two drugs may be very similar, but do

they actually behave in the body the same? You have to address the science of this question, but we have to live with the consequences.

I do not know if all patients benefit from both drugs in the same way, but I do know of U.S> patients that have received both drugs. In one case, there was a noticeable difference in response. Both drugs were received for over a year. Although the difference was not great, it does highlight the potential for benefit through choice and the possible necessity of choice.

Choice of treatment has been available in Europe for over a year. The EMEA concluded that choice was in the best interest of patients, and patient health has benefitted as a result. You can reach the same conclusion and ensure optimal patient care in the United States.

There is no reason for further -- to further delay approval. Efficacy has been established. What risks exist from ERT are manageable. The outcome of Fabry is known. It is premature death. To further deny access to treatment

is unconscionable. Patients have expressed their willingness to accept the existing drugs.

I must say again, Fabrazyme and Replagal represent the only currently available drugs for the treatment of Fabry disease. Our membership has expressed great support for a patient initiative that both drugs be available.

FSIG echoes the needs and desires of those we represent, and in this we do not endorse one single company or institution over another. We demand what is in the best interest of Fabry sufferers, prompt access for all to safe and effective treatment. Without it, we continue to suffer and die without hope.

The decision is in your hands, and we await your response. Thank you for your attention to this vital matter.

CHAIRMAN AOKI: Thank you. The next speaker is Tracy Myatt.

MS. MYATT: Hello. My name is Tracy Myatt. I have no affiliation with Genzyme other than I am very grateful to them for trying to help my

father. My Dad, Craig Cordell, died of Fabry in September of 2000 at the age of 59, and I am not going to talk about the details of his symptoms or anything, just to focus on his fight for treatment and how the benefits that he sought to gain, while they were unrealized in his case, can be realized by his two grandsons who also have Fabry's.

My dad was diagnosed in the early 1960s when not much was known about the disease. So he educated himself a lot by research and subscribing to orphan disease newsletters and such. In 1992 he was evaluated at Mt. Sinai, and became part of a research study at the National Institutes of Health in 1994, going up for annual evaluations as long as his health permitted.

In 1997 he was put on peritoneal dialysis, requiring about four to five treatments every day at home, and in that year he realized he was not going to be considered for clinical trials. His advanced symptoms placed him outside of the criteria.

So at that point, he began an aggressive letter writing campaign, writing to the FDA, the

participating hospitals, state senators, Department of Health and Human and Services. He really worked hard educating people on this, and often including Federal regulations, copies of those, talking about compassionate dose and trying to go that avenue, since he wasn't included in the clinical trials.

He even had his doctors, as early as 1997, lobbying for him, telling the participating hospitals of how he would be an ideal candidate for compassionate dose treatment, and even offering their services and their facilities.

In August of 2000, in response to our state senator's letter on behalf of my dad, Genzyme says, yes, we will give him the enzyme on a compassionate dose basis if the FDA will approve it, which the FDA did, and I am thankful to Genzyme and FDA for that.

It was another six weeks before all the releases and hospital arrangements could be made, and he actually got an infusion in September of 2000. But unfortunately, by that time it could not make a difference. When he went into the hospital, he was so

sick and his body so compromised that he developed an infection, peritonitis, while in the hospital and died six weeks later. But the day he got that infusion, it was like a major victory, because that's what he had fought for. It was just the chance.

He knew there was enzyme replacement out there, and he just wanted the chance to get it. He had been studied and felt he was deserving of benefitting from that. So I thank Genzyme for giving him that day. It was truly glorious, and even though he didn't have a chance to benefit from it, he knew that treatment was at hand and that his grandsons could possibly get that benefit in the future.

My son is seven. He has Fabry's disease, but has no symptoms as of yet. I have a 12-year-old nephew who is showing some early signs, burning in the feet and some GI involvement.

So my fight has taken on a new chapter now. With my dad, it was a daily fight dealing with the end stages of Fabry's, hearing his wheezing get worse every day, watching the fluid build up in his stomach and legs increase every day, monitoring his

blood pressure which got lower and lower every day, and each day we were waiting for treatment approval.

Now with my son, it is a daily concern anticipating the early stages. So I am going full cycle with this, anticipating the early stages. You know, is today going to be the day that we start noticing the Fabry's rash? Is today the day he comes to me and says, Mommie, my feet burn? Or is today the day that he has to sit out from PE class because he hurts too bad to participate?

Again, every day we are waiting for treatment approval. So what I'm trying to say is that every day is critical for these patients. This is a progressive disorder. So each day that the enzyme is missing from the body is another day of build-up in the cells, and each day that the enzyme is missing it is compounding all the other days that went before it, and each day that it is missing there is hundreds of Fabry patients, thousands, asking why, because there is enzyme replacement available.

I just ask that you please approve this treatment, approve both treatments, to keep the

disease that killed my father from attacking my little boy. Thank you.

CHAIRMAN AOKI: Thank you. The next speaker is Ricardo Borrego.

MR. BORREGO: My name is Ricardo Borrego, and I just want to disclose that I am actually a Fabry patient and have been involved in the Genzyme trials for the past three years.

I must say that since the inception of the trials when I did begin, because of having gone on and found where these things were going on and had found Mt. Sinai Hospital and their trials, I must say that my quality of life and the symptomatology that I experienced before has dramatically changed. It has dramatically changed my life.

Although histologically I do not have advanced end organ damage of any sort, the availability of the enzyme itself, knowing what it can do, only gives me the benefit, and anyone else that same benefit of preventing the disease to progress.

So with that, I just bring forward to you that, at least on a personal basis, this does have

benefit, and it has changed and it does improve what damage it does cause without treatment.

So I do come before you again with the hope that, not only the product from Genzyme is approved, but from the other company also, if that is also what is helpful to other patients with this disease. Thank you very much.

CHAIRMAN AOKI: Thank you, Dr. Borrego. The next speaker is Haya Howells.

MS. HOWELLS: Hi. My name is Jacqui Howells, and I'll make this quick, because my stomach is making a lot of noises.

I am here with my sister, Sabina Kineen, and it is amazing. My life mirrors Tracy's very much, and I have never met her before. I'd like to thank you for the opportunity to speak before you.

I would like to begin with saying that, unlike many of those who have spoken here today, I cannot give firsthand knowledge of the benefits of enzyme replacement therapy. No family members of ours have been fortunate enough to be involved with the trials.

You already have the facts and figures associated with this disease and its clinical trials. We hope to convey the frustrations and concerns of those who are awaiting approval of this much needed medication.

Our father, Fadel Ashmar, was first diagnosed with Fabry's disease back in 1984. Soon after my three sisters, my then six-year-old son, and myself were diagnosed with the disease. In the past year, my nine-year-old son and 10-year-old nephew have also been diagnosed and have begun to exhibit some of the symptoms.

In the 18 years that have passed since his diagnosis, our father has had many battles with this debilitating disease. Being a Registered Nurse in the family, I have been instrumental in coordinating his medical treatments.

In August of 2001, our father's creatinine level was 4.5. At that time, his physician had written a letter requesting compassionate use of one of the enzyme replacement therapies, stating the product offered hope for stabilization or improvement

in renal function.

For numerous reasons, this never happened. Within nine months, our father's creatinine level increased to the point of requiring hemodialysis, but he is still alive, which I offer condolences to Tracy and her family.

Since that letter was written, our father has been hospitalized at least ten times with twice being in the past week. He has had bypass surgery, a pacemaker inserted, in hopes of getting on a kidney transplant list. In addition, he is in chronic pain and fatigue, struggling to perform some of the simplest tasks.

This illness does not only affect the patient, but the patient's family. Our frustrations mount, because we know the treatment has been available, yet not accessible. We understand the FDA's caution, but we do not want to watch our father die, as so many others have, awaiting the approval of this medication.

Our hope is the enzyme replacement therapy will be made accessible very soon in order to stop the

progression of this disease or, even better, to reverse the damage already done. Our belief is that both companies should be given the opportunity to market their respective drugs, creating two lines of research, resulting in continued efforts for improvement. This would also prevent a monopolization of the market.

We ask you to please recommend the approval of the enzyme replacement therapy. I personally do not want to watch my children needlessly suffer from this disease, as my father and so many others have.

Again, thank you for the researchers and physicians and the people behind the scene, and thank you for giving me this time to share my concerns. Thank you.

CHAIRMAN AOKI: Thank you. The next speaker is Debra Johnson.

MS. JOHNSON: Hello. I am Debra Johnson. This is a lot more overwhelming than I thought it was going to be.

First of all, I really want to thank

everyone that has taken on this burden of trying to balance ideal science with all the ethics involved with providing human research. I know it has to be really hard for a lot of you.

I am sharing with you today a story that was written by Casey Nichols. He is a remarkable young man. He wrote a story the night before his father's funeral. If I don't get through it, a copy of it is available for you in the foyer out there. I have shortened it a bit so I can get the main points across, but it is an incredible story and it does involve a lot of people.

There once was a young boy out playing in the sunshine all alone. The birds sung to him and made him smile. He grew curious about the things around him and went deep into the forest to see more.

As he progressed, the sunshine slowly disappeared, and the boy grew cold. Soon there stood before him a ferocious and hideous looking dragon that blocked his path. The boy looked at the dragon and asked him why he blocked his way. Angered that the boy wasn't fearful and didn't run way, the dragon

roared, "You don't know who I am? I'm your dragon. I'm here to teach you about Anger and Hate, and then I'm going to take your life."

The little boy laughed. "Sorry, Mister Scary Dragon, but I'm just a boy. I already know about Anger and Hate and even death, but they are of no use to me. Only like to love and laugh, and you can't have my life, because I have so much to do."

This made the dragon even angrier, and the dragon howled. "Little boy, those things you cherish, love and laughter, are weak. They can't survive against anger and hate. But if you will not surrender your life to me now, I have plenty of time to teach you this lesson." The dragon blew flames around the boy, burning his hands and feet, and then disappeared.

The burns were painful, and they were deep. They were beyond the skin and the body. Even worse, no one but the boy could see them. It was a pain that would no one could seem to really understand. It never went away, and those that wanted to believe, how could they really understand?

from that point on, the boy's life could

have been very different. He could have learned anger and hate at that moment, but he didn't. His capacity to love and laugh only grew stronger. He grew into a man and was first blessed with a beautiful, strong wife and then with two boys. In time, they would soon learn that it was them that was blessed, all three of them to have learned to love and laugh from him.

The boy, now a man, didn't see the dragon for many years, but the pain in his hands and feet grew stronger, always testing his belief in love and laughter. The man grew more powerful through these things, and soon began walking through the woods along searching for the dragon in order to force the dragon to stop the pain.

He tried searching for natural and medical cures, but none had the slightest relief. He decided to fight back. As a creative man, he used his hands that the dragon had tried to cripple to create beautiful artwork that had always made others smile. As a caring man, he began to teach others how to draw.

without fear and without knowing, he had crossed a dangerous line with the dragon. Now the

dragon, unable to control his fury, had returned.

The man was uneasy, and the dragon smiled. "I'm here to teach you about anger and hate, and then I'm going to take your life." The man didn't laugh this time. He felt fear, because now it wasn't only about him. His wife and two boys were in danger.

The dragon released a sigh, "Now you can begin to see what it means to feel anger and hate." With tears pouring down the boy's face, who was now a man, "Now only stronger is my power to love and laugh, and never will I give up the joy of laughter."

The man ran full speed at the dragon and at the moment of impact when anyone else who might have witnessed it would have expected to see a horrific explosion or a great battle, there was only silence. The man was there lying all alone. The dragon couldn't be seen, but the poison that was once the dragon was now surging through the man's body.

The dragon was inside him and trying to take his life. His kidneys failed, and his heart was weakened. His doctors thought the end was near, and the man's boys and wife were stricken with grief. But

the man held on, and he knew that his life couldn't end. There was still much to do.

For ten years the man lived on, always holding on and sharing his power to love and laugh with all those around him, especially his family. At times, the dragon rose up from the depths of the man's soul and took pieces of his body, each time always believing it would be enough to teach him about anger and hate.

The dragon echoed in the man's head, "You have protected your family from me by containing me within yourself, but now you are too weak. I will take your life, and what you didn't learn from me, your family will.

The man knew that the dragon was right. He was going to die, but about those other things the dragon was wrong. He had taught them so well. His wife and boys would be fine, and hearing these words confirmed as he drew his last break, he heard his wife say those words.

They had loved each other in ways most could never imagine and, if his wife had never needed

to remember the good man her husband was, she only needed to look at her two boys, loving and laughing just like their father always had.

Thank you very much.

CHAIRMAN AOKI: Thank you. The last speaker is Gerald Walter.

MR. WALTER: Good afternoon, ladies and gentlemen. I know everybody is ready to get out of her and probably get lunch. So I will try and be quick.

Thanks for having me here. My name is Gerald Walter. I prefer to go by Gerry. I am here today to provide you with my personal perspective. I feel, you know, not really guilty but somewhat guilty in the fact that I am not one of the more severe Fabry patients, but I think I look at all of this from a little different perspective that I would just like you to appreciate.

At 48 years old, sort of on the cusp here, I guess, I am fortunate to not have any of the very severe consequences of Fabry's. I don't have any real severe kidney problems. I haven't had any strokes or

heart attacks so far, according to everything I hear. I am able to work and have a very productive life, and I'm fortunate for that. I'll tell you a little bit about that in just a minute.

I feel, though, I am being drawn closer and closer to the bell curve, the center of the bell curve where that 40-year-old life span originates for Fabry patients. I know that it increases a bit with dialysis and transplant, but I am not one of those people. So who knows what's up?

From where I stand, you guys are about the most important people in my life, being able to change the outcome of where this goes from here and, as I said, I kind of feel like I'm on the cusp. So maybe we don't have a lot of time.

I am reminded how serious this is, though, even though I'm not a -- I don't have severe problems. I have a brother that died of Fabry at 37. I'll get through that part and get it over with. My Mom has Fabry's. Two of my other brothers have Fabry's, my sister, a couple of nieces, nephew, cousins. So we are going to take a pretty hit with this if we don't

get something done fairly quickly, and I would really like the rest of my family not to have to say I lost two brothers or three brothers and so on.

You know, we have it throughout the family. I'm really the best of all of this in terms of impact, in terms of symptoms and in terms of productivity in my life. So I really, much more than for myself, the rest of my family and all these other folks really have some severe consequences, and probably for me to come.

I wrote a little lengthy stuff here, but I'll skip much of it for brevity. So just to let you know I'm not completely off the hook, the symptoms that I have -- and they are very classic, but you know, the chronic diarrhea, lack of perspiration, which are probably the two major things in my life that cause me trouble.

I have lots of the other things. I've had unexplained bouts of atrial fibrillation, traumatic edema in my legs, cystic kidneys, chronic anemia, tendinitis, body aches, shooting pains, you know, you name it, across the course of what happens to Fabry

patients, minus the very severe things. So I really am incredibly fortunate at this point in my life.

For me, the medical problems I have just described are fairly easy to deal with. I mean, I say easy in a certain sense. I mean I take medication for one thing or another. I work through the things that happen to me. The impact of the threat of early death is what affects me more so, based on the decisions I make, the things that I do in my life, knowing that the possibility of departing a little bit early is very real.

So really, what I'm talking about is, instead of making -- well, I make long term plans, but they are really short term plans in anyone else's mind. So my long term plans really consist of the next two, three, five years. You know, my goals are in my business, if I get just that far, I'll have made significant accomplishments in my life.

So what I really would like to do is make some long term plans that go into my sixties or seventies or maybe eighties, if I'm really an optimist, as I am.

As a 48, Fabry male, my current life goals -- I just kind of, you know, move from one short term goal to the next, being really fortunate that I got through that piece, and I don't mean to a doomsdayer, but the reality is there. I'm one of those folks that has a great potential to have some serious impacts.

So I guess what I'd like to share now is a little bit about my life. Before I became -- Before I knew about Fabry's I entered a profession that has caused me great pain in terms of the symptoms and impacts of Fabry disease, and even in my minimal way.

I am a lieutenant colonel in the United States Army. I have been on Active Duty for 18 years, and I have served 30 years in support of our nation's defense as Civil Service -- in Civil Service as a defense contractor, as a National Guardsman.

I reentered. Thirty years ago I entered the Air Force. I reentered the Army in 1994, and now have 18 years of Active Duty. So my goals are at the end of this year I am going to be selected -- I have been selected. I am going to be promoted to colonel. I'd like to get there.

In two years I am eligible for retirement at 20 years of Active Duty. I'd like to get there. More so, those kinds of things are for my family's sake even more so than my own. But I would like to have long term plans. I'd like to go back to Federal Civil Service. I'd like to sit where you are, and many of you are my age or older, and have debates in my profession like we are having this debate today.

So you know, I've come a long way. I have devoted my life to my country. I've enjoyed that. That's been a great thing for me, but I'd like a return, and not just for me but for all the folks who are in my situation.

I would really like not to be a casualty of bad timing, after all the things that I've come through in my life and been able to get over. So as I was out there, I've been in situations where I've been dodging bullets. I've been in situations -- I worked over ten years in munitions and explosives. I've made it through all that.

I have done the 10 and 15 mile forced road marches with weapons and gear in the heat and the lack

of -- not being able to sweat, it made that really tough. So you know, sometimes you start stripping off clothes, and your friends carry your weapons, and I've done what I've had to do to keep my job, to keep my career and support my country.

So as I said, I'd like to change my goals. I'd like to think that -- and I guess I'm about done with the -- I sort of really haven't read it, but I've covered all the points.

So what I heard today was no one disputed that the average life span for a Fabry male is 40 years old, sometimes increased to 50. I had heard some conversation about how the drugs get whatever it's called -- what's the term you use, GL-3 -- the junk out of my system.

So you know, I've heard you talk about that, and that's real, and it doesn't seem like there is much dispute about that. I have heard the dispute about process and statistics, which is very important. But you know, from my perspective, if you can allow me to not have diarrhea every day without relying on medication, I may even stay a few more years in the

military, but it's getting pretty tough with the physical requirements.

If you can allow me to sweat, the gentleman said how does this affect your heart or what benefits for your heart. Well, you allow me to sweat and not have diarrhea all the time, I'll take care of my own heart. You know, I stopped running in the military and started biking because I just can't -- You know, the heat is too bad. I can't play volleyball more than a couple of games anymore, and that's how I've lived my life.

I've been fortunate in one aspect in being able to do all these things. I worked through a lot of my things. They are still there, but I really want to be able to do more.

So I can take care of myself I you can give me something. So I would say, you know, do the minimal of allowing this to go on too long without some sort of approval. Let us take care of ourselves. Give us something, and if all the questions aren't answered, fair enough, you know. It won't stop us from continuing to research this.

You might lessons from guys like me. If I still die, you know, that will tell you something, but I'll be able to tell you in the meantime did I start sweating, did I lose the diarrhea, do my legs keep swelling up occasionally for no reason and I've got to explain that to the military so I can stay engaged in what I'm doing.

Just one other point. I was fortunate enough to also escape the Pentagon tragedy on 11 September 2001. I had a plane fly underneath my desk. If I can beat that, I can beat this.

Just to close, I guess -- As an aside first, I am currently enrolled in the Genzyme Phase 4 study. So I'm beginning to do my part to help you make this decision. I'm glad to do that. I'll let you know how it goes. I'll give you my business card, if you want to call me and ask me.

The financial association: As part of that study, I do receive transportation, lodging, per diem. I wasn't solicited or asked to come here for any funds. So I did this on my own.

I think that -- I guess my bottom line is

that I'd like to trade some of my GL-3 for a few extra years. A quick decision, and you folks can help me with that. Thank you.

CHAIRMAN AOKI: Thank you. This concludes this portion of the program.

DR. TEMPLETON-SOMERS: I'd like to announce to the Committee that the restaurant downstairs is reserving some space for you. So, hopefully, you can get through fairly quickly.

I would also like to give you a gentle reminder to refrain from discussing these topics during lunch and save your discussion for the open forum this afternoon. Thank you.

(Whereupon, the foregoing matter went off the record at 12:40 p.m.)

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

(1:37 p.m.)

CHAIRMAN AOKI: Thank you for coming back so quickly. I would like to bring the meeting to order.

Prior to launching into a specific agenda, a number of the Committee members have stated that they had some outstanding issues that they wish to address to the FDA and perhaps to Genzyme as well. So at this time, we will entertain those pressing questions that Dr. Fleming, in particular, had. The floor is yours, Dr. Fleming.

DR. FLEMING: Thank you. Well, what I would like to do, actually, is just provide a few comments on the earlier accelerated approval discussion, and then end with a question to the FDA. At the break, I was reading, and actually this sort of leads into a lot of what that first question is all about.

I think it is important to clarify the level of reliability of insights that a biological marker provides regarding treatment effect on a

clinical endpoint. In this discussion, I will approximate things by Level 1, Level 2, Level 3 where Level 1 is the most reliable.

If the effects on a marker reliably predict clinical benefit, then you have what we call a validated surrogate. As Dr. Kaiser pointed out, however, it is not required to have a validated surrogate for accelerated approval. If it is validated, it would be a basis for full approval, but these are fairly rare, and we could spend hours talking about the complexities of the science behind actually fully validating a surrogate.

Maybe the best example might be anti-hypertensive effects on blood pressure as a surrogate validated for stroke. The basis for accelerated approval I call Level 2 reliability. This is where the effect on the marker, in the words of the FDA, is reasonably likely to predict clinical benefit.

In the experiences that I am aware of, there have been two major areas where the FDA has implemented this strategy of accelerated approval. The classic examples were the initial examples in

HIV/AIDS where sustained, undetectable viral load has been a basis for accelerated approval, and in oncology where substantive anti-tumor effects have been a basis for accelerated approval.

The third level I'll call Level 3, and that is where levels of the marker correlate with the clinical endpoint. This is far and away the most common, and unfortunately, though, this is usually unreliable evidence about treatment effect, simply knowing that the marker is correlating with a clinical endpoint.

What can go wrong? Well, let me just try to briefly summarize a few key areas of the reasons that this paradox can arise. The first is that the marker is only statistically associated with what is the causal mechanism.

One example is if you have an HIV-infected mother, her CD-4 is statistically associated with risk of HIV transmission, but a treatment that would change CD-4 at birth wouldn't change anything. CD-4 is correlated with viral load, which is the causal mechanism.

Second, challenge with markers is how much of an effect, where, and for how long, and that matters. Classic example of that, many examples of that -- Classic example, post-MI patency. Of course, patency is a good thing to prevent future MIs, and yet lots of examples to show that it -- is it going to be two-flow, is it going to be three-flow? Is it 30 minutes, 60 minutes, 90 minutes post-MI? These matter in understanding how the treatment effect on patency will affect outcome.

CBER has seen examples of relative efficacy of acellular pertussis vaccines not accurately predicting -- the relative efficacy not being accurately predicted by key immune response markers such as FHA and protactin. These are correlated with outcome, but we have often been misled about which acellular pertussis vaccine has been most effective, if we simply looked at those immune markers.

A third issue is a treatment induced change on one of these markers may not represent a natural history change. Simple example of that is

natural history, CD-4 in HIV is certainly correlated with demise of the patient with age defining events and death, and yet IL-2 could -- am immune based therapy like IL-2 could substantially change CD-4 and not necessarily change the clinical endpoints, and right now NIH is doing a 6,000 person Esperi trial, because they recognize this uncertainty.

So I would put all of this together under -- The essence -- The essence of the scientific challenge, as I see it, in understanding whether a marker effect is reliably predicting a treatment effect is twofold.

First, is the clinical endpoint fully immediated through the biological marker, i.e., it's basically a biological and clinical issue. We understand that in the disease process it is influencing clinical endpoints, but do we adequately understand whether or not those various pathways through which the disease process influences the outcome are fully captured by the marker?

In fact, the examples I have just given are those examples that give us caution about whether

that is true.

The second fundamental and separate issue is: Is the treatment effect on the clinical endpoint fully captured by the effect on the marker? The treatment may have the intended effects on the marker, and yet it may have unintended effects. There are a wealth of examples.

One of the best is arrhythmias are clearly a risk factor for sudden death in patients post-MI. Hundreds of thousands of patients in the U.S. used encainide and flecainide because of this association. Ultimately, however, the effects of encainide and flecainide on death were substantially adverse, because there were substantial effects that were adverse, that were unintended, unrecognized, undetected that weren't mediated through the marker.

So I guess, in summarizing all of this, I would say in my experience, and I'm leading to the question, in prior accelerated approvals it has been predominantly in the areas of HIV/AIDS-oncology where, in those settings, there have been extensive prior data on which to establish that these markers are

reasonably likely to predict clinical benefit, and even there these issues are still being debated in those settings.

So in this setting with Fabrazyme, my question to you is, in essence, such clinical outcome data don't exist for a marker such as -- and I'm not going to just say quantitation of the GL-3 inclusions -- short term quantitation of the GL-3 inclusions. There is far less evidence, to my experience, to validate and address these complex questions that has existed in other settings where the FDA has entertained markers for accelerated approval.

I guess putting forward to the FDA, is that true or not true?

DR. WEISS: I would tend to agree that we don't have the wealth of experience in this particular disease or other types of similar types of inborn errors the way we do in HIV/AIDS and cancer as the two major classes of diseases where the accelerated approval mechanism has been most essentially used. But it's not that it hasn't come up in other settings and hasn't been addressed and considered in other

disease settings as well.

DR. FLEMING: Are there other disease settings that you could quote that would be more parallel to this, where this implementation has been done and where subsequent clinical studies were successfully carried out to ultimately show that we had valid effects on clinical endpoints?

DR. WEISS: I'm just wondering, actually, if it would be okay if I could actually ask Genzyme if they wouldn't mind addressing one of their particular situations. I mean, there is one that was addressed actually at an Advisory Committee a number of years ago with respect to the -- I don't know if Dr. Moscicki or Alison Lawton wouldn't mind, as one particular example. Would it be appropriate to ask one of you two to just address one particular situation?

We don't have the full story yet, but there have been some examples.

DR. MOSCICKI: Are you referring to Carticel as an example?

DR. WEISS: That is correct.

DR. MOSCICKI: In the Carticel development program there was extensive case series history that looked at some outcome measures over time, over a shorter period of time. In this case it was felt important in order to have approval under the accelerated mechanism in order to save patients from having destruction of their knees to carry through on a Phase 4 program. I believe this is what you are referring to.

In this case, it was thought to initially attempt a double blind, placebo controlled trial looking at a sham-like procedure or -- I'm sorry, actually a randomization to non-treatment versus treatment, but in a commercial setting patients all preferred to actually obtain treatment. So it was very hard to enroll into such a study in that kind of a setting.

So a subsequent post-marketing study was then designed in collaboration with FDA that was quite innovative, looking at time to event in patients who had undergone previous surgical procedures for their knee injuries, and then the time to event after having

then subsequently received the Carticel treatment.

This study rapidly enrolled, and is well underway now, looking at long term outcome in these patients for this time to event. Does that provide the points that you thought perhaps we might make?

DR. FLEMING: I would really need to look at this more carefully to understand whether it does, but even if it is relevant, it sounds like the study is still ongoing.

DR. WEISS: That is correct.

DR. MOSCICKI: On the other hand, it is supplemented by registry data which continues to show excellent outcome measures in those patients in terms of their functional capability for the knee.

DR. WALTON: I'd like to comment that I most certainly agree with you that this is a case where we do not have the body of clinical correlates of data between the surrogate and clinical outcomes, and ask in your deliberations, bear in mind that that is only one form of data.

The examples of cancer and of AIDS are, I think, ones where the agency has had great success in

use of the surrogate approach. They may not be the only circumstances, and this is, in some important regards, different in those circumstances, particularly in the circumstance, for instance, of cancer.

This is different in that we really believe we have an understanding of the biochemical defect, and biochemical and pathophysiological evidence are certainly among those that can be incorporated in the Committee's thinking, and ultimately the assessment of whether or not this is an appropriate surrogate would be upon the totality of the different kinds of evidence, either for, against or merely not present.

DR. FLEMING: I would have just one further comment. I would certainly agree that one needs to factor in, as the procedures indicate, totality of information. In addition to the clinical trial, what is understood biologically?

I would argue, though, that in nearly every setting that I've heard, surrogates proposed -- there is certain very strong biological rationale.

The complications that I had alluded to are certainly at least -- Whereas the biological rationale is present here, complications that I had alluded to, do you have the entire mechanism or what cell types matter, how long, how substantial? All of these kinds of things that have led us astray before are certainly things that are complications here as well.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. SCHNEIDER: I think the things that Dr. Fleming mentioned are all very interesting, but I don't really think they relate to this condition. You have a situation where you know there is a specific enzyme defect.

You know it leads to accumulation of this abnormal material, and using it as a marker treatment to get rid of that material is -- You know, you can never be 100 percent sure that it is the right way to follow a patient, but it's just -- It's inconceivable in my mind that that's not what is causing the defect in these patients.

If you want until you have absolute correlation between the marker and the clinical

effect, you wouldn't need the marker anymore. You know the clinical effect would work.

So I think you are getting a little too pedantic about this. To me, it's such a -- It's such a good marker. I think Genzyme should be complimented in doing such a wonderful -- in my mind, just a job of showing the effect of the treatment on the marker post-MI.

DR. FLEMING: I can't tell you how many cardiologists have told me, "It's patency, stupid." I mean, the question is how much, how long, how soon, and obviously, we need to discuss all of this, but --

DR. SCHNEIDER: Another thing is you asked for an example, and an example of where a marker has worked out is a disease that I've studied and got a drug approved for by the FDA seven years ago where children accumulated the amino acid cysteine in all of their cells, leading to severe kidney destruction.

We used as a marker the white blood cell cysteine level, and it turned out to be a very, very effective marker, and we still use it today to follow the treatment of these patients. We have a clearcut

genetic disease where -- I think it's a lot simpler situation than the ones you are suggesting, cancer treatment or heart surgery.

You know the enzyme defect. You know the material that accumulates. You know there is a terrible destructive effect of that material, and you get rid of that material. It seems to me pretty clearcut.

If you wait to get absolute proof of this, I don't think we will live long enough, any of us.

CHAIRMAN AOKI: Now Dr. Hunsicker.

DR. HUNSICKER: Well, as it says, it takes all kinds to make a horse race. Actually, in this I am closer to Tom than I am to you, Jerry. I'm right next to you, but --

The issue here is that there is not clearance of this nasty stuff from cell types, which could persuasively be the cause of renal disease. Now I'm not going to tell you what I think is the cause of the progressive renal disease. I will simply say that, if we have two applications to look at that come to diametrically opposite conclusions as to the

pathogenesis in a credible fashion, the answer is not reliably known.

That is where we stand today. The answer is not reliably known. Now I'm going to leave that then and go on to what I was going to say a moment ago.

First, I want to thank Tom for raising this issue, because I think that this -- There are two agenda items here almost today. One is the question of whether we should approve Fabrazyme in some fashion or what sort of recommendations we should make to the FDA about it. But the second is that we are going to be setting a precedent for how studies in renal -- progressive renal disease are done.

This is a critical issue, because we are now at the point where we are becoming progressively incapable of doing studies in renal disease based on the so called hard outcomes.

Now what is the problem in renal disease -- this has already been described by the sponsors today -- is that there is a very long latency between the initial events that cause damage to the tissues

and when you can measure anything in terms of loss of function.

As has been pointed out by the sponsor, you have to lose about half of your nephrons before you can measure a change in the filtration, irrespective of how you set out to measure it. It's not a matter of precision. It's that there is compensation of the residual nephrons, such that the GFR is maintained in the face of loss of nephrons until you have lost a great number.

There is a theory, which is debatable, but there is a theory that when you get to the point at which you have now lost enough nephrons that you no longer have a normal creatinine, that you have passed a threshold at which point you are going to have progressive renal insufficiency, irrespective.

So we would like in nephrology to begin looking at things before the changes in filtration have occurred. But when you do that, you are stuck with very long latencies.

Now a related issue that comes up with this is the issue of whether we can continue to

maintain the engagement of the pharmaceutical community in this business. The renal community, patients with renal failure or progressive renal disease, is actually not all that great in the larger scheme of things. It's not as large as the number of people with hypertension or with hypercholesterolemia or even with AIDS or whatever.

When you deal with something like Fabry disease, you are talking about a really tiny thing, and it's important that we not make it impossible for the pharmaceutical industry to address these questions.

So we have a real problem here. Then we get to the issue of what is particularly a problem here, maybe not across the spectrum of renal disease but certainly with respect to this particular renal disease, is that it is hard for me to imagine what more evidence they could have gotten about the relationship of any surrogate to the outcome, because what we know is that the stuff is in all the cells. Therefore, people with stuff is 100 percent, and there hasn't been any intervention that changes it, and the

only data that we have is the accident of biology that permits us to have the patients with a cardiac variant and the woman who donated her kidney was found subsequently to have heterozygous disease. I'm sorry?

DR. GOLDBERG: That is not a single case.

DR. HUNSICKER: Well, multiple cases. So this remains the total database on which we can form any hypothesis.

Then the question comes up, is it reasonable to permit this hypothesis to be put forward as a surrogate to get the drug on the market so that we can then have enough income flowing in to justify the continued development? That's really where we are.

Now what I come down to at the end of all of this, without trying totally to spill my case here, is that it seems to me that the whole system was not optimally served, because there is uncertainty on the part of the sponsors whether we are going to buy into this, because the data correlating this particular surrogate to the long term outcome is pretty thin, by anybody's measure.

They don't know, and we don't know, and I think the FDA doesn't know. I'm not holding the FDA responsible. I think we have come into something where we are now recognizing that we are going to have to deal with this in a much more intentional fashion.

The bottom of my discussion, Tom, is that this is the sort of a thing where I think the entire community would have been very well served, had the FDA convened an advisory group at the outset to determine what was an acceptable surrogate, so that the pharmaceutical industry could now say with confidence we can at least bring this question to you, get the thing out so we can afford to develop it.

Then the second piece is what then must be the absolutely nailed down, long term thing that justifies the early accelerated approval? I think that is really where the bulk of this discussion today is going to have to go.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: I agree with much of what's been said, and in particular with respect to the biological relevance.

I can understand the rationale that has been proposed with the endothelial inclusions, but I agree with Larry. At best, the evidence that that really is in line with the true pathogenic factors that are causing the major organ damage is not proven. But it seems to me something pretty clear.

We do know what is causing this disease. It's too much GL-3 in the circulation or somewhere, but that's -- But in any event, we have already pointed out that in another situation, HIV/AIDS, it is the load of the etiologic agent that is the surrogate, the viral load.

Here, we do have some mechanisms for looking at the load, and I would be willing to accept arguments that the plasma level of GL-3 is as good a surrogate as anything from a biological rationale as far as predicting that some therapy may ultimately be effective.

So I don't really understand why we jump from the simple observation of dramatically, consistently, persistently reduced GL-3 levels in the plasma with this therapeutic approach which I, like

Larry, congratulate the company on having devised as a reasonable surrogate.

Even there, there's still the lack of evidence that it really will correlate with improved clinical outcome, but as far as making an argument for it to likely, from a biological rationale perspective, be a reasonable surrogate, I'm much more willing to accept that of the bat than the somewhat, again, I think, circular reasoning that, I am still concerned, may have led to the selection of interstitial endothelial cell inclusions as the surrogate.

I still find it hard to believe that in a void a large group of individuals before the fact would have hypothesized on the basis of biological rationale that interstitial capillary endothelial inclusions is likely to be the best surrogate. Whereas, I think many people would agree, based on what limited understanding we have of this process now, that if there was some measure, the presence of this build-up of injurious substrate having been depressed by the therapeutic approach, you could argue that there is biological rationale to look into that

agent and see if it has a beneficial outcome.

So in summary, I'm still skeptical about being able to defend the biological rationale for interstitial capillary endothelial inclusions being the best surrogate. But I wonder if embedded in the data here is not an even better surrogate. That is this compelling evidence that the circulating levels, circulating albeit, of GL-3 is dramatically reduced by the agent.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: Well, I will address what you just said and then come back to what I was initially going to say. I think GL-3 exerts its effect intracellularly, and the demonstration that it does something in the lysosome is really very important.

Now that we know that the circulating levels correlate with those intracellular levels, I think you can use the circulating levels as a marker. I don't think you could before.

More important, I think that this is a very rare disease with terrible consequences, and

nothing that I have heard today tells me that this treatment is going to be -- is as fraught with consequence or complications as I would have thought.

It seems to be reasonably safe within the framework of this rather terrible disorder. Therefore, I think our major objective should really be to make sure that that Phase 4 trial gives us the information we need, and not to worry about whether or not this is a reasonable marker. It may or may not be, but we are not going to know unless we have a decent Phase 4 trial, and that's the important thing we should focus on.

DR. WATTS: Thinking about this as a clinician, I can't really buy the surrogate as a way of helping me manage patients. One of the concerns that I have had is which patients would be treated, at what stage in the disease, and for how long, and what clinical tool will be used to determine whether or not there is an adequate response, and how does that response justify the cost, the inconvenience?

I don't know whether this requires a central line be placed to give every two weeks, and

the associated risks with that, something that we need to know.

It's not a cure, but the only way, I think, to get an answer as to whether any of these surrogates are markers for real clinical endpoints is to get it out there and have a properly designed Phase 4 study to answer that question.

I have real concerns that the historical control part of the Phase 4 study is not going to be the adequate design to answer the question.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I have a very practical question for Genzyme. We were shown a lot of light microscopy, and the inclusions disappear. But do these cells, for want of a better term, look healthy under EM or other criteria? I mean, are they otherwise normal cells?

DR. RENNKE: Those cells that clear by light microscopy at the electron microscopy level look healthy. They look undistinguishable from normal cells.

Now this does not happen, as we pointed

out, in every cell type. It happens in every cell type but quantitatively differently. The endothelial cell clears much faster, and those endothelial cells are indistinguishable from a normal endothelial cell, including the electron microscopy level.

DR. WOOLF: Thank you.

CHAIRMAN AOKI: Dr. Rennke, do the nerves also look normalized or even after treatment, because I'm sure some of the biopsies must have shown you some nerves.

DR. RENNKE: In kidney biopsies it is difficult, but the people defined nerves. The topsy does not sample the areas where nerves occur, fortunately. The patients on skin biopsy -- those -- the perineural capillaries were assessed. The nerve itself is difficult to assess, because the myelin figures of the myelin containing cells will confuse the issue.

So one would have to focus the attention on the cell body of the cells. Now in the central nervous system and the sympathetic nervous system, it has been shown that those cells accumulate the GL-3.

We did not address this, because the biopsy sites didn't include, of course, ganglion cells and so on and so forth.

So the answer -- I cannot answer the question that you precisely asked. However, there is evidence that endothelial cells in Fabry's patients are activated, and they are activated as to their pro-inflammatory as well as pro-coagulant activity, and those are independent studies that come from Japan and from this country.

The markers for this activation have been published in reviewed journals, and therefore, the likelihood that the endothelial cell is involved in the pathogenesis of the damaging effect in the organs is very, very likely.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: WE have been told that it would take about a year and a half to complete the Phase 4 study and have the dataset available. I'm wondering if you had a monitoring oversight committee that looked at -- that had a continuous access to the patients if you could reach your endpoint sooner than

that, than the planned 18 months, and shorten the cycle and obviate the discussion around the table.

DR. TANDON: P.K. Tandon, Genzyme. We have independent monitoring looking at the data. They have not broken the blind. That's my understanding, and discussion could be brought to the DMC.

CHAIRMAN AOKI: Dr. Fleming?

DR. FLEMING: I think it is certainly relevant to look at what are the possibilities for early answers. Typically, when you are monitoring a trial that in fact is properly sized to clinically intended differences, the opportunities for early termination for conclusive benefit early arise when the true effect exceeds that that was postulated in your sample size calculation.

I didn't see the sample size calculation here, but for 14 events, by accrued calculation I did, it looks like you must be targeting a 75 to 80 percent reduction in these events. That's a pretty big effect.

So our biggest concern, I would think, is that, even if this study is carried out to its

completion and you have meaningful benefits, it could be of substantially smaller magnitude. I would be pleasantly amazed if the effect was so large that you would actually be able to terminate early. But this gets to an issue that, as I listened to my colleagues here, I am impressed with their level of confidence in the biology, not only that we understand the enzyme deficiency but we understand how that effect, in fact, in turn is mediated through these GL-3 levels, and that is the causal mechanism by which the range of clinical effects occur.

I've heard variations. Plasma GL-3 I've heard as a variation. I'm still troubled a bit, though, by the aspect that this is an effect that didn't translate into any observed clinical benefit in the Phase 3 and, of course, the explanation for that is early enough disease stage requires a much longer period of time. But in turn, if it requires a much longer period of time for the clinical benefit, it requires a much longer period of time for the biological marker effect to be in place as well.

We have very limited data. We have the

biopsies, the kidney biopsy out to six months even in the extension study, and that's the limit to that duration.

I would want to be very confident that this intervention effect, even if we think it's the right one, is going to be achieved in a way that is sustained for a long period of time. What does this mean? It means I myself would find it personally more acceptable to use the accelerated approval mechanism if I was very sure that the clinical endpoint studies of adequate duration could be carried out.

That leads to a serious question of my own I have here. If you give an accelerated approval and, if anything, you undermine the ability to even complete a study that I think is probably underpowered, what possible likelihood is there we are going to have continued adherence over a long enough period of time to get the real answers that matter to these patients?

CHAIRMAN AOKI: Dr. Hunsicker?

DR. HUNSICKER: Tom is always is a good person to set up the question. I wrote out what I

Thought were the three questions that we really had to answer in roughly this order.

First, are the data sufficiently good, as was weakly suggested by the sponsor at the end of the presentation, to give outright approval based on the fact that they had gotten very convincing evidence of plasma levels and clearance of the capillary?

I take the discussion I have heard to date to be not very encouraging for that particular thought, that we were going to give outright approval.

So you then move down to the question of: Is the surrogate adequate for accelerated approval, given ultimate documentation in another study? And if the answer to the first is no and the second is yes, then what is the nature of that study?

Now here is where I would like to get from both the FDA and from the sponsor a response, and it is along -- the question is along the lines that Tom has put.

We have discussed this as being a very long latency disease. We know that it is going to be more than three years for the people whom you treated

initially in this study here before they get to the point where they are having progressive renal disease.

I have already raised the question that, by the time people are losing renal disease, we may have a decreasability to treat, although that has not entirely been supported by other investigations in progressive renal disease, but it is entirely possible that we could have a negative answer to the confirmatory study in patients with more advanced disease, conclude the stuff was worthless and throw it out, when in fact there was the potential for very substantial benefit in treating earlier patients.

So my question to the FDA and to the sponsor is: How are we ever going to disentangle this issue, which is the critical issue for the long term in the management of these patients? So I would, with the Chairman's permission, ask for a response from the sponsor and then from the FDA.

CHAIRMAN AOKI: Dr. Goldberg?

DR. GOLDBERG: Well, we really appreciate the discussion, and many of the comments that have been raised are obviously things that we wrestle with

on a daily basis. We don't want to deprive patients. This is such a rare ultra organ disease that an entire patient population is the size of some of the trials that are done in some of the studies that Dr. Mann -- and some of the diseases that were being discussed.

One way that we could do this with the Phase 3 population -- and this is something that we raised to the FDA when we suggested an expanded approach to the confirmation in the post-marketing setting -- would be, because these Phase 3 patients had earlier -- they were younger and had earlier stage disease, most of them had normal renal function to begin with.

We could take those patients and follow them long term and compare them to the appropriate subset of patients in the natural history database. How that is done is certainly -- you know, we could use propensity scoring for those patients as well. But that's one way of following the patients of a shorter duration.

I should mention that there were ten patients in that initial -- in our Phase 3 population

who had -- by the MDRD equation, had an estimated GFR that was under 90. It is interesting to know that now 24 months into the extension period, eight of those ten patients still have stable renal function or slightly improvements.

So again, there's some additional evidence. One other point I really feel that I must make is that, you know, you do -- I think hypercholesterolemia is another example. If you take an Hmg CoA reductase inhibitor, I can lower cholesterol levels quite substantially in a very short period of time, but it's going to take a much longer period of time to see the clinical benefit.

I don't think any of you would expect to see a decrease in the incidence of myocardial infarctions, you know, in the period of follow-up that we are able to have in the size of the study, given this rare patient population.

So I think this -- It seems to me that this is a perfect setting for this surrogate endpoint, because it does clearly, as Dr. Schneider has mentioned, address this monogenic disorder. We have

an enzyme that is missing. We replace that enzyme. It trafficks to the appropriate lysosome within the cell. It decreases the abnormal substrate accumulation that was originally present.

DR. FLEMING: Just on this point, hopefully, we are not going to analogies to cholesterol lowering. Hopefully, we are doing much more than that, and thank goodness, we did clinical endpoint studies there; because you look at Gordon's meta analysis of 50 studies done ten years ago, and those studies showed substantial reductions in cholesterol that didn't lead to improvement in clinical endpoints, but it wasn't enough, and it's only later generation cholesterol lowering agents that actually have translated into clinical benefit, which we knew, because we did clinical endpoint studies.

So we got to have something better than that here.

DR. HUNSICKER: Could I get a response from FDA?

CHAIRMAN AOKI: Yes.

DR. WALTON: In response, I think, to the

question from both you and Dr. Fleming regarding the study, the ability to complete the study, the verification study, is very important to the FDA, and this has -- and we have certainly very clearly expressed that concern to Genzyme and, in fact, perhaps the second topic that is going to be discussed, the historical control proposal, is entirely related to that, as their approach to how to be able to ensure that a dataset is obtained, even post-approval.

So the ability -- The feasibility of obtaining the data post-approval is very much tied to the assessment with historical data -- the database proposal.

The concern that you have expressed about the verification study being done in one population and not necessarily the entire population, and certainly not the same population in which the AGAL-002 study was done, and ultimately perhaps not the population that will be repeatedly coming most to question in a physician's office about what to treat or whether or not to treat, is a very important one.

What one would do if the verification study in the more advanced patients were to fail to confirm the clinical benefit is a very difficult question, and in part we are going to be asking you to discuss that. You have probably seen one of our questions. We will be asking you to discuss that.

It is always a concern when the initial studies are done in one portion of the patient population, and the verification studies or later clinical studies are done in a different portion of the patient population. The ability to draw conclusions about the entire patient population can be uncertain.

DR. HUNSICKER: I want to make it clear that I see that there are two issues here. One is the current validation study as planned, which I think is very risky, frankly, because I think that it is going to be confounded by cardiovascular, cerebrovascular endpoints that we don't know and we have really no idea what the time scale is going to be on which that endpoint might be affected.

I am very concerned not only about the

possibility of Type I error. That is to say that we might find that the stuff was effective when it's really not. I am very concerned about Type II error. That is that in this promising therapy, which I think is promising, that we would not find convincing evidence, and then be pushed in the direction of disallowing it when, in fact, it might be beneficial.

I think the Type II error has to be avoided just as carefully as Type I, and I'm very concerned about the ability of the study as it was originally conceived, for that matter, to give us the power to answer that with sufficient reliability.

They are planning a .05 -- what percent power for .05 -- It's sort of a marginal powering, frankly, for that study, if everything goes well. And nothing ever goes well in clinical trials. We already know that, and it is going to get screwed up by drop-ins and -- well, not drop-outs, but certainly by drop-ins.

So that's a very difficult one, to start with. But even there, that doesn't answer the longer term issue, which is what is going to happen to the --

We heard testimony this morning of mothers who would like to get their kids when their feet start burning on this stuff, for whom the latency is of the order of 30 years before the endpoint we are looking at.

I'm just wondering how we are going to evaluate the effectiveness of this material in the long haul. I will say that part of my answer to that myself is that, while I have doubts the wisdom of truncating the randomized phase of the follow-on confirmation study, I think that it is absolutely essential that we do our best with Rubin's best help to figure out how to use the historic data; because I think inevitably we are going to wind up comparing against historic stuff, and we've got to get that as best we can before we go ahead.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: I would say I'm, you know, persuaded, as I think most of us -- many of us are, that here is a disease we understand the genetics of pretty well. We understand the biology pretty well, and we have a therapy that seems to address that very directly, and we've seen changes in global and some

intracellular markers of the disease.

But if we are to give accelerated approval, then we are required to show in post-marketing studies relationship to real clinical outcomes. The thing that, I think, bothers me the most is that, by giving approval right now, it seems to me, what the company is telling us is that we are going to then not be able to carry forward with what is a fairly good -- not perfect, but a fairly good randomized controlled trial with at least some possibility of giving us that information.

We are going to have to terminate that in the middle, and now move to a study design which, I guess, I personally find completely inadequate. It's an observational design, and it is actually weaker than an observational design, because it is using a different comparison group.

So it's really sort of a double cohort where you have issues of the selection of the historical controls as well as the usual observational problems with confounding and so on.

So I want to ask the company, are you sure

that -- I mean, I can understand how patients in your trial will want to go on the product once it's approved. But how sure are you that we can continue with the trial, and if we could continue with the trial perhaps in some abbreviated time period, for example, by redefining the primary outcome as only renal disease outcomes by adding some -- you are probably already doing pain scales and quality of life scales and so on -- perhaps by using a shorter P-value in order to shorten the course of this trial?

It just seems to me too bad to have to waste that trial information, which I think will be wasted if it is stopped at 18 months of follow-up.

MS. LAWTON: If I could just answer the first part of that question, just to let you know that we are actually more than happy to continue with the current trial as it is. However, obviously, we recognize that there are going to be a third of the patients in that trial who will continue on placebo.

So we can't guaranty the feasibility of that trial in a post-approval setting, because, obviously, we run the risk of those patients in the

trial may choose to drop out because they can now have an approved product available. That is really the problem that we've been trying to address in looking at alternatives.

I think the second part of your question I would like to maybe ask P.K. Tandon to address as far as some of the other endpoints. I think the trial wouldn't be powerful, but maybe P.K. would want to comment some more.

DR. TANDON: In terms of P-value, definitely I think we can entertain increasing the Type I at a rate from .05 to .1 if the Committee does that. That definitely is going to help. But as for the power calculations for other endpoints, we have not done.

We have focused exclusively discussing with the FDA on these hard endpoints like serum creatinine increase and cardiovascular and so on. So the focus has been on those events.

CHAIRMAN AOKI: Dr. Jennette.

DR. TANDON: Could I add one thing, please? I think the question is being raised about,

and I think the propensity score matters and all those kind of things -- I think that is a very powerful method. So I don't think we should discard them, saying that a simple observational study -- They are bringing the beauty of maintaining the randomized nature of the clinical trial as long as the outcomes are blinded. So we should think about that.

DR. JENNETTE: To continue this line of thought with respect to validation in the continuation trials, it wasn't clear to me this morning whether repeat kidney biopsies are going to be done later on. It was my understanding that the point was made that skin biopsies were going to be continued, but that there might be a termination of kidney biopsies.

That may be wrong. Could you clarify that?

DR. GOLDBERG: In the Phase 3 trials where we did our kidney biopsies, in the Phase 3 extension, you are correct. We did the last kidney biopsy. It was hard to ask patients to undergo more than three kidney and heart biopsies. So now it's optional, and most patients have opted not to do that. But we have

managed to get skin biopsies every six months into the extension trial to 18 months, and then yearly thereafter.

We will again continue to follow these patients for the total of five years. But we are also checking -- You know, as you mentioned before about plasma GL-3, we are getting samples to follow plasma GL-3 long term as well.

DR. JENNETTE: Well, with respect to Larry's point about the fact that there is progression of the glomerular injury to a certain point before the serum creatinine, certainly, and even the creatinine clearance will be able to indicate that there's been substantial parenchymal damage -- So I think, if it is feasible, you might consider putting some effort into obtaining that third kidney biopsy further out in the course to see if there is some difference in development of focal segmental glomerulosclerosis, if you do continue the randomized trial.

DR. GOLDBERG: You are talking about the -- I'm sorry. The Phase 3 trial is where the kidney biopsies were done. Three were done. That's already

an open label trial. We could try to obtain additional biopsies, you know, longitudinally and ask patients to undergo fourth or fifth biopsies.

DR. JENNETTE: So in the other -- the Phase 4 trial --

DR. GOLDBERG: Correct.

DR. JENNETTE: -- what is the design there with respect to pathology?

DR. GOLDBERG: There are no kidney biopsies performed in that trial. That is -- We were using progression of renal -- There is a composite endpoint looking at progression of renal function defined by a 33 percent increase in serum creatinine over a two-year period or progression to dialysis or transplantation, an additional cardiac progression based on predefined criteria.

I mean, we could do kidney biopsies. It's not part of the endpoints that were defined. No baseline biopsies were obtained on these patients.

DR. JENNETTE: There were baselines?

DR. GOLDBERG: Were not. They were not.

DR. JENNETTE: Were not.

CHAIRMAN AOKI: Dr. Jonas.

DR. RUBIN: I just want to make a follow-up comment on the issue of power. And, obviously, we are aware in the Phase 4 trial that it is-- 50 treated versus 25 placebo control isn't great. That is one reason why in this new proposal we describe the two control groups, potential control groups from the historical controls; because I really do agree with you that in the long term you are going to have to rely to some extent on historical controls.

To the extent that we can do as good a job or a better job than we are doing now by matching on a collection of variables, that other control group is going to be very powerful, and it does have bias potentially. There's no doubt about that, but it has the chance of greatly increasing the size of the control pool so you can see something from the treated by comparing the treated to the control.

It is a tradeoff, but at least it will have 110, and 85 of them will have some bias. But if you get the same sort of answer in both groups, you have more confidence.

DR. JONAS: I think that this is a very logical approach to a defined disease where there is a compartmentalized absence of an enzyme, and the treatment has been designed to replace the enzyme in those compartments. It's not perfect. It doesn't appear to get in every compartment, and it seems to generate an antibody response. But it has been very well studied, I think, to date.

I have -- I'm very hard pressed to try and come up with what I would have done differently to date in these studies. That is because of the nature of this particular disease.

I think that we have to reach collectively some sort of compromise between what gives us comfort in terms of the efficacy of this pharmaceutical and what is pragmatic for the patients and for the sponsoring company for the studies that are being done; because, you know, to achieve maximum comfort with this type of disease, one might want to study this for ten or 20 years in different cohorts and get the absolute perfect evidence that it is doing what we hope it is doing or that it is not doing.

That is just not going to be feasible. So I think that we are going to have to work toward some situation where we can strike that balance. It is not clear to me that a single study going a year longer or two years longer is actually going to generate what we are hoping it will generate.

I think that we have to deal with that and recognize that.

MS. KNOWLES: I would like to agree with Dr. Jonas' comments. I think that they are well spoken. I'd like to also say a couple of other things I think that are relevant to this discussion as well.

I've followed HIV since the beginning of its emergence in this country. I can remember when AZT was first approved. The sickest patients were the people who were put on AZT at that time.

Later after AZT did receive approval, other drugs got into the pipeline, into the research pipeline, and now we don't have, you know, a cure, but we have treatments. Some people can't take them. They don't work for everybody. But there certainly are a lot of people who are living longer and better

with HIV.

I think this provides a little bit of a historical framework that perhaps maybe could be generalized to your patients as well.

I think we need to strike a balance between making a treatment available along with useful research studies which may need to still be fine tuned.

DR. FOLLMAN: I'd like to talk about two issues that we seem to be focusing in on. Those are surrogacy and the Phase 4 study.

I'm sympathetic to Tom's argument that we might not have data here to really be comfortable with this surrogate endpoint as being correlated or having a causal effect on clinical outcomes. But this is a rare disease, and the mechanism that we think this is going to use will take a long time, it seems, to show benefits in terms of clinical outcomes.

So the question, to me, was we are going to have to have a theoretical surrogate endpoint or nothing at all. Listening to what people have talked about, I'm willing to accept this as a theoretical

sort of surrogate endpoint for this particular clinical trial for this disease.

That places a lot of burden on the Phase 4 study, because it could be that this is not a good surrogate. It doesn't predict clinical endpoints in the long run. So what is most important in my mind is to have a strong Phase 4 study.

So what I worry about is maybe we go forward with this surrogate, because it sounds good. We don't validate it. We can't validate it. And then we can't do the Phase 4 study either. So it sort of comes in, in some way.

We are talking now about buttressing this control group of 25 with 85 historical controls, something I am very wary of. So I'm willing to go forward with the surrogate issue in this particular case, but I think the Phase 4 study is very important.

I have also just been thinking about -- I saw a timeline earlier where it said the FDA would make a decision like in April or June or something like that, and the study is supposed to be over in December. So that is basically six months to have,

you know, the full Phase 4 study be done properly, done correctly.

So is that not right? But anyway, my point is I'm willing to buy the surrogate endpoint, and I think the Phase 4 study has to be thoroughly investigated and done properly.

MS. LAWTON: If I could just make a comment to that. Our date -- Our current date to the FDA to respond or make a decision is the end of April. The last patient who would be coming out of the current Phase 4 trial would be January 2004. We would then have to collect that data, do all of the analysis, and in our usual time frame when we calculate that it would be August 2004 before we could even submit this to the FDA.

The FDA would then have another six months to review that. So potentially you are looking at 2005.

DR. HUNSICKER: I'd just like to say for Dr. -- I can't see the name across the way. I think he is talking about that -- once the data collection is completed. We don't care what happens in the

interval between then and the submission of the data. Then people can be unrandomized.

What we want to do is to maintain the randomization as long as possible to make the most powerful case we can.

MS. LAWTON: Okay. So that would be January 2004. Yes.

DR. FOLLMAN: Right.

DR. HUNSICKER: Could I ask Dr. Rubin to give me again maybe a second cut with the help from his Amgen compatriot.

You said before that indeed the exposure is not necessarily identical to the information. Unfortunately, in this sort of a thing where you are looking at slopes, it cuts the wrong way; because typically you get your best information at slopes with greatest distance. So you will get more information as you get out.

What I really want to have a feeling for is what fraction of the expected information are we going to have at the end? That is to say, how dependent are we going to be on the stuff that you are

going to bring in from your -- from the historical cohort?

DR. RUBIN: Well, if we are going to be letting the randomized trial go to its completion, then we are relying on --

DR. HUNSICKER: Sure. But I'm making the assumption that probably the day after this stuff is available in the clinic that a lot of the patients who are currently randomized --

DR. RUBIN: We can make a calculation for the fraction of data that will be missing. What is very hard to do without unblinding the -- not unblinding, but -- yeah, without unblinding and looking at outcome data is to figure out the fraction of missing information that is there; because missing information has to do with how predictable the sequence of points are, and I haven't seen any of that data.

Like I said before, if you are measuring height, it doesn't -- fraction information is very little.

DR. HUNSICKER: We actually have data on

how difficult it is to establish slopes accurately within a limited period of time.

DR. RUBIN: Right. And if we have -- We have short term effects from the placebo controls going out different amounts of time, depending upon when they go open label, and that information -- if those are very straight and they agree with the (quote) "slopes," -- we don't have to do linear slopes -- If they agree with the slopes in the matched historical controls, then you have some confidence that the extended data on matched historical controls really are quite predictable and, therefore, the missing information is relatively small in extending the placebo controls out to termination of the trial, even though you haven't allowed them to terminate. Is that helpful? I'm not sure.

DR. HUNSICKER: Well, I think it's as good as you can do. And, yes, it is, therefore, helpful. I'm patient with you.

I guess I would like to raise one other question quickly of the whole group. A suggestion was made at one point along the line that this historic

control group would be a heck of a lot better if we actually had all of the creatinines, not just the creatinines that were obtained at the centers where the patients were being seen.

I know that it would be expensive. I know it would be difficult. I know it would be a pain in the neck. However, I am increasing, as I sit here, in confidence that, irrespective of what comes from the confirmatory trial, that we are not going to really understand the stuff until we have looked at it very long haul, and we absolutely need the best historical controls we can.

What about the possibility of getting those other creatinine data?

DR. GOLDBERG: Just to clarify, because I think that was maybe a misunderstanding in the FDA briefing document as well, we made every effort to not only get the data from the central site -- you know, the center of excellence, if you will, where the patients were referred, but from their primary care physicians as well.

It is very hard to do, and this was not

just in the United States. So we did that as much as we possibly could. So the data you have doesn't just represent the center of excellence.

DR. GRADY: Following up on that, is it not possible to perhaps attempt to -- I mean, a creatinine measurement is a very simple measurement. It's not possible to actually go to these participants and obtain a creatinine?

DR. GOLDBERG: This was -- That was not the design of the study. This was a medical records review. Some of the patients are dead, in fact. Sometimes next of kin were asked for consent.

So we could conceivably go back and try to modify the protocol and go back to those patients and get additional data, if that would be helpful.

CHAIRMAN AOKI: Dr. Sampson.

DR. SAMPSON: I'd like to follow up on Dr. Follman's comment and clarification for what you said and, I guess, further clarification from the FDA.

You were saying that you would like very much to see, somehow if this were acceleratedly approved, that be delayed so that it occurred in

January of 2004. I thought that was where you were going on this.

I'm wondering, is there any feasible way this Committee can offer that advice to you or if, once we accept the surrogate for accelerated approval, then you automatically will have the stuff on market, say, May 1st of this year.

DR. WEISS: We have a fair amount of authority. If there are issues that are contingent upon the confirmatory validation trial being fully enrolled with sufficient time, we have a fair amount of flexibility in terms of timing of things.

You know, if that is a point of advice, you know, we would certainly consider that.

DR. SAMPSON: Thank you.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: I just wanted to talk a little more about the historical control data. There had been some discussion about wouldn't it be nice if we could get more serum creatinine measurements on these patients or more further examination of the medical records.

To me, the real issue, the real problem I have with historical control data is that they weren't -- they were retrospectively asked to be in a study. They didn't have to take some active measures to be in the study. They didn't agree to be randomized. So they are fundamentally different in that respect from the Phase 4 patients.

To me, that's the bigger concern about why worry about combining that control group with the pristine one that we have.

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: Yes. I'd like to make a comment about the surrogate marker. I think there are some parallels with diabetes, because in that disease we used hemoglobin A1c as a surrogate marker for microvascular disease.

It took us about five years and a lot of NIH money to prove that that surrogate marker actually was a good marker for microvascular disease. I think this surrogate marker physiologically is much more attractive.

We have, I think, a simpler,

straightforward pathophysiology of the disease that causes what we are dealing with today, compared to diabetes which is so complex that very few people want to study it.

I think in this surrogate marker it is much more appealing, because it seems to be a product of the defect, whereas hemoglobin A1c is really not. The real problem I have -- In fact, it is the only problem I have with this surrogate marker is the company or no one today has addressed the mechanism by which this surrogate marker might cause the disease. I think that is one thing that Tom has pointed out.

In other words, does this accumulation of GL-3 -- is it just a mass effect or is this a toxic substance or how does this actually work? I would like the company to address that issue, because I am absolutely certain they have thought about it. And in fact, if it is a toxic substance, then there might be a product of the toxicity that we could also measure.

That would give us a handle on progression. So I think I like the marker, but I don't think anybody has really addressed on how it

actually is toxic. So maybe the company could say something about that.

DR. BRENNER: My name is Barry Brenner, and I'm advisor to Genzyme. Over the last 30 years, I have been engaged in studying the progression of renal disease experimentally in animals and in patients.

We think vascular disease is a prelude to the original injury, because we can simulate it in a laboratory very easily. If we infarct the kidney, we will induce a progressive glomerulosclerosis over time. We can infarct the kidney with microspheres. We can infarct it by tying off vessels, and the clinical equivalent exists, and that is cortical necrosis which is a macrovascular disease that leads ultimately to loss of kidney function.

Once the endothelium is damaged, there is both, by accretion of this material, encroachment on the lumen with ischemic changes and activation of the endothelium, as you've heard, to produce profibrotic factors, chemotactic factors, chemokines, cytokines and other inflammatory mediators.

So that injury is propagated from the

endothelium outward. We think all of these ultimately lead to the fibrotic sclerotic glomerular and to the interstitial changes.

With respect to a point that was made by Dr. Jennette, in the original context it was the unique findings in the heterozygotes, the cardiac variance of devoid endothelial involvement, glomerular capillaries, and interstitial peritubular capillaries that was so remarkably tracking with the benign nature of the disease.

When those vessels were filled in the heterozygotes and in the hemizygotes, there was the progressive renal disease. So the correlation from many patient observations, including some that you saw today,was very vivid.

The question came up, should you look at the endothelial cells in the glomerulus in the context of examining injury? The reason why that was not chosen is because in biopsies it often is the case that you don't get much glomerular tissue. You always will have peritubular capillaries in the histologic field.

So because of the tight correlation between glomerular endothelial involvement and interstitial capillary involvement when there is involvement, and the absence in both compartments when there isn't involvement, justify the use of one capillary compartment as surrogate for what might all of us agree to be the more relevant glomerular capillary.

I think it was wise to stay away from the glomerular capillaries simply for the reason of sampling error. I think that is why there was so much reliance and confidence in the use of this particular cell type.

CHAIRMAN AOKI: Dr. Brenner, could you stay there at the microphone just a minute?

DR. JENNETTE: A question, Dr. Brenner. Your work and others' has suggested that, rather than reduce profusion of glomeruli, perhaps increased profusion can lead to -- or at least pressures can lead to glomerulosclerosis.

Since the peritubular capillaries are really downstream from the arterial coming from the

glomerulus, is it conceivable that peritubular endothelial inclusions actually increase resistance after blood flow through the glomerulus and, in fact, in that mechanism are causing glomerulosclerosis rather than ischemic root?

DR. BRENNER: That's certainly a possibility, and I believe none of these are mutually exclusive. Anything that raises post-glomerular vascular resistance will raise the glomerular pressure. Angiotensin does it as a physiologic tenacity device, but high resistance -- We see it, for example in the sickle cell models where high resistance of the high hematocrit zone of the post-glomerular circulation is the root cause of the glomerulosclerosis that occurs in those sicklers who live 20 and 30 years.

So we believe the causation is very strong, as you imply, but it doesn't tell me that it is the only mechanism by which the glomerulus is damaged.

DR. JENNETTE: To me, that is a more attractive hypothetical basis for linking peritubular

endothelial inclusions and impairment of flow in causing glomerulosclerosis than ischemia to the glomerulus.

DR. BRENNER: Well, I would not say that all of these capillaries that are examined that are called interstitial capillaries are post-glomerular. There is a microcirculation that has to feed the glomerulus, and that is also present in the histologic section. And they examined them. They examined the vascular smooth muscle wall and the endothelium of non -- just endothelial capillaries. That is, only the capillaries that are bounded by a single endothelial cell.

So all of these were in the mix, and all of them showed resolution with enzyme replacement therapy over the 20 week period of observation.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: A couple of comments, maybe just to follow up first on Kathy's earlier comment as we talk about HIV/AIDS and how we began, as you noted, in more advanced patients in that setting and have had major successes as we have progressed.

I would just point out that for a number of generations of studies, we had the benefit of starting with clinical endpoint studies and learning about natural history and correlates as we went through that process.

I'd like to most specifically expand a bit on Dean Follman's comments on the historical control data and interpreting that. There is obviously a -- There has been a great amount of thought to what is the relevance and insights that we can get from control information beyond randomized trials, and many variations of what we call historical control data exist, observational based data, historical cohorts, etcetera.

Among the works that have been done, Stuart Pocock has written a manuscript now 20 years ago probably on the criteria that would be important to implement if we were going to use an historical control.

Essentially, the concept is the historical control database should be formulated much in the way of the way you would formulate the perspective

clinical trials, and it should meet a lot of the criteria that we would need to have in place in a perspective clinical trial to be interpretable.

So one of his criteria was the data should come from a clinical trial with high levels of follow-up. I think this is related to a point that Dean had made. This database from the experimental intervention is coming from people who were selected and managed in a clinical trial context, and that wasn't the case with the historical control, which can create some systematic differences.

A second issue is that there should be identical outcome assessment, and we have heard a lot of discussions about the nature of patterns of missingness in the serum creatinine data in the historical database.

We will talk about the validity of a clinical trial being inherently dependent on having high quality follow-up on the primary endpoint. Well, when we go to historical controls, it doesn't mean we can relax that important requirement. And as the FDA has pointed out, I think, even in this core subgroup

of 103 that were in the qualified data, 18 had one creatinine value, 22 had two, a median follow-up of 1.4 years, where 41 had less than one month follow-up.

If that was the randomized comparator in a randomized trial, I'd have serious problems with interpreting the information with that level of irregularity in follow-up.

We talk about, as Stuart Pocock does, the obvious point. You want to have balance in the baseline patient characteristics in the population, so the differences that you see can be attributable to intervention and not intrinsic differences in the patient population.

What we have seen from Dr. Rubin is some very sophisticated analyses. I don't have concerns with what Dr. Rubin has done. I have concerns with what we've been able to provide Dr. Rubin to empower him to do what he needs to do.

Specifically, as it has long been recognized, the covariates that are known and recorded are the tip of the iceberg of what distinguishes different people in the prognosis. So those issues

aren't able to be fixed with statistical modeling, even the most sophisticated statistical modeling.

Finally, Stuart says -- or Pocock says, and there should be no other differences of relevance, sort of a catchall. That's an awfully tough one, but you think about issues of same sites for referral practice comparability. You think about same points in time, going back to Dr. Hunsicker's comment sometime ago about, if there is time confounding and ancillary care is different, that can substantially influence outcome.

So a number of folks, a number of our Committee members, Dr. Grady and others, have pointed out issues of serious concern about whether the historical control experience -- what level of reliability does that provide relative to the clinical trial outcome information?

I go back to Adam's comments earlier, and I would strongly concur with your comments that one has to be rational, and in this setting to require 30 years of follow-up to answer the question is too high a bar. I completely agree.

The problem is, though, where is the middle ground compromise? We heard from the FDA a reminder that this is an orphan drug, and my understanding is we should and are making accommodations, and yet still, as we have been reminded, an orphan drug still requires substantial proof of efficacy.

Now if this wasn't na orphan drug, we wouldn't even be thinking about these issues in terms of whether they are remotely convincing, at least in my experience. We would want two adequate and well controlled trials and probably, in all likelihood, we would want to look at clinical efficacy endpoints.

So we are clearly moving away, and I strongly support comments from my colleagues saying you can't hold to that here. The question is what's a rational middle ground?

My own sense about this is this current what we are calling Phase 4 -- I truly think of as Phase 3 -- is of integral importance, and even if we just go the route of an additional one year to allow this study to complete its follow-up, it is barely in

a position to tell us the kinds of things that we want to know. But it does have substantial possibilities of teaching us significantly more, important clues about clinical endpoints and a lot more insight about the reliability of surrogates in the correlation.

The historical control data, I believe, is valuable but, I believe, does not come close to the value and reliability of the clinical endpoint study. So I would be thinking much more in terms of not doing anything -- whatever we do, not doing anything to negatively impact the ability to successfully complete that clinical trial, and then augment everything that we can with the historical evidence that we would hope to get, as a balanced and middle ground accommodation to the fact that this is an orphan drug.

There is an extremely important unmet need, but we have a commitment to these patients to understand reasonably adequately, as the regulations tell us that we need to understand, is this an intervention with adequately established, favorable benefit to risk before it is approved.

CHAIRMAN AOKI: Are you arguing then -- Are you stating then that the Genzyme protocol should go to completion to January 2004, as it is currently designed, and then adopt the historical design, since at that point in time they will go to market, assuming that it is approved? So that you would have continued observational information.

DR. FLEMING: The fundamental -- most fundamental important issue that I am recommending is that, whatever strategy we take, that that strategy ensures that we will be able to obtain the full information from this trial, maintaining adherence to the control placebo regimen through the planned period early in 2004.

My own personal view, about which I feel much more flexible after having stated that other point, is I would actually like to understand from that dataset, not just the effect on clinical endpoint, but to be able to much more clearly understand the duration of effects on the marker and on the clinical endpoint and the correlation, and all of that information taking then a much -- a reasoned

standard for what strength of evidence would be, but basing the assessment on that.

That would be my preferred approach, but under any circumstance the approach that we would take, I would urge be one that allows us to complete the placebo controlled trial without those placebo patients coming off the control regimen before early '04.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: I always seem to follow Fleming. There seems to be emerging a consensus, and I will phrase it slightly differently from the way that Tom did.

There seems to be emerging a consensus that we should get the most information that we can out of the what is now Phase 4 study. That is to say, we should try to keep it going as long as possible. I am going to leave to the administrators the issue of, if we recommend accelerated approval, what they do in order to achieve that follow-up -- you know, when you decide that the drug is available. That's on your backs, not mine.

What I want to emphasize is that the outcome of that trial will shed a good deal of light on whether Fabrazyme can slow the rate of progression of renal insufficiency in patients who have already reached some degree of renal insufficiency. It will shed virtually no light on any of the rest of the biology of this agent.

It is for this reason that I find myself ever more feeling the urgency of getting some more background information about these people.

Now this is a clinical trial's area here, and we are quite proper here in emphasizing the strength of evidence of clinical trials as opposed to epidemiological evidence. I will tell you all that I go home, and I take off my clinical trials hat, and I put on my epidemiology hat. When I put on my epidemiology hat, the approach I take is that some information is better than no information.

Where we are right now with respect to Fabry's disease is that the best information that we have about the total natural history is the result of the study that the sponsor has now done, because this

is a sufficiently rare disease that it hasn't been compiled like this in the past.

What I would like to say is that, in addition to following up the clinical trial data the best that we possibly can, I think that there is a very high priority on doing whatever you need to do to encourage the sponsor to extend and expand its observational database from the past.

We are going to be asking of that dataset whether patients have more frequent strokes or not, whether patients, in fact, have any change in the natural history of tingling in the feet or whatever the heck it happens to be; because there is none of this that is going to come out of that clinical trial that we are talking about right now.

So we really need to encourage the sponsor to extend as much as possible what we know about the natural history of this study, about which we know much less than we do about diabetes, to which you were comparing it earlier on.

DR. GOLDBERG: Could I make a brief comment? We are collecting data on strokes,

myocardial infarctions, etcetera, from the natural history database, and arrhythmias and things like that. But please bear in mind that you are getting -- When you do a medical records search, a serum creatinine is a very objective, concrete piece of information that you can follow over time.

Whether somebody has had an arrhythmia or -- You know, they say in the chart it's palpitations. We feel that is not documentation of an arrhythmia. Even an MI, obviously, there are several bits of criteria that go into that.

So it's not as clear a database, but one thing that we are also doing, in addition to the natural history database, that is well underway is we have a Fabry disease registry that is open worldwide. We've done the same thing with Gaucher's disease for which we have now data on thousands of patients, and it has been very helpful in helping guide physicians in the treatment of those patients more effectively.

DR. HUNSICKER: I'd just would comment that I will rest with my earlier comment, that some information, however imperfect, is better than none,

and where we stand in evaluating the background is very thin. The more you can thicken it out --

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: Yes. I just want to make a point. I may not be in the mainstream, but I feel a great urgency to get a treatment on the market for the patients here who basically have this disease; because there is really no other therapy available, in contrast to other diseases where we have alternatives.

Although I think we do need -- I agree basically with the speakers that we are really deficient in information of efficacy of this product. On the other hand, this product -- we at least know what it does to some extent. We know what the pathophysiology of the disease is, to some extent.

This is a progressive disease in 3500 patients in the United States, and from my point of view, there's some urgency to get this product or products available to the people who -- We could be wrong, but I think we are going to be right by getting a product to them on the market.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I must say that I feel that I am on the horns of a dilemma, because I'm terribly concerned about a comment that Larry Hunsicker made, that we are likely to have a Type II error.

If this trial goes two years and is marginally successful, what are we going to do a year from now? Are we going to say the trial failed; it's not good. What are we going to do? Are we going to come back and say five years from now, well, we're just going to have a five-year trial. What are we going to do?

We know the pathophysiology of the disease. I am assuming that there are animal models. At least, I hope there are animal models that can answer some of the -- fill the gaps in on the pathogenesis of this.

On the other hand, I can say, well, it's only another year until we finish this trial, and let's do it. We've got it. Let's try to mine as much information out of it as we can, and it's a classic clinical investigator that -- did you get it? Did you have a tube stored away somewhere to do something?

Do we know in this patient population that their antibody status is of great consequence or no consequence? I mean, are we doing that? What is happening to the urinary values of this material in patients who are having decreased renal failure? Are they filtering it less? Are they filtering it more? What's happening?

So my gut feeling is I'd like to go with a year, but, boy, as soon as -- It's almost irrelevant. I want the information, but I want the product approved.

DR. WALTON: Dr. Aoki, may I ask that, because of the time, and we have questions that it's important that we hear the focused discussion on the questions, and much of what was just said is very much tied to one of our questions.

CHAIRMAN AOKI: What I would like to suggest is that we take a ten-minute break now, and then come back and segue from this open discussion to a structured one in which we are going to discuss the issues directly, because you are right.

I think we have now aired all the issues

that are going to be discussed and, hopefully, we'll be able to move through this with some dispatch. Yes?

DR. ZERBE: Do I have the opportunity? Just a quick comment. I'd like to echo Dr. Schade's comment. It seems like the patients themselves are asking for availability, and we can reasonably and responsibly support that, provided three criteria are met.

First of all, that the labeling accurately reflects the level of knowledge that exists, and I think there is some work in the labeling itself that really focuses on the renal aspects. There is very little data that support efficacy otherwise.

Secondly, that we are quite confident in the safety. There hasn't actually been a whole lot of discussion on the safety throughout this, and there are a few niggling issues that I would like to hear addressed at the appropriate time.

There were the three patients that did have progression of renal failure. There was another patient that had a fairly substantial increase in proteinuria. None of that was explained in detail.

it would be nice to know more about those patients before we sort of sign off.

That is particularly important, because the benefit is at this stage pretty marginal.

Lastly, I think the future confirmation is essential. I think it's unlikely there is going to be a single trial that is going to do that. In fact, the better strategy would be not to focus on a single trial, but actually a strategy of a series of trials that could adequately, definitely in the long term answer the question, even with the drug on the market longer term.

So those are my comments.

CHAIRMAN AOKI: Thank you. Why don't we now take a ten-minute break, and promptly be back.

(Whereupon, the foregoing matter went off the record at 3:05 p.m. and went back on the record at 3:15 p.m.)

CHAIRMAN AOKI: Okay. Can you all take your seats. Dr. Woolf.

DR. WOOLF: I understand just before break that there is a knockout model of this disease. I'd

like to hear briefly about it, so perhaps it can shed some light on the pathogensis of the observations in humans.

CHAIRMAN AOKI: Is there somebody who could very briefly -- and I'm talking very briefly, like a couple of minutes -- talk about the knockout model for Fabry's disease?

DR. DESNICK: I'm Bob Desnick from Mt. Sinai, and I'm a consultant to Genzyme.

For the past 35 years I have probably diagnosed and managed more Fabry patients than anyone else in the world. We were the ones who cloned the gene and developed the knockout model, and the knockout model is a very good biochemical model of Fabry's disease.

In other words, it has the enzyme deficiency. It accumulates the substrate in all the key organs, and it has the lysosomal pathology. It doesn't have the endothelial involvement. So it is not a clinical model of Fabry disease, and the animals live a normal life span.

This is not uncommon with animal models of

disease. When you do knockouts, about half the time they don't have a clinical phenotype. But it provided us with a very good biochemical model and pathological model to evaluate -- to do the preclinical studies in Fabry's disease.

In that setting, and this is all published data, we are able to show very conclusively by giving the enzyme at doses that were high enough, we could reverse substrate accumulation and that, in fact, substrate delivery and clearance in the individual tissues was all dose related.

It was that information that guided us in our Phase 1-2 study where we selected our doses.

CHAIRMAN AOKI: And did you see the different responses of the different tissues as well? In other words, certain tissues reflected a greater change in GL-3 diminution than others?

DR. DESNICK: Yes. It's very much a function of enzyme delivery. The enzyme is taken up by the cells via the manno-6 phosphate receptor directly to the lysosome. So it's a beautiful model in which you can see, one, that you get the enzyme;

two, that it gets to the target site of subcellular pathology, and you can see reversal by light and electron microscopy as well.

So you can measure it quantitatively, and that's what we were able to do in the mouse model. We were able to show that we could, at appropriate doses, eliminate the material from certain organs, liver, skin, heart, and to a lesser degree kidney. It takes a longer time, because that's where you have the most substrate accumulation.

These clearances were all dose dependent.

CHAIRMAN AOKI: Okay, thank you.

DR. SCHADE: Just a quick question. I understand the animals lived a life span, but do they have any complications of the disease, any impairment such as cardiomyopathy or enlarged heart or any pathological consequence of the accumulation?

DR. DESNICK: So to date the only finding that we have in the two-year-old animals, which is the longest they live in our facility, is that they might have some mild cardiac hypertrophy and are similar, without the endothelial involvement, to the cardiac

variant.

CHAIRMAN AOKI: Okay. Now turning to the discussion topics, I am going to read some background material, and then we will address specific questions.

The following are observations regarding Genzyme's studies of Agalsidase beta:

The controlled study AGAL-002 conducted by Genzyme was designed with the primary objective of demonstrating a treatment associated effect on a histologic endpoint of "near-normalization" of substrate deposition in renal capillary endothelium on light microscopic examination.

A robust effect was observed in reducing the deposition of substrate in the capillary endothelium. Reduced substrate deposition was also observed in several other, but not all, cell types examined in renal, cardiac and skin biopsies.

Clinical efficacy was not observed. Among the secondary outcomes of Study AGAL-002 were the effect of the enzyme on pain and renal function. There were no changes in either group in renal function during the controlled study period, and there

was no treatment related difference in pain assessment.

AGAL-002 was not specifically designed or powered to show an effect on these secondary outcomes. The eligibility criteria did not specifically focus on patients who might be likely to demonstrate an effect on these measures.

Most patients developed antibody to agalsidase beta. Antibody formation has the potential to negate or lead to regression in the histologic findings prior to the time when clinically apparent decline in renal function would occur.

Adverse effects were observed in association with drug infusion. Some adverse reactions were severe.

Genzyme has requested marketing approval under the accelerated approval framework. This requires a determination that the studied surrogate is "reasonably likely to predict clinical benefit.

(a) Please discuss the relevance of the clinical measures studied and the importance of the observed results. To what extent should the results

on these outcomes influence the assessment of potential efficacy as may be predicted by the histologic results?

Would anybody like to take a crack at that one? Dr. Hunsicker?

DR. HUNSICKER: I have the last paragraph that you have just read, but it was appended to a first paragraph that was slightly different in focus. But let me try to do both of these.

First, it seems to me quite reasonable to assume that clearance of the endothelial material might well be associated with substantial clinical benefit. So I think that this measurement is relevant.

You asked about other things. I think that it is very reassuring that the majority of cells similarly have clearance of this material, because I do think that it is beyond question that the disease is due to the retention of this material in some cells somewhere, and the more cells that clear it, the more reassuring it is. So I think the fact that it is cleared by multiple cell types is substantially

reassuring.

The clinical measures are all negative. I do not take that as a worrisome thing at all, and that, I think, may be the focus of what you were trying to get at. Particularly with respect to the renal outcome, one would not have expected that -- Let's say one were to take diabetes or some other glomerulopathy with patients who had creatinines that averaged 0.7, 0.8 at the time of entrance into the study -- that one would have seen anything at all, even in 100 percent effective therapy by the end of five months.

So the fact that there is no renal outcome as measured by GFR in no way surprises me. Similarly, I believe that the absence of a response to pain probably reflects that it is going to take a heck of a lot longer to reverse that, if indeed it ever is reversible, once it has occurred.

So I do not take the negative findings in any way as weakening the hypothesis that this is a surrogate for the ultimate endpoint that we want.

CHAIRMAN AOKI: Anybody else who would

like to answer that? Yes, Dr. Watts?

DR. WATTS: I completely agree. I have trouble understanding exactly what the question meant, but failure to show clinical improvement in renal function and pain or cardiac function certainly is not disturbing, given the short nature of the study.

CHAIRMAN AOKI: Thank you. Dr. Fleming.

DR. FLEMING: Well, clinical data on clinical measures certainly are -- as we look prior to an approval, are generally a very important part of what we look for as we try to assess benefit to risk. Obviously, they hold the potential of telling us something very important directly about whether the intervention is affecting clinical measures, and they are also very important evidence contributing to our assessment of the reliability of surrogates.

I can accept the position here that these measures are expected to be not substantially affected in studies of small sample sizes and short duration. It is of interest to me that, for all nine measures that were put forward, that globally one had a sense of nothing happening, and some of these like pain, I'm

not as convinced that we shouldn't have seen anything.

There was no net pain effect, but globally I can accept the fact that this certainly doesn't conclusively rule out benefit. I am, however, aware that it hasn't added any encouraging evidence.

It does, though, tell me that it is certainly to be expected that, if we have clinical benefit, it will be a longer term achieved benefit, and it does provide the sobering realization then that one is going to be looking at the need for understanding longer term biologic activity.

If you are going to expect longer term clinical benefit as we interpret these markers, it has to be not just what have we shown short term, but is there adequate evidence to ensure that we are going to see longer term GL-3 efficacy as well as longer term safety.

So the lack of clinical evidence here is not irrelevant. It certainly has implications for our overall sense of what it is going to take to show benefit.

CHAIRMAN AOKI: Okay. The next question

is: Please discuss the quality and --

DR. ZERBE: Just a point of clarification. My understanding on the pain was that, in fact, there was improvement in pain. The problem was that there was a substantial improvement with the placebo group as well, which means that, you know, it's very difficult to interpret, but it isn't as though nothing happened.

DR. FLEMING: Well, then I would amend what I would say to say there was no evidence that there was a treatment induced effect on pain beyond the well known placebo effect.

DR. ZERBE: Agree completely.

DR. WATTS: It's hard for me to get at all the data, but I think it's a different explanation than that. When you are doing a study with multiple endpoints and you have a heterogeneous population, it's doomed to failure.

As I read it, the pain scores on a ten-point scale were 1.9 versus 2.2, which means most of these people didn't have pain and, therefore, most of these people had no margin for improvement.

CHAIRMAN AOKI: Okay. Please discuss the quality and strength of the histologic data. Please include in your discussion the importance of substrate accumulation in the renal capillary endothelium to the pathophysiology of the kidney dysfunction, and the relative importance of substrate accumulation in other cell types. Dr. Jennette.

DR. JENNETTE: I'll be reiterating, I think, comments that others have made. I think there is absolutely compelling evidence that the inclusions in endothelial cells in the microvasculature are dramatically improved, reduced by the agent.

I think what is very comforting, and Larry has already alluded to this, is that in fact, although not focused on as much, there is evidence that there was significant reduction in the inclusions in many other parenchymal cells in the kidney, in the heart, in other tissues.

So even though that wasn't the primary endpoint, it certainly adds some support in my mind to the contention that the intracellular accumulations which, I think, we all suspect is the prime mover in

the pathogenesis, are improved.

I would reiterate that I think the observations on quantitation of GL-3 in plasma, even though that is not the site at which it is causing the injury, more than likely, in the urine, even in the tissue, although those data were incomplete and were not discussed in any detail as a consequence, all of those parameters of histologic and biochemical analysis -- the bulk of this substrate which must be somehow -- it's not completely elucidated -- causing the disease is diminished and in some instances substantially, in others less apparently.

So I am encouraged by the pathologic evidence says a reduction in the bulk of the substrate, which is independent of the clinical issue.

CHAIRMAN AOKI: Any additions? Dr. Barisoni?

DR. BARISONI: Yes. I would like to add that, while I agree with Jennette and the histologic data are really strong, and the fact that there are no major changes in other cells such as podocytes, it is probably not relevant at this time. It might be

relevant in 20 years when FSGS may develop due to podocyte disease, but we can't prove it now, and you might have it anyway. So --

CHAIRMAN AOKI: Thank you. Okay, let's move on to the next one.

Please discuss the ability to extrapolate the short term histologic response data to the longer time frames when clinical benefit might be expected to occur.

I think we just answered that. Okay.

DR. HUNSICKER: Okay. Thomas nominated me. At best, from -- Well, first of all, the -02 trial simply demonstrated clearance of the substrate. IT didn't demonstrate anything clinical. At best, what we are going to get from the now Phase 4 trial is information about the impact of this therapy in patients who already have existing renal insufficiency or are proceeding rather rapidly.

That we have a fair shot at getting some information about. Longer term information is not going to come from either of those two trials, and unfortunately, must come in the long haul from

comparing where we are in the future from where we have been in the past, and that is inevitable. It is unescapable.

An issue which I think you did glide over, which is the issue of antibodies, is something that we might address right now. That is to say, what is the likelihood that the fact that there is an antibody response will affect the long term effectiveness of this drug?

CHAIRMAN AOKI: Let's address that when we come to it.

DR. HUNSICKER: Okay. You want to keep that one separate.

Short of that particular short term thing, I think the best we can hope for from any of these trials is evidence that this drug will affect in the relatively short term the rate of progression of renal insufficiency in patients who have existing renal insufficiency.

Now that is not necessarily -- It's unfortunate that that is all we are going to know, but that's not necessarily a criticism. That's all we are

setting out to know, and that's all that it is reasonable to think that we are going to be able to find out about within any realistic time of evaluation of this kind of an agent.

Therefore, I think that we have to accept that what we are going to know is relatively limited and that the long term truth is going to have to come out in post-marketing surveillance.

CHAIRMAN AOKI: I agree with that. Dr. Fleming?

DR. FLEMING: Well, I had -- I mean, I see (b) and (c) as separate issues, and I see the studies that we -- Phase 3 study as giving us direct information about (b), and concur that there is impressive information on the primary endpoint. But I see (c) asking a very important extension issue, and that is I would think we would all -- I would assume we would all agree that, if this short term effect that we have seen in five months weren't sustained for very much longer, that in this chronic setting here it would be far less plausible that we would see clinical benefit.

So this is a critically important question. As a statistician, I would say I have no clue what the answer is. I understand biologically that we can be hopeful. We have a little data, and its glass is probably more than half-full in that data when we talk about the extension study, but it does, in fact, give some suggestion in some of these cell substrates that there is a certain fraction of people that don't have the sustained at least zero level benefit.

So it seems to me that, unless there are some strong biological arguments that people can give for why it is almost certain that what we see will be sustained, I would say at least statistically the evidence that we have indicates that there is an important level of insight here that we remain to gain. That insight can be gained by both historical experiences -- well, cohorts followed for long periods of time as well as randomized comparative trials, and those sources of information, I see, will be valuable to being able to answer this more clearly in the future.

CHAIRMAN AOKI: I agree. Any other comments? Dr. Jennette.

DR. JENNETTE: With respect to the Phase 4 trial again, I would suggest considering the possibility of renal biopsies at the end of that study or at some point. Even though they are not baseline biopsies a, hopefully, dramatic difference in some pathologic parameter in addition to endothelial inclusions might be very informative. So I would advocate considering adding that to the protocol.

DR. HUNSICKER: Could I reply to Dr. Jennette? God knows, I don't want to have anybody say I don't want more information, but let me -- Just so that the sponsor is not pushed in the direction that I think is not likely to be productive, let me just go down some of the problems.

First of all, what you are going to be interested in is not persistent removal of the complexes. I think that we -- I frankly agree with you, we can now follow with the serum levels. It seems to me that if the serum level is zero that we can assume that things are going better in that

regard. That's been a fairly good correlation.

With respect to evidence of progressive disease, what we would be looking for is differences in the amount of renal scarring or some measure of renal scarring, whether it be glomerular dropout or interstitial scarring or whatever it happens to be.

In fact, since people are starting at different points, and since in fact people can have relatively normal histology -- I mean function and still have terribly abnormal histology, what you can say is that these people are going to be coming into the study with very, very different degrees of histology.

You add on top of that, that this will have to be an additional informed consent, which will not be uniformly done. So you are going to have a nonrandom group of people responding to it.

So what you are going to have is a readout at the end of the study in a nonrandom selection of patients in whom you don't know how much change there has been since baseline, because you didn't do it, in an area in which nobody has yet provided a convincing

way to rank people in terms of fibrosis.

I personally feel that this is absolutely hopeless, and I would not personally encourage the sponsor to go down that route.

DR. JENNETTE: Just one comment. Bear in mind that the serum creatinine and the creatinine clearance are surrogate markers for the injury, which can be viewed directly in the biopsy. Of course, that's a pathologist's bias.

DR. HUNSICKER: Well, I know that, but I would say also that the injury in the kidney on a biopsy -- the injury present in the kidney that is biopsied is a surrogate for the clinical outcome. So I don't think we are any closer.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: I thought the question was more directed at whether or not this clearance of the substrate persists. You know, the sponsor has a lot of ability to get that information in the patients that they are now following in their open label studies up to three, four, five years, and it provides a lot longer follow-up than the Phase 4 trial.

I mean, I think additional biopsies in people who have been using the drug for a long time could be useful, but probably all we want to know is does this persist for multiple years.

DR. GOLDBERG: Could I clarify that? You know, we have committed to, and we are doing those serial skin biopsies, and I showed you in the primary presentation that we're looking at superficial skin capillary endothelial cells now.

The latest data that we showed you is out to 30 months into the extension. So it's a three-year period of follow-up for the patients who were originally on Fabrazyme, and between 95 and 100 percent of the patients had zero scores out at 30 months to 36 months.

We have similar data that we would be happy to share with you on the deep vessel endothelial cells.

DR. GRADY: Yes, and I Think that's excellent, but it is three years out of what could be a lifetime of treatment, particularly in people who are developing antibodies to the treatment.

DR. WALTON: Dr. Aoki, may I clarify what the question was about. I'm concerned this one may have also been misunderstood. I apologize if the questions I've written have not been entirely clear.

This question is a lead-in to the next one, and in this one, because there has been great concurrence that the clinical benefit on renal failure is going to be a relatively longer term outcome, and we are discussing the possibility of a surrogate being likely to predict that clinical benefit, that it seemed reasonable to assess whether or not there was confidence at this time, given the data in hand at this time, that the histologic information we have would be sufficient to carry through, through the time period that might be needed for the clinical benefit.

If one were to have an acute assessment of a surrogate that appeared to show a treatment effect and a clinical benefit were to be unexpected for 15 years, but that that surrogate would need to persist in its altered state for all 15 years, one would want to have a reasonable degree of confidence that that persistence of the surrogate would be maintained.

So the question is, given the data that you have heard, can you be reasonably confident in presuming that the histologic effect you have seen will persist out to time frames, however long that might be, for when the clinical differences might be appearing?

DR. HUNSICKER: Confidence is a rather subjective term. Let me, therefore, respond in a slightly different way.

If the enzyme keeps working in the lysophagosomes the way, way in the future that it has in the past, the likelihood is that it will continue to be effective; and if it continues to be effective, we are assuming that that is what is going to lead to the ultimate clinical benefit.

Now why would the enzyme not be able to continue to do that? If there were something that I can't imagine right offhand that said that the enzyme changed its character every ten years the way the flu bug does every year, then maybe that would be the case. But there is eery reason to believe that the same enzyme is going to do the same thing 15 years

from now as it is doing now.

So the only likely reason that it might not do that is if there were a failure in delivery. The best we can do about that is the most likely cause for failure to deliver is something that changes the clearance mechanism.

About that, we actually have some information in the short haul, and it is the part that Dr. Aoki suggested we defer until later on, which is the impact of antibody. Short of the issue of the impact of antibody, I can think of no reason why, if this stuff clears the glop out of the cells today, it will not continue to do so 15 years from now.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: A circumstance under which the long term maintenance of this primary endpoint would not have clinical outcome that would be advantageous would be if, in fact, that correction doesn't correct the true pathogenic process. I don't know what the pathogenesis is.

The hypothesis that has been put forward by Genzyme is feasible, to a certain extent, but for

in fact, if the accumulation of the substrate in the podocytes is the primary mover in focal glomerular scarring, and Helmut Rennke and Dr. Brenner have suggested that in some circumstances at least injury to the podocyte is a prime mover, then if the inclusions remain there, as we have a suspicion they at least remain a little bit longer, and that's the true pathogenic factor, then eliminating the inclusions from the endothelial cells won't have an effect.

If it's the mesangial cells, likewise. Now having said that, I will refer earlier to the fact there is some evidence that there is reduction in the bulk of the deposits even in those cell types. But that is aside from just talking about the endothelial surrogate.

So at least to me, there are conceivable ways by which you could have correction of the endothelial cells. They are closer to the circulation. Maybe there is a better effect. The podocytes are further from the circulation. But in any event, if the pathogenic process is still moving

forward even though the endothelial cells are cleared of the inclusions, they are not going to have a clinical benefit. But I don't know that. It's all hypothetical.

DR. HUNSICKER: But I don't think that was quite what I heard you say. You said, if the pathogenic hypothesis is correct, is the histologic correction that we have seen likely to persist?

DR. WALTON: Yes. That was the question in this part.

DR. HUNSICKER: And I think the answer to that is, yes, it is reasonably likely to persist.

DR. WALTON: The question Dr. Jennette was discussing is really the next part of the -- the next element of the question.

CHAIRMAN AOKI: Okay. After this, we wills be asking for a vote.

Please discuss if capillary endothelium substrate deposition, specifically as assessed in Genzyme's study AGAL-002, is an appropriate surrogate for the purpose of accelerated approval. That is, is "near-normalization" of renal capillary endothelium

reasonably likely to predict a clinically meaningful effect?

Discussion, and then vote.

DR. HUNSICKER: My discussion is my vote. So I'll wait until my vote.

CHAIRMAN AOKI: Okay. Why don't we take a vote. Why don't -- We are starting from the left. Committee members.

DR. WATTS: What are the options?

CHAIRMAN AOKI: Dr. McClung?

DR. WATTS: Yes or no, or can we have a "don't know"?

CHAIRMAN AOKI: No. You can make statements. I have never known Dr. Watts not to have a statement. Dr. Grady.

DR. GRADY: This is kind of the key question, though. I mean, it seems a little odd that we have no discussion of the absolute key question.

CHAIRMAN AOKI: Oops, I missed that.

DR. GRADY: Well, I just said this is the key question, and it seems a little odd that we have no discussion of the absolute key question.

CHAIRMAN AOKI: No, I invited discussion.

DR. GRADY: Oh, okay.

DR. HUNSICKER; I will start out some discussion and offer it up for people to shoot down.

Again, is it a reasonable surrogate? Reasonable is not defined. I believe it is the best hypothesis that we can put forward today. There is more support for this hypothesis than for any other pathogenetic hypothesis that I have heard put forth.

Therefore, it is reasonable to take this hypothesis, because the alternative is having no hypothesis to take forward, and we've got to start somewhere.

CHAIRMAN AOKI: Thank you. Dr. Jennette.

DR. JENNETTE: I agree.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: I agree also, and I think there are a number of other examples of genetic disorders in which getting rid of the offending material led to tremendous improvement in the patient. I think we have to just make that leap of faith that this will be another one of those.

CHAIRMAN AOKI: Is there anymore discussion? Dr. Grady?

DR. GRADY: Not being a nephrologist, I would just like to ask our nephrologist colleagues. I guess the thing that confused me the most was the podocyte issue. So, yeah, it seems quite clear that we've got this substrate. It's cleared from some cells, but particularly given the data we are going to review tomorrow, there was some suggestion that the proper cell to look at for clearance is the podocyte.

If we were doing that right now, I think we would have a much different view, because there was some clearance from podocytes but not nearly the huge and marked effect that we saw in the endothelial cells.

So does somebody know something about this?

CHAIRMAN AOKI: There is a pathologist.

DR. HUNSICKER: I am a nephrologist, and I know nothing about the pathophysiology beyond what we have heard talked about today about this particular disease. However, I can say generally that the

correlation between renal function and glomerular scarring is much less strong than the correlation between interstitial scarring and renal function.

So that if I were to look somewhere for the definitive, most likely thing to reflect on what is going to happen in the kidney, I would actually look in the interstitium before I would look in the glomerulus.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: I have not ruled out the possibility that the podocyte is the main target. I haven't ruled out any other possibilities either, smooth muscle cells in the muscularis of the arteries, mesangial cells, wherever.

As far as it being a surrogate marker, there is also no evidence that there is not a reduction in the bulk of substrate in the podocytes. In fact, there is some soft evidence that there might be some reduction, and the reduction in the endothelial cells may be a more sensitive marker that, in fact, there is a reduction in the podocytes. We just can't detect it by our current methodology.

So I'm not sure the podocyte isn't still the target. I'm not convinced there isn't a reduction, and I suspect there might be a reduction. So it does concern me some, because I have had the concept reinforced by data in other pathogenic mechanisms that lead to focus segmental glomerulosclerosis that the podocyte may be involved, but that still doesn't prevent me from concluding that this is a reasonable surrogate now, suggesting that improvement here may reflect some improvement even somewhere else in the pathogenic process and ultimately the clinical outcome.

CHAIRMAN AOKI: Dr. Jonas.

DR. JONAS: I actually had a question about the podocyte accumulation of material. It seemed to me -- and I'm wondering if my impression was correct -- that there was the potential for great individual variation in response to enzyme administration in the podocytes.

In the material that we got, there was a photo micrograph of a cell with greatly reduced storage. Yet the aggregate information doesn't show

such enormous reductions in storage. I was wondering if anybody could shed some light on that.

DR. RENNKE: As you know, when the change is so dramatic, as it is in the podocytes, it is difficult to assess minor changes. It is much easier to say yes or no. We had the distinct impression that in the treated patients that there was a reduction in the density of the lamella. This is what is the weak spot, if you want.

On the other hand, there was some cells in which this was much more dramatic than in other cells. This was not only between patients but also within patients. So the change is not uniform, but again it may be an issue of sensitivity.

DR. BRENNER: Could I add a point or two here? In these natural experiments of the female heterozygote, the cardiac variant, there is occupancy of the podocyte by GL-3 for 50, 60, 70 years. There have been examinations of the morphology of those cells.

The ability of the podocyte to serve as the final barrier to prevent the transglomerular

movement of albumin and other large molecules is a function of the point where they join, the tight junction so called, slit diaphragm.

Unlike the glomerulopathies, primary and secondary, where there is heavy proteinuria and a direct correlation with slit diaphragm abnormalities, the slit diaphragm in the female heterozygote has been examined and is normal, despite the accumulation of GL-3 within the cell body.

So there is a difference in the injury mechanism between how, on the one hand, where there is proteinuric states that slit diaphragm deteriorates and in this case, in the asymptomatic female heterozygote, where it does not deteriorate, even though the cell has the intract material.

As to why the enzyme replacement therapy doesn't seem to have the same magnitude benefit on the podocyte as the other cells may in part be due to contact with the enzyme; because again, if the barrier is intact, not a great deal of enzyme in concentration reaches the non-blood site of the glomerular capillary. That is the urinary aspect, which is where

the podocyte lives.

The other is that, for all the other cell types that were examined, there is a rather finite turnover of cells. So when you begin to infuse enzyme, cells are shed from the kidney. The cells that now come and replace those shed cells are now in an environment where the enzyme level is restored.

So there is no stimulus for reaccumulation. The podocyte, a very terminally differentiated cell, may reside in its capillary wall for years without turnover. So it may be persisting, not seeing enzyme and, therefore, much less affected.

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: Can we assume that there are no accidents of nature the other way, accidents of nature the other way that people who have the severe podocyte disease have clinical renal disease in this condition? We've only heard about it -- that is, these people are relatively asymptomatic when they are accumulated. Are there examples of the reverse that we haven't been told about?

DR. BRENNER: I think the correlation is

that where there is severe renal disease in addition to podocyte disease, there is vascular endothelial disease. So the correlation still comes out very tight.

In the absence of vascular endothelial disease, podocyte involvement appears benign.

DR. WOOLF; No proteinuria?

DR. BRENNER: To my knowledge -- Well, there may be mild proteinuria by 60 or 70, but there is no clinical renal disease of the type that leads to renal failure.

DR. WOOLF: Thank you.

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: Yes. I would just like to ask one question of the FDA in reading this question, which is somewhat confusing to me. The question is this: If the answer to this question is yes, and the first sentence is a little different than the second sentence, because the second sentence refers to renal capillary endothelium -- If the answer is yes, does that imply that this is then the surrogate marker that will be followed in Phase 4 studies or future studies,

and is that problematic if renal biopsies are not going to be done?

DR. WALTON: The two sentences were intended to focus on the same finding; that is, the primary endpoint of the capillary endothelium. Your question as to what problems that --

DR. SCHADE: My question is, if it is going to be renal capillary, then in future studies if the skin is measured, then you are going to have a surrogate marker of a surrogate marker.

DR. WALTON: Ah. Okay, I'm sorry. Now I understand. The question, I think, is really meant to focus on the renal capillary endothelium, since that was the primary endpoint put forward. But of course, you've heard the data that there are pretty much the other organ -- Capillary endothelium is entirely consistent.

So for our purposes, we really don't -- are not really particularly distinguishing between them. In answer to your question, though, I think what I want to clarify is that the requirement on accelerated approval really does not actually require

that the surrogate ever again be looked at.

I think we would all be very interested in that, but the regulatory requirement does not require that that surrogate ever again be looked at. It requires that the clinical benefit be studied.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: I can't think of a better surrogate endpoint for the renal thing. I can think of the easier one. The data that I have heard convinces me that measuring serum levels of GL-3 correlate with clearing of these deposits from all the organs that this enzyme will clear them from.

Now whether this enzyme clears them from all the organs from which they need to be cleared is a different issue, but it seems to me, until we know which renal cells or other cells have to be totally cleared to see an effect, I would be just as happy looking at serum levels of GL-3.

CHAIRMAN AOKI: Okay. Dr. Fleming.

DR. FLEMING: I wanted to hear my clinical colleagues' comments before commenting, because I -- there is much insight here that influences my own

thinking about this.

I struggle with this issue, because as the accelerated approval guide indicates, establishing -- in essence, establishing the adequacy of a marker to serve an accelerated approval can be based on an array of different sources of information, epidemiologic, therapeutic, pathophysiologic, etcetera.

Where I am struggling, as I at least have already articulated, is that we have an uncommonly minimal amount of information in those first categories, epidemiologic and therapeutic. So I am relying extremely heavily on insights from my clinical colleagues from a pathophysiologic perspective.

On one aspect, and maybe I misunderstood, I thought there were one or two comments that said we are going to use renal capillary endothelium, and we endorse it as an adequately established surrogate endpoint, because it is the best one that we can come up with.

I would think that I probably misunderstood, because that certainly wouldn't be a basis of saying we would use this specific marker,

because the best one we may come up with may not be adequate. There has to a very strong -- since this is the essence of the validity of this marker, a very strong biological explanation. And I've been hearing many aspects that I find obviously extremely relevant.

Where I struggle with this is, as I think about it again, is this specific marker providing an adequately comprehensive capturing of the biological mechanism by which this disease process is going to induce clinical endpoints, and specifically if it is renal capillary endothelium.

I have heard other comments that at least have suggested there may be more comprehensive aspects to measuring what enzyme replacement therapy is doing, although I am finding it reassuring. It appears, when you look at those other measures, too, they do seem to be influenced, although what is critical here -- and we have said it, but it needs being stated again; and in fact, I think the FDA clarified their reason for asking the preceding question was for this purpose, and that is: We are looking in some cases ten, 15, 20, 25 years down the road, and it is an extraordinary

situation for us to say that these effects here are in fact going to be a reliable comprehensive capturing of what these mechanism shave to be in order for us to achieve this long term clinical benefit.

CHAIRMAN AOKI: Thank you. There is Dr. Hunsicker again.

DR. HUNSICKER: It was my "it's the best we can do." So I have to respond to that, Tom.

DR. FLEMING: Actually, I wasn't sure it was yours, Larry, but if you want to respond, go ahead.

DR. HUNSICKER: It was, and I shall respond without any embarrassment at all. What I said was that it is the single most likely pathophysiologic hypothesis that has been put forward. There are no data to support it beyond what we have already talked about, which is these experiments of nature, and indeed it is that that makes it the single best hypothesis.

What I want to extend that is that I think that bringing the experience of the AIDS or cancer things into this is in a way misleading. We have a

situation where it is, in principle, impossible to get closer to it than this.

That is why I said we have the opportunity of taking this surrogate and the things that are correlated with it, which are clearance from other cell types as well -- we have the opportunity to take this surrogate or we are left without any surrogate at all.

Now that's what I mean by the best of all surrogates. I don't think that we want to get ourselves into a position where there is, in principle, no way to proceed, because there cannot be convincing evidence until you have done the experiment, and you can't do the experiment because you can't afford to do it and follow people for five years because the target population is too small.

DR. GRADY: But, you know, this is just not the best surrogate. That's clear, because it is a multi-system disease. I think, you know, serum GL-3 actually seems to me to be the best surrogate.

Had the company come to us only with that, we would have said, oh, yeah, but how do you know you

don't clear it out of cells. So it seemed particularly important to look at a variety of cells and maybe the most important one would be the kidney, because that is the most important functional problem associated with the disease. But we would like to see this therapy help the heart disease, the cerebrovascular disease and pain and os on and so on.

So in some ways, I think GL-3 is a better surrogate marker, because, you know, it may predict effects on --

CHAIRMAN AOKI: You said the plasma GL-3?

DR. GRADY: Plasma GL-3 is a better surrogate marker, and it's great, because you don't have to go taking hunks of people's kidneys.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: I agree completely with that statement, but it just asks here is this an appropriate surrogate marker. I think it is an appropriate surrogate marker for many of the things we have said today.

I agree with you. I think the serum or plasma GL-3 level is as good, maybe a better

surrogate. I think it's an appropriate surrogate marker, maybe not the best, probably not the best.

DR. HUNSICKER: I think we stand in history in a very different position now than we did when this study was done. If you think of this, this is an inclusion disease which is intracellular. There is no assurance that getting it out of the blood is going to get it out of the cells.

It was critical to show that this stuff got it out of the cells. Now that we know it gets it out of the cells and that you can follow that with a clearance out of the serum, we don't need to do the biopsies so much anymore. I would be very happy now to follow skin biopsies and serum. But until we knew we got it out of the cells, we didn't know that this had anything to do with what we were talking about.

CHAIRMAN AOKI: Okay. At this point, I think we can start the vote again. Dr. McClung.

DR. McCLUNG: Well, it is no surprise that I don't know whether this marker will predict a clinical outcome, but I think that it is both intuitively attractively and biologically plausible

that it does and that it is an appropriate marker for the purposes that are being discussed. On that basis, my answer to the question is, yes, that there is -- it is reasonably likely that the marker will predict a clinically meaningful effect, at least in the legal sense of the word reasonable, if not in a statistical meaning.

CHAIRMAN AOKI: Thank you, Dr. McClung.

DR. FOLLMAN: Based on the discussion, I would say there is -- it is reasonably likely to predict a clinical outcome, that this is an appropriate surrogate marker for this disease at this point in time. So I would agree.

CHAIRMAN AOKI: Dr. Barisoni.

DR. BARISONI: Based on the discussion, I agree, too, this is a reasonable marker.

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: Yes.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: I always have trouble with yes/no questions. But I'll try to be very brief, to say that, certainly, the testimony that has been given

relative to the pathophysiological rationale is extremely important.

My own sense about this is the lack -- the substantial lack of the clinical evidence that we would typically expect to have and uncertainties about comprehensiveness of capture and longer term effects leaves me with enough uncertainty that I'm not willing to say it is established, although I do believe that, with additional evidence potentially from sources such as the ongoing clinical trial, that at that point the evidence could in fact be sufficient for me to have answered yes.

CHAIRMAN AOKI: Was that a yes or no? Abstention?

DR. FLEMING: Well, that's a current no, if I'm forced to say yes or no. But I think issues are more complex sometimes than yes or no.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: Yes.

MS. KNOWLES: Yes.

DR. JONAS: Yes.

DR. JENNETTE: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes, once again.

DR. SAMPSON: Yes.

DR. HUNSICKER: It is reasonably likely in legal terms. It meets the requirement. Yes.

CHAIRMAN AOKI: Thank you.

DR. SCHNEIDER: Yes.

DR. GRADY: Yes.

CHAIRMAN AOKI: Fourteen to one. Okay. Use of this product is associated with risks. It is difficult to balance the risks of definable adverse effects with efficacy that has not been directly observed, but may be only predicted from a finding on a surrogate endpoint. Please discuss how you balance risk with any benefit that may be inferred from these data.

Who would like to open the discussion? Dr. Hunsicker.

DR. HUNSICKER: Is it out of order to discuss the major concern that has been raised, which is the infusion reactions, before we answer this issue here?

CHAIRMAN AOKI: I think -- Can we address this question using the infusion reactions and the antibody problems as the risk, taking that in context. How would you respond?

DR. HUNSICKER: The reason that I suggested that is that I think that the issue of the infusion reactions deserves some discussion, and it is part of the infusion reaction part of this. I think that, until we have discussed the infusion reaction thing, which is the most serious risk that has been presented to date, it is very hard to discuss intelligently the balancing of risks and benefits.

CHAIRMAN AOKI: Dr. Walton.

DR. WALTON: If you would like to defer this -- On that basis, if you would like to defer this question until after -- somewhere, I guess, toward the end of the next one, that would be perfectly fine.

DR. GRADY: But I think we should -- You know, one comment is that we have hardly a clue what the risks are, because the number of people that have really been studied in a rigorous way is so small that, you know, confidence even around zero out of 50

or 60 is fairly high. I mean, everything about this is more or less uncertain.

DR. WEISS: This is a difficult question, we realize, but it's the issue not only of -- maybe we don't have a lot of information on the risks, but also we don't have information right now on the real benefit. It is one thing to assess the risks in context with something that provides the mortality or irreversible morbidity benefit, but when -- and this is not unique to this issue, but when you have something that is being considered for an approval based on a surrogate that has -- for which it is reasonably likely but not yet, you know, shown that there is clinical benefit, it puts the context of the risks in a somewhat different setting.

So that was the nature of some discussion about this question. But agree that we are perfectly comfortable with deferring this discussion until after the next question has had some discussion.

DR. WALTON: Also, even at that point you may feel it difficult to discuss. I think that this was a -- This is always an important question to ask,

the risk/benefit balance, but if you feel that you really just have insufficient information to provide much advice, then I think that is the appropriate comment and not to wind up belaboring it, later on.

CHAIRMAN AOKI: Yes, why don't we just come back to that. We are deferring that one. We will come back to that after we have discussed -- I think we do have a chance to talk about infusion reactions and the antibody titer, certainly the antibody titer.

Okay, number 2 -- You want me to read this or do you want to read it yourselves?

DR. HUNSICKER: The audience doesn't necessarily know what the question is, and -- They all do? Okay.

DR. WEISS: Maybe you can just give everybody a second then to just make sure they have had a chance to read it, and then we can start with the questions.

CHAIRMAN AOKI: Okay. Who wants to take the first one: Please discuss your interpretation of these data. Dr. Hunsicker?

DR. HUNSICKER: I interpret this section, actually, as asking about whether the antibodies will affect the long term usefulness of the agent and not really directing right now at the issue of the toxicity. So let me address that.

First, it is futile to ask the question what is going to happen after ten years of the use of this stuff in a study that has only gone on for a year or two years or something like that. This is unknown. It cannot be known until the long haul, and that is properly deferred to analysis and post-marketing survey.

The real question is what do we know at the end of this study with what we have now? What we know is that a very large fraction of the patients become immunized effectively, as far as I can see, all of the people who don't have any enzyme. The people who have some residual enzyme don't become sensitized.

When they become sensitized, they appear not to have any change in the area under the curve of the circulating material. It may, however, be bound to antibody. There appears not to be a difference in

the amount of either plasma level or cellular clearance in those patients who have or have not -- and maybe you are going to comment about that later on -- developed antibodies.

So it appears not to affect the long term effectiveness of the enzyme in clearing the intracellular materials.

Now I would like to offer just as a speculation one possibility that this might be the case. You will remember that this enzyme is only effective in the lysophagosomes at a very reduced pH. My guess is that what is going to happen when people develop antibodies that bind to the thing is that, in fact, it is going to accelerate the clearance into precisely those same components, the same compartments, where the acidic pH is going to disassociate the antibody, and the enzyme is going to do precisely what it did in the first place.

Now it is always difficult to ask a person what his explanation -- Well, it's not difficult. It's dangerous to ask a person what his explanation is for a finding when he already knows what the finding

is, because it is my experience that it never takes more than 30 nanoseconds for me to understand precisely what's happened, whether that is what's really happened or not. However, it is my understanding that there is not, in fact, any visible effect of the fact that there is antibody present on the effectiveness.

I find it very easy to believe that there would not be, because of what I have just said about the possible way in which the thing would be handled.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: I appreciate very much what you said, Dr. Hunsicker. I think that is very appropriate.

My take on this is that there are a number of other disorders in which replacement therapy in people who have very low levels of whatever it is has been treated as foreign tissue, and people have developed antibodies.

There are a number of other disorders where we have also accepted modest immune responses of one kind or another as the price of therapy. So if we

know that this stuff works, all of the side effects that have been described to date seem very minimal.

We know how to deal with high antibody levels, if we have to, in many situations. These people are not going to be any worse off if they get high antibody levels than they are now without any of the enzyme around it all anyway.

The big question, of course, is whether we are giving them high antibody levels and a high fever and yet they are going to get no effect out of this. I still think that most of them would feel that this is a small price to pay for the chance of being relieved of their symptomatology and having prolonged life.

So I think that these findings do not disturb me, and I see no findings that suggest a waning of enzyme activity.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: One of the advantages of GL-3 level, serum GL-3 levels as a marker would be to provide an easy answer to this question, because looking at histology it is going to be awfully hard.

You see skin biopsies that are clear, and then there is something there, and then they are clear again. That may simply be sampling variation.

I wonder if the sponsor has information on serum plasma levels of GL-3 that correlate with antibody levels.

CHAIRMAN AOKI: So the answer to the first question is probably not.

DR. GOLDBERG: Did you want us to comment on the correlation between plasma GL-3 levels and antibody levels?

The antibody levels do not inhibit the reduction of the plasma GL-3 whatsoever. By the way, there is data from Turner and colleagues on another lysosomal storage disease supporting exactly what Dr. Hunsicker says about actually facilitating uptake.

I might also mention, in the pharmacokinetic part of our Phase 3 trial we did look at leukocyte uptake of Fabrazyme at visits one, seven, and 11. Indeed, there was a modest increase in the uptake by the 11th infusion, but it did not in any way inhibit the reduction of plasma GL-3.

CHAIRMAN AOKI: Okay. We will just go on to the next question. Dr. Hunsicker?

DR. HUNSICKER: Which one is the next question?

CHAIRMAN AOKI: "In light of the need for long term" -- 2(b).

DR. HUNSICKER: I think that it is already part of the plan --

CHAIRMAN AOKI: Turn on your mike.

DR. HUNSICKER: I think that it is already a part of the plan to monitor tissue levels as in skin biopsies and plasma levels as these studies continue, and I think it would be important for us to make sure that the antibody -- that the enzyme activity continues to be active for as long as the studies go on, and that should continue to be collected. But it's not something we need to do anything about now.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I actually interpret it a little differently. If this drug were approved, should one monitor antibody status to time immemorial?

I think it would probably be easier to

measure GL-3 and, if there is a change in that, go ahead and measure antibody rather than every year or two years or whatever. I would want to see a biologic effect -- a change in biologic effect, and GL-3 seems to be as good as any.

CHAIRMAN AOKI: Okay. Two(c) --

DR. FLEMING: There is no -- Just on this issue, there is, obviously, at this point no evidence as yet about what relationship antibody loss -- antibody formation would have with ultimately long term clinical benefit.

DR. HUNSICKER: I interpret the data as showing no evidence that the antibodies cause long term change in activity for the period of time that we have had to observe these patients.

DR. FLEMING: That's right.

DR. HUNSICKER: And we need to continue to follow it as long as we can, and that's all we can do. I think the other question is, is there any reasonable basis for thinking that the antibody, which is relatively benign at the present moment save the issue of infusion reactions which we are going to talk

about later on -- is there any reason to think that the antibody level or the antibody problem will get worse or that there will be a change in the future?

My answer to that is somewhat hypothetical, but in fact, the experience of repeated injections of normal proteins into the body tends to be that you actually have the antibody response go down rather than up. That, in fact, is what is being seen here.

So that there is no *a priori* reason to believe that the antibody response would develop more problems in the future. Further, as already has been ascertained by Dr. Jennette, there is no evidence for an immune complex disease, which is the other thing. So that I think that the potential for further worsening of the impact of the antibodies is small.

DR. FLEMING: So is the conclusion that that is adequately, confidently known, that there needn't be any further exploration of that as data do emerge on clinical effects?

DR. HUNSICKER: You know, this is a nice conversation. We are doing it in public. But I take

-- First of all, I have a principle about the evaluation of long term adverse effects. I believe in the clinical trial you can only evaluate for adverse effects that are as frequent as the effect that you are trying to get that's a favorable effect. Everything else is almost by definition underpowered.

So I think that, with the exception of major adverse effects, the proper place for the evaluation of them is in post-marketing surveillance. That's what we actually have to do anyway. You know, uncommon adverse effects simply cannot be ascertained with enough confidence in clinical trials to be able to say much, and we have to depend upon post-marketing.

DR. FLEMING: I'm interpreting this question to be inclusive of that source of information as well. I interpreted this to mean in light of the need for long term, lifelong treatment --

DR. HUNSICKER: Yes.

DR. FLEMING: -- we need to explore this in the future with whatever source of long term evidence we would be obtaining.

DR. HUNSICKER: Oh. You mean do we need to look for further evidences of antibody mediated damage?

DR. WALTON: I think you are quite right. This 2(b) is to hear about how important that evidence is, and it will be in 2(c) we ask you to distinguish when that data might have to be obtained. That is the question of pre- or post-marketing.

DR. HUNSICKER: It is hard for me to know precisely what I would be looking for. There is no early evidence, Tom, of immune complex disease. One could ask to look for evidences of immune -- or monitor for immune complex injury, and certainly that in terms of case report forms would be reasonable.

Is it worth doing a renal biopsy to assure at the end of some larger period of time that there is still no evidence of immune complex deposition? I think that's marginal.

CHAIRMAN AOKI: Dr. Jonas.

DR. JONAS: Wouldn't it be reasonable to draw some inference from the experience with Gaucher's disease and chronic infusion of lysosomal enzyme?

DR. GOLDBERG: With the caveat that every protein is different from one another. In Gaucher disease we see about a 15 percent incidence of antibody formation, and patients generally tolerize over time, just as Dr. Hunsicker said.

Fortunately, there again we have not seen any significant impact on efficacy in the many hundreds of patients -- Pardon me?

DR. HUNSICKER: Or toxicity.

DR. GOLDBERG: Correct, or toxicity. No evidence of immune complex disease at all.

DR. HUNSICKER: See, the net effect in the kidney at least, if you are talking about immune complex -- I've just been thinking about my suggestion about immune complex, and I want to back off it. In the net effect, what you are interested in is renal function.

So even if you were to get some immune complexes, if his kidney function is better because he no longer has the Fabry's problem, then you are still ahead of the game. So I think the answer is you don't really need to do anything other than figure out what

your primary outcome is.

CHAIRMAN AOKI: Okay. Let's move on to the next, 2(c).

DR. HUNSICKER: (c)(i), yes, it is reasonable to permit these data to be evaluated after marketing approval. And (ii), I hear a consensus that probably serum levels of GL-whatever the heck it is --

CHAIRMAN AOKI: GL-3.

DR. HUNSICKER: Yes, GL-3 possibly together with skin biopsies would be adequate to assure that we are continuing to clear the material.

CHAIRMAN AOKI: Any other comments on 2(c)(i)? Okay, how about 2(c)(ii)? All right. We are at 3.

DR. WEISS: Excuse me, Dr. Aoki. I don't know if -- Could we go back then to the question that we skipped on 1(e) about the risk/benefit? Actually, question 2 doesn't really address the infusion reactions which people had mentioned were the primary concern, may or may not be related to this whole issue of antibody generation. But people seemed to think that was important to draw into addressing question

1(e) about balancing theoretical or real risk with potential benefits as can be inferred on the basis of the surrogate.

I was just wondering if we could have some brief discussion on this particular question still.

DR. HUNSICKER: Okay. Since I seem to have taken the lead position of proposing things to be either agreed to or disagreed with.

The major adverse effect that was measured and is ascertained and is unquestionably increased in frequency is the reactions. These have been serious enough to cause hospitalization in a very small number of cases.

I take it -- this is going to be a sort of peculiar way to answer the question, but the fact that 100 percent of people from the randomization trial were willing to roll over into the full trial indicates that, from their point of view, the hope of a long term benefit, even if it is not yet proved, is worth what they have paid for it in terms of what appear to be very temporary discomforts.

Therefore, I personally believe that the

answer is, yes, that the potential for benefit overweighs the documented but very minor toxicity of the infusion reaction.

That is one that we haven't discussed, and I wanted to have some discussion. So I would appreciate it if other people would comment on that point.

CHAIRMAN AOKI: Dr. Levitsky, would you like to comment on that?

DR. LEVITSKY: Well, I think I had. The only thing that is troubling me is at what age you would feel comfortable exposing people to even that short term risk. Children, early adolescent children apparently can have some severe early complications of this disorder, and I would not like to deprive them of the chance to participate in such a trial, and also to benefit from the drug, should it have benefit. But I am a little uneasy that one should set criteria for entry perhaps associated with age criteria.

DR. HUNSICKER: That does bring up an interesting question. This study may have been started or the whole program may have been started

before the FDA rules came in, but I thought that it was required that we get at least some information about children.

DR. WEISS: If something is for an orphan indication, they actually can be waived from the requirement of actually conducting trials in children. Not that we wouldn't love to see that information.

As you may know, the pediatric rule is being challenged currently. So we are no longer actually able to -- Even had this been a disease of much more commonness and affecting children as well as adults, at this point there is a stay on our ability to implement that rule until further actions may be happening. But the short answer is that you are correct, that there is no information on young children, and any comments that the Committee would like to make to that effect would be very useful. Genzyme may have some experience as well.

DR. GOLDBERG; Just a point of information, we have committed and we have begun in Europe a pediatric trial which is now enrolling patients and is ongoing.

With respect specifically to the question of when one might begin therapy, I am of the understanding that there was recently a consensus paper accepted by the Annals of Internal Medicine. Both Dr. Desnick and Dr. Brady were key authors on that paper. Perhaps Dr. Brady could comment on when he thinks it would be most appropriate to start therapy.

DR. BRADY: Well, this is a very important question, actually. We, too, had been interested in a pediatric trial. Based on our results with Gaucher disease, if you can get these people enzyme therapy before they become symptomatic or even badly symptomatic, your outcome is almost guaranteed to be much, much more successful.

We've seen this. We have people in this area who received enzyme with authenticated Gaucher disease completely asymptomatic throughout their life. I think this might possibly obtain in certain cases with Fabry disease as well.

So we are extraordinarily anxious to initiate this therapy as soon as we possibly can in

these people. And I think it's axiomatic. It is almost easier to prevent something from becoming pathologic than it is to reverse the pathology. So we are extraordinarily hopeful that this will be undertaken and undertaken soon. Thank you.

CHAIRMAN AOKI: Thank you. Dr. McClung?

DR. McCLUNG: We have sort of drifted off on the question of pediatric use, but let me come back to the infusion reaction and ask real succinctly for those who obviously don't see these kinds of problems often whether there were any serious or sustained sequelae.

We have been told about the frequency with which these events happen. They were acutely defined as serious as adverse experiences are defined, but were there really any clinically serious or, importantly, any sustained consequences of those reactions?

CHAIRMAN AOKI: Dr. Goldberg?

DR. GOLDBERG: There's two issues here. One is to distinguish severe from serious, and many of these were severe but not serious. There were a few

serious, as you mentioned. These were not sustained.

Again, I would like to defer to Dr. Dominique Germain who came from Paris, who has had extensive experience both in our clinical trials and in the commercial experience, to tell us about the real life issues of the infusion reactions. By the way, the severe reactions were primarily chills, severe chills.

DR. HUNSICKER: That's what we talk about when we think about approaching this problem with rigor.

DR. GERMAIN: Thank you. My name is Dominique Germain. I am a geneticist working in Paris. In addition to the six patients originally enrolled in the Phase 3 Genzyme trial and now initiated therapy with Fabrazyme for 32 additional patients. Among these patients only three of them had experience these last two years, mild to moderate infusion related adverse events.

The 29 additional patients haven't experienced one single adverse event. This brings us to a total of 19 infusion related events out of 818

infusions which have been performed. So that is less than one out of 40.

They were all mild to moderate, and not difficult to manage them conservatively.

CHAIRMAN AOKI: Dr. Woolf.

DR. GERMAIN: There was maybe an additional issue about these IgE seroconversions. So we had experience with two patients. One is in Lyons and has developed positive IgE testing in the blood, and the other patient is under my personal care and has developed positive skin test.

An interesting point is that we have been able to successful rechallenge both of these patients, and interestingly, the patient at my site we had to discontinue clearly reported to me that after discontinuation of therapy, pain had reoccurred in the extremities, chest pain, frequent -- We have now been able to successfully again rechallenge him. He has received eight new infusions of Fabrazyme without any single adverse event.

CHAIRMAN AOKI: Thank you. Dr. Woolf.

DR. WOOLF: It's not that conventional

infusion reactions has me concerned. It's some of the IgE mediated. There was one patient, I think, who had a near anaphylactic reaction in the clinical trial or at least it certainly sounded that way.

So my question really relates to how is this drug going to be administered once it is approved? If the family doctor can do this in his office, I would be very concerned. But I don't know how this would be done in rural areas of the country.

This drug does have rare but significant side effects, and I think there needs to be appropriate warnings.

DR. HUNSICKER: Is there not experience with the long term administration of anti-hemophilic factor, that in fact this is also associated with infusion reactions, as I recall. I think that what we are talking about is virtually superimposable upon that experience.

That doesn't mean that you should blow it way, but you know, people get AHG at home.

CHAIRMAN AOKI: It probably be done in an infusion center, though, probably, unless you had no

choice. But certainly, an infusion center would have that familiarity.

DR. HUNSICKER: It might be well to do that, at least initially, until we know what --

DR. WOOLF: I mean, hemophilia is a little different disease even, life threatening in minutes to days.

DR. GOLDBERG: Just to clarify, we certainly recommend that these infusions be carried out by experts and in centers of excellence whenever possible. Absolutely. I might also mention that the "near anaphylactic reaction" was not an anaphylactic reaction. The patient did have some mild decrease i blood pressure. One question is whether it is, in fact, vasovagal.

DR. GRADY: And the other question on the other end of the sort of pediatric issue is what about older patients who have multiple comorbidities who may be the more susceptible or perhaps just more -- in whom these reactions might be more toxic?

I mean, I presume we are not considering any sort of restrictions for age or comorbidities.

Obviously, the people in the trial were relatively healthy.

DR. HUNSICKER: We had data presented to us on -- I thought it was children, and one child who had developed the IgE and then -- It wasn't a child? Oh, I take it back. But to then get to the answer after this discussion to the FDA, my reading is that the potential for benefit outweighs the observed toxicity.

CHAIRMAN AOKI: Okay. Why don't we move -- Dr. Fleming?

DR. FLEMING: Before commenting, just a quick reminder that I need. If we look at the targeted regimen, 1 mg/kg two weeks, could I find out, under that regimen for how many patients do we now have complete safety data through six months, a year and three years?

CHAIRMAN AOKI: Dr. Goldberg?

DR. GOLDBERG: Well, at 1 mg/kg, let me just go through trial by trial. So in the Phase 1-2 trial there were only three patients that were on 1 mg/kg initially, but the vast majority of those

patients have remained on therapy now, and in fact are perhaps the longest follow-up.

We have the 58 patients from the Phase 3 trial, another 13 patients from the Japan bridging study, and then a commercial use in Europe --

DR. FLEMING: How far out? How far? Remind me, the 58 and 13.

DR. GOLDBERG: The 58 patients, that study, they are out about three years now on average. The Japan study -- Actually, if we could pull up the slide from the primary presentation that has our clinical development plan, it has the timeline of when the studies began.

DR. FLEMING: I don't need that.

DR. GOLDBERG: Okay. Then in addition to that, in Europe and in the international experience, I think there are in the vicinity of perhaps another 150 patients who have been on drug for varying lengths of time, and the Phase 4 patients, the --

DR. FLEMING: That l50, on this regimen?

DR. GOLDBERG: Yes. I mean, on 1 milligram. Everybody is getting 1 mg/kg every two

weeks.

DR. FLEMING: And they have been followed?

DR. GOLDBERG: Well, the drug was approved in August of 2001 in Europe. So increasing use over that period of time. Then the more advanced patients in our Phase 4 trial, there is again the 76 patients. The longest patients out are about two years now. Two-thirds of them are on treatment.

DR. FLEMING: Okay. Well, just to quickly then respond to this. I would agree with what the FDA says here, and that is it is difficult to balance risks of defined adverse events with efficacy that is a projected efficacy, that is not an established efficacy.

As Larry has pointed out, the favorable aspect of this is that the safety profile largely looks quite favorable. There are the severe infusion reactions. I needed these numbers just to get a sense that -- to more or less quantitate the statement that what we don't know is long term effects. We don't know also rare effects.

We have approximately 100 people out to

three years. So we can rule out serious events that would occur with risk one in 30, three percent. Things could be happening less than three percent out there. We do not have the data for that.

Over a year, we can be a little more confident. We can rule out things probably at a level of about two percent or greater. So essentially, we have some known but seemingly acceptable, if this is the totality, what I'm hearing, and I understand the logic that, if what we have seen is the totality of what we will see in safety, then against what we would hope -- and of course, always you have to put your prior on how likely you think what we are hoping will be realized. If you believe it will be realized, then clearly this is favorable benefit to risk.

So we left with various levels of uncertainty that we have about whether we will realize the benefit that is at this point only promised. The short term safety risks are seemingly acceptable, although not totally trivial. But what is also very important here is that we really don't know about longer term and certainly rare but significant events

that could be occurring.

CHAIRMAN AOKI: Ms. Knowles.

MS. KNOWLES: It would be my thinking that any adverse events would be ultimately put into a package insert. Right? Okay. So, hopefully, you know, if these infusion reactions are still continuing to be a problem, or if there are new things that crop up, those will be added.

CHAIRMAN AOKI: Okay. Moving to --

DR. WALTON: Yes, to the degree that adverse events are known or as they become known, they certainly would become part of the information provided.

CHAIRMAN AOKI: Question 3.

DR. WALTON: Dr. Aoki, for this question and the next one, we will appreciate it if you could read the questions into the record.

CHAIRMAN AOKI: Okay. This product is intended for long term use by patients with Fabry disease. If marketed on the basis of an accelerated approval, the product must be studied further to describe and verify the clinical benefit. If the

verification study were to yield inconclusive results, there would be uncertainty as to the clinical benefit of the product, and FDA would need to consider withdrawal of approval of a product that might, in fact, be beneficial.

Quest 3(a): Please discuss how FDA should approach verification studies, including the degree to which sensitivity to important, but small amounts of benefit should be sought.

DR. WALTON: Dr. Aoki, may I clarify two things at this point?

CHAIRMAN AOKI: Certainly.

DR. WALTON: One is that the question is contingent upon the aspect of the regulations that state that, in the failure to verify the clinical benefit, the FDA may withdraw the approval. I just wanted to remind the Committee that that is a formal part of the regulations.

The second is to clarify that this entire question is not focused so much upon any particular kind of verification studies, but just verification studies in a more general sense.

CHAIRMAN AOKI: That's very helpful. Any comments on this question?

DR. HUNSICKER: You have heard a consensus that we do not know at the present moment that this infusion had any beneficial effects whatsoever. What we know is that it does something that we agree is reasonably likely, I think, was the word, to have benefit in the future.

How the FDA should approach the verification studies is, first of all, with respect to what you can get from the sponsor, you should get as much as possible, as much as possible in terms of keeping the patients in the currently planned Phase 4 study as long as possible to get as much information as possible from that.

As I have already said, my opinion is that you also need to get as much information out of the historical and the registry stuff that you can, because I think, inevitably, your evidence is going more and more in the future to come from comparison with other -- you know, past historical patients.

I think that you should not, however,

consider that those are the only data. I was very impressed this morning with what was presented by -- and here I show my constant problem remembering names, but it was Grun-something or other, Grunfeld. I was very impressed with his data.

I'm told that there are 30 abstracts that are already being presented in Europe from other use of this agent that is not sponsored by the sponsor. I think that the FDA should take into consideration all of the available evidence that is there at the time. Some of it will be harder than others, and I think that you are going to do this by, presumably, presenting it to a group and saying is this now reasonably persuasive.

I would say further that it is potentially -- it is possible that you will not have an absolutely definitive, across-the-board statement as to the efficacy. You may, for instance, be able to say with great confidence that it reduces the rate at which patients who are already in moderate renal insufficiency progress toward renal failure, but you may not be able to say anything else with a hell of a

lot of confidence at all.

So this issue of reviewing may be ongoing for a period of time. So I would not consider that you should make this a deadline by which there must be absolutely nailed down proof, but that you shouldn't give up until you actually have pretty well nailed it down.

That's a very long answer, but does that help you?

DR. WALTON: I think that you have brought in some parts of what we are asking in the part (b) of the question as well, which is what should the agency do if faced with a study that was planned to provide the verification data but was unable to do so.

I think your -- What I'm hearing you say is that we should then just try again.

DR. HUNSICKER: Let me be very precise about that particular issue. I understand that the company has a complete commitment to getting as much information out of this study as can be done.

You are well aware of the fact that the minute that this stuff becomes available commercially,

there is an ethical responsibility to reconsent every patient in that study, to be certain that they are willing to continue in that study when the material is available now commercially on a standard of care, whatever you want to call it, basis.

I cannot predict what -- Well, I can predict what is going to happen. I think the majority of patients are going to stay with the study and do it, and that is something over which the company will have no control.

You may have some control in -- to be sort of foxy about this -- in the amount of time it takes you to determine how to respond to the company's request. But once you have given them the authority to market the stuff, they will have no control over this at all.

That means that, in fact, we are going to have to depend upon, to the extent that the question is not answered, epidemiologically derived information, and we are going to have to do the best we can.

I don't think -- Specifically, I don't

think that you should remove this agent simply because this study fails to give a definitive answer.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: Well, I am going to start with what, to me, is a much easier part here, and only answer a, for me at least, easier part right now, which is 3(a) rather than 3(b), and defer for 3(b) for a bit.

It seems to me that in 3(a) the 00800 randomized trial that is now approaching within a year its completion on its blinded phase is my greatest hope for being able to provide the clearest answer on clinical effects, because of my strong belief that the randomized comparator trial will give us the clearest indication of what benefit is.

If benefit is truly profound in its nature, then clearly historical data can also serve as a basis for identifying that benefit, because the magnitude of the signal exceeds the magnitude of the source of bias. But I am truly hoping in 3(a) that the basis for the verification, if you should go ahead with the accelerated approval, will be the 00800

trial.

It is for that reason, as I noted earlier, that whatever you choose to do with accelerated approval, I would surely hope it would be minimally impacting the ability of that study to maximally retain patients on the duration of follow-up on placebo and intervention that the study was designed to achieve.

In this setting, of course, with that information, there will also be -- and this may be a different question. But of course, there will also be opportunities after then full approval will be given for follow-up studies in a traditional post-marketing manner with active and passive surveillance to be able to address these issues of safety that we recognize also have to be addressed in the longer term.

DR. WALTON: I think that you are more addressing what we are going to be -- what we are asking in question 4 in terms of your emphasis on what type of study. At this point, I think we are asking to understand in the first part --

DR. FLEMING: There is a little bit of 4

in the sense that I see you get into the historical aspect of it. But the essence is the 00800 is what I see -- what I personally would hope you would be able to have as the verification study for -- whether you are providing accelerated approval or not, for clinical benefit.

DR. WALTON: I think -- Yes, I think part of this question is also some -- we are asking for some advice on how sensitive verification studies should be to a clinical effect. That is, a verification study can be powered for sensitivity to a massive effect or it can be powered for sensitivity to the minimally meaningful effect or anything in between, and advice on whether -- whether or not you have any advice on how FDA should go about viewing proposals in that regard of the sensitivity of the study.

This is in a fair degree getting into consideration of how we think about Type 2 error for verification studies.

DR. FLEMING: An immediate thought on that point. The 00800 trial has as its strength a

randomized comparison over three years of follow-up. So as its strength, it also is going to provide us a longer time frame to see the realization of clinical benefit.

Negatives to that trial or weaknesses of that trial are that it certainly isn't powered to the minimally clinically relevant benefits that we might hope to be able to achieve. By my sense in a quick back of the envelope calculation, I think with 14 events you are targeted to having very high power to pick up about a 75 to 80 percent reduction.

I could readily -- In fact, without question, I would think a 50 percent reduction in those clinical events would also be very relevant, but would take a much -- on the order of 88 events instead of the 14 to 16 events that we are targeting here.

So what you are asking is certainly very relevant. This study is potentially our best opportunity at this point to be able to look at longer term effects using a randomized comparator placebo that is the freest of sources of bias. But the reality is there is a very real chance that we could

still have an intervention that has clinically meaningful effects that won't be established by that trial. Hence, we will be dropping into the 3(b) question shortly.

I would again urge that we do everything we can to maximize the likelihood that 3(a) will be answerable based on that nearly completed randomized comparative trial.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: The way I read this would be that suppose that the endpoints were not met, but that you showed a significant reduction in decline between the two groups. Well, no. Okay, either. I can waffle also. But it didn't meet *a priori* the -- That's still very important. I mean, we are taking our best guess at what we agreed was a pretty good surrogate. At least most of us did, and based upon that a study was designed that may or may not be successful, according to the predetermined guidelines.

If we are rigid about it, we could say, well, you didn't get the 14 events after three years; you didn't get their verification. Pull the drug.

But suppose, in fact, you cut the decline in half, but you didn't meet the target. Would that make sense, and I would submit it doesn't.

So I would be very sensitive. If I found an improvement, I would probably be even -- If it were .06 or .07, and you can keep on cutting the salami as thin as you want, if I found a meaningful -- what looked like a meaningful clinical trend -- I'm speaking as a clinician, not as a statistician -- I would continue doing it, continue using the drug.

DR. FLEMING: Could I have a clarification, because I was just interpreting that scenario as a 3(b) scenario. I was interpreting the scenario where you do not -- because you used the word inconclusive, where you typically -- statistically, we use the word conclusive, meaning the standard for strength of evidence of a single positive study, meaning that you achieve the primary endpoint with something approximating a one-sided 025.

So I was interpreting 3(b) to incorporate, among other situations, this situation where you see a trend, but it's not conclusive.

DR. WALTON: Yes, that's exactly right.

DR. HUNSICKER: I would like to just suggest that we may be missing the boat entirely here, and I would like to suggest another scenario, which is that the study, in fact, doesn't show a very big prevention in the decline in function or in clearance in those patients who already reached a certain degree of renal insufficiency, but that meanwhile back at the ranch, the folks in Europe have done a whole batch of studies on congestive heart failure and have shown that there is consistent reduction in left ventricular mass in patients who have been treated.

It is very clear that the study that we are looking at is powered to look at a renal effect and a subset of the patients that may not be representative of all the people.

So I am much more concerned about a Type 2 error which is not the one that says, in fact, there is a real effect on renal function but we didn't see it to meet our criterion. Rather, I am worried about the Type 2 error which says we looked for the wrong endpoint.

That is something we just are going to have to be very open-minded about. When push comes to shove, when you come back to look at this in whatever period of time it is, about a year from now, and this study has been concluded, however the heck it was concluded, you are going to look at that time at the totality of evidence from all source.

Some of that evidence is going to come from this Phase 4 trial that is defined and is going to be completed as well as they can. Some of it is going to be from the sponsor's studies that are based on epidemiologic extension, as we have heard described. Some of it is going to come from stuff that's been done by other people like Dr. Grunfeld that has absolutely nothing to do with the company, and we are going to look at everything we see there to see if there is, in fact, evidence of a meaningful clinical benefit.

I personally think that it is rather fussy, if that's the right word, to try to be too precise about how we are going to interpret the outcome of this study, which we know is underpowered

at best -- we've just heard about that -- when we don't know the setting in which that data is going to be -- those data are going to be reviewed.

So I guess I am saying I don't know -- I don't think I would pin it all on exactly how that study comes out. It is the totality of confirmatory studies that is going to be important.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: In regard to the accelerated approval, 3(a), I am concerned about a particular scenario which, you know, maybe will play out here where you adopt a surrogate not on the basis of data but on a theoretical rationale of how it affects the process, and everyone agrees it is a rare study, and so we can't really get data for it, and we have to go with those theoretically compelling or plausible surrogate endpoint.

Then under accelerated approval, as I understand it, at some point the drug is approved, and everyone can get it. So any ongoing study where we really are placing all of our bets to show clinical benefit is harmed in a great way, because all the

patients will get it.

So at the end maybe the sponsor will say we should use historical data or, you know, the study is separate from so much cross-over, it's really uninterpretable. We have a P-value of .20 but, you know, look at all these circumstances. Should we continue the drug being approved?

So you have a situation, if it plays out like that, where you effectively approving a drug on a theoretical surrogate endpoint. You know, when I read this originally, I thought, well, the sponsor is concerned about all this cross-over, and I thought, well, this must be a concern in every accelerated approval study where there is this potential for the drug to be approved and then the study that is ongoing to be contaminated, more or less, by the approval.

So that is a concern I have about accelerated approval, and it is a concern I have here in this study that the sponsor is proposing, the Phase 4 study.

DR. WEISS: And I think your concerns are quite valid. They are concerns that, you know, we

have discussed and raised as well.

Part of the regulations indicate that usually these post-marketing studies are ongoing at the time of approval, and true, this one is ongoing. There are times, though, when, you know, the post-marketing study is actually even further along.

In many scenarios that I think we addressed earlier, the post-marketing verification is actually obtained within the exact same population that the reasonable surrogate is taken from. So it's less of an issue. It's become sort of a nuance, if you will, of at times doing -- proposing to do these verification trials in a somewhat different population than what were studied in the major trial that would be coming forward for efficacy, just like -- and then the issues that Dr. Hunsicker has raised several times about, you know, you may -- The verification study may prove something in a particular subset, those with more advanced renal disease, and if shows something in there, they require some extrapolation perhaps back to less severely affected; and if it doesn't work in there, then there's questions about what does that

really mean for the product.

So I don't have an easy answer, but you have raised and highlighted the concerns.

DR. HUNSICKER: This is an important enough question, Dr. Aoki, that I really would like each of the members of the Committee to say something about it. You have heard a lot from Tom and from me. You've heard a little bit from -- I can't see that far across the way, but from a couple of other colleagues, but I'd like to have people polled, if you would be willing to do so, for at least a terse statement about what their thought is that FDA should do.

DR. FLEMING: Well, I would still -- I would really like to follow up with Karen's point, just for some additional general discussion, because I think Dean has gotten right at the essence of a critically important issue.

The concept of accelerated approval is one that is very appealing in the sense that, for patients that have very serious diseases, it clearly is well understood that there is a need to get promising interventions to them as soon as possible.

The prices paid for that are, first, that those interventions are being delivered at a time when there is less than the traditional amount of confidence about whether benefit to risk truly is favorable.

Other consequences are these issues that are not trivial as well, and that is the kind of information that we need -- and, remember, accelerated approval isn't full approval. It is in a sense a conditional approval where it is expected that studies will be underway or will be able to be completed that will provide a traditional adequate amount of insight about whether or not the intervention is truly beneficial.

Traditionally, we have relied on randomized trials as the source of that information. We have had lots of discussions about that today. But in settings such as this, it would be naive to think that proceeding with a placebo controlled trial of sufficient duration and size to be able to understand benefit would be highly implausible, both from the perspective of being able to enroll people, as well as

to be able to sustain the control arm without a substantial amount of cross-ins where those cross-ins could significantly dilute what is the true level of benefit that we would hope to be able to document.

So again, I come back to what we had heard in the beginning is a rationale for accelerated approval here is that we have 00800 well underway, and it is exactly right. It is a well configured situation where it is going to give us the potential for establishing benefit, and we truly should hope it will, and we truly should do whatever we can to maximize the opportunity that it will.

Yet we realize that, even if it is well conducted to its completion, it will only, with likelihood, show benefit if benefit is very substantial in magnitude.

So my major concern is, if that study is compromised or even if it isn't compromised and it doesn't show benefit, but we have been reminded -- or it doesn't conclusively show benefit, I'm sorry. But we have been reminded is orphan drug doesn't mean that there still isn't a requirement for substantial proof

of efficacy, and accelerated approval doesn't mean that you have fully established benefit.

That awaits then post-accelerated approval, and where I don't know the answer and I would want to find out from my colleagues here how should the sponsor and FDA proceed to provide a timely validation of true clinical benefit in the event that accelerated approval is provided here and 00800 doesn't provide substantial proof of efficacy.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: Accelerated approval, it seems to me, is based on the need to use the drug imminently in some subgroup of patients who are very sick and who will, hopefully, benefit even if there is less than optimal evidence of efficacy and some risk.

I guess the question is, you know, if the drug gets accelerated approval, is that automatic approval for all patients with Fabry's disease, some of whom are ten years old and, while they may -- You know, they may have important issues with pain and quality of life or don't have imminent risk for morbidity and mortality.

I mean, that's your -- It would be approved for any patient with Fabry's disease. Is that correct?

DR. WEISS: Well, we didn't have a specific question about that, but I would certainly be very interested. We oftentimes in approving products, whether it is accelerated or conventional approval, look at for whom the product should be indicated for.

Many times, and not all the time, this is actually the people who were studied in the efficacy trials. But there is always some assumptions and extrapolation that one has to take and some sort of leaps of faith in even extrapolating from the people who were in the clinical trial to the larger population.

There are times when we have gone on to extrapolate and we extended indication to individuals beyond who were in the clinical trial, and some of it is based on a number of factors, including the plausibility that, if it worked in one particular -- or the overall population of this trial and there is no inherent reason why it shouldn't work in other

groups. But oftentimes people, extremes of age or more advanced disease, etcetera -- in the conventional development program with a more common disease, there tend to be additional studies in these other populations.

DR. GRADY: I mean, I think to many of us it seems that what we are doing with accelerated approval is trading off or giving away the potential to really complete the ongoing trial in the best possible way. So that what we are most worried about is that, if we give accelerated approval, that that trial will be compromised and that we won't get any answer, really, with regard to efficacy.

The question in my mind is to what group of people and, you know, how important is this -- I guess we're trading about a year of early access to the drug potentially for getting any information on efficacy in the Phase 4 trial.

DR. HUNSICKER: One of the subsections of something -- and I don't recall it as being quite here, but there is an understanding that typically with accelerated approval there would be an

understanding that the agent would be used essentially exclusively by people who are highly expert in the area. I know that this has come up with respect to transplant related drugs and things like that.

Is that part of this here or is there the potential? I'll tell you the rationale that I have. IT seems to me that the community of people who are truly expert in the use of this agent are, as a group, fairly committed to the idea that we've got to find out whether this stuff works or not, and I don't know whether you could enforce this but at least you could invite the circumstance where it was being used, as was being suggested before, at centers of excellence, all of whom have agreed to do almost a census of information about what's happened as a consequence of it.

That would have the potential over a period of time of giving some more information beyond the specific trial. Everybody here, I think, thinks that that specific trial should be adhered to as closely as possible what they said that they were going to do. But beyond that, is there the potential

for more or less keeping this in the hands of people who are likely, in fact, to submit data about the outcomes?

DR. WALTON: That portion of the regulations that you are recalling for accelerated approval are for a different circumstance of accelerated approval. It is when that constrainment on what setting the product may be used in is necessary in order to ensure its safe use and due to particularly marked concerns about the risk/benefit balance, and that sort of constraint will -- is a way to improve the risk/benefit.

That is a separate element of accelerated approval than the approval on the basis of a surrogate.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: I would like to respond to two things. One was the comment about the issue of who should be able to benefit from this drug or not benefit from it. As a pediatrician, I am very concerned about the pediatric issues, because I am sure that there will be 12 and 14-year-old children

who have severe pain syndromes from this who deserve to be treated with it.

If we are -- If our wording is not careful, we will have a lot of insurance issues which will mean that those children may not have access to the drug. We see this with a lot of other drugs presently. So we have to be very careful about that.

Yet I don't propose that this drug at this stage should just be used for children who carry the genetic diagnosis but are symptom free. That is one issue.

The second issue, however, is the answers that you request to the questions in 3. My response to this is that I deal much better with the reality than with the hypothetical. For instance, if you were to tell me at the conclusion of this study that the data on renal disease were inconclusive but the Fabry's rash went away, I would say, well, that doesn't sound like it's worth what we are doing.

On the other hand, if you were to say to me that the data on the heart disease looked awfully good -- it wasn't quite there yet, but it looked

awfully good, I would like to take another look at that.

I would suggest that my response to this is, when those data are in, let us look at it again.

DR. WEISS: Thank you. We would definitely plan to come back to the Committee in that case.

DR. McCLUNG.

DR. McCLUNG: Well, again, I would like to just amplify a couple of other points, to say that with regard to the verification studies, we are in a bind that we will never get out of; because if the current Phase 4 study goes to completion and is successful, what it will demonstrate is that there is benefit in patients who have moderate renal impairment.

That doesn't say that it will be of benefit in patients who have cardiac problems later on, and it doesn't say that it is necessarily of benefit in patients who don't yet have clinical evidence of benefit, and it will be impossible, just because of the duration of the latency period and the

small number of individuals involved, to show that initiating therapy in an adolescent will have benefit on clinical outcomes that don't happen for 20 years.

We will be on a different stratosphere about thinking about this disease and having therapeutic interventions before that time happens.

So I think the FDA ought to be focused on verification and be cautious about the types of patients for whom the drug will be approved based upon the outcomes of those verification studies.

I'm concerned, too, about Type 2 error. So I think having -- not requiring the same level of confidence that we would have in other larger, more easily studied diseases would be appropriate. And if there is a clinically meaningful effect that a group of experts can define, I would be comfortable with that. But to extrapolate from one endpoint in one group of patients who have one level of involvement and manifestations to the entirety of the population who has the genetic problem is an even bigger leap that I am less comfortable with.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: Correct me if I'm wrong, but the Phase 4 study is only renal disease. We have no data for any other manifestation at all, and nor will we ever get data other than during the treatment process. I mean, there will never be a study that randomizes people to placebo simply to look at cardiac disease.

So we are going to have endpoints, and people will compare what their septal thickness is or some other manifestation of cardiac disease and say, yes, the septum has decreased. Some years later they are going to say, well, the myocardial infarction rate is X, but what was the comparison group?

It's going to be terribly confusing. In fact, I don't think we are ever going to be able to answer that at all, other than, getting back to Larry's point, we will have to use some historical data which everybody will dump on because it's historical data, but we have no other choice.

By the way, you know, looking at septal thickness is, in reality, nothing but a surrogate marker for clinically important heart disease, and

someone is going to have to verify that in this disease, that in fact that surrogate is important.

I mean, we heard about flecainide and encainide. Fluoride made bones very dense. They were terrifically dense. It made them very brittle. So I don't think that this trial -- It is going to, hopefully, answer some questions on renal disease. We may be able to tease some other data out, but the clinical data for other organ systems we won't have, and I think we are just going to have to accept that and then deal with the uncertainties.

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: Yes. I just want to agree with Dr. Grady. I think we are making a tradeoff. I think it is very clear that, if this drug receives accelerated approval quickly, we will lose some data from ongoing trials. That is a decision I'm willing to take, because I actually give this body and the rest of the researchers out there a lot of credit, because I think, once this drug is used in a whole lot of people that we will see a lot more information.

We are already getting information from

the European experience. Now it may not be a controlled, double blind, randomized trial, but it will be a -- There will be many experiences in good trials coming out.

I think, if in fact, it turns out in several years that we don't see an improvement in renal function, in spite of the fact that we see a decrease in plasma GL-3, we will be a lot smarter. We will have a mechanism of why that is not working. We will be measuring something else.

In other words, I agree it is more difficult to get really good data. But I also believe that, once people start using this drug, we will be designing trials in the various populations that aren't even being addressed in the current trials that will give us a whole lot of new information.

So I think it is important to get this medication into people who really need it. Then the challenge, and I think it's a challenge for the FDA is, when they require post-marketing trials, to be certain that it is not so invasive that it excludes half the populations.

So I think like kidney biopsies are not a good idea if there are other surrogate markers. In other words, I think what I have seen in some clinical trials that have disturbed me is that the trials were so invasive -- and I can talk about diabetic neuropathy trials, etcetera, in which I had to do seronerve biopsies. I think there is a tendency to be overly aggressive and invasive.

Whereas, we can do many measurements now. We can do cardiac thickness, etcetera, without invasion. I think the challenge is to design noninvasive trials in which the entire population who have these will participate.

So to me, I'm willing to take the tradeoff, because I think all of a sudden we will gather information rapidly that we would never get if we hold up on approval of this drug.

DR. FLEMING: Could I comment just on this point before we move on?

CHAIRMAN AOKI: No. We are -- It's past five now, and we are just halfway through the questions.

I think we will just curtail the discussion on 3(a). Let's move to 3(b): Consider the situation of a post-marketing verification study where the result is inconclusive; for example, an inability to complete the study as designed --

DR. WALTON: Dr. Aoki, actually, I think we've heard discussion on that rather well mixed in with all this discussion. If neither you or one of the other members has something to say that you felt was not said, we would be comfortable with moving on to question 4.

CHAIRMAN AOKI: Okay. Let's move to question 4. I've been asked to read this one:

Genzyme is currently conducting a randomized, controlled study to provide the verification of clinical benefit that they believe the histologic measure predicts. Genzyme proposes to change this study design to a single arm, open label study of treatment with agalsidase beta. In order to support this proposal, they have provided a database of information on creatinine levels in patients with Fabry disease. Genzyme proposes that this database

can form an external, historical control group for comparison with the data in the proposed open label treatment study.

Genzyme initially proposed a method for analyzing the historical data to provide a historical disease progression rate. FDA reviewed the proposal and identified several areas of concern. Genzyme recently proposed a different method to analyze the historical data in order to provide a historical disease progression rate. This new proposal lacks sufficient methodological detail. FDA is unable to determine whether it is potentially suitable to provide a historical disease progression rate.

(a) Please discuss the quality and strength of data in this historical database, particular as regards the intended use as a historical control.

We did discuss this in pretty great detail earlier. I don't know if we need to do more than that. What do you feel, Dr. Walton?

DR. WALTON: If the Committee members feel that they have already expressed any opinions they

have on the existing database then, that would be fine.

CHAIRMAN AOKI: Please discuss, to the degree feasible, the advantages and disadvantages of the recent Genzyme proposal for a method to use the historical data.

DR. HUNSICKER: Let me make a comment here about this, trying to take all of these things into account. But I want to ask a question first.

That is, let's say that somebody is going to gather to look at this evidence in a year. What possible outcomes are there? Clearly, one outcome would be your data is now conclusive, and it's the final approval. One outcome could be there is now clear evidence of total inefficacy, and there is withdrawal.

Is there the potential of saying the case is not yet conclusively proved, and we are going to look at something in yet another year, or not? In other words, is continued existence in the status of conditional approval possible?

DR. WALTON: The agency has discretion

about how to evaluate the data and what actions to take. Just as the accelerated approval says that FDA may approve, it is also not an automatic event that the product is automatically withdrawn if some event does not happen by a certain date.

I think that your question really was what we were asking for advice on in the previous one: What should FDA do? But the -- and the reason we were asking is because there are choices that can be made.

DR. HUNSICKER: Well, then to respond to that, going back to the previous question my recommendation is that you do not limit yourselves, when you look at these data in another year, to a definite yes or a definite no, that you acknowledge the possibility that it is still going to be inconclusive and that we need more information. That's number one.

Having said that then, what I think is that the historic database is not lacking simply because of absence of -- it's not affinity; what do you call it? -- propensity scoring, and it is not inadequate because of problems in the modeling shape.

It is inadequate because it's from a different era.

That doesn't mean it is totally inadequate, but there is an inadequacy that cannot be fixed. Therefore, you have the requirement, from my point of view, of getting the most information out of the stage 4 trial that you can get using its current design, even knowing that that may not be conclusive, but you've got to go for that, and I would not personally like to see anymore dilution of that design than is absolutely required to fill in for the loss of data that is inevitable or that is unavoidable.

So my answer to your question is that it is not a modeling problem. It is an era problem. It is a selection problem. Those are not fixable issues, and therefore, you must restrict your primary analysis of that particular thing to the way it was originally designed, supplementing only to the minimum extent necessary.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: I agree with what Dr. Hunsicker said, that the problem with historical data is that it is not really comparable to the data we

have here. The models and methods that Dr. Rubin proposed are, you know, appropriate and cutting edge, but they are not -- they are only as good as the data that are fed into them.

So I'm skeptical using the historical data. I also wonder why it was proposed, actually, because you know, this won't be approved, as I understand, until April, and then the Phase 4 study will be five-sixths of the way done. It is a three-year study, and you would be missing maybe seven years of data that might be contaminated.

So I didn't see the compelling reason for using the historical database, to begin with. So as what was mentioned earlier and what we have all said, I think the most important thing to try and do is to try and get the dataset for this study as currently as it was designed and to continue it as best we can.

Maybe that means, you know, delaying approval. I'll say it. You know, maybe instead of in April, you make a decision later on, and that will have the benefit of improving the integrity of the Phase 4 study.

DR. GRADY: Well, let me just make a quick comment, because -- and you might speak to this. There was all this language about rolling the study over. I mean, I think I am very much opposed to rolling that study over into now an open label study with historical comparisons. I think that is also what several other Committee members have said.

You may have trouble in completing it according to its design, but I would certainly like to see you try.

MS. LAWTON: Just if I can comment on the comment made earlier about why did we propose the historical data. I think it is important to point out that we actually proposed that getting on for two years ago now when we didn't even have anywhere near as much data as we now have on the Phase 4 study that is fully enrolled and ongoing.

So I think that is an important point, because we saw that as an option for how we could move forward with accelerated approval at that time.

I think the other comment that I would like to make is, as far as the propensity scoring

method -- and I'll maybe ask Dr. Rubin just to come up and comment -- the long -- the opportunity to collect much longer term data in these patients may actually be one way to ensure the power of this Phase 4 study.

DR. RUBIN: I think it is important to distinguish between the original proposal, which is just to take the historical dataset as a comparison for the open label, randomized, and to use it instead in this method for generating trends to impute the serum creatinine data for the placebo controls when they are no longer on placebo.

When they are no longer on placebo can be because it goes open label or it can go until it continues, then impute them longer term; because once the study is over in two or three years, they are not going to be on. If you want to understand something about long term progression, you are going to have to turn somewhere.

There are all these issues with the historical control data. It is from a different era, and there are different types of people, and you can try to adjust for that to the extent possible, and

that is what this propensity scoring is designed to do.

I want to make the point that, in fact, the subset of the historical control data that we were calling the chosen, the 85 chosen historical controls, are a different set of people than the, I think it was, 101 that FDA was showing as to be the group that Genzyme was proposing; because in those 100 people or 103 -- I don't remember the exact number -- there are 15, 20, who are not completely but quite different from anyone in the randomized group of patients.

We are aware of that, and we attempt to try to adjust for that, to the extent possible. The other point that was made a couple of times is that there are more data. There are more variables that are possible to control for.

It still won't be perfect. It will still be from a different era. There will be other variables that are hidden. In the historical dataset, there are missing values. We adjust for those missing values to the extent that we can, but it's better to not have missing values. It's always better to not

have missing values.

So we can do potentially an even better job of selecting a subset of the historical controls than we've done so far, and maybe there won't be 85. Maybe there will only be 70 to provide information about the longer term progress, but still I think you can't deny that that's useful information.

You have approximately 50 randomized treated and 25 randomized control, and if someone comes up and gives you 60 people who look the same with respect to age, baseline serum creatinine, sex, la-da-da-da-da, 20 covariates, use of ACE inhibitors, whatever it is, and they look similar, you're going to say, ah, irrelevant, let me do another randomized trial when you can't do a randomized trial? I don't think it makes sense.

You are going to have to rely eventually on historical data. I think it is very useful to get some experience with it now when you can actually compare it to the results of the randomized trial.

DR. GOLDBERG: Please understand, with respect to the contemporary nature of the historical

control: As I mentioned in the primary presentation, 71 percent of the creatinines have occurred since February of 1996.

For example, many of these patients are on ACE inhibitors and are, I think, treated in the modern era. I --

CHAIRMAN AOKI: Dr. Sampson.

DR. SAMPSON: I just wanted to underscore Dean's comment, that it would be absolutely superb to see the randomized trial finished in the double blind phase, and I would encourage the FDA to do whatever they can legally and, if possible, to have that occur.

I don't think there is anybody that is saying the historically controlled study or the kind of this outline of the propensity matching that Dr. Rubin has presented can't be a secondary analysis and certainly supportive and adding further information to the primary completion of 008.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: I am going to reinforce, but I think it's worth reinforcing both Dean and Allan. I concur. I believe the essence of what will be most

reliably learned from the 00800 trial will be the randomized comparative part, and again as we have urged, to do whatever is possible to allow us to maximally achieve the insights from that study.

I just did a quick calculation. I think, if the renal events break out 8-6 in the right direction -- of course, that's eight of 25, six of 46, which is a 32 against 13. That's sort of the edge, just to give you a sense of what it's going to take. That's the edge of what it would take to be traditional strength of evidence for a positive result.

So as I was saying earlier, it's powered to a 75 or 80 percent reduction, meaning if it is 75 or 80 percent, you have a 90 percent change of observing at least a 60 percent relative reduction. You are going to have to see a 60 percent relative reduction.

Now it's in this context, I would say here, and it's exactly what I think Allan has said, the historical evidence will be relevant, supportive analyses. When we do any clinical trial, we do

supportive analyses in addition to the primary analysis; and if things are close, this kind of supportive evidence certainly could be helpful and, of course, it could go in the wrong direction, and it has to be then given equally objective attention in that manner, as will other secondary measures that will be especially important if they are clinically relevant endpoints, although all of this should be done with a great deal of care to ensure that you are not data dredging, i.e., to keep the distinction between a confirmatory analysis and an exploratory analysis.

So the historical data is of some relevance, but the essence of the information for this 00800 trial is going to come, I believe, from the randomized comparative component.

CHAIRMAN AOKI: Okay. Can we move on to the part (c), 4(c)?

Based on the information Genzyme has provided to FDA at this time, please discuss whether the new analysis method can be conclusively assessed to determine if it is suitable to provide a sufficiently accurate and precise prediction of the

renal progression rate.

DR. FLEMING: Weren't we in essence just answering (a), (b), and (c)?

CHAIRMAN AOKI: No further?

DR. WALTON: I think this was a relatively small question. As we had highlighted in our presentation, there were elements of the proposal that we felt had been unspecified and that we felt would be important to fully specify for knowing what that method could do.

If the Committee were to -- felt that this isn't worth discussing, then j--

DR. FLEMING: You gave an excellent -- I think it was Dr. Hunsicker who pointed out that the FDA presentation, clinical and statistical, was superb. You gave a very careful and detailed exploration of the strengths and weaknesses. It seemed to me you are already well on top of what these issues are all about.

DR. WALTON: And if that's the Committee's opinion, we are perfectly happy with moving the discussion forward.

CHAIRMAN AOKI: Okay. How about 4(d)?

Please provide recommendations regarding how Genzyme and FDA should focus efforts to verify the potential clinical benefit of agalsidase beta. These efforts might include: Completion of the verification study as a randomized, controlled study -- I think we have heard a lot about that, and we do want that to happen; renewed efforts to develop a more extensive historical database prior to developing analytic approaches to the historical data; further development of Genzyme's newly proposed analytic approach; other approaches the Committee may wish to recommend.

I think much of this we have also discussed, except for the "other approaches." I think the other approaches that might have been suggested were delaying the approval so that the 008 can go to completion, and completed to January of 2004 at which time the historical database would be implemented.

DR. WALTON: If I might take the opportunity to sum up what I think I've heard, and then --

DR. FLEMING: Could we -- If you are about

to, could we just -- one or two more comments?

This is such an important issue, and I think we have largely addressed it, as you have said. Where I am struggling is I still don't know the answer to this question myself, if 00800 isn't viewed to provide adequately favorable evidence, and it potentially could. As we've said, we really, truly hope that it does, because if it doesn't, it puts us in an extremely difficult position of understanding if, there is an accelerated approval then, how we can avoid the false negative by withdrawing the agent if there are trends, and yet still being able to verify those trends.

If the effect is fairly modest and yet still important, that is my greatest fear. In fact, often that's where we are in clinical medicine. We make important advances, but they are incremental. That's where I would always argue randomized trials are most reliable, if we have to rely on historical evidence.

We can say we can release this and just look at what happens in the broad clinical practice.

That may work. For rotovirus we can detect in its inception, because it is so rare. It would be so rare to occur.

If we, in fact, induce a very large clinical benefit, we can detect it. But as we have said earlier, 250,000 patients a year used encainide and flecainide, and it was tripling the death rate, and nobody recognized it. It was recognized only when a 200,000 person clinical trial was actually conducted.

It is extraordinarily difficult to say I am going to recognize meaningful differences, but if they are not overwhelming in their size -- So that the challenge that we often have is to be able to discern this, and if in fact, as I am hearing, clinical benefit will occur for a longer -- in a longer time frame, that makes it even more difficult if we are going to rely insights from broad clinical use.

If it is highly effective, okay, and in shorter term that will show up. That will be reinforcing, although if that's the case, I hope 00800 is a positive study. But if it is a more subtle

effect longer term, how do you distinguish that from no effect?

In fact, if you see no effect, aren't we going to have to go two, five, eight, 10, 15 years before people would finally say, okay, there is no effect, and I can no longer say it's something that is going to show up longer term.

The truth negative here -- If there is a true negative, can you truly say we are going to be able to prove a true negative in clinical practice without a control, when in fact a true positive could look like a true negative for a long time. So somebody, when you are seeing a true negative would not be convinced that it was a negative.

So my struggling here still is we think that this is an agent that could provide substantial benefit. Please keep intact the current trial that has a very good chance of showing it. If you think it is moderate but clinically important benefit, I have no clue to how to advise you, how we are going to be able to show that if you give an accelerated approval at this time. That's my reality check on not having

an answer as to how we would do that.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: I just wanted to comment on Genzyme's analytic approach. The main problem -- The thing I don't like about it the most, I guess, and the thing that is most assumption dependent is where you would have the 25 controls in the Phase 4 study and you are augmenting those with 85 historical controls.

That seemed to be, you know, unnecessary. What I would prefer to do is, if the study -- If this is approved in April or so and the 25 controls start getting product in June, you will have -- Those 25 patients have five-sixths of their data when they were on placebo properly, and one-sixth where they have been crossed over. I would just do the imputation for that one-sixth of their total follow-up time, using just those 25 controls and not augmenting it.

DR. HUNSICKER: I was going to suggest rather fliply that the answer to (d) is a classic A on the SAT. That is to say, one, two and three, but not four.

What we have heard is we need to complete

as much as we can the current randomized study, but it is highly likely that we are going to need to develop other data sources as well in order to get confirmation, either positive or negative, because in my mind it is a very real possibility that we are not going to get a clean definitive answer out of the study.

That means that number 2 and number 3 are going to be required.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: This is a little bit of a different suggestion. I am, you know, trying to think of some clinical outcome you might measure, and one of the problems -- I think what we are talking about here is a preventive outcome, which is difficult. It is really much more immediate to treat some problem related to the disease.

I can see that pain and quality of life are subjective, you know, variable and difficult to measure. I was actually wondering if you couldn't, however, do a very short, quick trial of treatment for hypohidrosis. I was struck by what a problem this is.

It may be very easy to measure it with skin impedance or something like that and to show an actual clinical benefit for that outcome.

DR. MOSCICKI: The measurement of sweat is a problematic issue also, unfortunately. In the original trial sweat was measured using a very state of the art methodology called QSART, and the results were somewhat equivocal because of variability.

Again, in the methodology there was a positive trend that was identified, but it wasn't statistically significant in terms of the changes of sweat in these patients.

DR. GRADY: How many patients were in that trial, and how long was the duration of treatment?

DR. MOSCICKI: There were 22 who were subjected to QSART. Those were the patients in the United States, all of whom had to travel to one single center in New York City in order to have a QSART done on a regular basis.

So some of these endpoints, while they sound interesting, are also very problematic in terms of how to try to approach them. I must say, you know,

the current trial has been an enormous effort. We have combed the entire world in garnering patients in order to just get this trial enrolled to get this kind of group of patients.

There are many other diseases, and the one perhaps that I have worked with the most in the last ten years is Gaucher disease where it is a multi-systemic disorder, and we certainly can't -- We can't prove every single system that is involved in a clinical trial setting to be affected or to be improved.

In fact, in Gaucher disease the early studies could not show the effects on bone, because that took a very long time, as the situation we have here. Again, that's where a registry situation actually was extremely useful in the ability to pick up this kind of post-marketing benefit and to be able to look at this.

The registry in Gaucher disease has approximately 2,000 patients now that have been followed ten years, and the data has been extremely useful, I think, in helping to continuously confirm

the real benefit.

So there are other methodologies that could certainly supplement a trial effort in approaching this. Delaying approval is an extremely serious proposal, if that is at all to be considered by the panel.

I think you have heard the plea of patients here today as to the impact, and I know that, if I talk to the patients, there has been an extreme sensitivity to this current trial even having a placebo element involved in it and having an irreversible change potentially in the kidney as an outcome measure that those placebo patients have to progress to.

Finally, I might call your attention to the possibility that, by using something like the innovative statistical methodology that's been proposed to you today, we might actually solve some of the power problems that also concern the panel so greatly; because it would allow us to actually increase the duration of follow-up in an open label way.

Unfortunately, in a placebo controlled trial not only are we constrained by the issues of the size of the population that we can get to go into these trials, hence sample size, hence power, but we are also constrained by how long it is plausible to actually ask a patient to stay on intravenous injections of a placebo every other week, traveling to a medical center in order to do that. It's very hard to ask someone to do that for years.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I'd like a clarification from the FDA on (d)(i). Are we talking about completing the trial as originally described for the full duration without approval of the drug or with approval of the drug and trying to maintain the integrity of the trial, which most of us will agree will be impossible?

DR. WALTON: I think that we were asking for advice largely, in fact, on the importance you place on the different kinds of evidence and on the importance of, in this case, getting the evidence that will be capable of making an assessment from the

randomized study.

DR. WOOLF: So this is prior to approval?

DR. WALTON: Well, I think we are all of the mind that it will be very difficult to conduct the randomized controlled study in the post-marketing situation. So the expectation is that all of that randomized experience is liable to be in the preapproval circumstance.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: If I had Fabry's disease or a relative with Fabry's disease, I would want access to an agent that was going to have some clinical impact. I think, while there are issues of having patients receive a placebo injection every other week, I think there is also a problem in having a drug out there where everybody gets an injection every other week of a drug that doesn't have a clinical benefit.

I think it is important to do everything possible to show that this therapy helps people. It not only changes the plasma levels of GL-3 and changes the inclusions in the cells, but it actually helps people.

DR. GOLDBERG: Can I just get a clarification?

Dr. Follman mentioned an approach which would be, if the accelerated approval were given in April, that five-sixths of this study would be complete, and just impute the last bit of data on the 25 placebo patients. That seems to me to address many of the concerns of everyone and allows access to these patients who are in desperate need of therapy.

I was just wondering -- I didn't hear much discussion on that, and is that a plausible approach that would be a good balance here?

DR. FLEMING: So you're saying, if we were at a point where, let's say, six months, a certain period of months before you would have hit the earlier intended time period, and you had at that point 12 events instead of 14, you are going to do some kind of imputation?

DR. WALTON: Well, this wasn't a suggestion we had made, obviously. This was brought up in the discussion. I think at this point it is difficult for FDA to assess that without having the

details of exactly what is involved before --

DR. FLEMING: Well, it's fairly easy to say that imputation would not provide additional strength of evidence and restore what you would have had, had you been able to continue the trial to the longer term to be able to achieve the 14 events.

DR. HUNSICKER: The imputation would presumably -- Only the additional information at all, if it conveyed information from the baseline -- from the group of people who are being added. It is consistent with what I said, which is that you should use the data from the randomized trial to the extent possible, and only use the other information to the extent that was necessary to repair the damage done to the randomized trial.

Does that make any sense to you?

DR. WEISS: Can you clarify what you mean by damage to the randomized trial?

DR. HUNSICKER: We use the information from the randomized trial to the extent possible. Well, for instance, then everybody who has reached an endpoint by six months is where he is. That's what it

is. You only use the data from the prior -- the historic control dataset to give you enough information to complete imputing the results in those patients for whom we do not have complete data. That's all you use it for.

Then you can impute -- I agree with what Tom said. To some extent, you know, we get into large arguments when we are designing clinical trials over what is going to be the primary outcome and what is going to be the next five, and we should do that. But the fact is that, when push comes to shove, we do them all.

I am sure that what you are going to wind up doing is present the results of the trial as it was, truncated where it was, with the data that you have, and then you are going to impute a little bit more and see where you get from that. Then you are going to do a batch of more general imputation to see what we would have had if we had incorporated all the people.

You are going to present all those data, but the FDA and you have to agree on what is the

primary one simply, so that we don't wind up with five tests of the same hypothesis.

I don't think that we can do this right here at this table. I think we have to leave that to the FDA to work out with the sponsor.

DR. FLEMING: I might just try to say something simple. The hour is late. The simple concept is that I would think many of us who at least are strong believers in the importance of randomization is that what is important here is to achieve maximal, complete information in the randomized trial, following these people as long as possible under the placebo comparison.

That will give us the most interpretable evidence where it is true that other sources of information will be supportive and relevant, but I wouldn't consider them part of the primary fundamentally because of the distinction between bias and variability.

The sponsor is pointing out correctly, we'll get more data at you, and that can reduce variability. But I have always said I would rather

have a somewhat smaller, more reliable, unbiased assessment than a somewhat larger assessment that has irregularities and uncertainties.

So the pure and important analysis here will be the randomized trial, hopefully in a study that is well conducted with quality follow-up, with maximal duration of follow-up per what the intention was of the trial, where then supportive evidence comes from historical studies that they are doing that will be important supportive data and any other important source of supportive evidence that you can identify.

CHAIRMAN AOKI: Any other? Dr. Jennette.

DR. JENNETTE: We have spent a lot of time talking about this Phase 4 so called component, and I certainly favor its completion, and I would be very much influenced if it showed a very positive effect. But I must say that my decision at this point about whether or not I think this potentially valuable therapeutic agent should be released on the market would not change if that study was completely negative, because I don't think that study would prove that it is not effective.

I share Dr. Schade's optimism that, in fact, the post-marketing distribution and availability of the agent worldwide will result in unanticipated observations that, if it is a valuable therapeutic agent, will demonstrate that.

Now to an epidemiologist/statistician, I am sure that really rubs the wrong way, but at this juncture my optimism is that the post-marketing events, in fact, are going to be more valuable than what we could do in a few months of extending the premarketing machinations.

DR. FLEMING: But just so I can share your optimism, could you convey to me, if it isn't effective, if it truly isn't effective, then the scenario that you have just indicated is what we would see in the trial, and can you give me a sense of how long it is going to take under this post-marketing surveillance scenario to be able to establish with adequate conclusiveness that it isn't effective, since the regulations for accelerated approval indicate that there needs to be a timely way to get a reasonably reliable assessment of whether there is efficacy?

So in this scenario, you have just indicated that if it is effective, you are optimistic that this kind of supportive evidence could come forward. But I am equally concerned that, if it isn't effective, where lack of observed benefit for some period of time could be attributed to noise, could be attributed to the fact that in truth there is a delay.

How could you reassure us that within a timely manner this approach would allow us to identify an agent that truly isn't effective?

DR. JENNETTE: I can't.

CHAIRMAN AOKI: Are there any other questions, Dr. Walton? Dr. Weiss?

DR. WALTON: No. We have no other questions. I think we would like to thank the Committee for very extensive discussions and very helpful comments and advice. It's been a very difficult application for you to discuss, and we very much appreciate your helping us.

CHAIRMAN AOKI: Thank you.

(Whereupon, the foregoing matter went off the record at 5:50 p.m.)