DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

# Endocrinologic and Metabolic Drugs

# Advisory Committee Meeting

Tuesday, October 21, 2008

11:45 a.m.

Crowne Plaza Hotel
Silver Spring, MD

C O N T E N T S

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

Kenneth D. Burman, Acting Chair
Paul T. Tran, R.Ph., Designated Federal Official

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Roger Packer, M.D.
David Schade, M.D.
John Teerlink, M.D.

FDA PARTICIPANTS (Non-Voting)
Julie Beitz, M.D.
Anne Pariser, M.D.
Lisa Kammerman, Ph.D.
Claudia Karwoski, Pharm.D.
Lynne Yao, M.D.

P R O C E E D I N G S

**Call to Order**

DR. BURMAN: Good afternoon. I would like to start the Open Session. For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held in the Lincoln Room immediately following the meeting today.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I would also like to remind everyone present to please silence your cell phones if you have not already done so. I would also like to identify the FDA press contact, Ms. Karen Riley. If you are here, please stand. Thank you very much.

I would now like to proceed with the introduction of the committee. If we would start on the FDA side.

**Introduction of Committee**

DR. BEITZ: Good afternoon. My name is Julie Beitz. I am the Director of the Office of Drug Evaluation III.

DR. PARISER: I am Anne Pariser. I am the Acting Deputy Director of the Division of Gastroenterology Products.

DR. YAO: My name is Lynne Yao. I am a medical reviewer for the Division of Gastroenterology Products.

DR. KAMMERMAN: Lisa Kammerman. I am the statistical reviewer for the submission.

DR. KARWOSKI: Claudia Karwoski. I am Acting Director for Division of Risk Management in the Office of

Surveillance and Epidemiology.

DR. FLEGAL: Katherine Flegal. I am an epidemiologist with the Centers for Disease Control and Prevention.

DR. ROSEN: Cliff Rosen, endocrinologist, Maine Medical Center.

MS. HOUSE: Tiffany House, Pompe Patient Representative.

DR. FELNER: Eric Felner, pediatric endocrinologist at Emory University in Atlanta.

DR. JOAD: Jesse Joad, pediatric pulmonologist, from the University of California at Davis.

DR. AOKI: Tom Aoki, Division of Endocrinology, University of California at Davis.

MR. TRAN: Paul Tran, Designated Federal Official for the EMDAC Advisory Committee.

DR. BURMAN: Ken Burman, Chief of Endocrine at the Washington Hospital Center and Professor of Medicine at Georgetown University.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. HENDERSON: Jessica Henderson. I am the Consumer Rep from Oregon.

DR. THOMAS: Abraham Thomas, Chief of Endocrinology, Henry Ford Hospital, Detroit, Michigan.

DR. PROSCHAN: Mike Proschan. I am a statistician from NIAID.

DR. PACKER: Roger Packer, Executive Director of Neuroscience and Behavioral Medicine and Chairman of the Department of Neurology, Children's National Medical Center in Washington.

DR. HANOVER: John Hanover, Chief, the Laboratory of Cell Biochemistry and Biology in NIDDK, NIH.

DR. TEERLINK: John Teerlink, Director, Heart Failure, at San Francisco VA Medical Center and at University of California, San Francisco.

DR. FOGGS: Michael Foggs, Chief of Allergy and Immunology, Advocate Health Care, Chicago, Illinois.

DR. HOLMES: Greg Holmes, Chairman, Department of Neurology, Dartmouth Medical School, Hanover, New Hampshire.

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

DR. VELTRI: Rick Veltri, Industry Representative, Schering-Plough Research Institute.

DR. BURMAN: Paul Tran will now read the Conflict of Interest Statement.

**Conflict of Interest Statement**

MR. TRAN: The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular government employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 U.S.C. Section 208 and Section 712 of the federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal government employees who have potential financial conflicts when it is determined that the

agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal government employees with potential financial conflicts when necessary to afford the committee the essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves Biologic License Application 125291, Myozyme (alglucosidase alfa) 2000 liter product scale sponsored by Genzyme Corporation, for the treatment of late-onset Pompe disease.

This is a particular matter meetings during which

specific matters related to Genzyme Corporation, Myozyme, 2000 liter production scale will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to the FDA invited industry representatives, we would like to disclose that Dr. Enrico Veltri is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any particular company.

Dr. Enrico Veltri is employed by Schering-Plough Research Institute.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may

have with any firms at issue.

Thank you.

DR. BURMAN: Thank you.

We will have Open Session Introductory Remarks by Dr. Pariser, Acting Deputy Director, Division of Gastroenterology Products, CDER, FDA.

Dr. Pariser.

**Open Session Introductory Remarks**

DR. PARISER: Thank you, Dr. Burman. Good afternoon. I would like to thank everyone again for their time and careful consideration of these issues. I just wanted to remind everybody that now we are in the open session, so only disclosable information can be discussed and no trade secret or confidential information should be discussed in this session.

I would also like to clarify for the committee that we are here this afternoon to make a decision on the approvability of the 2000 liter product only in the late-onset Pompe disease population.

This decision should be made considering only the data that has been vetted and reviewed by the FDA, which would include the LOTS trial. There may be some other data that may be presented, but this data has either not been

submitted to the FDA or would not have been given adequate time to review it. It is up on the slide.

This includes the Taiwanese infantile data, the LOTS extension study, the two small clinical studies from Europe, the MTAP program, the Pompe registry, and the worldwide postmarketing registry data.

The decision today should be made solely based on the LOTS data that will be presented during this session.

DR. BURMAN: Thank you.

We will now proceed to the Sponsor Presentation. Before Genzyme's presentation, I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will now proceed to the Sponsor Presentation.

**Sponsor Presentation**

**Introduction**

[Slide.]

DR. KUTA: Thank you. My name is Alex Kuta. I am the Vice President of Regulatory Affairs at Genzyme Corporation.

[Slide.]

We are here today, as Dr. Pariser said, to discuss

the clinical data supporting the approval of alglucosidase alfa manufactured at the 2000 liter scale for the treatment of late-onset Pompe disease.

Today, we will have an overview of Pompe disease presented by Dr. Priya Kishnani, Chief of the Medical Genetics Division at Duke University. Dr. Kishnani is a world expert in Pompe disease. She was a principal investigator in our 1602 study and the infantile-onset study and was an investigator in the LOTS study that we will discuss today.

Our clinical experiences with the 2000 liter scale will be presented by Dr. Ed Kaye from Genzyme Corporation and the statistical methodology will be discussed by Dr. P.K. Tandon of Genzyme Corporation, as well as Dr. L.J. Wei from Harvard University. Dr. Wei's specialty is clinical trial methodology.

[Slide.]

In addition, we have the following experts with us available to the committee.

Dr. Hwu from the National Taiwan University. Dr. Hwu is an investigator in the infantile-onset study that led to the original approval of Myozyme in 2006 and is also the sponsor of the investigator-sponsored trial with the Taiwan

experience of 2000 liter drug in infants in Taiwan.

Dr. Robert Leshner is a neuromuscular disease expert from George Washington University and was an investigator in our late-onset treatment study.

Dr. Ans van der Ploeg was a principal investigator in our LOTS study at Erasmus Medical Center in Rotterdam and treats one of the largest patient populations of Pompe disease in the world.

So, what I would like to do now is give you a little regulatory history on how we got to where we are today.

[Slide.]

Initially, as part of development, the Myozyme clinical development process started in 2003, and it started with the infantile-onset study or 1602, and this utilized the 160 liter scale material. We felt given limitations on product and given the severity of that disease population, that was the place to start development.

But we also realized that the late-onset study or the late-onset patient population was critical to understand, so, in order to do that, we initiated a late-onset natural history study, also referred to sometimes as LOPOS, the Late Onset Prospective Observational Study, and

we used this to help guide our development of the Late Onset Treatment Study that we will discuss today.

You can see shortly after we finished the Late Onset Natural History Study, the Late Onset Treatment Study began. This study used the 2000 liter scale material.

The original BLA that was submitted included both the 160 liter and 2000 liter scale, and we had approval for the 160 liter scale. Again, this approval was based on the data from the infantile-onset patient population.

FDA made the determination that these two products were not comparable at this point and so we worked with them to gather data that would hopefully allow us to have the 2000 liter scale product approved. So, we submitted an sBLA that included additional analytical data and clinical data for consideration of the 2000 liter scale.

In discussions with the FDA, they indicated to us that they still did not have enough data to indicate that the products were comparable and indicated that the 2000 liter scale was a new product. And so we submitted--we were requested to submit a new BLA.

This BLA was based on the LOTS data that we had here with the 2000 liter experience.

During this time when we were looking to have the

sBLA under review and while we were having some restrictions with the 160 liter scale, we initiated a treatment protocol called MTAP or the Myozyme Temporary Access Protocol.

The idea here was that we would be able to make drug available to patients during this intermediate period of review, so that the 2000 liter scale could be used in late-onset patients in the United States.

This was a treatment IND or a treatment protocol, excuse me, and it involved 168 patients at 81 clinical sites.

[Slide.]

So now what I would like to do, based on the agency's assessment of our data--actually, I am sorry--one other thing I just wanted to indicate that worldwide, Myozyme is produced at the 2000 liter scale, is approved in 43 countries worldwide and there are greater than 750 patients outside the U.S. that are being treated with this product.

So now what I would like to do is based on FDA's assessment of comparability propose Genzyme's indication for this drug.

Alglucosidase alfa is indicated for the long-term use in patients with late-onset Pompe disease and it has

been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.

We have also proposed here a definition for the use in late-onset patients, and we propose that this be limited to patients with symptom onset greater than 24 months of age without hypertrophic cardiomyopathy that is characteristic of the infantile population.

What I would like to do now is have Dr. Kishnani address the natural history of Pompe disease and put this recommendation into context for us.

Dr. Kishnani.

**Overview of Pompe Disease**

DR. KISHNANI: Good afternoon.

[Slide.]

My name is Priya Kishnani and I am a pediatrician. I am also a clinical and biochemical geneticist. I work at Duke University Medical Center. Over the past 18 years, I have spent my career on Pompe disease.

I serve both in the capacity of a clinician and also a translation researcher. Over the years I have seen more than 150 patients with Pompe disease across the disease spectrum, infantile, as well as late-onset Pompe disease

patients, and I have also cared for patients throughout the world and provided guidance to more than 100 cases.

[Slide.]

Today, what I am going to try and do is discuss the clinical spectrum, the natural history, the pathophysiology, and factors affecting treatment outcome of alglucosidase alfa in Pompe disease.

[Slide.]

Pompe disease is a metabolic myopathy characterized by cardiac, skeletal and smooth muscle involvement with a continuum of disease severity.

At one extreme we have the infants who present within the first few months of life with hypertrophic cardiomyopathy. These babies progress very rapidly. They are very hypertonic and they die within the first year of life. This is what we call infantile-onset Pompe disease.

Then, we have patients which have a later onset that is beyond the first year of life. This includes both juveniles as well as adults. They have a slower progression. It involves primarily the skeletal and respiratory muscles, no cardiac involvement or minimum cardiac involvement.

These patients have a longer survival but with

marked morbidity and the outcome in these patients is also very dismal. It ultimately results in death but, here, it is really primarily due to respiratory failure.

The deficiencies due to the lysosomal enzyme, acid alpha-glucosidase or GAA, and, as a result of this deficiency, there is accumulation of the substrate, which is glycogen, which leads to muscle tissue damage, ultimately resulting in functional impairment and then in a permanent disability.

This is a very rare disease with an estimated incidence of about 1 in 40,000.

[Slide.]

Now, Pompe disease presents as a spectrum. Here is a photograph of a baby in the terminal stages of the disease. Here is a photograph of an adult, also in the terminal stages of the disease. You can see that there is really no difference between the two. They are both unable to move, they both cannot breathe spontaneously, they both require feeding assistance. The outcome in both is also the same, and that is death.

The difference really is the rate of clinical deterioration, much more rapid in the infant as compared to the juvenile or the adult, and the other real difference is

the presence of hypertrophic cardiomyopathy in the infant and without it in the adult.

[Slide.]

Now, talking about the natural history, infantile-onset Pompe disease is rapidly progressive and often fatal, and this is really supported by a study, a retrospective chart review of 168 cases with infantile Pompe disease. Here, the median age of death was 8.7 months.

This is a baby 8.2 months, someone that I have treated, and this little girl, as you can see, is in the terminal stages of a disease, completely unable to move, has minimal to no head support at this stage, and this little baby actually died shortly after this video was taken.

This is really a chest x-ray from a child with infantile Pompe disease emphasizing that cardiomegaly or cardiomyopathy is a significant part of the disease.

[Slide.]

Now, I would like to talk about the natural history of late-onset Pompe disease. And there are two parts to this. One is that the disease is clinically heterogeneous, and, two, that it is progressive and debilitating.

In terms of clinical heterogeneity, what I want to

emphasize is that at any stage, a patient with late-onset Pompe disease, be it a child under 15 years of age or an adult over 60 years of age, there are significant risks for respiratory and weak chest support.

I want to show you two videos. These are both patients that I followed, an adolescent and a 60-year-old female. You can see that both have tremendous weakness in hip, spine, and knee extensor weakness, and what it results is in a difficulty and ability to climb or to rise from the lying down position.

The difference really is in the age at which these patients have presented.

[Slide.]

I next want to make the point that the disease is relentlessly progressive and debilitating. It is not one that can spontaneously remit.

Here, you can see that with each added year since diagnosis, the patient with late-onset Pompe disease is at significantly increased risk of requiring wheelchair and ventilator support.

Here, I want to show you two videos, both are of the same adult. This was taken--she is 45 years old and you can see that she has significant difficulty in rising. And

here you can see her shortly thereafter. The disease is clearly progressive. You can see this patient is having significant difficulty in now rising. In fact, she is unable to do this task.

Over the course of time, this is a patient who will ultimately require wheelchair and ventilator assistance. I also want to point out here is that this is a patient who currently remains untreated with enzyme replacement therapy in the United States.

[Slide.]

Now, in terms of the pathophysiology of Pompe disease, I think there are two factors I want to talk about. Central to the disease is really the accumulation of glycogen in the lysosomes, and. via these 2 EMs, I want to emphasize different stages even while the glycogen is intralysosomal or if the glycogen has now seeped out of the lysosome and now becomes large lakes of glycogen.

In the early stages or in the fibers where it is resolved and where the glycogen is intralysosomal, there can be an impact of enzyme replacement therapy resulting in clearance of the glycogen. But, in this stage, which is blown up further here, you can see that now with this large lake of glycogen and its extravasation into the cytosol,

this is a point of what I call no return or no response to enzyme replacement therapy.

The other point is the important role of defective autophagy in Pompe disease resulting in its pathology, and this affects the Type II muscle fibers more than the Type I muscle fibers.

[Slide.]

Here, I really want to say that there is differential involvement of muscle fibers in Pompe disease. In this cartoon, if you can see here, here is the normal muscle cell with normal muscle fibers neatly laid out, and here is lysosome performing its job clearing the glycogen because of the presence of acid alpha-glucosidase.

Here, in this situation, you see an affected muscle cell. There are variable muscle fibers in different stages of involvement, normal muscle fibers, muscle fibers where the glycogen is still intralysosomal, and muscle fibers which are completely damaged or where there is irreversible damage because of extravasation of the glycogen outside the lysosomes.

Furthermore, I want to emphasize this from an EM of an adult patient of mine. You can see neatly lined muscle fibers, completely disrupted muscle fibers. That is

showing that there is a lot of heterogeneity even at muscle level in this disease.

[Slide.]

Now, extent of glycogen clearance really depends on the condition of the muscle tissue prior to treatment, and via these four slides, I want to emphasize this point. These are all stained by PAS, and here you can see a pretreatment in this particular patient that the glycogen is not as abundant as it is here.

The muscle architecture is well retained and well preserved, and so here, after six months of enzyme therapy, you can see nice clearance of glycogen, maintenance of the muscle architecture.

Now, in this situation where there is much more involvement with some preserved muscle fibers. But several which have extralysosomal glycogen, you can see that even after 12 months of enzyme replacement therapy, the response is not as robust and there is still presence of glycogen that's there.

There are other factors besides the presence of glycogen, clearly, the stage of muscle fiber in the sense is the glycogen intralysosomal or extralysosomal, and other factors, such as defective autophagy, the role of

antibodies, high-sustained antibodies in terms of the response to enzyme therapy, and, of course, even the underlying genotype of the patient.

So, for example, a patient who has two underlying deleterious mutations, what we call cross-reacting immunologic material-negative, these patients will be unresponsive to enzyme replacement therapy.

[Slide.]

So, in conclusion, Pompe disease is a severe and progressive disease.

There is profound clinical heterogeneity as I have shown you in the late-onset form of the disease and, if left untreated, the outcome is dismal, resulting in death in the infantile-onset, wheelchair and ventilator dependence, and often an earlier death even in patients with the late onset form of the disease.

I make this statement, not because it is written in the literature or documented in textbooks. This has been my personal experience. I have lost many, many babies to this diagnosis. I have been the harbinger of bad news to many of the families, saying take your baby home to die.

I have also given the bad news to many children and adults with this disease. I have watched many of them

decline over the course of time, the inability to run, the inability to climb stairs, inability to walk, ultimately, the inability to do basic tasks, such as dressing and undressing themselves, basic toileting skills, what one patient said to me, "a loss of human dignity," and ultimately, the commitment to wheelchair and ventilator dependence.

I have also seen patients, children and adults, with this disease, and I have lost them to this disease.

These are examples of some of the patients that I follow, children, adults, and you can see that across the disease spectrum, there is clinical heterogeneity, but I really want to end on a note of hope.

Here is a child who is now 9 1/2 years old. This little boy started on enzyme therapy when he was 3 months of age. This boy lost a sibling to the disease at 11 months of age. The two of them had the same underlying genotype.

This child is now functioning at a very high level. He is a fourth grader. I had the privilege and the honor of seeing him two weeks ago in Moline, Illinois. This boy is now playing baseball and, other than having a label of Pompe disease, he functions in no different a capacity than the children that we see day to day.

With this, I really want to conclude by saying that the hope that we had when we started these trials in infants, I think we carry the same hope today with the children and the adults, the hope that if we pick them up early, maybe we can make them normal functioning adults.

The second hope is that if we catch them late, we can at least stabilize the disease and not have them committed to the inevitable, the fear which they have, the wheelchair and ventilator dependence, and the death which the loved ones that they have face on a day-to-day basis.

With this, I would like to end and I would like to introduce Dr. Kaye, who is a child neurologist by training. He currently works as Group Vice President at Genzyme Corporation. Prior to joining Genzyme, he served as Chief of Metabolism at Children's Hospital of Philadelphia.

Dr. Kaye has a long-standing interest in neuromuscular diseases particularly with Pompe disease.

**Clinical Experiences with 2000 L Alglucosidase Alfa**

DR. KAYE: Thank you, Dr. Kishnani.

[Slide.]

What I would like to do today is review our clinical experience with 2000 liter alglucosidase alfa in the late-onset patients.

[Slide.]

My objectives will be to review the Late Onset Prospective Observational Study, a natural history study, also, to look at our Late Onset Treatment Study results and, finally, to discuss an age criteria for use of 2000 liter material.

[Slide.]

Our late-onset observational trial was a prospective observational study of 58 ambulatory and patients free of invasive ventilation and it was of 12 months duration.

The study was conducted to characterize the clinical progression of late onset disease. We used this to understand the natural history, to inform our selection of endpoints, and also the estimates of sample size.

We added a 6-minute walk test at the end of the study to look at the reproducibility of this potential endpoint, and this was during the time of discussions about endpoints with the FDA. So we don't have prospective information on this particular endpoint.

We do have the ability that we have established a baseline level and also a rate of decline in the percent predicted FVC from this study.

[Slide.]

Now, one important observation that was made as part of the study was the association of 6-minute walk test and FVC with the use of assistive devices.

If we look at our 6-minute walk test and looking at patients who were less than 300 meters, now, this was the median that we observed in the LOPOS patients. The patients who had a decreased ability to walk had a greater increase in the use of assistive devices for walking.

Similarly, looking at the FVC, in patients who were less than 55 percent predicted, this was the group, this was again the median from our LOPOS, and this group that had a weaker pulmonary function had a greater incidence of using non-invasive nocturnal ventilation.

[Slide.]

The decline in our FVC was observed over a 12-month period. These patients declined 3.6 percentage points, and it suggested that this test was a sensitive indicator of progression of the disease and also potentially useful in regards to clinical meaningfulness.

[Slide.]

The LOTS trial underwent a number of considerations before beginning the trial. We knew that it

was a rare and clinically heterogeneous disease and that it would be a challenge to find enough eligible patients.

We also realized that Pompe was a neuromuscular disease and it was associated with two important symptoms, the loss of mobility and respiratory failure. This limited the number of endpoints that we could use and hence, some of the considerations about 6-minute walk test and FVC.

We did not know what to expect when treatment began. Patients would either stabilize or they could improve. We did know, however, that the extent of muscle damage may determine the magnitude of the response to treatment.

Importantly, we knew that we had one chance to perform a placebo-controlled clinical trial, because commercial therapy was available to patients and patients had to choose to go in and stay into this trial.

[Slide.]

The endpoints that were chosen really referred to the musculoskeletal and also the respiratory components. So, a co-primary endpoint of a 6-minute walk test distance was used, and this was supported by secondary and tertiary quantitative muscle testing in the arm and the leg.

This particular test measures the force or the

strength in the muscle and was used to support the 6-minute walk test distance. Also, the respiratory percent predicted FVC was used to capture the respiratory symptom with tertiary supporting evidence in the percent predicted maximum expiratory pressure and maximum inspiratory pressure. A quality of life instrument was used, the SF-36, but we didn't see a difference between the two cohorts.

[Slide.]

The study design consisted of a randomized, double-blind, placebo-controlled trial with a 2:1 drug to placebo assignment. All of the patients received 20 mg/kg drug or placebo given intravenously every other week.

This was a multi-center and multi-national study. It was a large study of Pompe patients, the largest to date, and it comprised a significant number of the known patients. It was in eight sites in three different countries.

The patients were stratified according to baseline disease severity and based on what we had observed in LOPOS, again above or below 300 meters or above or below 55 percent.

[Slide.]

The entry criteria consisted of being at least 8 years of age. And we used this particular age because it

was the reference standard limit and also was an age that we could ensure test compliance from children.

All patients had to be ambulatory, and they could not be invasively ventilated.

They also had to demonstrate some evidence of lower extremity muscle weakness, diminished pulmonary function and diaphragmatic weakness.

[Slide.]

You will hear a lot later about the statistical analysis plan. What I will say about the data to come is what we used was a linear mixed effects model with a robust variance estimation, and also an ANCOVA analysis looking at the change from baseline to Week 78.

[Slide.]

108 patients were screened, 90 of which were randomized into the trial, 60 into the treatment group and 30 in the placebo, again remembering that it's a 2:1 assignment.

Almost 90 percent of the patients completed the study, and this is really due to the dedication of the patients who chose to stay in the study despite the fact that commercial therapy was available.

[Slide.]

The patient demographics was not different between the two cohorts. There was a slight imbalance between the male and female. But again remember that this study was stratified according to the baseline severity. So, we stratified according to the 6-minute walk test distance and percent predicted FVC and, as you will notice, the two cohorts were comparable.

Also, these patients were ill when they entered the study. They were at a 50 percent walking ability on the 6-minute walk test compared to normal and about 55 percent in their percent predicted FVC compared to normal. They were in the moderate to severe category according to the American Thoracic Society Guidelines.

[Slide.]

These are the results of our 6-minute walk test, the co-primary endpoint. The placebo-treated patients showed a 3-meter decline from baseline to the end of the study. In contrast, we saw an increase of 25 meters in the treated group that was maintained until the end of the study. The difference between the two groups was 28 meters, and this was statistically significant using the LME or the ANCOVA.

[Slide.]

In support of the 6-minute walk test, we saw quantitative muscle test leg and quantitative muscle test score that had a similar pattern of response to what we saw in the 6-minute walk test. Now, these were not statistically significant but trended in the same general direction. Also, these patients had evidence of weakness while they were in the trial.

Their baseline in the arm was about 55 percent and about 35 percent in the leg, and we know, Dr. Kishnani talked about the progression, the leg is always more affected than the arm in these patient groups. So what we saw in these studies represented what is seen in the clinic.

[Slide.]

Next, is our co-primary endpoint for percent predicted FVC. The placebo patients went down 2.2 percentage points over this 18-month study. This is similar to what we observed in the LOPOS data and, in contrast, patients on drug stabilized and went up 1.2 percent with an overall difference of 3.4 percentage points. This was significant at the LME and the ANCOVA.

[Slide.]

In support of the FVC was the maximum expiratory pressure. This was significant using ANCOVA and, again, the

similar pattern that was seen in the FVC.

Supportive data was using the maximum inspiratory pressure that also showed a similar pattern of change.

[Slide.]

We looked at prespecified subgroups to see if we could see a consistent improvement across these various subgroups and what we observed was that it always was in favor--the treatment effect was always in favor of drug, the alglucosidase alfa and never in favor of placebo. This was for a 6-minute walk test distance.

[Slide.]

Looking at percent predicted FVC, we saw again in these prespecified subgroups the treatment effect was consistent among all groups in favor of drug, none in favor of placebo.

[Slide.]

To put these treatment effects responses in context, we looked at the effect size. The effect size is the treatment effect divided by the standard deviation. So patients with late-onset Pompe disease were compared to two other approved products, Aldurazyme and Elaprase, for other lysosomal storage diseases.

The effect size from what was seen in patients

treated with Myozyme compared to Aldurazyme and also to Elaprase was in the same range. Also, looking at percent predicted FVC effect size was comparable to what was seen using Aldurazyme.

[Slide.]

Now, I would like to talk about the safety results from our LOTS trial.

[Slide.]

The adverse event rate between the two cohorts, if we look at any adverse events, we can see that these two cohorts were obviously sick patients, it was a 2:1 randomization. So we saw more events in the treatment group. In fact, in this population, there was one patient that accounted for 50 percent of the adverse events.

They were similar except for anaphylactic reactions that were seen only in the treatment group. Focusing on the serious adverse events, we saw that both groups had approximately 20 percent in frequency. Most were unrelated to treatment.

There was one patient death in the treatment group that was also unrelated to drug. We had 4 serious adverse events in the treatment group, 3, or 5 percent, 3 out of the 60 that were seen with anaphylaxis, there was 1 episode of

tachycardia and 2 related events were seen in the placebo group.

[Slide.]

Now, focusing on patients who had anaphylaxis, 3 out of 60, or 5 percent, experienced anaphylactic reactions. Two of these patients had IgE-mediated reactions. These patients were identified by having respiratory and cutaneous symptoms. Interestingly, both patients were rechallenged and are currently on therapy at the present time.

One patient has experienced angioedema of the tongue and was discontinued due to the reaction.

The FDA had noted a fourth patient that was classified as anaphylaxis. This particular patient had a history of asthma and was on albuterol twice a day. The symptoms during the infusion consisted of intermittent mild to moderate wheezing, that recovered within a few minutes each time by slowing down the infusion rate and treating with albuterol.

On discussions with the investigator, the physician stated that he did not believe that this was anaphylaxis, so Genzyme did not record it as such.

I will also bring to your attention that none of the patients had cardiovascular compromise in response to

these anaphylactic reactions.

[Slide.]

Looking at the production of anti-GAA antibodies, we assayed this in two standard ways, the ELISA and also confirmed by the radioimmunoprecipitation. All of the patients who were treated seroconverted. The median time to seroconversion was 4 weeks and the peak titer was 6,400.

In this patient group, 61 percent of the patients decreased from peak titer by greater than 2-fold at the end of the study.

[Slide.]

We looked also at the titer and the effect on safety and efficacy. We divided patients into quartiles, the lowest quartile having the lowest antibody level, the highest quartile having the highest antibody level. So, in regards to the serious adverse events and infusion-associated reactions, we did not see a difference between patients with low or high antibody titers.

Looking at the results, the 6-minute test walk and the percent predicted FVC, again, looking at patients with low versus high, we didn't see a difference. Surprisingly, the patient group that walked the farthest was in the highest quartile. But we didn't see an increase in the FVC,

and our interpretation is that there was no difference based on the antibody levels.

[Slide.]

One question that needs to be discussed, should there be a lower limit in which patients received 2000 liter. In the study, I remind you that 8 years of age was used as a cutoff, but this was chosen as a practical way of ensuring test compliance.

Also, the FDA has mentioned in the briefing document about 18 years of age. Listening to Dr. Kishnani and talking about the biology of the disease, there doesn't appear to be any difference between a 5-year-old or a 55-year-old with late-onset disease since they respond in a similar way. So, we can't find a biologic rationale for restricting to this age group.

[Slide.]

Another proposal would be to look at hypertrophic cardiomyopathy as a way of differentiating infants from late-onset Pompe disease. This is what was mentioned by Dr. Kishnani. The proposal would be to look at 2000 liter material that should be given to patients with Pompe disease without hypertrophic cardiomyopathy and older than 24 months.

[Slide.]

To support the use of 2000 liter in a younger age group, we did look at our pivotal study and looked at patients who were diagnosed at less than 18 and also had first symptoms at less than 18. We realized this is a small cohort, but the effect size was similar to that of older patients.

[Slide.]

Now, we also tried to support some of the data by looking at patients from Taiwan. Now, I need to mention, as Dr. Pariser had said, that this is new information to the FDA. The information was received at the end of August, so they have not had an opportunity to review it. But we thought this was important information to share.

This was a single-site, investigator-sponsored prospective study of infants with Pompe disease, and it was conducted by Dr. Paul Hwu, who is here in the audience today, at the National Taiwan University Hospital.

This was protocol-driven and it was IRB-approved. There were 11 patients that were treated with alglucosidase alfa. And all of these patients are the entire group that presented to this institution, and many of these patients were treated earlier. That is because Dr. Hwu had performed

newborn screening, and 6 of the 11 patients were identified by newborn screening.

However, when they were treated, they were all symptomatic and had hypertrophic cardiomyopathy. Also, all of the patients were CRIM positive and their exposure was 71 weeks.

The efficacy parameters were similar to what was done in the 160 liter material pivotal trial and spontaneous safety reporting occurred.

[Slide.]

Looking at this information, this was our pivotal trial, patients who were compared to a matched historical control of 61 patients. We noticed that almost 100 percent were dead by age 18 months, 90 percent by 12 months. This was compared to patients who received treatment.

Looking at the event-free survival, you notice that there is an increase that was seen in patients receiving the 160 liter material. Also, in this group, 6 of the patients were in the historical group that came from Taiwan, 3 of the patients who were in this group were from Taiwan. Two of these patients subsequently went on and to die.

Looking at these results, again, not comparing

this because this is not a matched historical control, but what we did see is that all the patients are alive and free of invasive ventilation at this time.

Five out of the 6 patients who were of walking age, are walking independently, and we know that no patients with the classic infantile onset ever achieve walking ability.

[Slide.]

We also looked at cardiac response in this patient cohort. It was about 7 standard deviations above the mean, and decreased by 78 weeks nicely. This was almost identical to what was seen in our pivotal infantile trial using 160 liter material.

[Slide.]

The safety data was comparable to what has been seen in other populations and so 3 out of 11 patients had AE reporting. There was an IgE-mediated anaphylactic reaction. This patient continues to receive treatment.

[Slide.]

So, overall, the risk/benefit that we see using the 2000 liter material is that there is a demonstrated clinical benefit. This has been shown by improved distance walk and stabilized pulmonary function in late-onset

patients.

This is significant given the natural history of a progressive muscle weakness and loss of functional independence. The response in the Taiwanese infants is reassuring for use in younger patients.

In regard to the safety risks, the infusion-associated reactions were mild or moderate and transient. The anaphylactic reactions were infrequent and manageable, and the majority of the patients continued to receive treatment despite the anaphylaxis.

There were high levels of IgG antibodies to the drug but no observed evidence of clinical impact.

There was a favorable risk/benefit profile given proven clinical benefit in a very rare population with no other treatments available.

Now, I would like to turn it over to Dr. P.K. Tandon from Biostatistics.

**Discussion of Statistical Methods**

DR. TANDON: Thank you very much, Ed.

[Slide.]

I am P.K. Tandon. I am a biostatistician.

[Slide.]

In this presentation, we will be focusing on four

topics today. Number one is statistical challenges in the study design for Pompe disease, changes in the primary efficacy analysis plan, final efficacy analysis, and the last is rerandomization discussion which will be headed by Dr. L.J. Wei.

[Slide.]

As you heard from Dr. Kishnani and Dr. Kaye, there are some statistical challenges in designing LOTS trial. This is obviously a very rare disease, limited number of patients available for clinical trial, a single chance to conduct a placebo-controlled trial given a commercial setting.

Most importantly, there was a lack of longitudinal natural history data on 6-minute walk test in Pompe disease and a concern that, in a progressive neuromuscular disease, long-term follow-up is needed.

[Slide.]

Original primary efficacy analysis plan was basically Week 52 trial, two co-primary endpoints, 6-minute walk test and FVC, and the two treatments will be compared using ANCOVA with repeated measures.

[Slide.]

After the trial initiated, we amended the primary

efficacy analysis plan.

Why was the plan changed? As I stated, there was concern that 52 weeks would not provide sufficient information. And there was external information coming out from Elaprase trial, which is the three-arm trial, one of the arms, which is biweekly, was not statistically significant at 52 weeks in 6-minute walk test.

Our product is also biweekly, so we were concerned about that maybe that if we prolonged the trial, that we will see an effect.

Also, we want to make sure that it will decrease the chance of false negative study.

What was changed?

We applied fixed information-based design with interim analysis to possibly extend the patient follow-up beyond 52 weeks and the cap was at 78 weeks. The trial will end at 78 weeks. It doesn't matter what happens.

All these changes were prospectively defined in the protocol and the statistical analysis plan and agreed to by FDA.

[Slide.]

At Week 38, with all the data available, an independent statistical center reporting to Data Monitoring

Committee performed an analysis. Using pre-specified rules, the Data Monitoring Committee recommended trial extension to 78 weeks.

Extension to 78 weeks depended on estimated variance and not on the estimated treatment effect. Therefore, no statistical penalty needs to be applied at the final analysis.

Most importantly, Genzyme did not have access to interim analysis results until after study completion.

[Slide.]

Final analysis when the trial was completed, pre-specified testing of LME model assumptions was performed, and these assumptions, like linearity and normality, and variance/covariance of structure, these assumptions were found to be violated.

One of the most important things I want to point out here, the estimate of treatment difference in the slope, which is the primary endpoint, was not changed. But appropriately, we applied commonly used robust methods for standard error estimation.

Also, the key supportive analysis was ANCOVA test comparing baseline to Week 78, and that is FDA's preference.

At that time, rerandomization test was one of the

prespecified sensitivity analyses.

[Slide.]

FDA has chosen to focus on sensitivity analysis on rerandomization test as the primary efficacy analysis. However, we believe there are problems with that approach.

We are very fortunate to have Dr. Wei with us, and Dr. Wei has been working with us on this topic. Dr. Wei is a Professor of Biostatistics at Harvard, and he is the leading authority in the clinical trial methodology.

He will demonstrate that application of rerandomization test is not appropriate in this trial.

Thank you.

L.J.

DR. WEI: Thank you very much, Dr. Tandon. I was told every person deserves 5 minutes of fame in his life or her life. This is my 5 minutes, I think.

[Slide.]

I would like to share with committee members the very interesting issue about rerandomization test. The problems arise if we use a minimization treatment allocation rule.

Now, think about very typical clinical trial setting, think about the LOTS study. We have 90 patients in

the study. Let's go back to the original, the very beginning of Day 1, what happened in this study.

First, the patients show up. We are going to decide if the first patient should be assigned to treatment or placebo. Now, the LOTS study required 2:1 ratio, so we like to have at the end, have 60 patients by treatment, the drug, and the 30 by placebo. That is the goal.

So, you said, well, this is a very simple example, I mean I can toss a coin. The coin you have got heads, the heads is two-thirds, the tail chance is one-third. First, the patients show up. I toss a coin. If I get head, I assign this patient to drug. If I get tail, I assign the patient to placebo.

So, I continue tossing the coin every time a patient shows up, and independently toss a coin 90 times. You say, well, that is very simple, why do I need statisticians to do this kind of work.

Well, life is more challenging. I don't want to say complicated, but the thing about this case LOTS study, we have 8 centers, international centers, and also we have two factors we want to be balanced. Each factor has two levels, so think about you have 4 levels times 8, which is 32 strata, 32 strata, and you have 90 patients, and 90

divided by 32, you roughly have only 3 patients on average for each stratum.

So, the alternative way, we said let's use a permitted block design for each stratum, treating like 32 independent mini-trials, we do this block design.

Now, I cannot do this because, you know, just there is not enough patients in each stratum. So, in this case, actually, very commonly people use a so-called minimization rule, or we call this a dynamic allocation rule.

So, if you allow me to illustrate this a little bit. So, every time a patient shows up, we actually ask ourself if the patient assigned to placebo, what is the imbalance, what is the measure of imbalance between drug and the placebo group.

Then, I ask myself if the patient assigned to drug, then, what is imbalance between this treatment and the drug. Then, I wanted to know if I minimize in this imbalance, which one I should use.

Now, you can use a totally deterministic rule to assign those patients. But, generally, they did a great job. They actually utilized the stochastic minimization rule, not a totally deterministic.

So, I have done myself, in the '80s, it took me many years to study this clinical trial design. Think about the trial is over, 90 patients accrued, and then we ask ourselves, we have 90 numbers now, and 60 were in drug, 30 in placebo, you ask yourself, gee, is there a treatment difference between these two groups or not.

So, you can do all kinds of things, right? You can do T test or whatever you want. Now, there is a school of people, they are very interested to do the following, so-called rerandomization test, and this is not a new idea at all.

Back in--Tom can tell us--maybe back 50 or 60 years ago, you know, even R. Fisher, I think talk about this, the rerandomization test. So, Cyrus Mehta is here, and I actually did quite a bit of work to try to promote this rerandomization test.

You know, personally, I really appreciate FDA actually tried to use this one to promote our idea.

[Slide.]

Now, allow me to use just one minute to explain this very simple idea, how do we do this rerandomization test. Think about this LOTS study. We have 90 patients and think about the trial is over now. You have 90 patients in

front of us, the first patient, second patient, third patient and fourth patient.

Let's take a special case. We use 6-minute walk before and after. That means the last observation minus the baseline 6-minute walk.

First, the patient actually had 35-meter improvement. The second patient is 20-minute, 30-meter improvement. The third one is 21 and the fourth is 40.

So, you have 90 numbers in front of you which actually truly observe the numbers sitting in front of you. Then, you ask yourself I did this minimization rule, actually, what is the realization I got from the drug, placebo, and the then drug-drug, and et cetera.

This is one realization I actually obtained by using this minimization rule. Now, combining this second row and the third row, you know which one is the placebo, which one is drug, and now what is the response. So you can construct, for example, two-sample T test, very simple, right? You standardize this, right, you got a 2.15.

Then, you ask yourself, say, wow, 2.15 is how unlikely, if I get this 2.15, if there is no difference between the drug and the placebo, and I said, well, listen, I don't want to build any model, I don't want to use any

model to analyze data, I am going to do the following.

I am going to say I am going to use the same minimization rule, regenerate the sequence, drug, placebo, placebo, drug and et cetera. You generate another sequence of 90 symbols in front of you. That is one simulation.

For this simulation, you just simply ask yourself can they break up those observed sequence and you observe the value. Now, for this single simulation, you compute a two-sample test, you got a value of 0.63. And then you do another one, you have got a 2.4.

Now, you can generate this many, many realizations, for example, I can generate 10,000 guys and build this using this 10,000 guys, construct a reference set.

[Slide.]

Now, think about if I just toss a fare coin, one-third chance to placebo, two-thirds chance assigned to drug, you construct this 10,000 test statistical value. That is the horizontal line and the vertical line is the frequency. So you plot a histogram. You tell me what is the number most likely when there is no difference between the two groups.

Look, that is a very nice shape, symmetric, around

zero, left-hand side is the negative value, right-hand side is the positive value. How do you figure out p-value? This is the number we got, for example, it should say 2.15, for example. It should be on the right-hand side of area, of the blue bar, which is, for example, 0.03.

Now, this is very nice because, actually, this test has nothing to do with the model, you don't have to assume normal distribution, just kind of parametric assumption.

Bob Smythe, a good friend of mine, and I wrote a paper. We said, well, you know what, I think this randomization rule, even it's not tossing a fare coin, probably, this distribution is still symmetric around zero.

Sure enough, we can allow a little bit of less randomization for the allocation rule to have this very nice asymptotic

ytool.

[Slide.]

So, what is the problem with our LOTS study? Now, LOTS study actually because we use the minimization rule, which is not totally randomization, it is relatively deterministic. So, if you construct this 10,000 simulation like we did using the minimization algorithm, look at this

histogram.

The histogram, centered here at zero, the big mass on the right-hand side are the positive value, very little value is on the negative, then, you ask yourself, wow, if there is no difference, the changes between placebo and the treatment should be zero, right? How come this guy is not a center zero?

So, in fact, we are in trouble because we cannot use this test to get even valid statistical inference.

[Slide.]

Here, it is very interesting. I think if you have enough randomization, the rerandomization test may be considered as a sensitivity analysis. But, in my opinion, this is not a primary analysis even for that crossing point.

In our LOTS study, the p-values obtained from the rerandomization test for 6-minute walk cannot be interpreted. I think, in my opinion, because this bias the issue probably is invalid.

Thank you for your attention.

**Summary**

[Slide.]

DR. KUTA: I would like to close our presentation with several summary remarks.

[Slide.]

First, full approval is warranted for the 2000 liter scale alglucosidase alfa for use in late-onset patients. We have shown you today that the Late Onset Treatment Study was a large study for this type of patient population. It was well controlled, and it met its co-primary endpoints of 6-minute walk and percent predicted FVC.

Improvement in muscle strength and stabilization of pulmonary function are clinically meaningful in this progressively debilitating disease, as Dr. Tandon and Dr. Wei just described.

The global clinical experience and outcomes will continue to be collected and analyzed through the Pompe Registry and through ongoing post-marketing studies.

We would submit that the value and feasibility of an additional clinical study comparing the 2000 liter with either placebo or 160 liter scale at this point is not clear.

[Slide.]

I would like to leave you again with our proposed indication where we propose that alglucosidase alfa is indicated for the long-term use in patients with late Pompe

disease. And. regarding the use of an age cutoff again, I would submit that the 2000 liter scale be limited to patients with symptom onset greater than 24 months without hypertrophic cardiomyopathy.

Based on the disease characteristics as defined by Dr. Kishnani earlier, this is very clear.

Regarding safeguards for restricted distribution, we are confident that REMS can effectively manage the distribution post-approval of this product.

Certainly, there is more to learn about Pompe disease and how to manage it. But we would ask you to consider the totality of the evidence which we have before you and consider full approval for this product.

Thank you.

DR. BURMAN: Thank you very much.

We will now proceed to the FDA presentation and there will be time for discussion later.

**FDA Presentation**

**Alglucosidase alfa 2000 L Advisory Committee**

**and Statistical Review**

**Lynne P. Yao, M.D.**

DR. YAO: Good afternoon. My name is Lynne Yao, and I am a medical officer with the Division of

Gastroenterology Products at the FDA.

While I am waiting for my slides to load, I just wanted to say thank you to Mr. Paul Tran and to our Lieutenants Wesley Shehara and Cecily Reece for getting this advisory committee meeting together. It took a lot of effort and we really appreciate it.

I will also just tell you that I will be presenting the clinical data on the LOTS as it relates to the 2000 liter product and my associate, Dr. Lisa Kammerman, will present the Biostatistics section, and my associate, Dr. Claudia Karwoski, will present issues regarding the REMS.

[Slide.]

Dr. Kishnani elegantly reviewed the Pompe disease background, so I feel it is probably okay to breeze through these slides.

The only thing I want to point out is that, in fact, as Dr. Kishnani has pointed out, that the disease actually represents a spectrum from the infantile onset being the most rapidly progressive and leading to death at a very early age, to the adult onset in which progression is measured in years to decades as opposed to months.

Also, I want to point out that the amount of

endogenous or native enzyme activity is different between these groups as well with the GAA activity lowest in the infantile onset and oftentimes not present compared with higher GAA activity in the older onset groups.

Now, again, these are general terms that I would like to point out and there is certainly overlap as Dr. Kishnani has pointed out. It is a spectrum of disease.

[Slide.]

Now, I really want to review the regulatory history of the drug because I think it provides a very important clinical context and regulatory context for our discussions today.

[Slide.]

In July of 2005, Genzyme submitted an application to the FDA seeking approval of both the 160 liter and 2000 liter production scales for alglucosidase alfa.

The data that were submitted from this application included efficacy data on the classical infantile-onset disease only. It was compared with the untreated, age-matched historical control and again only the 160 liter product was used.

The inclusion criteria for this study were very specific, included that you must have been diagnosed with

Pompe disease prior to the age of 6 months, that you were to have started treatment by the age of 7 months. You had to have cardiac hypertrophy and you were not to be receiving invasive ventilatory support.

Now, these were all again based on what we have heard about the disease, important criteria to include in terms of the inclusion criteria. Also, many of these patients, as you have heard already, declined very rapidly and require mechanical ventilatory support, therefore, the company suggested that we use a primary efficacy endpoint of ventilator-free survival at 18 months of age, which we felt was appropriate.

As it turns out, there was an 83 percent ventilator-free survival at 18 months of age compared to only a 2 percent survival, patient survival in the historical control group.

[Slide.]

During the FDA's clinical review, however, it was noted that the 160 liter and 2000 liter products may not be comparable. This was based on product quality attributes, nonclinical and clinical pharmacology assessments.

Therefore, we asked Genzyme for additional information to support the comparability of these two

products. But again in order to maximize the hope to approve the product within the first review cycle, Genzyme withdrew the 2000 liter product from the application and said only approval for the 160 liter product.

Thus, in April of 2006, the 160 liter product was approved in the United States for the treatment of Pompe disease.

[Slide.]

Listed on this slide is the actual indication for the 160 liter product, and that is that Myozyme is indicated for use in patients with Pompe disease. Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas the use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

[Slide.]

By the first quarter of 2007, Genzyme had reported to the FDA that there was a critical drug shortage of the 160 liter product. In discussions with the FDA, Genzyme actually agreed to develop a Myozyme Temporary Access Program that would allow 2000 liter product to be given on a case-by-case basis to patients over the age of 18.

These patients had to be pretty severely affected including use of invasive ventilation or be wheelchair bound, and the 160 liter product at that point became available to patients only less than the age of 18.

In October of 2007, Genzyme submitted a supplemental application seeking approval of the 2000 liter product. Again, there were concerns relating to product differences and that these product differences may lead to actual differences in biologic effect between the 160 liter and 2000 liter product.

We found that there was insufficient clinical data to establish the comparability between these two products.

[Slide.]

Unfortunately, with the submission, and we have heard previously that there were no head-to-head studies available between these two products, and the clinical data that we had to review really just included four small studies in which infants received 2000 liter product.

We matched patients for the criteria of the infants that were treated in the 160 liter approval process and we found 7 patients who were 2000 liter treatment naive and that were available for comparison.

[Slide.]

This slide shows just basically a rough efficacy comparison between these two products that our FDA reviewers wrote and we found that there was a trend towards a decreased efficacy based on 18-month ventilator-free survival and median time to the ventilator between the 2000 liter group and the 160 liter product group.

Thus, we really could not establish the comparability between these two products. And it is very important to note that we are talking about N equals 7 and N equals 18 here so that the patient population was really, really too small to draw any definitive conclusions.

[Slide.]

So, in April of 2008, FDA requested based on this review that Genzyme submit a new application with clinical data to support the separate licensure of the 2000 liter product actually as a new drug.

Also, I want to point out that in April 2008, the MTAP was closed to new patients, and recently Genzyme reported to the FDA that they are aware of at least 53 newly diagnosed adult patients in the U.S. who are waiting to receive treatment, but cannot obtain access to the drug due to the closure of MTAP.

[Slide.]

Genzyme agreed with the FDA that there was insufficient clinical evidence to establish comparability of the 160 liter and 2000 liter products and thus submitted a new application in support of the 2000 liter product.

In this application, Genzyme is seeking approval of 2000 liter product in the treatment of late-onset Pompe disease and, as you have heard from Dr. Kaye, that would include both juvenile-onset and adult-onset disease.

The data that would support this application include efficacy and safety data on one study, AGLU02704, or the Late Onset Treatment Study, or LOTS.

[Slide.]

You have already heard about the study design and that includes that it is multi-center, multi-national, double blind, randomized, placebo-controlled. There were patients age 8 to 70 years who had been diagnosed with Pompe disease, but who had not received previous treatment.

We have also heard that they were assigned in a 2:1 ratio by a minimization algorithm to receive either the 2000 liter product or placebo. The original planned treatment period was 52 weeks and the dose was 20 mg/kg/dose.

[Slide.]

The study objectives included to evaluate the effect of 2000 liter product on functional endurance as measured by the 6-minute walk test, to evaluate the 2000 liter product on respiratory muscle weakness as measured by the forced vital capacity and a percent predicted fashion in the upright position and also, of course, to evaluate the safety profile of the 2000 liter product.

[Slide.]

In order to understand the analysis of the primary efficacy endpoints, I would like to just review the definitions of the endpoints and how they relate to Pompe disease.

The 6-minute walk test is a measurement of functional endurance. Patients are asked to walk along a 100-meter flat corridor for 6 minutes at their own pace. They are allowed to use assistive walking devices and are allowed to stop.

The normal ranges for healthy adult women average around 500 meters, and for healthy adult men about 580 meters, and up to 700 meters in healthy adolescents. It also has been pointed out that it has been used as a primary efficacy endpoint in other enzyme replacement therapy approvals.

Again, this is based on its ability to evaluate global physical performance.

There are some limitations and that includes that this does not actually reliably predict time to ventilator or death. Again, this test relies on patient effort and motivation.

[Slide.]

The second primary efficacy endpoint or forced vital capacity is the measurement of the adequacy of respiratory effort. Normal values have been established and they are based on age, gender, height and ethnicity.

Generally, values are reported as a percent predicted normal with an abnormal value of being about less than 80 percent of the predictive normal value in the healthy population. Again, this FVC has been used in other enzyme replacement therapy approvals and the same limitations apply to FVC as they do for 6-minute walk test.

[Slide.]

Well, what about the patient population? The major inclusion criteria and exclusion criteria are presented on this slide. Patients had to be 8 years of age or older, had to have the disease diagnosed by GAA activity, had to be able to at least walk 40 meters, had moderate to

moderately severe changes in FVC at baseline and a drop of FVC from the upright to supine position.

Exclusion criteria also include that they would not have invasive ventilatory support, that they had not used enzyme replacement therapy or GAA in the past, and there was no restriction to the use of concomitant medications.

[Slide.]

So, the primary efficacy endpoints that were measured in LOTS, just to clarify, on the original protocol were listed as a measurement of meters walked during the 6-minute walk test at 52 weeks, adjusted for those baseline characteristics.

Measurement of upright FVC as a percent predicted at 52 weeks adjusted for baseline.

There are numerous secondary, tertiary and exploratory efficacy endpoints that I will not review as part of this presentation, as none of these will be the basis for our approval.

I just want to point out the original statistical analysis was a repeated measures analysis of the difference in the 6-minute walk test at 52 weeks adjusted for baseline differences, and that the FVC would not be reviewed if the

6-minute walk test was found not to be statistically significant.

[Slide.]

This is a timeline of the protocol and statistical analysis plan amendments over the course of the study. As you can see, the LOTS protocol was received by the FDA in May of 2005, with the first patient enrolling in September and the last of the 90 patients enrolled by March of 2006.

The last patient completed the study by September of 2007. Highlighted in red are the three protocol amendments that were received by the FDA, and highlighted in blue are the three statistical analysis plans that were submitted to the FDA.

I would just like to point out in summary that there were three protocol amendments and three statistical analysis plan amendments that were submitted to FDA, that spanned the entire length of the LOTS trial.

I would now like to turn the presentation over to Dr. Lisa Kammerman, who will discuss the important study design, statistical analysis issues regarding the LOTS study.

**Lisa A. Kammerman, Ph.D.**

DR. KAMMERMAN: Thank you. I am going to review

the changes to the study design statistical analysis plan, which are really important to understanding and interpreting the results from the study.

The changes to the endpoint in statistical methods were made while the study was ongoing and again after the data were unblinded and analyzed. As you have already heard, further complicating the interpretation of the results is the way subjects were assigned to treatment groups.

Instead of using a blocked randomization scheme or some other type of randomization scheme, a minimization algorithm was used instead. And this really necessitates the need for rerandomization tests to assign statistical significance to the results.

[Slide.]

While the study was ongoing, the design was changed from fixed duration of 52 weeks to an adaptive strategy. At the time we were given two reasons for this change.

The first was to determine the optimal duration of the study, and the second was to make comparisons over the entire duration of the study. I have highlighted the second reason because I want you to keep this in the back of your

mind when I review the results from this study.

The changes to the strategy also necessitated changes to the endpoint and the analysis. But I also want to point out that we never--FDA never really agreed to these changes to the protocol and the statistical analysis then.

I think we were probably taken a little bit by surprise when we did see the proposal, and the final statistical analysis plan arrived right when the final interim analysis was being done--I shouldn't say the final, but when the interim analysis was done.

[Slide.]

The endpoint that was prespecified in the original protocol was the 6-minute walk test at 52 weeks. To accommodate the adaptive design and to include all the 6-minute walk test assessments throughout the entire study, the prespecified endpoint was now changed to a slope. So linear slope estimates the rate of change in the 6-minute walk time over the duration of the study.

The prespecified analysis was also changed. Originally, it was a repeated measures analysis, but it was a change to a linear mixed effects model with a model-based covariance matrix.

These changes were made while the study was

ongoing but before the data were analyzed.

[Slide.]

So, what was this adaptive strategy? The idea was either to stop the study at 52 weeks or to extend it. I might add at one point they were considering doing an interim analysis and perhaps stopping even earlier for efficacy. But that didn't appear in the final protocol amendment.

The idea was to compare the average increase in meters walked relative to baseline using a longitudinal model to assess the changes in differences between treatment groups.

An interim analysis was done after all the subjects completed 38 weeks. According to the rules, the study would stop as previously planned, at 52 weeks, or be extended an additional 13 or 26 weeks. So, after the interim analysis was done, a decision was made to extend it by 6 months to 78 weeks.

[Slide.]

The advantages that were stated in the application when this adaptive strategy was adopted was that the longitudinal approach uses all the data, all the assessments of the 6-minute walk test. There is a gain in the power of

the statistical test, and that the interim data can be used to determine the correct time for stopping the study.

These points are very important to interpreting and understanding the results from the study.

[Slide.]

You have seen this graph. Genzyme just showed this a little bit earlier, of the change from baseline in the 6-minute walk test of the 2000 liter product versus placebo. This vertical line indicates when the interim analysis was done.

Along the X axis I show the number of subjects who contribute to each of these means in the standard errors. So, at the time of the 38-week interim analysis, there were 55 subjects receiving Myozyme or 2000 L, and 29 on placebo.

At the time of the interim, you can see that most subjects had four data points, baseline, 12 weeks, 26 weeks, and 38 weeks. The idea behind the adaptive strategy is that we can't add more patients because it is a rare indication but that we can add more visits and have more data points contributing to what was assumed to be a straight line.

So, by having a better estimate of the straight line, it reduces the variability and, in theory, would make it easier to detect a treatment difference if it exists.

What you can see is after 38 weeks, actually perhaps probably starting a little before 38 weeks, the 6-minute walk test starts to plateau among subjects receiving 2000 L.

Even if the data don't follow a straight line, one could probably still argue that the straight line is measuring an average rate of change throughout the study.

[Slide.]

Here are the summary statistics. These are just the raw means for the 6-minute walk test, the 2000 L and the placebo treatment arms. In average, those subjects at baseline could walk around 320 or so meters. On average, those in the 2000 liter product improved by about 26 meters, whereas, placebo decreased on average by 5 meters for a treatment difference of 31 in favor of 2000 L.

What is interesting is that the median change from baseline to the last observation in the 2000 L treatment group was 16 compared to a mean of 26, suggesting that there is skewness in the change from baseline among the 2000 L group.

[Slide.]

Here are the results for the prespecified analyses of the primary endpoint. The prespecified analysis was this linear mixed effect model, the model-based variance in

meters per month. The point estimate is 1.2 meters per month for the 2000 L treatment group and about essentially no change in the placebo group with an average increase of 1.3 meters per month for the 2000 liter versus placebo.

This result was not statistically significant, 0.09, when using the classical type approach, rerandomization results were not available.

After looking at the model and the analyses, and doing some diagnostics, it was determined that certain assumptions in the model were violated including normality and the linearity of the data, and also the construction and assumptions of how the variance and covariance was going to be made.

I know this is a little complicated, but it is important to understand that. So, after the data were changed, the Applicant adopted a robust variance estimator, which is very robust and is more forgiving of misspecifications in the model.

I actually agree that this is probably a better approach. But it still raises the question of whether the Applicant would have proceeded with a robust variance if the initial model had been statistically significant especially if the second model had been statistically non-significant.

[Slide.]

The analysis of covariance was a supportive analysis and, with this analysis, the Applicant's analysis gives a p-value of 0.04. The rerandomization p-value, which I believe is the appropriate value, gives a p-value of 0.06.

I have just written a few notes down here that this endpoint and this analysis was not the basis for the adaptive strategy, and it is not consistent with the rationale for using slopes, which was the prespecified primary endpoint, and the LME, which was the prespecified analysis.

[Slide.]

So, some of the pros of the analysis of covariance is that it has many fewer assumptions than the LME model. It addressed the clinical question of interest which is what is the difference between treatment groups and the change from baseline to the last observation.

The cons is that again it wasn't the basis for the adaptive strategy. It contradicts the Applicant's rationale for using LME and slopes. A big issue is that of missing data, which we haven't yet addressed.

By using the last observation, what we are saying is that we are using last observation carried forward. So

we are not accounting for subjects who have discontinued study because there is that one death, or patients, for example, with anaphylactic reactions.

[Slide.]

I am going to turn right now to the issue of rerandomization by starting off talking a little bit about stratification.

So, why do we stratify in clinical trials? It is always a good idea to stratify patient enrollment and analyses by variables known to be related to outcome. I think this is a really nice example.

Along the Y axis, we have the distance walked at the last observation. Along the X axis is the distance walked before they started treatment.

You can see it is a fairly nice straight line, so it is highly related. And it's a really good idea to stratify, and stratified analyses can sometimes give us misleading results. So, the question becomes how do we stratify patients and how do we do our analysis.

[Slide.]

There are two schools of thought. One is the stratified randomization, which you are probably all familiar with, so within particular strata, subjects are

assigned at random to treatment groups.

In the case of LOTS, for example, if we had used stratified randomization, each subject would have had the same chance of receiving the 2000 L, 2 chances out of 3, regardless of who had entered the study before they had been assigned to treatment.

So, every subject is independent of the one who enters before in terms of treatment assignment. With stratified randomization, we can obtain p-values from classical analyses that are usually straightforward, not always.

Some examples are T tests, F tests, get the test statistic and look it up in a table for the p-value.

[Slide.]

So, the second approach is the minimization algorithm, which was used for LOTS. As you heard, the goal was to maintain a 2:1 balance of treatment to placebo. This is done by examining the ratio of the number of subjects assigned to 2000 L to the number of subjects assigned to placebo.

If there is a large imbalance within a site or with one of the strata, then the subject is given a higher probability of being assigned to the treatment that will

bring the ratio closer to 2:1.

In LOTS, the probabilities of assignments were 100 percent, 90 percent, 50 percent, 10 percent and zero percent. The 100 percent would be if there was imbalance within a site and zero again if it was imbalance. So, if placebo was being favored, then, to get the 2:1 ratio to favor 2000 L product, that subject would be deterministically essentially assigned to 2000 L.

Unfortunately, the Applicant hasn't preserved the original list of allocation probabilities so we can't evaluate the distribution of these probabilities and see if somehow these probabilities are causing the difference between the rerandomization and the classical test.

[Slide.]

With the minimization algorithm, because all assignments are not equally likely for each subject, the analysis becomes complicated. I think Dr. Wei did a nice job of explaining the rerandomization.

The idea is to recreate the experiment, in our case the clinical trial. So you pretend every time you do one of those rerandomizations, you pretend the study is starting over again.

So, if the first person was enrolled in the 2000 L

group, say, with 50 percent probability, for the next rerandomization or the first, we would flip a coin and assign that person to placebo. But what is important to remember is that for each rerandomization, we again apply the minimization algorithm.

So, we again examine the assignments within sites, stratum, and determine the probability of the next person to be assigned to the treatment or placebo.

In the study, the first person had I believe a 90 percent chance of being assigned to 2000 L, and that person then had, for all the rerandomization, out of the 10,000 rerandomizations, that would mean on the average 9,000 of them would have that person being assigned to Myozyme or--I am sorry, 2000 L product.

So, the idea with the rerandomization is that there is no difference between treatment and placebo, that when you plot all those T statistics, you will get a nice distribution, the expected value will be zero.

An example of the rerandomization is Fisher's exact test.

[Slide.]

In our analysis, or our preferred analysis, rerandomization is that this accounts for the order in which

patients arrive. It accounts for the changing probabilities of assignment and why do the methods give us different results.

One possibility is the allocation procedure started with the first subject, variation is to let the study run for maybe 10, 15, 20 subjects and assign everyone 50-50 chance of being assigned to treatment or placebo and then start in with the minimization. But, in this case, the first person had a 90 percent chance.

Another possibility is that the order of arrival matters. Finally, when it mentioned about the distribution, argument is being made that the histogram is showing that the rerandomization test is inefficient.

I would argue really that probably the allocation procedure is inefficient.

[Slide.]

So, just to give a few quick plots of the data, this one shows the cumulative distribution of assignment to treatment versus the order of entry. So, the red line is assignment to the 2000 L product, blue is placebo.

Here, if we look at the median, so 50 percent of the placebo subjects--it is hard to see this sideways--arrived. By Patient No. 40, who enrolled in the study,

about 50 percent of the placebo arm had been enrolled as compared to the 2000 L treatment product. It was closer to 50.

If the accrual to the treatment arms had been identical, these two lines would overlap.

We also have some suggestion that the final endpoint change from baseline is a function of when subjects entered. So I fit a straight line to the data, change from baseline versus order of entry.

[Slide.]

It's a weak line, but what you can see is down here among the subjects who enter in the first half of the study, there are some individuals who had relatively large decreases from baseline. There were none later on.

Up here, there are a few individuals who had high changes from baseline. These people down here are pulling the line down and the ones who enter later are pulling the line up

[Slide.]

Interestingly, when I plotted the order of entry versus study site, here is about the patient or number 45 who entered in this study. You can see that there is this one study site, 26, from the Netherlands, who had the