largest enrollment in the study. They enrolled 22 subjects I believe. So, they accounted for half of the subjects enrolled in the second part of the study.

We see down here, these two sites enrolled, this one almost all their subjects within the first half of the study, this site, 47, within the first half. These were both from the United States.

[Slide.]

FVC is really not at issue no matter how we look at the results, no matter which test, which endpoint, the results are statistically significant.

[Slide.]

To summarize the results, there are numerous changes that affect our ability to interpret the results. While the study was ongoing, it adopted an adaptive strategy which necessitated a change to the analysis from repeated measures to linear mixed effects.

After the study was unblinded and the initial prespecified analysis was done, the prespecified model was modified to one with a robust variance. Additionally, FDA is emphasizing the analysis of covariance, which was a supportive analysis.

The endpoints again were changed from 6-minute

walk test at 52 weeks to a slope. After this study was unblinded, an additional prespecified analysis was done and we are now using ANCOVA. This essentially changes the endpoint once again from the initial one, which was 6-minute walk test at 52 weeks to a slope. So now we are at change from baseline to the last observation.

[Slide.]

We believe the p-values from the rerandomization tests are the correct p-values. They are almost always the correct way to proceed, to recreate the clinical trial including the minimization algorithm and the order of entry into the study.

The prespecified analysis was not statistically significant. The model assumptions were violated and once it was modified, it was statistically significant by the Applicant's analysis, but not by ours.

One might argue that it still measures the average rate of change over the study.

[Slide.]

The analysis of covariance might be the most appropriate model in this situation given the issues with the violations of the model assumptions for the linear mixed effects.

It addresses the clinical question of interest and makes many fewer assumptions. However, it is not the endpoint that was the basis for doing the adaptive design in the first place. It contradicts the Applicant's rationale for using longitudinal models for analysis and for using the slope as the best endpoint.

There are also the missing data issues, the analysis of covariance is using the last observation carried forward. Remember there are discontinuations due to anaphylaxis and one patient couldn't continue because that patient died.

I will turn it back to Dr. Yao.

Lynne P. Yao, M.D.

[Slide.]

DR. YAO: To continue with our analyses, we also looked at a few subgroup analyses that include the effect of age and baseline GAA activity, the effect of immunogenicity, and some exploratory and responder analysis to the efficacy endpoints.

[Slide.]

If we look at the age group comparisons--again these are based on patients at the time of their first infusion--and break them down by age categories, patients

less than 18 years all the way up to patients 70 years of age, we see that in the lowest age group, there were only two patients enrolled in both the 2000 liter treatment group and the placebo group.

In fact, if we look at the youngest patients in the study, those patients less than 30 years of age, there were only five patients or 8 percent of the patients less than 30 years of age at the time of the first infusion in the treatment group, and only 10 percent of the patients in the placebo group who were less than 30 years of age.

Also, remember that the patients over the age of 30 generally have a more attenuated form of the disease. Thus, there were really insufficient numbers of patients studied in the LOTS trial to assess efficacy in the juvenile onset population.

[Slide.]

Why is the juvenile onset population of interest? It is so because patients tended to have more rapidly progressive symptoms, they have a generally worse overall prognosis and, if treated with enzyme replacement therapy, may require the longest course of treatment.

Therefore, a definition of the juvenile onset population based on their clinical diagnosis should be

established. We reviewed patients in the LOTS trial based on their age at diagnosis and their age at first symptoms.

If you look at patients who were diagnosed under the age of 18 years, there were 11 patients total in the LOTS trial. However, two of these patients we excluded because they were diagnosed before the age of 18 but actually did not manifest symptoms of their disease until their 20s. Their diagnosis was made based on a family member with the disease. So, therefore, there were only a total of 9 patients who were diagnosed under the age of 18 years in the LOTS trial.

[Slide.]

If we look at the age of first symptoms, there were actually 14 patients who reported symptoms before the age of 18 but actually were not diagnosed until after the age of 18. In fact, 8 of these patients were actually over the age of 40 at the time of enrollment and 3 were over the age of 50.

There were also 9 patients of these 14 who were over the age of 25 at the time of diagnosis. Therefore, we really do not believe that this patient population represents the true juvenile onset population.

We would propose a practical definition of

juvenile-onset disease as those patients who developed symptoms and were diagnosed with Pompe disease less than the age of 18. If you look at this, then, there were 9 patients studied in the LOTS protocol with this definition.

[Slide.]

If we look at the efficacy of these 9 patients in the late onset study, we see that for both primary efficacy endpoints and for both treatment arms, we see a worsening of their results at the end of the study.

We also note that there is a treatment effect between the placebo group and the 2000 liter group. But this treatment effect appears to be attenuated compared to the 28 meter treatment effect we saw overall.

Thus, we see that younger patients appear to have more rapid progression of disease.

[Slide.]

If you look at GAA activity, again, GAA activity roughly correlates with the age of onset of disease, younger patients having lower GAA activity. We found 10 patients in the LOTS trial with a GAA activity less than 1 percent, 6 randomized to the 2000 liter group and 4 assigned to the placebo group

Again, these patients tended to be younger with 5

of these 10 under the age of 18 at the time of diagnosis.

[Slide.]

If we look at the efficacy data on these 10 patients with GAA activity less than 1 percent, we also see, we have again both primary efficacy endpoints in both treatment arms, we see worsening at the end of the study.

Again, there is a treatment effect seen between the 2000 liter product and placebo, but this treatment effect appears again to be attenuated. This also supports the finding that younger patients, lower GAA activity, more rapid progression of disease.

[Slide.]

So, in summary, the juvenile-onset patients, again, they have generally a worse prognosis, their GAA activity is generally lower and there are really insufficient efficacy data from LOTS in the juvenile-onset population to really assess efficacy properly.

We also would submit that the efficacy data suggest a trend towards decreased effectiveness of 2000 liter product in younger patients and patients with low GAA activity.

Again, I want to make sure that I point out that these small numbers of patients were not powered in

appropriate numbers to really make any statistically significant conclusions.

[Slide.]

I want to move on to the immunogenicity of the 2000 liter product. The development of immunologic responses to enzyme replacement therapy remains a major concern. The impact of immunogenicity on both safety and efficacy of the GAA may be substantial.

Again, if you develop antibody to the enzyme, it may lead to decreases in efficacy, as well as increases in safety concerns. Most infantile-onset patients do not produce any native enzyme for their immune systems to recognize and, therefore, the administration of a recombinant enzyme is more likely to elicit immune responses than in the adult-onset patients, most of whom make some native enzyme.

Also, inhibitory antibody formation is of interest because clearly, this could lead to decreases in efficacy.

[Slide.]

These are immunogenicity data comparing the 160 liter product and the LOTS. I just want to point out that there was an 89 percent of patients, of the 18 in the LOTS trial, who developed antibodies to GAA, and 10 percent of

patients who developed inhibitory antibody.

In the LOTS trial, all patients--and they were late onset patients treated with 2000 liter product--developed antibody, and 30 percent of these patients developed inhibitory antibody.

Thus, it appears that the 2000 liter product may be more immunogenic than the 160 liter product. These findings were somewhat unexpected given that infantile-onset patients should be expected to be at higher risk for developing antibody responses.

[Slide.]

This slide shows the effect of the inhibitory antibody on efficacy. I told you that there were--if I go back to the last slide--there were 18 of 60 patients who developed an inhibitory antibody. But we wanted to look at the subgroup of patients who did not tolerize to the treatment; that is, they had a persistently rising IgG titer at the end of the study in association with the presence of inhibitory antibody.

If we look at the 6-minute walk test data on these 4 patients, it turns out that they had a significant or a substantial worsening at the end of the study compared to other treated patients.

[Slide.]

This slide shows the individual 6-minute walk test data on all 90 patients that were enrolled in LOTS. Along the X axis we see the time in weeks and along the Y axis we see the change in distance walked during the 6-minute walk test.

As you can see, there were 4 patients who had improvements much more dramatic than the rest of the treatment group, and there were no such improvements in the placebo group. If we remove these 4 patients from the analysis, in fact, the treatment effect is decreased by 41 percent.

[Slide.]

Well, what was it about these 4, what we call "high performers," and was there something about their specific characteristics of the subgroup that we could identify?

In fact, 3 of these 4 patients developed inhibitory antibodies to the enzyme, which again seems a little bit unusual that they would develop inhibitory antibodies, but yet perform in such a high level.

It turns out none of these patients actually had persistently rising IgG titers; that is, they developed some

tolerance we believe to the enzyme product. They had an improvement on an average of about 194 meters. Again, that is compared to 28 meters difference in the treatment effect in the study.

There is a biological reason potentially to describe this phenomenon, and that is that the inhibitory antibody may actually act as a carrier protein bringing the enzyme to the target cell and leading to less mistargeting of the enzyme.

[Slide.]

Also, placing the study findings in the proper clinical context is a critically important but difficult task; that is, what level of improvement constitutes a clinically meaningful response to treatment.

The FDA review team is aware from discussions from your dedicated patient representative, Ms. Tiffany House, that a practical definition of a response to 2000 liter product could be stabilization of disease or prevention of further decline.

Therefore, an important issue we would like to ask the Advisory Committee is to consider the definition of a meaningful clinical response based on these primary efficacy endpoints.

Genzyme also attempted to define a clinically meaningful response based on the primary efficacy endpoints in the LOTS trial. Originally, they defined a responder as a patient who improved at least 54 meters in the 6-minute walk test and had at least a 15 percent improvement in the percent predicted FVC over baseline.

I would say that this was their originally defined responder. The response thresholds were actually lowered in the third statistical analysis amendment. As you recall, the statistical amendment was received by the FDA after the study finished, the last patient finished.

Also, I want to point out that these definitions really were derived from non-Pompe disease populations and, therefore, may not really be applicable.

[Slide.]

Nevertheless, if we look at the responder analysis based on Genzyme's original criteria, we find that 2 patients walked more than 54 meters in the 6-minute walk test and improved by at least 15 percent, and there were no patients in the placebo group.

Again, it is difficult to make clinical conclusions based on the lack of information about endpoint thresholds in Pompe disease.

[Slide.]

I want to now turn our attention to the background and to discussion of the safety analysis.

This slide presents the background of the safety analysis. The major safety issues relating to all enzyme replacement therapies really relate to the immunogenicity of the product. We know that the immunogenicity may be relating to side effects or safety issues concerning anaphylaxis, infusion reactions and also chronic immune reactions.

Overall, I should say that the safety profile of the 2000 liter product is comparable to the 160 liter product based on the LOTS data, and I would like to point out some of these differences.

[Slide.]

Overall, there were 27 serious adverse events, and the term "serious adverse event" is a regulatory term that is defined as an adverse event that leads to hospitalization, permanent disability, death, or birth defect.

There is 1 patient in the analysis of these 27 that died. There were 19 events in 12 patients in the 2000 liter group and 7 events in 5 patients in the placebo group.

Again, most of these SAEs were not related to treatment with the 2000 liter product. However, anaphylaxis did occur in the 2000 liter treatment group, but not in the placebo group.

[Slide.]

Overall, we found an incidence of about 7 percent anaphylaxis, 4 patients out of 60 and, actually, 2 of these patients withdrew from the study due to this complication.

This is compared with an incidence of none in the placebo group and about 5 percent in the 160 liter product trials.

As you have heard from Dr. Kaye and others, Genzyme does not agree with our classification of 1 patient who developed anaphylaxis. But I should point out that we had our data reviewed by the Division of Pulmonary and Allergy Products at FDA, by an allergist who agreed with the classification of 1 patient. We also used the definition based on the consensus conference convened by the NIAID, and the reference is listed for you here.

[Slide.]

Infusion-associated reactions are those reactions defined as likely to be related to medication that occurred during or within 2 hours after completion of the infusion or

by the discretion of the investigator.

You can see based on our review that there was a total of 297 infusion reactions broken down by treatment group versus placebo, 29 patients in the 2000 liter and 15 patients in the placebo group, roughly equal I should say frequencies within patients; that is, about 50 percent of the 2000 liter group and 50 percent of the placebo group sustained infusion reactions.

But really what is more I think important to point out is that the types of infusion reactions within these groups is different. We see that within the 2000 liter group, many of the infusion reactions that were sustained were really significant or strongly suggestive for allergic and anaphylactic type reactions, whereas, in the placebo group there were none such type reactions and mostly really included headache and nausea.

[Slide.]

If you look at the instance of delayed onset infusion reactions, again, the placebo group actually had more delayed onset reactions, and I should say that that is defined as a reaction that occurred 2 hours after the completion of the infusion up to 48 hours after completion of the infusion.

Again, what I really want to point out is that if we look at the types of infusion reactions sustained in a delayed fashion between the two groups, we see that there was one episode of delayed onset anaphylaxis; that is, an episode of anaphylaxis occurred after the observation period, and 2 episodes of urticaria that the sponsor--I put an asterisk here--the sponsor has recently told us that these episodes of urticaria actually started before the 2-hour observation concluded. But we were not aware of that at the time these slides were initially made.

[Slide.]

Also, other potentially important adverse events that may be immunologically mediated include skin and kidney adverse events.

More skin reactions were seen in the 2000 liter group compared to the placebo group, and some of these skin reactions were concerning for allergically mediated skin reactions. In fact, we have noted immune complex mediated skin reactions in the post-marketing surveillance of the 160 liter product.

Also, urinary abnormalities have been seen in higher frequency I should say in more patients in the 2000 liter group compared with the placebo group. Again an

episode of immune complex mediated glomerulonephritis has been reported with treatment in an earlier form of recombinant GAA.

Many of these findings, however, may develop only after long-term exposure and LOTS may not have uncovered the true risk for the development of these chronic immune adverse events. Therefore, we believe that longer term follow-up is required to assess the true risk of these types of immune complex mediated events.

[Slide.]

So, to conclude, I would like to review the FDA review team findings. You have heard about the study design and statistical issues including that there were changes made to the study design and the statistical analysis plan while the study was ongoing and after the data were unblinded.

There was allocation of patients using a minimization algorithm and rerandomization tests.

Taken together, these findings raise concern regarding the robustness of the study conclusions that can be made.

[Slide.]

There was a 28.1 meter difference between the

treatment group and placebo group at 78 weeks with a p-value of 0.06 based on ANCOVA, and this is the p-value again based on what Dr. Kammerman describes as a rerandomization inference which we believe is the correct p-value.

If we use the prespecified analysis, there was a difference of 1.2 meters per month with a p-value of 0.09, and there was no rerandomization inference performed for this analysis.

[Slide.]

For FVC, we note that there is a 3.4 percent difference between the upright FVC percent predicted between the 2000 liter group and the placebo group at 78 weeks, and all the analyses that were performed were statistically significant for this difference.

We also want to point out that FVC could be considered a surrogate endpoint. But, if so, it must be verified with further clinical study.

[Slide.]

There are insufficient number of juvenile-onset patients enrolled in LOTS to evaluate the efficacy of the 2000 liter treatment in this group.

Low GAA activity appears to be associated with younger patients and a possible attenuated response.

There have been no clinical trials to date evaluating 160 or 2000 liter product in juvenile onset-patients.

[Slide.]

Immunogenicity of the 2000 liter product appears to be greater than the 160 liter product. This increase in immunogenicity may lead to increases in anaphylaxis and infusion reactions.

[Slide.]

Finally, delayed onset anaphylaxis, which has not been previously described with the 160 liter product, appears to be present with the 2000 liter product, and chronic exposure to the 2000 liter product has not been adequately studied and patients may be at risk for development of immune-mediated skin and kidney reactions with chronic exposure.

In closing, the Review Division at FDA is clearly aware that Pompe disease is a rare progressive disease for which there is only one treatment approved in this country, the 160 liter product.

We are also clearly aware of the critical drug shortage of the 160 liter product, as well as the urgency that the Pompe disease community feels in approving a

product that will allow patients who are unable to receive any treatment at all to be given some chance at treatment with the approval of the 2000 liter product.

Therefore, this Advisory Committee was convened to help answer questions we at the FDA have regarding the approval of the 2000 liter product.

As part of these questions, we are asking the Advisory Committee in one of our questions about communication plans and restricted distribution of the 2000 liter product should this product be approved.

I would now like to introduce Dr. Claudia Karwoski, who will discuss the background information for this question.

Claudia B. Karwoski, Pharm.D.

DR. KARWOSKI: Good afternoon.

[Slide.]

Just a little background. A REMS or a Risk Evaluation Mitigation Strategy is a risk management plan that utilizes tools beyond routine labeling to ensure that the benefits of a product outweigh the risks.

They are generally designed to meet specific risk minimization goals and these are essentially the same as a RiskMAP, which is terminology that has been used over the

past few years except that REMS today can be required by FDA and are enforceable.

As such, FDA can actually determine that a REMS is needed at the time of approval to assure the benefits outweigh the risks.

[Slide.]

REMS can include a number of elements including patient labeling, medication guides or PPI for patients, communication plans for healthcare providers or other healthcare professionals and elements to assure safe use, which in the past has been termed restricted distribution.

These can include that prescribers have certain training or certification in order to prescribe the product;

That pharmacies or healthcare settings be certified, that the administration of a drug be limited to certain healthcare settings;

That the drug is only dispensed after documentation of safe use;

That each patient is subject to certain monitoring, or that each patient is enrolled in a registry.

[Slide.]

Drugs that offer important benefits should be considered for a REMS in one or more of the following

situations:

If the risks are serious and preventable;

If the safe and effective use may call for specialized healthcare skills or settings;

When the benefits justify the risks in only a limited patient population;

Or if the product is in a class of products with similar risks that have required REMS.

[Slide.]

So, if the 2000 liter product offers important benefits and is approved, a REMS should be required to address the following issues:

First off, the established name for both the 160 liter and the 2000 liter is the same as is the dose for both products. This can lead to confusion between the products and maybe even the belief that the products are interchangeable so strategies should be employed to address this potential for medication error.

Currently, the 2000 L product is potentially more immunogenic than the 160 liter product.

Patients with infantile or juvenile-onset Pompe disease may be at increased risk for these immune-related adverse reactions.

So, again, the REMS should be targeted to the use of the 2000 liter product in the intended population.

[Slide.]

The sponsor has proposed a plan for the distribution of the 160 liter product that they have been using for quite some time.

This plan includes training and communication, including an in-service and training to staff who treat the infantile-onset patients, training to their preferred distributors, which is a small number of distributors, notification to parents of the infantile-onset patients that they are being treated with 160 liter product.

There is also annual recertification of the infantile onset staff.

A disclosure statement from sites administering to both populations that they acknowledge the difference between the indications of the two products.

The 160 liter product is packaged or will be packaged with the intended patient's name on the packaging and, finally, clear labeling for the 2000 liter product which gives a clear indication for use.

[Slide.]

So far as we can tell, the sponsor's proposal

really focuses on the distribution of the 160 liter to only infantile-onset patients, but it doesn't appear to focus on preventing the 2000 liter product from being used in the infantile or juvenile-onset patients.

[Slide.]

So, some additional strategies may be considered. Some of these may have already been considered by the company but we haven't gotten these sort of details.

The communication efforts should be expanded to healthcare professionals that treat all forms of Pompe disease, and those that administer or will administer the 160 and/or the 2000 liter.

Enrollment, training, and certification of all facilities that administer the 2000 liter product, and then distribution to the 2000 liter product only to those certified facilities.

Enrollment of all patients being treated with the 2000 liter product. This will allow for determination whether the patient is eligible for the product, as well as it can serve as a repository of adverse events and with linkage to the specific product.

[Slide.]

The company may also consider packaging both the

2000 liter and the 160 liter specifically for the intended patient, and then verification at the certified site that the patient is enrolled in REMS, and that the product that they have, that is to be administered, is for the intended patient.

[Slide.]

In order for any REMS proposal to work to minimize risk, a definition of patients that are eligible or not eligible for the 2000 product is needed.

This concludes FDA's presentation.

DR. BURMAN: Thank you.

We will now move to the Open Public Hearing.

Open Public Hearing

DR. BURMAN: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

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

relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

We have a total of eight Open Public Hearing announcements, and there will be four minutes for each. Speaker No. 7 will be speaking on behalf of the AMDA Society, will have eight minutes.

The first is David Hamlin.

MR. HAMLIN: Good afternoon. My name is David Hamlin. I am here today to speak on behalf of the United Pompe Foundation, Pompe patients and their families.

First, I would like to share our concern on the issue of approval of Myozyme from the 2000 liter scale and what it would mean if it were not approved.

I think everyone here knows that Myozyme in its current form is not the final answer in the treatment of Pompe. That being said, Myozyme has made a difference in the lives of Pompe patients here in the U.S. and many countries around the world.

Myozyme is vital to keeping patients as healthy as possible while a more effective treatment can be developed. For some of these patients, the effects of Myozyme have been minimal; for others, it has been more profound.

The sooner a patient can begin therapy, the better the results may be. We now have patients that have not been able to begin therapy due to Myozyme from the 2000 liter

scale not being approved for commercial use.

Although most of these patients are still able to walk and breathe on their own, this can change at any time. Many of us know that due to an accident, illness, or progression of this disease, a patient can go from walking and breathing on their own to being on a ventilator and wheelchair overnight.

While MTAP has allowed continued treatment, some healthier and recently diagnosed patients have not been able to begin therapy. Although MTAP allows patients to receive Myozyme from the 2000 liter scale at no cost, there are still associated costs and issues these patients face every two weeks.

Some MTAP patients have to travel hours to get to a center that is approved and absorb the costs of travel themselves or find some type of assistance, such as our organization, that will help cover these costs.

If the Myozyme from the 2000 liter scale is approved, these patients should be able to find a facility closer to home to eliminate the difficulties and burden of having to travel long distances.

Secondly, I would like to speak to this issue as a parent of a Pompe patient who has been treated on Myozyme

from both the 160 liter and the 2000 liter scale.

Our 20-year-old son Eric was one of the patients that was walking and breathing on his own one day and on a ventilator and not able to walk the next at the age of 13. Eric has spent considerable time on Myozyme from both scales.

Eric began receiving Myozyme through the Expanded Access Program in April of 2004 at the age of 16. It was our hope that Myozyme would at least stop the progression of Pompe. For the first 10 months of treatment, Eric received Myozyme from the 160 liter scale, and over the next 18 months, from the 2000 liter scale.

Before beginning ERT, Eric could not even support himself on his hands and knees. After being on treatment for 12 months, we started taking videos of his exercise to track his progress, if any. Since beginning ERT, Eric has made great gains in areas such as strength, pulmonary function and quality of life.

You can see some of his improvements in this video. One of the most important improvements has been in his pulmonary function. He has gone from 23 percent of normal to 45 percent, allowing him to be off of his vent for up to nine hours at a time. Eric is now able to walk 25 to

30 feet in his gait trainer.

Having been on each scale of Myozyme, Eric now has a promising future and is planning for it.

In closing, I would like to say after Eric has been treated and has shown improvement on both scales, I have absolutely no reservations in urging that the drug being produced at the 2000 liter scale be approved so that all patients can begin treatment.

Thank you for allowing me the time to speak.

DR. BURMAN: Thank you, Mr. Hamlin.

Mr. White.

MR. WHITE: Good afternoon. My name is Brian White. I am age 45, married, two boys 13 and 11, diagnosed with Pompe disease in 2003, and have been on Myozyme since the summer of 2006.

In response to your question, no is my answer.

I can't speak to you today about stratification, randomization, and those types of things. What I can speak to you about, though, is the devastating impact this disease has had on my life and my family, and the benefits I have had of being on Myozyme.

Up until about 2001, I was a normal person. I was playing basketball, I was camping with my kids and my

family, and the disease hit out of nowhere. Since then it has been a steady, steady degradation downhill.

Right now my forced vital capacity is 30 percent of what a person my size should be. I can't sleep without a BiPAP, I can't lie down on the floor to watch TV, to wrestle with my kids, play with my dog.

Life is hard. Walking to the restaurant last night was hard, sometimes even I have to think to remember to breathe. Sitting in church, driving a car, sometimes I say take a breath, Brian. So it's hard living with this disease.

My leg muscles and arm muscles are impacted, not as much, but also, I am weak, I can't squat down. My balance has become shaky. The impacts are not just physical also. They are also mental, it has affected my job, my self-confidence, even my self-esteem as I have tried to maintain my role in society as a parent with two children does. It has been a difficult process.

Right now 30 percent, I look at it as on the bubble. If I drop down to 20 percent, my quality of life, in my opinion at least, will be impacted dramatically. I probably won't be able to do the things I can still do. I will be into a world of, you know, 24-hour tracheotomy, and

things like that, and it is a world I don't wish to go to.

I started Myozyme in August 2006 when it became available commercially. I did not get into LOTS because of my low forced vital capacity. To me, it was a no-brainer, my life was just going downhill. It was the only choice I had. I didn't even think twice about it even with the possible side effects, I went in and did it.

What it has done for me, it has not--I don't play basketball anymore, you know, I don't do the things I used to do--but what it has done for me, it has stabilized me.

My forced vital capacity had bounced up to about 31 percent, I think it was 26 or 27 when I tried to get into LOTS, 30 percent was the cutoff. It stabilized that. It has basically allowed me to continue my life the way it is today, which is what I am trying to do and kind of what my goals are.

The enzyme has been a major, major benefit and it has allowed me to stay there.

In kind of concluding, I sat on a committee. I work in the natural gas business and I sat on a committee, and we developed some standards. And when it came time to vote--it took us about two years--when it came time to vote, the chairman, a wise man from Texas, looked at us and he

said, "Don't let great get in the way of good."

What he meant was we could work two more years on these standards and make them better. But he knew that, if we voted and approved these standards, they would be a great help in the natural gas business. We went ahead and we did that.

So, I guess that is kind of how I look at this process and your group. Don't let great get in the way of good. There may be future therapies that are better, but this thing, this therapy does a great, great service to us that need it.

Thank you very much.

DR. BURMAN: Thank you, Mr. White.

Ms. Eggers.

MS. EGGERS: Good afternoon. My name is Dianna Eggers and I am 48 years old. I am here on behalf of my brothers Ron and Scott and myself. We all have Pompe disease. You can't even imagine what it is like for our mother who has to watch all three of her children suffer from this devastating disease.

My brother Ron has been on Myozyme for two years today. For the first year he was on 160 liter commercially and now he is on 2000 liter for the second year under the

MTAP program. He has had no adverse events and has steadily improved continuously under both.

My brother Scott is not on Myozyme yet but hopes to be on it in the near future. It is extremely difficult for our family to watch him progress with this disease.

I have been on Myozyme for 2 years and 8 months, the first 2 1/2 years under LOTS and the extension study, and the last 2 months under MTAP. I was fortunate I was on the 2000 liter Myozyme from the start, and also had no adverse events.

My life before Myozyme was one of constant struggles to perform normal every-day tasks. It took tremendous effort for me just to go through my normal work day. My job as an accountant requires me to work 45 to 60 hours a week at times. I was slowly losing my independence and becoming dependent on other people to help me with my daily tasks at home.

My life now has changed dramatically. I have regained my independence, I am able to go shopping by myself and walk freely around the store without using a shopping cart. I am also able to work my 45 to 60 hours a week and still have energy to do outside social activities and hobbies after work and on weekends.

It is my hope that Myozyme is approved and will become available for my brother Scott and all the others that are waiting.

I thank you for your time.

DR. BURMAN: Thank you, Ms. Eggers.

Mr. Harvey.

MR. HARVEY: My name is Jeffrey Harvey. I am 38 years old and I have Pompe disease. I spoke at an FDA Advisory Committee meeting in February 2006 advocating the approval of Myozyme.

It was my hope then that Myozyme would be approved and that it would as least stop the progression of my disease. Myozyme was approved and I have been treated with it since June 2006. In June 2007, I started receiving the 2000 liter product through MTAP.

After I started treatment, my disease stopped progressing and I eventually started noticing small improvements. I started having more energy and experiencing less fatigue. About a year ago I realized that it had become uncommon, instead of the usual case, for me to have neck pain from strain at the end of the day.

These small changes, along with the preservation of the capabilities I had two years ago, in one sense seem

like a minor improvement. But, compared to the state I might be in if my disease had continued its progression, the improvements make a major difference in my current and future quality of life.

I am able to continue working part time. I rarely have to go to bed when I am not tired because of neck, back, or shoulder pain. I also hope that I will continue to see small improvements.

I know that right now with the 2000 liter product not approved, and MTAP not open to new patients, there is no way for new adult patients to start Myozyme therapy.

The thought that someone newly diagnosed and a condition similar to mine a couple of years ago might continue to deteriorate rather than potentially be stabilized and have small improvements that can have a large impact on the quality of their life is rather distressing.

I also have some apprehension for my own situation if the 2000 liter product is not approved. I don't know how temporary the Myozyme Temporary Access Program is. If I lose access to Myozyme, I don't know whether or how fast I might start to decline again, or if i will lose ground that I won't be able to make up.

I urge you to advise the FDA to approve Genzyme's

biological license application for the 2000 liter Myozyme.

Thank you.

DR. BURMAN: Thank you, Mr. Harvey.

Mr. Salbato.

MR. SALBATO: I have adult-onset Pompe disease. My entrance into the medical system began just out of high school when it was discovered that I had elevated liver enzymes from a routine blood test.

I was outwardly normal with no obvious signs of illness. Doctors could find nothing wrong and told me to get on with my life. But I knew something was wrong. Looking back, I believe it was in the fourth grade that I received the first clue.

I distinctly remember telling my mom that I had a headache and could not go to school so that I could avoid Field Day in which I would be forced to perform a sit-up in front of my classmates. I was always a poor runner, PE class, and particularly physical fitness testing were particularly traumatizing.

In my teenage years, I began having issues with fatigue and frequent headaches. As an adult, it had become more and more difficult to maintain normal levels of activity. Pushing myself too hard would lead to profound

fatigue.

The quest for self-understanding led me to spend countless hours in the medical library trying to determine what was wrong with me. My persistence led me to finally obtain a diagnosis more than four years later.

During this time, I began majoring in biology and I obtained in a Bachelor's and Master's Degree in biological science before working in biotechnology for five years. I am now working on my Ph.D. in a laboratory that studies gene therapy for Pompe disease.

I began my participation in Genzyme trials, first in May of 2004, with the LOPOS observational study, and then in November of 2005, I began LOTS. LOTS brought real hope that my life was going to get much easier. Convinced I was receiving placebo since I was not having any infusion reactions, I did not have any expectation for improvement.

After the third or fourth infusion, I began to notice something. I began to feel lighter on my feet and more invigorated. I could more easily raise my knee from a sitting position and felt strong enough to run again.

Eventually, I learned that I was indeed on treatment and I wasn't receiving a psychological boost but a physical one. I improved approximately 40 meters in the 6-

minute walk test at the 12-week assessment and began running the 10-meter time test. My CPK, a marker for muscle damage, fell by 30 percent during this time when it had previously been very stable over the preceding years.

My vital capacity remained stable or slightly improved and my maximum inspiratory and expiratory pressures have also improved slightly. People close to me have noticed that my gait has improved, and I seem to fatigue less easily.

In the nearly three years that I have been on Myozyme, I have not regained the ability to do a sit-up, nor do I have the endurance to run long distances. But I have maintained what I initially gained.

I think it is important for people to understand that even though I have adult-onset form of disease, I do not believe there is a discrete onset of disease. It has been proven that we can lose up to 40 percent of our muscle strength before it becomes obvious that something is wrong.

It may not be realistic to expect dramatic reversal of damage that has taken so long to manifest. I have been told that the adult-onset patient experience on Myozyme is that they tend to regain what they most recently lost. This has been the case for me.

If there is anything we have learned in the numerous ERT trials it is that it is easier to prevent than to reverse the progression of this disease. Myozyme has the capability to change the projectory of disease progression. I can only imagine how differently my life would have been had I started before pathological changes began to occur.

I feel that it would be a travesty if Myozyme 2000 liter does not get approved due to a lack of treatment response robustness. I think it should be up to the patients to determine what is clinically meaningful, and I personally believe my improvements are very real and very meaningful.

Thank you.

DR. BURMAN: Thank you, Mr. Salbato.

Krystal and David Hayes, please.

MS. HAYES: Hello. My name is Krystal Hayes. My main purpose today is to tell you how well my daughter Hayley responded to the 2000 liter product.

Hayley was diagnosed in June 2006 at the age of 6 months with infantile-onset Pompe disease. At that time, Hayley began infusions of Myozyme that was produced at the 160 liter scale. She received 32 infusions under the 160 liter scale Myozyme with significant cardiac improvement,

however, only minimal physical gain.

Because of this, Hayley was enrolled in a double-dose study where she would receive treatments weekly instead of every two weeks. During the year-long study, Hayley received treatments of alglucosidase alfa produced at the 2000 liter scale.

The study was completed in September of 2008 and Hayley's physical abilities improved remarkably in just 52 weeks. My first example of how her physical ability has improved is that after 6 months on the 2000 liter scale, Hayley passed the barium swallow study that she had previously failed twice. She was unable to eat by mouth for one year before passing the swallow study. What a joy it was when she could finally put food in her mouth.

Secondly, in Hayley's first year after her Pompe diagnosis, she became ill many times. During this first year, Hayley was taken to the ER three times with one requiring an admission to the hospital for pneumonia. She received antibiotics 9 times and had 3 rounds of steroids all within her first year of infusions.

Thankfully, since Hayley started infusions under the 2000 liter scale, she has only received antibiotics once and has had no ER visits or hospital admissions due to

illnesses.

Hayley has also been oxygen-free for over a year now. I feel that now Hayley's body is stronger and able to fight illnesses better than it used to. For the last month, Hayley has been attending preschool and has stayed healthy, and we all know how difficult it is to keep children well in that environment.

Next, I will talk about Hayley's physical improvement. Right before Hayley started infusions through the 2000 liter scale, Hayley could sit for a maximum time of 9 minutes, and if she began to reach for something, she would fall down.

Hayley was unable to get into or out of the sitting position independently. She could only bear weight on her legs for a few seconds and could not maintain the hands and knees position independently. Hayley would sit on a tricycle but not make any effort at pedaling and, when placed in a walker, she wasn't able to move it. Rolling was the only way she would go from one place to another.

At this time, Hayley can sit completely unassisted and can get in and out of the sitting position independently. She can scoot on her bottom to go anywhere she wants, and she is pretty fast, too.

Hayley can get into the hands and knees position and maintain it briefly, and also creep with assistance. She assist with pedaling a tricycle and came make about five pedal rotations on her own. She can also move independently in an adaptive walker for short distances.

As far as language goes, one year ago Hayley could only say "Mama." Now, Hayley can say well over 100 words and can even speak in four- to five-word sentences. Her lip closure is improving and her smiles are much more pronounced than they used to be.

The last point I would like to make is that Hayley's heart was severe affected before diagnosis, And, after receiving infusions through both scales of Myozyme, her heart has continued to improve, and is now very close to normal.

In closing, I would like to say that Hayley has benefited from both scales of Myozyme. But more physical gains have been noticed since she was put on weekly infusions through the 2000 liter scale.

On behalf of Hayley's entire family, we would like to say how thankful we are for Myozyme. Without it, we know we wouldn't have our beautiful little girl in our lives.

We hope the FDA will make the right decision in

approving the 2000 liter scale of alglucosidase alfa. If efficacy is the issue, then, Hayley obviously never regressed while being on the 2000 liter product. We have personally seen how effective this medicine is and how it has helped our daughter to become more independent and happy.

Please approve this medicine so that the adults with Pompe disease are able to receive treatment to improve their quality of life.

Thank you.

DR. BURMAN: Thank you.

Mr. Fox will now present. Mr. George Fox is representing the Acid Maltase Deficiency Association, and is speaking on behalf of many members of that society. Mr. Fox has been given up to 7 minutes to speak.

Mr. Fox, please proceed.

MR. FOX: Thank you.

Good afternoon. My name is George Fox. I am here today to speak on behalf of the Acid Maltase Deficiency Association or AMDA. I will also be speaking on behalf of some of the late onset Pompe patients that couldn't make the trip.

As you can see in the video here, are some of the

faces of the people that are affected by Pompe disease, as well as you will hear a piano being played by Johan Barker, who also has adult-onset Pompe disease and is on the 2000 liter Myozyme.

My son Phoenix has Pompe disease and is currently receiving Myozyme manufactured in the 160 liter bioreactor. Even though this therapy has not been perfect, it has corrected his cardiomyopathy, which I feel has enabled him to still be alive and with us today.

I feel it is important to note that even if a treatment is not 100 percent perfect, if the treatment allows a patient to spend their life with the ones they love, then, they have been given the most precious gift of all, the gift of life.

I feel that the same situation applies to the adults who are receiving Myozyme manufactured in the 2000 liter bioreactors. These are individuals who have no other treatment option at this time. Without any type of treatment, these patients will most likely die or have to endure invasive ventilation well before they have had a chance to live their lives.

If you are affected by Pompe disease, you may notice the progression when you begin to have difficulty

climbing a flight of stairs or losing your breath while running with your friends. It is not long before you sense that walking becomes more difficult.

Soon, all of the things that used to be simple are now labeled as tasks. During this time, these individuals may have noticed that breathing has become more and more difficult with each passing week.

After many tests and sometimes years of not knowing what is wrong, you are finally given the correct diagnosis of Pompe disease. Unfortunately, some will never get diagnosed correctly, and there is a good chance they will die of respiratory failure from an unknown condition.

Thankfully, with the advent of 2000 liter Myozyme, those who are correctly diagnosed with late onset Pompe disease now have renewed hope in the form of a proven product. This is a treatment that has been shown to help many in the U.S. and around the world.

In the international Pompe community, there are many blogs and e-mails from people diagnosed with Pompe disease who talk about how much better they feel and how much more energy they have after starting Myozyme from the 2000 liter reactor.

Some people state that even though they may not

feel a huge difference in strength, they may be able to use their BiPAPs less or sleep better throughout the night. There are other people who say they are able to come off their ventilators a couple hours a day, which I feel is an incredible feat.

I can tell you from firsthand experience there is nothing more deafening than the sound of a ventilator being turned off. My son is able to come off his ventilator about an hour or so each day. When the continuous sound of artificial ventilation suddenly stops, you immediately think something is wrong even if you were the one who turned the ventilator off.

When this happens, the person diagnosed with Pompe disease is then able to leave the ventilator behind and even if for a brief moment, not have to rely on a machine to live, I personally cannot think of a more liberating feeling.

Even though some affected by Pompe disease state that they don't feel any stronger with treatment, they quickly mention they are not getting any weaker either. For these patients, to know that this horrible disease has stopped its downward progression is an incredible thing indeed.

Instead of slowly sinking into the confines of a wheelchair and ventilators and likely an early death, most late onset people with treatment with 2000 liter Myozyme are able to stand their ground and ward off the unruly consequences of substrate accumulation.

If the 2000 liter treatment stops disease progression, and is safe and well tolerated, then, it needs to be approved for use in the United States. This 2000 liter treatment has already been approved in many other countries.

Being able to increase production of Myozyme is very important for the future of these enzyme replacement therapies. It is imperative that these products be produced in larger capacities so that not only can more patients be treated around the world but that, ultimately, we can bring down the cost of manufacturing these drugs.

These benefits can then be passed to the next generation of people with rare diseases. Currently, the 160 liter product cannot supply the adult patient population, and the Temporary Access Program hasn't enrolled patients for almost a year.

As of right now, the 2000 liter product is the adult patient population's only option. So I ask you to

find it in your hearts to help bring this drug to the people who desperately need it.

Now, I also have a couple of quotes here from some patients affected by Pompe disease, who wrote in to me and said here is our quotes, and these are people that are on 2000 liter product from around the world.

For instance, Cynthia in Australia writes, "Myozyme gives me small steps forward and none going back."

Joyce Rapp says, "Myozyme has improved my energy and stamina. For example, I am able to walk farther than I was prior to starting treatment, I no longer fall like I used to."

Trevor Paret, in Canada, says, "Without Myozyme, I would definitely not be here today. Myozyme saved my life."

Hilary, in Oregon, says, "Myozyme helped me get back on the ski slopes."

Helen Walker, also in Australia, says, "I am now able to plan for the rest of my days, living by myself, in my own home, looking after myself, all because I am treated with Myozyme from the 2000 liter vat."

Bob Morrison says, "How about Myozyme doesn't seem to be doing much; that is, until I stopped taking it."

Rebecca Brooks writes, "Myozyme delivering me from

a life of compromised dependence and pain to a vital expressive contributing active life of renewed possibilities."

So, I would say that these are the reasons why Myozyme needs to be approved, and these are the people you need to be thinking about when you make your decision.

Thank you.

DR. BURMAN: Thank you, Mr. Fox.

We have one more presentation by Laura Case.

DR. CASE: My name is Dr. Laura Case. I am a physical therapist, and I am on faculty at Duke University. I have been a physical therapist for almost 30 years, 30 years next month. I have worked with individuals with neuromuscular disorders my entire career, and I have seen many patients with Pompe disease.

I do have disclosures to make. I have received honoraria from Genzyme Corporation in the past and am on the Pompe Registry Board of Advisors. I received no support for coming to this meeting or attending.

I am here today, not to report any research data or to comment on it, but simply as a voice from the clinic to speak to what I have seen over the years in terms of the devastation of the natural history which you have heard

about and the benefits that I have seen in individuals on enzyme, and to express my concern for the individuals with late onset Pompe disease who currently don't have the opportunity to consider enzyme replacement because of the limited quantity.

I, too, have seen children who were so weak they could barely move and whom I could not help and have seen children with infantile-onset Pompe on enzyme that can now walk and run, which has been extraordinary. It has been unparalleled in my career.

I have also seen adults in whom the progression of disease has led to a loss of ambulation and significant disability, and have seen adults on enzyme who report to me decreased pain, decreased fatigue, increased function, an increased ability to participate.

To me, as a physical therapist, that is significant because I firmly believe that in the presence of a disorder in which the natural history is progression, even stabilization is an improvement.

I am really just here to voice my support for individuals with Pompe disease, to voice my support for the physicians and scientists working to find answers, and to support the FDA in their quest to take good care of

patients, in the hopes that someday and, hopefully, someday soon, all individuals with Pompe disease who are interested in enzyme replacement will have the opportunity to make that choice.

Thank you.

DR. BURMAN: Thank you very much.

I personally would like to thank each of the participants on behalf of the committee who participated in the Open Hearing Session. Thank you very much.

We are ahead of schedule a little bit and, with your permission, we will take a 15-minute break. I have 2:25, and we will reconvene at 25 to 3:00 and have the discussion.

[Break.]

Discussion and Questions

DR. BURMAN: I would like to call the afternoon session to order.

We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

I would also like to mention that we will try to get all the business done and adjourn by 5 o'clock. Many

people have planes and transportation they have to meet.

We certainly want an active, full discussion, but also would like it focused on the questions that have been derived by the FDA. What I would like to do is I am going to introduce the first two questions and read them, and ask for Dr. Pariser's clarifications, if that is okay.

With regard to the first question, the preamble is that the 160 liter product is the only commercially available alglucosidase alfa treatment in the U.S., and it is indicated for the treatment of all forms of Pompe disease. The 2000 liter product was not found to be comparable to the 160 liter product and, therefore, deemed to be a different drug.

Only a single study exists to support the effectiveness and safety of the 2000 liter product in the treatment of late onset Pompe disease. To provide substantial evidence of effectiveness, FDA's reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect, such as mortality, and is statistically very persuasive--i.e., has a very low p-value that indicates the result is highly inconsistent with the null hypothesis of no treatment effect.

FDA believes the 6-minute walk test is the relevant parameter for deciding the efficacy of the 2000 liter product. The results of the analysis between 2000 liter product and placebo for the 6-minute walk test at the end of the study, adjusting for baseline and based on rerandomization inference using ANCOVA, gave a p-value of p equals 0.06.

Furthermore, after an initial look at the data, the Applicant changed its statistical analysis of the 6-minute walk test. The Applicant has proposed alternative statistical analyses that were discussed at this meeting.

Although the change from baseline in percent predicted FVC appears statistically significant, it was not the prespecified primary endpoint. Based on the Applicant's statistical analysis plan, the formal hypothesis testing of FVC was not to be performed if the 6-minute walk test analysis failed to reach statistical significance.

Additionally, the use of FVC is not a recognized clinical benefit endpoint, nor is it a validated surrogate marker in Pompe disease.

Question No. 1 is a discussion question, a vote and a discussion question, and Question No. 2 is related as a discussion. So I will read both if that is all right.

Question No. 1. Do you believe LOTS has established the effectiveness of the 2000 liter product? We will vote Yes or No after full discussion.

a. If not, should an additional study be conducted to determine whether the 2000 liter product is effective in treating late onset Pompe disease?

b. If additional study is recommended, should a head-to-head study versus the 160 liter product be conducted, or an alternative study design? We will discuss that.

Question No. 2. Please consider the following decisional options for the 2000 liter product and state which option, based on the evidence presented, is most appropriate. We would like to choose a, b, or c.

a. Not approved. If no approval is recommended, then, the 2000 liter product can be made available to adult-onset patients under a treatment IND, whereby the Applicant may charge for product as part of the conduct of an additional study or studies. These studies would be conducted to further evaluate the 2000 liter product. We will discuss that.

b. Approval under Accelerated Approval, Subpart E, whereby the 2000 liter product can be approved using the

FVC as a surrogate endpoint reasonably likely to predict clinical benefit, and a verification study to demonstrate clinical benefit of the 2000 liter product would be required of the Applicant during the post-marketing period.

If you believe this is the most appropriate decision, please recommend a study design for the verification study, such as head-to-head comparison versus the 160 product.

c. Regular Approval based on the 6-minute walk test findings in LOTS.

Those are the first questions that we are going to discuss.

Paul recommends that we should No. 3, as well.

Question No. 3. If an Accelerated Approval or a regular Approval is recommended, please consider the following:

a. The LOTS trial enrolled an inadequate number of patients with juvenile-onset Pompe disease. Only four patients were under 18 years of age at the time of enrollment, one of whom was exposed to the 2000 liter product, one patient aged 16 years.

Only nine patients in LOTS developed symptoms and were diagnosed with Pompe disease under the age of 18, six

of whom were exposed to 2000 liter product. Should the indication for the 2000 liter product be restricted to the adult-onset population only, i.e., patients who were diagnosed and had symptom onset over 18 years of age? We are going to vote Yes or No on that.

b. If you recommend approval for a restricted age group, adults only, what safeguards should be implemented to avoid use of the 2000 liter product in patients less than age 18, such as communication plans or restricted distribution? See attached REMS template.

c. Should additional studies be required as post-marketing commitments to assess efficacy? Vote Yes or No.

If Yes, please describe the design of the studies.

d. Should additional studies be required as post-marketing requirements to assess safety? Vote Yes or No.

If Yes, please describe the design of the study.

Dr. Pariser, would you like to make any clarification points or comments?

DR. PARISER: Just the same clarification, I guess, we made at the start of this Open Session, is that the data presented in the LOTS is the data that we need to use to make the determination of effectiveness and safety, and that FDA has not vetted and reviewed some of the other

data that was presented.

I just wanted to provide that clarification.

DR. BURMAN: Thank you.

Any other clarifications by the FDA?

[No response.]

DR. BURMAN: I think what I would like to do is open the floor for discussion, focusing on the questions and the issues that we want to discuss, and hope for an active interesting discussion.

Yes.

DR. PACKER: I have two questions, one, I think first to the FDA, and the second to Genzyme representatives.

The question to the FDA is concern about the analysis of the juvenile onset or the younger onset patients. Even though you defined the juvenile onsets of having symptoms before a certain age, many of them didn't receive treatment until later.

So, how are we going to use the data to assess that--if they would have gotten treatment at an earlier age at a juvenile point, they wouldn't have benefitted since we have no data for that, and isn't it sort of a self-fulfilling prophecy if you say, well, you take someone who had juvenile onset that may have worse disease, delay the

initiation of treatment and then think that any therapy is going to be of any significant benefit?

DR. YAO: I would first state that I think that that is true. I think the data that have been presented clearly show that beyond a certain point, we are not going to expect to see very much improvement. If we get stabilization, I think that that is what we would all hope for.

I think the point about the juvenile onset--and again the age cutoff is admittedly arbitrary and really used as much as a definition that we sort of use clinically in medicine to define the difference between an adult, say, and a child. But I also think that what we are really looking at is how many patients were actually studied, that we can actually say we looked at this group.

That is what our big concern is with the LOTS protocol is heavily weighted towards older patients. So, if we are going to approve the 2000 liter product, I think it is important to know that there really are no data out there.

The infantile treatment group, which was the 1602 study, studied infants, and the LOTS trial studied, you know, the mean age was 45, as you saw, 8 patients total

under the age of 30. We have a whole group of patients there that we just don't have any data on.

So, we can argue what might happen, but we just don't know.

DR. BURMAN: Dr. Yao, if I might, correct me if I am wrong. When the FDA approved Myozyme two years ago, there were 18 patients who were infant onset, and yet it was approved for juveniles and adults without any data in that group.

DR. YAO: That is correct. Again, I think the fundamental difference between the initial approval and what we are talking about right now is that at the time that 160 liter product was approved, there was no other treatment available.

So, even though the data were only obtained in those infantile-onset patients, and there were only 18 patients, the benefit to those patients was clear, and we wanted to make sure that patients, all Pompe disease patients received access.

The difference in this situation is that we have an approved product, we have the 160 liter product that has been approved in this country for use.

DR. PACKER: But it is not available. Is that

true, it is not available?

DR. YAO: That is correct.

DR. PACKER: So, what is the benefit if it's--I am raising the question--what is the benefit if it is approved but not available?

DR. PARISER: Well, right now the 160 liter product is being made available to patients less than 18 years of age here. I mean it is approved for all patients. We are not suggesting that juvenile patients not be treated, but, right now the juvenile patients, those under 18, are being treated with the 160 liter product. It is those over the age of 18 that are receiving 2000 liter through the MTAP program although not all patients are receiving it.

DR. YAO: I also might add on to what Dr. Pariser has just said. The MTAP program was specifically opened and was treating patients over the age of 18 with 2000 liter product, and Genzyme--please correct me if I am wrong--have stated that the availability of 160 liter product for patients under 18, the current supply is okay there.

DR. BURMAN: Could I ask--that is an important point.

DR. PACKER: I would love to hear that clarification.

DR. BURMAN: Yes.

DR. BEITZ: I just wanted to clarify on the indication statement.

DR. BURMAN: Sure. I think Genzyme is going to answer that one question, if we might, and then let us go to you, the availability of 160 and 2000 for each group.

DR. McDONOUGH: My name is Jeff McDonough. I believe the question is regarding the sustainability of supply for these various populations in the United States.

What was said this morning, just to clarify, is that for a definition as was proposed in our indication for the 2000 liter material, 24 months of age with no cardiomyopathy as being those patients eligible for 2000 liter, or another way of saying it, the 160 liter material would be reserved for infantile-onset patients with cardiomyopathy aged younger than 24 months, we could supply using the 160 liter material indefinitely for that population.

If we were asked to supply the totality of patients who are aged 18 years or younger today with the 160 liter material, we would not have a sustainable way to provide for that population going forward. We would not have either the current inventories or manufacturing

capacity to provide for that population going forward.

Does that answer the question, Mr. Chairman?

DR. BURMAN: Yes. Thank you.

Dr. Beitz, did you have a question?

DR. BEITZ: I just wanted to clarify what was said about the approved indication for the 160 liter. I think we showed in FDA Slide No. 7 that the indication statement actually clarifies the limitations of the data that we had and also states that use in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy. I just wanted that in the record.

DR. BURMAN: Thank you.

DR. PACKER: And I had that one second question. Could I do that? It is more to Genzyme. We heard a lot of the data they presented. But then it was also mentioned briefly that the quality of life data did not show any difference or was not useful in the evaluation.

Could we get a little bit of update? We have heard a lot of families and groups talk about how this has affected their lives. What were the results of the quality of life data on the 2000 trial and, if it didn't show benefit, why do you think it did not show a statistical benefit?

DR. SKRINAR: Alison Skrinar, Genzyme Clinical Research.

Slide on, please.

[Slide.]

As a secondary endpoint, we looked at the SF-36 PCS score, physical component summary score, looking at the impact of treatment on physical health status. From the baseline mean scores, you can see that these patients are 1.5 standard deviations below the mean, indicating that by SF-36, PCS score standards that are 1.5 standard deviations below the mean, they are diminished in terms of their physical health status.

However, we do not see an increase in the Myozyme group or a decrease in the placebo group using this instrument. We believe that this is because (a) it is not a disease-specific instrument, (b) were likely to be underpowered relative to other studies that have been performed to demonstrate the effect of treatment using the SF-36.

Finally, and we believe most importantly, that we have stabilized the walking ability and pulmonary function in these patients, and the magnitude of the changes that we observe are not likely to have the patients perceiving a

difference but that the value is in preventing the progression of the muscle weakness.

Now, I would like to just ask very briefly, Bob Leshner, one of our investigators, to comment on his experience.

DR. BURMAN: I think we are okay for the moment unless the committee wants to hear that. I think we are okay. Thank you, though, very much for that clarification.

Dr. Proschan, you had a question, as well?

DR. PROSCHAN: Yes. I am wondering, is Dr. Wei still around? Good.

I was a little taken aback by the rerandomization analysis because I didn't see anything on that in the briefing package. So it was kind of surprising to see this. You know, proponents of minimization have argued that you could use this kind of approach, that it would be a valid thing to do. And yet your slide CC62 seems to show that even if there is no treatment effect whatsoever, you get a mean that is not zero. It is something positive.

I am wondering, is the issue here being caused by the 30/60 randomization or the fact that you are using an ANCOVA that is adjusting for imbalances? I mean are the people who say that it is valid to do this just wrong?

DR. TANDON: P.K. Tandon from Genzyme. I just want to clarify this issue about rerandomization. We just came to know a few weeks ago about FDA's cushion on this thing when they asked to do analysis on ANCOVA using rerandomization tests.

Dr. Wei.

DR. WEI: Thanks, Mike, for the question.

First, I would just like to emphasize one point so we are all on the same page for the ANCOVA, which is to measure the changes, right, from time zero to the last observation.

The conventional method p-value is 0.035, the rerandomization test p-value is 0.06.

[Slide.]

Michael, if you look at this picture on the screen, think about it. If there is no difference between the two groups, so the difference of 2 means or the change is identical to zero in a population sense.

Your statistical value in the expected sense should be zero, otherwise, it is bias. So, here is one situation we don't have like toss a coin, complete randomization, or even like permit a block design. We use the so-called minimization rule. That is what caused this

problem. The center is now zero, so I cannot say this guy is on bias test even, it looks like it's a bias test.

Does that--

DR. PROSCHAN: So, you are saying even if you just did a simple T test, you would have this problem?

DR. WEI: Yes, yes. You could do simple T test, 2 sample T tests.

DR. PROSCHAN: Because I mean the proponents of minimization have said that you can analyze it this way, because opponents of it have said hey, I don't know how to analyze this data, it is not really randomization, and the proponents have said well, you could analyze it this way. But you are saying that is just not right.

DR. WEI: Well, Michael, you need enough randomization in the location rule to assure me you have enough room to break up the response sequence and that you realized assignment but, because of this minimization rule, we cannot break them up. So that is the cause of the problem. Thank you.

DR. BURMAN: Thank you.

Dr. Joad, did you have a question?

DR. JOAD: Yes. I just wanted to ask the person from Genzyme who was talking about feasibility for the 160

product, is there enough of it that you could do a study in the age 2 to 18-year-old, if that was something we would want? That is the group that really hasn't been studied at all yet, and I am not talking about everybody who needs it but enough for a study comparing the 2000 and the 160.

DR. MEEKER: David Meeker, Genzyme.

I think there is sort of two questions. One is what is the goal of that study, and so we can address that separately. Comparing the 2000 and the 160 in a head to head, the size of that trial we believe would be in excess of 500 patients to show a non-inferiority design that there was no difference. That is something that we absolutely could not supply with the 160.

There are approximately 70 patients under the age of 18 now, and that is a pool that will grow. And our point is, is that with our current 160 liter supply, we could not indefinitely supply that population or allow an increased number of patients to come into that pool, where as Dr. McDonough previously stated, using the biologic definition for an infantile onset of hypertrophic cardiomyopathy with onset of symptoms less than two years, we can commit fully to treating that population. So we would not be able to do the trial.

DR. BURMAN: Thank you.

Ms. House.

MS. HOUSE: Hi. I had a question about going back to the classification of juvenile onset. The FDA classifies infantile and juvenile, adult onset. But Genzyme just went with infantile and late onset.

I would like for maybe Dr. Kishnani or Dr. van der Ploeg to address the FDA's breakdown and what they think about it, should it be broken down like that. And, on Slide 48 of the FDA's presentation, where they talk about how to break it down, is that even a proper way to break it down or would you advise something different.

DR. KISHNANI: Priya Kishnani, Duke University.

I think that the definition of infantile Pompe is very clear. It is patients who presented the first year of life with the hypertrophic cardiomyopathy. Any patient that presents after the first year of life or even if you want to take a conservative approach, after the first two years of life, it is a continuum of disease spectrum.

They do not have the cardiac involvement. Their primary symptoms are skeletal and respiratory muscles, and the cause of death or disability in these patients is really due to respiratory failure.