In the infants, the real cause of death is cardiomyopathy and the progression of it. So, to us, as treating clinicians, we prefer to think of this as a continuum, as one part of the disease spectrum. Juvenile, adults all are late onset Pompe disease patients.

DR. BURMAN: Would the FDA like to respond?

DR. van der PLOEG: My name is Ans van der Ploeg. I am a pediatrician in metabolic diseases and Clinical Chairman of the Pompe Center in Rotterdam. We are currently treating 90 patients with Pompe disease.

I am involved in the research in Pompe disease since 1985, and we treat patients with Pompe disease for the last 10 years. Of the 90 patients we treat, 20 are children, and that are infants and children.

I would like to say two things. First, the question of Tiffany, juvenile patients, indeed, I completely agree with Dr. Kishnani, is a spectrum of disease, and indeed it is true some of the juvenile patients have a more severe form of the disease since it is a spectrum.

We also have shown in a large survey that we conducted with the International Pompe Association, that a subset of the patients below 15 years of age have a more severe form of the disease. But the majority of children,

and, in fact, 50 percent of the children, have the same set of mutation as the adults with Pompe disease and, in fact, there is a spectrum.

We have also shown that the onset of disease and the time the patient becomes wheelchair dependent and ventilator dependent is dependent on the age of onset, so the disease duration.

In fact, it is really spectrum. And, in fact, if you are a juvenile patient who presents with symptoms at 16 years, and you become 24, then, you are still the same patient. And when you are at 24 and starting to have symptoms with the same set of mutations, you are growing older. So it is really a spectrum of diseases.

I would also say something about patients with juvenile form of disease that we treated as part of the pediatric LOTS study. That was a study that started, in fact, in February 2005. Five patients were enrolled. This was a Genzyme-sponsored study. It was a study that lasted for 1 1/2 years and after that it was an investigator-driven study.

In this trial, five patients were enrolled, age of 5 to 18 years. These patients were ambulant and had proximal muscle weakness. What we found in these patients

is, first of all, and I think that is very important in this respect, is that the patients tolerated the enzyme well and maybe you have a slide here that I can present. Slide on.

DR. BURMAN: I think we really would like you to be very succinct. I appreciate you coming, but please finalize your comments.

DR. van der PLOEG: My comment is here, that in effect, and if the slide is on--

[Slide.]

The effect you see, here are the patients, 5.9 to 15 years, and you see the age of symptoms, 1.1 to 11.6. But I would like to have the second slide because I think that is the most important one.

[Slide.]

Patients were exposed for 74 weeks and, in this trial, none of the patients has infusion-associated reactions, and the highest titer that we found in these trials was 6,400 in this trial.

So, still after 3 years there are no infusion-associated reactions, patients did not deteriorate over the last 3 years, and there were 3 patients with a low pulmonary function who continued to show age-related improvement, and one showed a significant improvement from 57 to 75 percent

FVC.

DR. BURMAN: Thank you for coming.

Dr. Pariser.

DR. PARISER: We certainly agree that there is a spectrum of disease and where you draw the line, I don't think anybody knows. What is described in the medical literature is not a general classification of late onset, but childhood, juvenile, adult, although the definition of that really varies depending on who you ask.

Our concern is--and I will echo some of the comments that were just made--is that the younger you are when you are diagnosed, the tendency is for the disease to progress more rapidly.

So, what we have is an information vacuum, what do you do with the 3-year-old, the 4-year-old, the 5-year-old, who tend to have a much more rapidly progressive disease as opposed to the patient who is diagnosed at 20, and would tend to have a more attenuated progression.

This, we don't have any information on but that did lead to our concerns about the noncomparability of the products.

DR. BURMAN: Thank you.

I would like other members of the committee to be

involved and raise any questions or comments that they have.

Eric.

DR. FELNER: I mean I guess is the age, this 24 months that the sponsor has put on, I guess the age for the 2000, is that FDA driven or is that driven--because I mean I don't think you need an age especially, I am in pediatrics, so we are the last to get any medications approved and they are always approved for the adults.

I think in this case what is much more important is the progression of the disease in the 3-year-old. If they don't have cardiac disease, they don't have infantile onset. I think everybody has explained that to us today, and I think it is something that we should all take.

So, if the patient doesn't have cardiac disease, I think we should be at least looking at the question of can they get the 2000 liter regardless of what their age is, knowing that it is likely going to be 2 or above, or 1 1/2 or above.

So, can we make that as part of the question? I think it would make it easier for me to be able to vote on this, is if you can say any patient that doesn't have cardiac disease regardless of age should be able to get the 2000 liter.

DR. BURMAN: When you say can get it, you mean from a production standpoint or from an FDA standpoint?

DR. FELNER: I mean at least as Genzyme has explained today, if you take the 18 and below and you say all the 18 and under can have 160 liter, they are not going to have enough product for that. They have explained that, this is the problem.

So, simply put, if we think that the 2-year-old and the 3-year-old have the same disease as the 30- and 40-year-old, which it sounds like from the experts that they do, they should all be lumped into the same group.

At least that would be my opinion. I think it would be much easier to vote on this and make sense of it in a condition that is very progressive--and you don't have a lot of time to see benefits. But I think that would make it easier.

Cardiac disease, 160 liter, that has been well shown biochemically from the bench research to the clinical patients, and then anything not cardiac 2000 liter. I think that would be easy to vote on, easy to understand.

DR. BURMAN: Dr. Pariser.

DR. PARISER: The 24-month cut point did not come from us. That was Genzyme's suggestion. If you are looking

at the classic infantile, it's the patients that are diagnosed at less than 6 months of age with cardiomyopathy. So, if you are looking for a continuum, it would pretty much have to be 7 months and up without cardiac involvement. But just what we are seeing and what I think the literature does support is that the younger you are when you are diagnosed, your disease does tend to progress more rapidly.

DR. BURMAN: Dr. Felner, if we followed your suggestion, there really, as was pointed out in the last study, there are very few, quote, unquote, "juvenile" patients who received the medication, the 2000 liter.

DR. FELNER: There are few, but I mean again maybe this is because I am in pediatrics and we see this commonly, we never get the medications. We don't get them approved, and so, if you want to wait, obviously, you want to try to get studies done, I think it is going to take time. But I don't think there is enough--I mean in many things we do in pediatrics, we have to rely on adult data.

Whether it be time issue while we are waiting for the post-marketing studies or some other study to be performed, I think why not let the 2-year-old have it who may even have much more of a chance for benefit than the 10-year-old, or the 1 1/2-year-old, however way you want to

look at it. But I think that it's hard to exclude.

I think all the non-cardiac should be grouped into one group. We know there is no data on it. But this is not a condition like--I mean this is a progressive condition, this is not a well, the morbidity is a little bit and, eventually, it will be recovered when we finally get the medication approved.

DR. BURMAN: Dr. Teerlink had a question first.

DR. TEERLINK: Actually, I have three questions. The first is a multi-part one in regards to the 6-minute walk test. We are obviously being asked to look at treatment effect size here that is about 28 meters.

Coming from the cardiovascular arena with pH, drugs were approved on the basis of the 70 meter, in which 70 meter was in the small study, and then, when they did the 200 to 300 patient studies, that treatment effect, as often happens, decreased down to 40, 44 meters, and was approved.

So, I am a little concerned that in small studies, treatment effects tend to be amplified, and we are already dealing with a relatively marginal treatment effect here. In a small study that may or may not be really truly representative of what a larger study would have been if one were to be able to be feasible.

The issue that I have is what about unblinding effects in terms of the infusion-related adverse effects. The 6-minute treadmill is a self-limited treadmill. It is relatively objective but is potentially affected by unblinding. That is one part of the question.

The second part of the question is I am still trying to struggle with Dr. Wei's and the FDA's interpretation of this rerandomization. My current feeling of what Dr. Wei basically said is, basically, he said that based on the distribution because of the strange randomization scheme, we basically cannot distinguish between the effects due to randomization and the effects due to the treatment.

So, if you are basically saying that, then, that means that the data set that we are working with is so hugely confounded by this randomization scheme, that whatever treatment effects we are seeing can't be interpreted.

Now, I would love to have you help me out of this. But, as of now, that's where I am at.

The final thing is the ANCOVA that presented includes the last observation carried forward, which in general is biased towards treatments especially if there is

a dropout among the treatment group.

So, have there been sensitivity analyses, which include worst case imputation for the 6-minute walk test in the worst case scenario? That's the first question.

DR. BURMAN: Dr. Yao, do you want to address that?

DR. YAO: Shall we go with the first part of the question first? Okay. I need Slide 53.

To start answering the question, yes, we were interested in the effect of a possible unblinding in effort-based activities like the 6-minute walk test and we looked at it from two different perspectives.

We looked at it the first way, which was to say in patients who dropped out of the study or discontinued, there were actually 4 patients who withdrew from the study based on the--the direct quote is "wished to receive commercial product," and one could speculate that the reason that they withdrew from the study because they wished to receive commercial product, they believed that they were not receiving the treatment.

If you look at the 6-minute walk test in those 4 patients, actually, 3 of them were placebo treated and 1 was Myozyme treated and their average 6-minute walk test was minus 28. So, that suggests that from one end.

The other end, which is also interesting, is patients who actually perceived maybe that they were receiving treatment, we heard a gentleman in the open session discuss the fact that he didn't have any infusion reactions and he thought maybe he was in the placebo group.

Well, we looked at that, too, we looked at patients who had numerous infusion reactions and our cutoff was basically just 10. We said anybody who had more than 10 infusion reactions, let's just see what is going on there.

In fact, there was one placebo patient and I think it was three--let me just double-check--there were five patients that had more than 10 infusion reactions, four in the treatment group and one in the placebo group. The one patient in the placebo group who had more than 10 infusion reactions improved by almost 60 meters, 59.2 meters.

Again, these analyses are not presented to imply that they are in some way significant. But I think they point to the fact that this is a difficult test to interpret.

DR. TEERLINK: But your sense is that the unblinding due to infusion related adverse events is probably not a major contributor to this, is that correct?

DR. YAO: Correct.

DR. WEI: I only had 5 minutes. I have done this research for 15 years. I am really pleased that you actually catch the meat of the whole problem.

You think about this clinical trial. After you have 90 patients to finish up, you have 60 treated, 30 in the placebo, how do we make an inference out of this 90 patient data? You have a different way to look at this data, right?

A very important part is how can I use this 90 numbers to make a future inference? That means I have a future patient I want to treat. Do you really believe there is something for future patient, or you only worry about this 90 patients?

Of course, I worry about future patients. Rerandomization tests, there is a fundamental problem. That means you fix this 90 patients' responses, you rerandomize those guys and you ask yourself, for those 90 patients, is there a difference between the two groups, which is the 30 against the 60.

So, anything you come back. The only thing you can answer, do you think for this 90 patients do we have any difference between the two groups, which to me is not very interesting in some way, because I really wanted to make the

inference for general populations. Sorry, go ahead.

DR. TEERLINK: But the answer to that question that you just posed is based on the data we have on those 90 patients, we can't make an inference between whether there is an effective treatment difference.

DR. WEI: No, no, no. Based on rerandomization tests, we cannot tell, but you have to go back to the fundamental conventional method. For example, just T test, you have 60 numbers, 30 numbers, you compare two means, like Michael said, let's perform a T test. If my T test value is 2.15, I say what is the p-value. I said greater than 1.96.

In this case, it's 0.035.

DR. TEERLINK: I am far from a statistician, but my understanding is that the reason they did the rerandomization scheme is because the T test is not necessarily appropriate in this setting because there wasn't truly a randomization, that there was a minimization allocation procedure, which violates some of the assumptions of a T test. So, consequently, the rerandomization procedure was invoked--

DR. WEI: No, sir; sorry

DR. TEERLINK: --by the FDA.

DR. WEI: Sorry. Can I answer you before FDA

answer it? The fundamental assumption for our clinical trial--you have 90 patients. You are assuming those 90 patient is a random sample of a well-defined population, so all the conventional method is built on this assumption.

So, you can argue, say this 90 patient may not be a well-defined sample from a population. That's why people are wanting to do the rerandomization test. Even we use a minimization rule, allow the patient to the placebo and drug group. There is no bias in multi-center.

Think about it, you have eight centers internationally, right. You have such a complex allocation rule and they actually give you the assignment rules to centerize, somewhere in United States. So, this lady is so smart, she cannot even figure out what is the assignment rule. So, basically, there is no bias involved even when we use a deterministic minimization rule.

So, minimizing rule is commonly used for this setting. This is no violation for my conventional inference unless you argue with me and say hey, listen, this guy is not a random sample from a well-defined population. Then, we will say what are we going to do here? We have 90 patients, and you cannot make an inference.

DR. BURMAN: Thank you. I think there are a lot

of statistical questions. But let's move on.

DR. TEERLINK: I will give up. The second question was actually going to be on the unblinding effects of the FVC. Finally, one of the big issues for us is to try to help, you know, approve drugs that will help people feel better, live longer. And we have no evidence in this study that helps people live longer. So then the question is does it make people feel better.

We have already seen the SF-36 data which said it did not help make those people feel better that way, and one of the criticisms of that was that it was nondisease-specific. I think actually one of your panelists may be at the center that has done some of this work, but there is the Rotterdam Handicap Scale, which was presented in an article by Hagerman from Rotterdam suggesting that it is a relatively disease-specific measure of patient reported outcomes. I would be interested in seeing--and I know that was measured during the study--so I would be interested in seeing that, and secondly, the fatigue score.

DR. KAMMERMAN: There are two questions still that are outstanding. One was the LOCF and the worst case scenario. I agreed that totally can bias the results. I haven't looked at it yet. I don't know if Genzyme has or

not, but that definitely needs to be looked at.

With respect to rerandomization, the ideal scenario would be to list all the possible allocations. So the common one would be if you have 4 subjects, list all possible outcomes, and then compare what you have to the distribution.

So, that is probably almost an impossible task. That's why we have the rerandomization. Presumably, it represents what we would see with all allocations. But it is hard for me to believe that we can use classical tests in this situation because we didn't randomly select from the pool of patients.

They came in a certain order, and that needs to be reflected. There are constraints on the randomization, the probabilities, different strata, and so on.

I am wondering, perhaps, if there was a programming error. I don't know if you have looked at that, if you have had two separate programmers actually do the rerandomization and implement the minimization because they can be very difficult to program.

DR. BURMAN: Thank you.

Time, believe it or not, is getting to be an issue because it is going to take a while to go over the

questions. But I certainly want to have a full discussion.

Dr. Packer, you had a question before?

DR. PACKER: It was just a reply to Dr. Felner. I didn't think we needed to re-ask the questions. If you look at Question No. 3, if there is an agreement that it should be approved, then, by the time you get to Question No. 3, there is a question should it be restricted to a population.

I certainly agree with Dr. Felner, being a clinical trials person in pediatrics, that we have a lot of problems getting access to drugs for pediatric patients. I think Question No. 3 will address that question without having to restate the questions.

DR. BURMAN: Thank you.

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

DR. HANOVER: I would like to just extend this a little bit and ask maybe the FDA with their experience, we have experience now with a number of enzyme replacement therapies, and this issue of whether it is age appropriate or not.

I would like to ask what has been the experience with those other enzyme replacement therapies with regard to developmental issues, have you seen, for example, a dramatic increase in either loss of efficacy or increased risk in the

pediatric age group that would make us worry about these age issues since we have very limited data in this scenario.

I guess I would argue that knowing the molecular mechanism of this drug gives us some advantage. It is not that we can say we have no data about this type of thing. I would like your comment on that.

DR. PARISER: It becomes a little bit difficult when you are trying to compare some of these diseases because they are so different. What was very unique here is that instead of the situation where the pediatric patients are the last to get it, this would be a case where the pediatric patients were the first to get it, and it was never our intention that this would be restricted.

The 160 was approved for all patients and it was never our intention that this would be restricted from the younger patients. So, what we are faced to here is not an FDA approval issue. This is a manufacturing limitation issue. It is not FDA wanting to in any way, shape, or form stand in the way of the younger patients getting the drug.

Now, with the other diseases, what is unique also about Pompe disease is you don't get CNS manifestations of the disease, and that is not true in a lot of the MPS diseases where you get progressive CNS disease.

It really becomes a much more complicated issue to study and, in some of these, Hurler's; for example, treatment of choice in under 2-year-old's is bone marrow transplantation, and the issue of not just in the peripheral manifestations of the disease but also the continued CNS progression since it won't cross the blood-brain barrier.

It gets really pretty complicated.

DR. BURMAN: Thank you.

Dr. Foggs.

DR. FOGGS: Systemic anaphylaxis is one of the most ominous outcomes for any therapeutic intervention, and it seems as though, if we look at the data for the 160 liter product, the rate of systemic anaphylaxis was 5 percent, 6.7 percent for that in the 2000 liter product except for this one discrepancy which Genzyme indicates they did not interpret to be reflective of a systemic anaphylactic reaction.

I would tend to agree with that interpretation to the extent that this particular patient had known asthma, was treated with a short-acting beta agonist, and happened to experience wheezing.

We have no other data in the account that is given to us. But one thing we do know, that it is not customary

for systemic anaphylaxis to spontaneously resolve with decreasing the rate of infusion of a product because it is mediated by allergen-specific IgE, which would not result in the continuation of that particular immunologic reactivity in association with a rate reduction.

I would like, since we are trying to account for some discrepancies in the 160 product and the 2000 liter product, to have some specific commentary on the part of the FDA as to why this particular clinical presentation was interpreted as systemic anaphylaxis.

DR. YAO: I would be happy to provide that. I am hoping that we have my slide set here, and it may not be, but it was in my updated slide set, Slide No. 51.

We had the same concerns regarding again issues of immunogenicity and the most severe form of allergically mediated adverse event, which would be anaphylaxis.

[Slide.]

You can see that what we asked the sponsor to provide are case reports forms. We actually had, I believe there were 8 or 9 patients in which we had concerns that there might be evidence of an event of anaphylaxis, and the sponsor had reported those three.

These are the symptoms that were reported actually

in patient 29708 that occurred during at least I believe it was two infusions, it was at least one. Again, we asked our Division of Pulmonary and Allergy Products, and we had an allergist in the Division who has specific expertise in immunologically mediated adverse events and enzyme replacement therapies to review this.

Of the other 4 cases that we had, she did not agree that those were anaphylaxis. But, in this one case, I believe that she had the case report forms including the vital signs. That is what led her to believe that this was indeed a case of anaphylaxis, and yes, we disagree.

We also would state that based on the NIAID definition that Samson, et al. had published, that the clinical--you know, I am not the expert here obviously--but the clinical definition of anaphylaxis does not necessarily relate or correlate with the presence of an IgE-mediated event. So, we were using that definition.

DR. FOGGS: I think that is an important discrepancy because you can have degranulation of tissue mast cells and circulating basophils with mediated release independent of an immunologic process.

If you are going to call it anaphylaxis, unless we are getting specific about what is now an obsolete

terminology called anaphylactoid reactions, I think it is important to be specific about mechanistically what is operative in association with the endpoint that constitutes the therapeutic side effect.

I think that is important because there are many agents, an example of which is vancomycin, which is rate dependent in its association with systemic manifestations that could be interpreted as anaphylaxis, when, in fact, it is not by medical definition considered to be anaphylaxis.

That is important if we are looking at the 160 lot which had the same rate of anaphylaxis if you subtract this one patient.

DR. BURMAN: Thank you.

Again, we do have a time issue because we have to vote and talk, and what I would like to do is Dr. Holmes and Schade have asked to raise questions, and I guess Dr. Veltri, as well, and then Tom. Then, we will go on to the voting.

DR. HOLMES: I will try to be real quick here. I just want to make sure I understand the issues. The issue is that with the 6-minute walk test, you guys find a nonstatistical difference and they do not, your 0.09, their 0.04. You are saying this shows no efficacy as far as

walking. I just want to be sure based on your statistical analysis of their preliminary study design.

DR. YAO: There was a treatment effect of 28 meters with our p-value of 0.06, and the sponsor's p-value of 0.04; that is correct.

DR. HOLMES: The 0.04 and 0.06 is what I was worrying about today with all the statistical talk. I just want to be sure.

DR. YAO: That's correct.

DR. HOLMES: Then, you would say, well, certainly that is not a robust phenomenon no matter whose results you believe or what statistical analysis you believe, right? I mean that is not very vigorous.

I think what we are supposed to find is that if you are going to approve one randomized clinical trial, it is supposed to be quite robust with one trial. I think that is what the instructions were.

The second thing is that everyone seems to agree that as far as vital capacity, it was significant. But yet you guys seem to be throwing that out, that that is not clinically significant.

If that is true, why did this protocol get approved in the first place, what was the thinking when it

was first approved? It seems to me like we are changing our mind now that forced vital capacity is a nice thing to measure; but it doesn't have any meaning, therefore, it is not important.

DR. YAO: I would say that for both efficacy endpoints, and for efficacy endpoints in a disease like Pompe, it is difficult to find efficacy endpoints that we can really hang our hat on.

While not perfect, I think the idea would be the 6-minute walk test would be the primary efficacy endpoint with the FVC actually a sequential co-primary endpoint; that is, if the 6-minute walk test were significant, then, the FVC would be used.

We are in a situation now where we are having some difficulties in establishing that robustness of clinical conclusion, and that is why I think the FVC becomes more relevant in this situation.

Again, the forced vital capacity has not been really studied in Pompe disease. But we have discussed it in the Division and in the Division of Pulmonary Products about using it as an efficacy endpoint in patients with potential restrictive lung disease, and they agree that it could be used. I do want to bring that up.

DR. PARISER: I think what we also have to point out is the magnitude of the change. There was a 3 percent difference between the two, which is very small. So the results can be statistically significant but the clinical meaning is in question.

DR. BURMAN: Thank you.

Dr. Schade.

DR. SCHADE: Yes. I would just like to raise the issue and agree with Eric, the issue about the availability of the 160 lot for juveniles.

It is true that the FDA did approve it for use of the juveniles. But I also read the package that was sent to me from the patients and interested people, and they pointed out that in addition to the approval, the FDA then included a statement that there was not adequate data to support the use of this in the juveniles and adults, and so then the patients in the packet pointed out that therefore their insurance company had actually denied them coverage.

So, although the product is approved, because of the language, it gives the insurance companies a good out of not to approve the payment of this product.

I am very concerned that, in fact, the 160 lot is not universally available just because it was FDA approved,

because the language that went along with it. So, because I have not seen any pathophysiological data that the disease is different in the juveniles and the adults, I think it is very artificial to separate it on an age basis when I don't see any pathophysiological difference between the disease whether you are young or old.

It may progress a little more quickly but that is not a pathological difference. I would agree with Eric that--I am an adult endocrinologist and I have many more drugs than Eric does--but I would hate to see the juveniles, who really stand to benefit longer and more from this therapy, to be denied based on just an age difference when there is no pathological difference.

DR. BURMAN: Thank you.

Dr. Veltri.

DR. VELTRI: i was going to comment along the same lines in the sense that here we have a therapy which, as opposed to many of the adult therapies, you know, here was the first therapy in the infantile form, and it was a much harder endpoint as opposed to a functional endpoint, ventilator-free survival.

The FDA apparently is concentrating on the juvenile but, by the protocol definition where you required

an age of 8, as I understand it, to have a meaningful forced vital capacity, the protocol itself perhaps denied the ability to maybe explore the juvenile form appropriately.

But I would be remiss to believe that, you know, even though the genotypes are probably the same issue, and that is glycogen storage, that clearly there is a cardiomyopathy definition for the infantile. But this is a progressive disease and it is hard for me to believe that that continuum doesn't exist.

I think it would be difficult to do another trial, at least a placebo-controlled trial, in the juvenile form. There may be other designs, and I do think that the data, although there are statistical issues here, and I was also confused--I am going to get to the question in a minute--but I was confused by the fact that what was in the briefing documents as part of the analysis was different than what was presented here.

My question is this. There was that one case of the late onset anaphylaxis, and it wasn't clear to me whether that was a patient who also had anaphylaxis early, as well, or whether that was just an isolated late, just manifested as a late.

DR. YAO: I can answer that question by saying

that the information that we had from the data sets that were submitted to us, indicated that this episode of anaphylaxis occurred late and that it wasn't a progression or continuation of an event that began early.

Also, again I think just to make sure that we are talking about the same thing, and I guess I will throw this in as a pediatrician, too. I mean I am concerned about the availability of drugs to treat conditions in the pediatric population.

We can slice or dice and discuss or debate the age that we decide is most typically or most clearly defining a particular disease population, and everybody knows that that is doomed to failure because we have stated clearly that this is a spectrum, that doesn't start on Day 1 and end on Day 18, or doesn't start on age 1 and end at age 18.

I think what I want to make sure that the committee understands is that we just don't have the data on the 2000 liter product in younger patients. So, if we choose to approve for younger patients, then, we are just taking it on faith because LOTS has not adequately studied these patients.

The second thing is that again, I just want to make sure that it is clear, that the 160 liter product is

approved in this country. We are not talking about a situation in which it is either approved or there is no treatment available.

There are manufacturing issues in terms of supply, but it has been approved in this country.

DR. BURMAN: Thank you.

What I would like to do is ask Dr. Fleming for his comments. We would like to try to vote on the first question in about 10 minutes.

DR. FLEMING: Thank you, Mr. Chairman.

I have waited until the end because there are so many statistical issues, and I wanted to have whatever time I had to try to summarize at least my sense of the key issues from a statistical perspective, but actually to lead to a question that is a clinical relevance question even more so than statistics.

I think the FDA hit the nail on the head for what I wanted to begin with. You are going to ask us a question about whether or not we think there has been effectiveness shown. And that is an important question, but it is not totally well defined.

Do we mean statistically significant effects on whatever the measure is, or do we mean statistically robust

results, and, in fact, you are correct.

The goal of clinical research is not statistical significance. The goal of clinical research is statistically reliable evidence of clinically meaningful effects, and those clinically meaningful effects ideally would be on clinical efficacy measures. And that is the ultimate, have you got persuasive robust evidence of that.

Or short of that, could this be a Subpart H accelerated approval where you have got clear indications of effects on biomarkers, and you are right. The bigger the effect on the biomarker, the more persuasive that could be clinically.

So, the design of the trial that you signed off on wasn't off-line even if it was based on 6-minute walk test and FVC, if the effects were really big.

If the effects are more modest, are they enough to still establish biologic activity from Subpart H.

There has been a lot of discussion of statistics here, and I don't want to go through it all. I am going to not go through most of it, but just a couple of things that I think are to be highlighted. John was getting at some of them.

When you look at 6-minute walk, how robust are

these results from the magnitude of the effect in the nature of how the trial was designed. I am so pleased that the sponsor did a randomized trial with blinding. I don't want to miss the fact that that was a major achievement in this setting.

With that achievement, however, there are still issues - was the blinding maintained, and not just from a symptoms perspective, but everybody that got therapy, got antibodies, and nobody that didn't, didn't. Could that have unblinded?

This is an effort-based test, the 6-minute walk. Last observation carried forward is a mindless approach. To LOCF somebody who has died or to LOCF somebody who has had anaphylaxis makes no sense, and I think that probably is leading to some bias in overestimate.

The aspect about an adaptive method, we could spend an hour. We have spent enough time. But the bottom line to this is you can't let the data drive the hypothesis you are testing because you can't interpret the p-values, and you are going to get biased estimates.

It is confusing. I have tried to go through the protocol as it existed originally where it was clear that it was a 52-week repeated measures analysis. By the way, that

is far more the traditional way we have used 6-minute walk in all our disease settings, is what is the difference at 16 weeks or 52 weeks or 78 weeks. That was originally the case.

It got changed and as I track it through, all of a sudden what appeared was the use of the slope and the use of LME. I don't know where it came from, and that's okay if it's truly coming from independent of the data. But the changes got made very late and they have to be implemented without any knowledge of the relative efficacy. Because you can't change the endpoint, you can't change the analysis method when you see the data.

I can't tell if this was done. They are saying the right--I am glad, they are saying the right things, they did it based only on a variance estimate without seeing the data. But I can't tell for sure if that was the case.

But even if it was, what is frustrating to me is--and it's not necessary to find out if it was, because that is not my major concern. What is frustrating is they did make the change, they assumed a linearity.

Clearly, FDA had a beautiful slide. From zero to 38 weeks, you get this great separation, then, it's parallel, you know, with linearity. So, they actually

didn't gain something by doing this. And then they added additional complexities with variance, covariance structures that most of you don't care to want to know about what that is all about. But the bottom line is FDA is right.

They did something with a robust estimate, but would they have done it if the p-value hadn't been dropped from 0.09 to 0.04. You have got all these multiplicities.

The bottom line is we get into these adaptive methods to change things in mid course, to make things better, and this is what we often get - a lot more confusion.

The bottom line is to this, my sense is that there is an effect, it is not highly robustly shown. There is an effect of 26 to 28 meters on the 6-minute walk. I am disappointed that it doesn't grow after the first 9 months, it is parallel after that.

I am disappointed that the secondary endpoints of QMT, leg score, arm score, the percent predicted, MEP, MIP, they are all just marginal. The quality of life doesn't show a difference. Only two people responded by their prespecified measure of what is robust, a 54-meter improvement and a 15 percent increase in FVC.

The problem is we are not seeing that. We are

seeing much more modest effects. We are seeing much more modest effects on FVC. What we are seeing, though, my sense is more robustness of FVC. That is why the concept of saying we are seeing an effect, it is more robust on FVC, now, that maybe gets into Subpart H. But here is my question.

I listened to the Open Public Hearing. I am impressed with what appears to be a substantial opportunity and need and effect. Then, I look at the data and it is much more modest. I would have thought, what I would have loved to have seen would have been data in the adult setting on indications of death, indications on--I know, there is only one death--indications on ventilator dependency, indications on use of walking device, quality of life.

These are all the things I am hearing in the Open Public Hearing that we are getting, and I am not seeing any evidence of that. I am not saying it is not true. But the evidence that we have at this point, actually, I would have thought the protocol made sense because you would have seen a bigger signal on 6-minute walk and FVC as they were planning.

We are seeing an effect but it is more modest. Why should I not be disappointed that we haven't seen more clear

clinical efficacy benefit even as a signal, if not statistically significantly established, based on what we are hearing from the Open Public Hearing?

I am not looking for a sponsor response actually, because I would really like an unbiased--

DR. TANDON: I just wanted to clarify one point.

DR. BURMAN: Mike, you had a quick comment?

DR. PROSCHAN: I think there are a lot of lessons to be learned. One of them, I don't think minimization is a good idea. The other thing is you don't want to use your primary analysis, have it be very model dependent. For your primary analysis, you want something that is going to be valid without having to make a lot of assumptions.

The LME with the model-based variance I think is a big mistake. Adaptive methods, I think they have their place. I have done some research on adaptive methods. They have their place, but not the kind of thing where, halfway through the trial, when you hadn't planned to do something, then, you come back and change the outcome, which I think is troubling.

I think there are a lot of statistical problems. Having said that, though, I mean I look at the totality of the evidence, and I come to a little different conclusion.

I mean I find that the evidence does support that there is an effect. Now, is it clinically meaningful? I don't know. I am not a clinician, and I am always wary of clinicians who say this is clinically meaningful, this isn't, and I wonder how they got that.

When you look at the subgroups, when you look at the secondary endpoints, they are all going in the same direction. They are not--you know, as Tom says, they are marginal. Some of them are a little over 0.05, some of them are a little under. But I think there is a consistent pattern here of a benefit.

As I said, I can't say whether that is clinically important or not. But I think, when I use the word robust, I mean do you get about the same results when you do different methods of analysis, and I think you do.

I think they did a Wilcoxon test. They got something a little under a 0.05, so they are getting around 0.05 with several different analyses. So, to me, the results I would call them robust. They are not big. They are not big effects, but they are consistent effects across different analyses, relatively consistent.

So, I think there are all kinds of statistical problems, but I am persuaded by the totality of the

evidence.

DR. BURMAN: Thank you. I wish there was much more time to discuss all these complex issues. This is obviously an important problem, and I do think we have to move on to the vote because the FDA also wants, after we vote, for everyone to have a very succinct discussion of why they voted the way they did.

Does the FDA have any other thoughts before we move on to the voting, a question or any other clarifications?

[No response.]

DR. BURMAN: Okay.

Tom, do you have one thing?

DR. FLEMING: Part of my comment was an effect could be an effect that is adequately, reliably established on a biomarker is reasonably likely to predict clinical benefit, or an effect could be truly establishing clinical benefit.

If you think one or the other of those are true, does that mean you vote yes for this question, and then you get to the distinction later?

DR. PARISER: Yes, because then you have to decide under Question 2 in which way it would.

DR. BURMAN: Thank you for that clarification.

We will be using the new electronic voting system for this meeting. Each of you has three voting buttons on your microphone, Yes, No, and Abstain. Once we begin the vote, please press the button that corresponds to your vote.

You will have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, I will read the vote from the screen onto the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as to the reason why they voted as they did.

If there is no further discussion on this question that is critical, we will now begin the voting process. Please press the button on your microphone--I will read the question in a second--that corresponds to your vote.

Do you have the question up there? Yes.

The question is Question 1. Do you believe LOTS has established the effectiveness of the 2000 liter product? Yes or No.

[Vote.]

MR. TRAN: One person did not vote. Can you revote? Every person press again, please.

[Vote.]

DR. BURMAN: Interesting. I will read these into the record. 15 people voted Yes, 1 No, and zero abstain.

What we would like to do now is to go around the table, all the voting members, and explain your vote succinctly in as much detail as you think important.

Dr. Schade, do you want to start?

DR. SCHADE: Yes. I voted Yes because I think that the study, the weight of the whole study demonstrated efficacy.

DR. HOLMES: This is Greg Holmes. I voted Yes, as well. I thought it was a very difficult decision to make. But I think the predominance of evidence shows it has some effect. I don't think it is robust, but I think there is some effect, beneficial effect.

DR. FOGGS: I voted Yes based upon the evidence submitted. Even though I would like to have seen additional evidence, I think because of the rapid progression of the disease and those who are affected by it, forces me to vote Yes to make the 2000 lot available.

DR. BURMAN: Thank you. Maybe also you could go back, Dr. Schade--I should have mentioned it, I apologize--when you explain your vote, if you voted for approval, then,

you vote for approval under accelerated approval or regular approval based on the findings.

Sorry for the confusion. My vote didn't get recorded. My vote is Yes. But we would like to explain Part 2a and 2b, just mention if you voted for approval, what kind of approval.

Dr. Schade?

DR. SCHADE: I would vote for 2b.

DR. BURMAN: I think 3 is a separate question that we can address after this.

Dr. Holmes?

DR. HOLMES: Yes, 2b.

DR. FOGGS: 2c.

DR. TEERLINK: I voted No, and I voted No because I did not believe that there was any statistically persuasive information here that there was a clinically meaningful difference.

I think we are being given a false choice. The option for this company is to just make more 160 liter generators, biogenerators if they needed to. We don't have to say oh, because the 2000 liter is the only thing available, we have to do this.

I think if we were going to apply the standards

that I feel are very, very important for not only helping our individual patients, which I thought the patient discussions were compelling. But we need to also protect the public health, and that is our job here.

I don't think that they have, on the basis of their clinical data, provided that information. Of note, they didn't show the Rotterdam score or the fatigue scores, which were the patient-specific scores that I had asked to be shown. But I know that they were not statistically significant. There is no difference in those scores.

There were no sense of patient-specific improvements in anything, and if they really want to show a clinically meaningful difference, we have patients here who said, hey, it has kept me off a ventilator, it has made me be able to do all this dramatic benefits, well, then, as we have for every other drug, we should ask them to show it.

So, we are now approving a drug to give a 21, 28 meter benefit in walking that may be a statistically significant difference, and balancing that against 100 percent of patients developing immunogenicity and 6 percent being exposed to the risk of anaphylaxis.

So, when I look at the risk-benefit ratio, I can't conscientiously vote for approval.

DR. HANOVER: I voted Yes. My feeling was the drug differed little from its predecessor, and I believe the efficacy and safety of the drug was established. 2b.

DR. PACKER: I voted Yes. I thought that there would be no real good way, given the endpoints in this kind of a chronic disease, to get the robust endpoints that maybe everyone would be statistically very happy with, and I would do this as a 2c. I don't see that there is another trial that is going to give us a better answer.

I think there are ways, with Question 3, to try to regulate this approval to some degree. But I think, given the total weight of the study, I would vote to approve this and with regular approval.

DR. PROSCHAN: I voted Yes. I think I explained my rationale just before the vote. I also would go with regular approval.

DR. THOMAS: Abraham Thomas. I voted Yes and I would vote for 2b. I do have a lot of concerns for the study. As a clinician, I see very little effectiveness, and I think this study is fraught with design flaws in terms of the statistical analysis and changing during the middle of the study, which in general I would find unacceptable.

The fact is there is not enough of it to go

around, which is the only reason why we are even considering this vote. But I say 2b because I have some concerns about a slippery slope that will happen.

It is very easy at this point, if this is approved completely, to then start shifting more of the patients from 160 to 2000, and in the patient comments that we heard earlier, many of them started on 160 and were switched to 2000 because of availability.

I don't know if 160 did something for them and then 2000 is doing anything for them than just maintaining the effect from 160. So, when do we decide you go from 160 to 2000, and we are using the excuse of resources that we can't make more.

So, there is a very slippery slope on when we switch from 160 to 2000. So, as a result, even though I vote 2b, I think there has to be some more studies done to clarify this issue.

DR. HENDERSON: Jessica Henderson, Consumer Representative. I voted Yes. I could go for either 2b or 2c. I agree, I am concerned also about the slippery slope and the comment made about access according to health insurance. If the 2000 is less expensive than the 160 in particular, which I suspect it would be, I could definitely

see the norm being that health insurance mandates that patient start on 2000 and only go to 160 if 2000 fails. So that is a concern.

I would also like to see more studies with the outcomes studied that the patients talked about today.

DR. FLEMING: By law, FDA has to have established substantial evidence of efficacy and favorable benefit to risk to approve an agent.

If we look at what would be true clinical measures, such as improving survival time, delaying time to ventilator dependency, improving time, longer time before you have to walk with a device, improvement in quality of life, I would accept any of those as being direct measures of clinical efficacy.

Modest improvements in FVC and modest improvements in 6-minute walk have not been validated as valid surrogates in this setting, hence, I don't understand how these data provide a single trial robust establishment of clinical efficacy.

However, the Congress has allowed for the concept of having reasonably likely to predict clinical benefit with evidence of clear effect on biomarkers that are making it reasonably likely to establish clinical benefit.

When we look at the effects on 6-minute walk, 26, 28 meters, and no additional effect over the last nine months in that period of time, that is half of what the team was targeting initially as a defined response, and it is half of what has in other disease indications been validated as being sufficient to document that you are a little bit better or you are a little bit worse.

From the perspective of FVC, the American Thoracic Society said a 15 percent difference is clear evidence of clinical benefit, so those measures, with big effects, could be interpreted in the context of clinical efficacy.

That is not what we are seeing here, but we are seeing evidence of an effect on biomarkers, particularly on FVC. But I think it can be justified to argue that patients should be given immediate access through expanded access with follow-up validation of this experience. So, I vote Yes, and I vote for 2b.

DR. BURMAN: I vote for 2b with the following comment. This analysis of the safety and efficacy of replacement therapy in Pompe disease represents a difficult complex decision. In my view, on the one hand, there is a discordance between the subject of analysis of efficacy--for example, patient testimony--and the subject of surrogate

endpoints, and yet, on the other hand, the strict quantitative scientific analysis of physical, chemical, and clinical data.

It must be commented that there is no other treatment modality for this often devastating disease, and there are technical issues regarding the supply. Perhaps in this context, we can compromise to some extent our usual standards of unequivocal compelling efficacy data.

This agent seems relatively safe in the short term. To be certain, however, long-term post-marketing studies of efficacy and safety are required. However, on balance, I think the agent should be approved with close post-marketing studies.

Tom.

DR. AOKI: I voted to approve and with 2b. I think in a very real way, this is very similar to the first approval for the 160 L product. This basically is the only game in town for non-infants if the supply issue is correct.

So, I think in a sense we are driven to accept this based upon that realization. Also, I agree that my sense of all the data suggests that it has a beneficial effect. I agree that not one particular thing is robust.

I am kind of puzzled by the 6-minute walk, which I

believed failed or is close to significance because it basically measured two things or three things actually, not only muscle strength, cardiac performance, but also pulmonary function.

If you watched that video where the boy was walking with the walker, he was getting literally tired while he was walking that 10 or 50-foot path, 50-foot path.

So, it seems to me that may be why the 6-minute walk was not such a good choice, because it's a multi-system tester rather than forced ventilation capacity, which is essentially one, you are testing respiratory muscles. You are not asking the heart to simultaneously carry a 140-pound person 25 feet.

DR. JOAD: I voted Yes. As a pulmonologist, I would have to say I was impressed by the FVC data over the minute walk, 6-minute walk data. I do not believe the 3 percent difference is meaningfully, clinically, like I don't think anybody would perceive a difference in that degree of difference.

My concern is that the difference happened in the first 26 weeks, and then appeared to be parallel. So it's really important to know. My sense that that is an important difference is dependent on my understanding of the

disease, that you expect what would be the placebo to continue to decline where the treated would stay flat.

I don't think we know that. So I am really hoping somebody can come up with a 2b plan that is a real plan that can follow it out over time. I am worried that it may not be ethical or practical to do a placebo-controlled study anymore, and I am not sure whether it is feasible or useful to do a comparison between the two production methods. But I will stick with 2b and Yes.

DR. BURMAN: Thank you.

Dr. Aoki, did you vote for--which part, 2b or 2c?

DR. AOKI: 2b.

DR. BURMAN: 2b. Thank you.

DR. FELNER: I mean I think the effectiveness at least was shown reasonably and it is really the only option available as far as treatment goes. I think immediate access should be granted but, obviously, follow-up validation data.

I think the study that might be considered is going to be very difficult because of the spectrum of disease, and that may be another reason, in addition to some of the others that have been mentioned, is why you won't get a tremendous difference in some of these tests. Some

patients are much more severe than others, and when you look at the differences, they might not all come out. But I think 2b with this follow-up data should be done.

MS. HOUSE: I vote 2c. I think that in this case, you have to take the disease into consideration, and it is a degenerative disease.

While LOTS may not have demonstrated profound improvement, when you are talking about a degenerative disease, I think that stabilization is what is most important.

We know that without any treatment, what is going to happen is that you are going to continue to decline and, to me, it was very relevant, that just looking at the raw data, not the statistical analysis, that there was some improvement. That would never happen without treatment.

So, for that reason, to me, that is clinically significant. I have been in studies, I have done the different quality of life surveys. And when you are doing them, the questions they ask are not something that you would necessarily change in one year or even a year and a half. It is something that two or three years, five years down the road, you are going to say wow, you know what, I can suddenly do this again.

You are going to notice stabilization first and that is what I noticed in my own experience. So, to me, having any sign of improvement in the treatment group compared to decline in the placebo group is significant. And that is why I vote Yes.

DR. ROSEN: I voted yes and I think, to echo Tiffany's comments, I think one problem is that we--Yes and 2b incidentally--is that we tend to underappreciate that the difference is that there is progressive loss, and that is so very important in deteriorating disease, whereas, the improvement is quite minimal. And I believe we are really underpowered in this study to see a major effect because of that, plus the heterogeneity in the cohort of adult patients makes it difficult.

I was impressed with the FVC. I must say, though, the sponsor really, some of the things they did in terms of the interim analysis, the data changes, the design changes are really deplorable, and we wouldn't tolerate it in a normal situation. But this is a situation where there really aren't many options.

On the other hand, I would like to also comment on the FDA's subgroup analysis because I think that can be very misleading for the juvenile cohort that is so small that

when you say there is no effect and it is deterioration in the disease, I would agree with you. But if you just look at Slide--I think it's Slide 47--that at 70-week termination in the 6-minute walk, the treated group was minus 0.8 and the placebo group was minus 0.20.

So, you could take the data and say, gee, there was a huge negative effect in the placebo group, and what you have in the treated group is no change. And this comes back to what we heard from the public hearing and also what Tiffany mentioned, and that is there is progressive deterioration.

But I think subgroup analysis is tremendously risky in terms of drawing conclusions about what we should be saying when we are talking about 6 subjects or 9 subjects with the placebo group.

I think the FVC was one of the original endpoints that the FDA had decided on and, even though it may not be clinical significant, it certainly met the endpoints. So that is why I voted for 2b.

DR. FLEGAL: I also would vote for 2b, and I agree with the comments about subgroup analysis. I think there are a lot of sort of ambiguities here with the heterogeneity and the statistical changes in the analysis are a little bit

unfortunate.

Also, I think both of the tests are somewhat imperfect as well because they both depend on effort and they are not fully standardized. That could have affected the results one way or another. So, I think that is part of the picture.

Because of that, I think it would be good to have further study to really demonstrate clinical benefit because the tests we have right now are not really clearly demonstrating that and I think it is important to go further. But I think the patients should have access to this, and there should be follow-up.

DR. BURMAN: Thank you, all. I think that is everyone for that. The official vote was 16 Yes, 1 No, and zero abstain.

We will be discussing in the next question the nature of any study design. Thank you.

With regard to Question 3, if an Accelerated Approval or a regular Approval is recommended, and we are asking you regardless of how you voted to assume that the answer to this is Yes, that there was voted approval, or regular Approval, Accelerated or regular Approval:

a. The LOTS trial enrolled an inadequate number

of patients with juvenile-onset Pompe disease. Only four patients were under age 18 at the time of enrollment, one of whom was exposed to 2000 liter product, one patient aged 16.

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; that is, patients who were diagnosed and had symptoms onset over age 18? We will vote yes or no in the same manner that we just did.

DR. PACKER: Can you restate that?

DR. BURMAN: Sure. Should the indication for the 2000 liter product be restricted to the adult-onset population only; that is, by the FDA definition, patients who were diagnosed and had symptom onset over 18 years of age? Vote Yes or No.

DR. FLEMING: You are restricting to late onset but, within the late onset, you are asking, is that correct? Is the question should you allow the entirety of the late-onset population or should you restrict it to the subgroup, is that the question?

DR. BURMAN: Right. Don't forget Eric's comments

about the differentiation and the discussion of the continuum.

DR. PARISER: If the committee wants to consider a different age range from what we have listed, then, you are free to do so.

DR. BURMAN: Eric, do you have any comment?

DR. FELNER: I think Roger had said it well, that if you vote No for this, it is going to be assumed or at least somebody has an avenue to treat at any age with the non-cardiac disease, and maybe that is all it should be. So just leave it as it is so we don't have to change anything.

DR. PARISER: Say that again.

DR. FELNER: If you were to say No on this question, and that means anybody who has non-cardiac disease can get the 2000 liter product. Right? If you voted No--

DR. PACKER: That is my understanding, that it isn't really the age. It depends on how you define these things. But I think No means that you could give it to everybody who has non-cardiac disease. You have the ability to do it.

DR. BURMAN: Again, time is an issue, but it still isn't that clear that way, and I wonder, Dr. Pariser, could we modify the question?

DR. PARISER: Yes, you can modify the question. We are looking to see if there is an age restriction or a restricted distribution that should be in place for this.

DR. BURMAN: Does the committee have a feeling for it?

DR. TEERLINK: Typically, one of the things, you usually approve drugs based on the patient population studied, which regardless of who actually got into trials, usually is given, saying, okay, these are your inclusion criteria and then based on your inclusion criteria, we will approve it for that group.

So, that one option would be the 8-year-old and above. The other option is to say, well, we think we understand the pathophysiology of this disease, and we believe by all the extensions of everything else that others have said here, that we should just go with the pathophysiologic process in which case then it should be however the late onset is designed is pathophysiologically.

So for me, the decision is actually between those two approaches to the question, do we base it on the inclusion criteria for the trial, those who are allowed to get in the study versus what we believe in a kind of thought experiment, what we believe is the pathophysiology.

I might be tempted to restate it between those two options.

DR. BURMAN: We really have to move on, and the FDA would like us to specifically vote on this question as posed and then in the discussion we can have disclaimers.

So, the question posed is, if I am quoting the FDA correctly--

DR. PARISER: No. What we really want to know if there should be any kind of a restricted indication. Now, where you want to cut that, you can decide. It does not have to be 18.

DR. BURMAN: How about if we voted on this question and then when people go around, they give their opinion?

DR. PARISER: That's fine.

DR. BURMAN: Is that all right with everybody? Thank you.

Let's move ahead and vote on the question as written with any caveats in your discussion.

Should the indication for the 2000 liter product be restricted to the adult-onset population only; that is, patients who were diagnosed and had symptom onset over age 18? Vote Yes or No.

MR. TRAN: Please press the button part.

[Vote.]

DR. BURMAN: That is always interesting. For the record, there were zero Yes votes, 16 No votes, and 1 abstain.

I think this would be an appropriate time to go around quickly and maybe this time we will start on this side, Dr. Flegal, to give your opinion, and then any discussion succinctly you think ought to be done in the post-marketing study and for follow-up.

DR. FLEGAL: Well, I just felt that there was no clear reason to cut it at this arbitrary age. This appears as far as I understand to be a continuum and that we should not be denying the possible benefits to other late-onset patients who are younger than 18, so I didn't see a compelling reason to restrict it.

DR. ROSEN: I agree. I think it is completely arbitrary about age 18, and I think it would set a bad standard without any data to say that if you are below 18, you have a different disease or something is different about it than above 18.

DR. BURMAN: Would you like to make any comment regarding follow-up with the REMS template or anything like

that?

DR. ROSEN: I think the REMS template is a reasonable idea. I think it is really incumbent on the sponsor to produce a study that is respectable and reasonable, and gets at this age issue a little more carefully. REMS looks like a template of how to approach that.

DR. BURMAN: Also, if anyone, as you go around, has comments regarding what study you would propose, that would be important for the FDA to know, as well.

MS. HOUSE: I voted that it should not be restricted because I personally think that it's a mistake to try to distinguish between juvenile and late onset. Pompe disease, I think it is much more appropriate infantile, late onset, because the cardiac involvement, there is a clear delineation there.

I think there is just too much overlap between GAA activity, age of onset, rate of progression, any type of classification would be a mistake and could end up leaving patients with no access to therapy.

DR. FELNER: I think my comments before should cover it so I don't take up any more time.

DR. JOAD: I voted it should be available for

everyone. But my real wish would be a 2000 versus a 160 study in that 2- to 18-year-old age group. It would answer so many of our other questions, it could be longer than this one was. It would be ethical because they both work, and I think it would be really a great thing to do.

I understand about the type 2 error in the power analysis, that show no difference. But, if there were a difference, it might show up with less.

DR. AOKI: I voted no age restriction and I also agree, I would love to see a 2000 L and 160 head to head. But, failing that, I certainly would like to see a REMS study.

DR. BURMAN: Thank you. I voted No and certainly think there should be a REMS template. We are going to be discussing in the next question, additional studies. But I agree that there should be at least a 1- to 2-year study of the 2000 liter versus the 160, analyzing the PFTs and the walk test, as well as perhaps even muscle biopsy to assist glycogen storage in the muscle after treatment.

DR. FLEMING: I voted No. I don't have a good sense about whether there is an important interaction by age for benefit to risk. But I have been reassured by the concept that in voting for approval with Accelerated

Approval, we will be getting post-marketing evidence that will provide very important necessary enhanced insight about benefit and risk, and that insight will allow us to have a better sense about whether there is interaction by age.

So, given the reassurance that we would have proper validation trials under the concept of Subpart H, I find it appropriate to be more inclusive here in this Accelerated Approval.

DR. BEITZ: Could I just jump in for one second?

I just wanted to clarify that when we talk about REMS, that has to do with communicating risks and benefits to patients and prescribers, and restricting distribution perhaps to certain patients.

It doesn't really talk about studies. Studies should be viewed as a separate entity from REMS, just to clarify.

DR. BURMAN: Thank you.

DR. HENDERSON: I voted No, and I agree with Tiffany that it is an access issue. That is why I voted No. I think that there should be required enrollment in a registry so that we can continue follow-up and get more information on this, and including quality of life that is beyond the quality of life outcomes that are measured now.

DR. THOMAS: I voted No and I think based on the trial, I would suggest that we use the trial inclusion criteria, which is 8 or more. The other thing is I am not sure in my mind that these two products are equivalent. So they definitely should have a different name.

Further along that line, if we agree that the disease is more severe the earlier you are, and if 160 might be a better product, then, we should make sure that those who are under 8 get 160.

I would think in terms of the REMS, there should be some documentation saying that you have to prove that you do not have cardiac disease to be on the 2000 because that might be something that is accidentally, people start on 2000 inappropriately when one sees a better choice.

In term of studies, I think there should be some type of comparison with 160, and I think one of the endpoints, which I don't know the feasibility of but I would think is possible, is we should use some non-invasive imaging.

We can look at fat and content and muscles on MRI, and we can also look at NMR spectroscopy, which we do for diabetes studies in terms of flux. So that might be something that is considered in terms of the efficacy, as a

surrogate for biopsies.

We can clearly look at muscle increase if there is an alteration by MRI. It will add to the cost of the study, but I think it is fairly reasonable to do.

DR. PROSCHAN: I abstained because, you know, from the statistical standpoint, I can't really tell whether there is a differential effect of treatment by age. And so I think that would require some medical judgment as to whether that is plausible. I don't have any medical judgment. So I abstained.

DR. PACKER: I used to have medical judgment before I joined this committee. But I voted No because I don't think we can restrict it to these patients.

I did vote initially, and I agree with that, that there it should be a 2c, but I think in a very restricted population. The children who are having more rapid disease, I think this is the opportunity to do the appropriate study to see if there is a difference in those children.

So, I would have a restricted study, not for all the patients. Also, I would probably do stratification, not based only on age, but residual enzyme activity, rate of progression, and things like that, and actual functional level of the child entering so you could get away from some

of this heterogeneity--so you might be able to get an answer.

I am very worried about ever doing a 160 versus 2000 study because, first of all, I don't know if the 160 is going to be available, and I don't think you are ever going to have enough numbers to do a comparative study with all due respect unless you have an unbelievably robust separator.

I do want to see a restricted study. I could care less about the REMS, but I want to see a restricted study in the younger patients who are deteriorating faster with lower activity.

DR. HANOVER: I voted no basically to allow maximum flexibility of treatment in both populations. I would like to see oversight and I guess I would focus that oversight in very careful monitoring of even both kinds of drug, and I don't disagree with having each have a separate name so that it can be an ongoing monitoring process.

DR. TEERLINK: I voted no. I would have very limited faith, actually, no faith in post-marketing studies to be able to answer any clinically significant issues in terms of proving efficacy. I think we have never seen a post-marketing study to give us any indication of whether

something works or not.

In terms of an active controlled trial, comparing 160 liters to 2000 liters, I would point out to everybody that 160 liters has not been studied in the late-onset patients so we don't know actually what its baseline value is or whether it works or not. So I think an active controlled trial is very difficult to do.

DR. FOGGS: I voted No. My primary reason for voting No was so as not to deprive those individuals who are in restricted age brackets from the potential therapeutic benefit of the treatment.

I would like to see head-to-head studies and also as has been mentioned, some more tangible evidence of efficacy in the form of muscle biopsies and other markers that could be correlated to the natural history of the disease being impacted by the specific treatment.

DR. HOLMES: I voted No. I would use the criteria they used for the study, starting with age 8. Obviously, I would like to see more studies, too, comparing the 160 and 2000. I wouldn't be so much concerned whether one is better than the other. If they were both comparable, I would be happy.

DR. SCHADE: Yes. I voted No. I would like to go

on record as being opposed to a comparison study between the 160 and the 2000 because I think that would interfere with a good post-marketing study and be a waste of resources.

I happen to believe the sponsor that the numbers involved would be large, certainly larger than 90, because you are comparing two treatment groups rather than a placebo and a treatment group.

But my real concern, and I concur that, to date, post-marketing studies have been very problematic, that doesn't mean they can't get better, and we have a lot of very good surrogate markers for muscle disease.

So, I think I would like to see the resources of the sponsor be devoted to a very good post-marketing study and registry. When you are dealing with which everybody seems to agree a progressive disease, I think then you can look at a large cohort and if nobody actually progresses, I think you can make some reasonable conclusions, whereas, if everybody progresses, then, you get into problems about rates of progression and it does become difficult. But I think a good post-marketing study is feasible.

DR. BURMAN: Thank you all very much.

There are two more questions and we will take them in order, and then go for explanations of each.

The question at hand is: Should additional studies be required as post-marketing commitments to assess efficacy? We have had a little discussion of this already, and we are asked to vote Yes or No.

To read it again: Should additional studies be required as post-marketing commitments to assess efficacy?

The next question is going to be on safety. This is efficacy.

DR. PARISER: Could I provide a clarification?

DR. BURMAN: Please do.

DR. PARISER: If you voted for Accelerated Approval, by regulations, then, that does require a post-marketing study.

DR. BURMAN: But you would like, as a representative of the FDA, some discussion on what those studies should be?

DR. PARISER: Yes, but if you did vote for Accelerated Approval, you pretty much have to vote for another study.

DR. BURMAN: Thank you.

DR. FLEMING: Not pretty much, you have to, it's the law. So, if you are 2b and you have an Accelerated Approval, we must complete a validation trial, and that

validation trial is not on other biomarkers. That validation trial is validating the benefit to risk profile, establishing efficacy on an established surrogate or on a clinical efficacy endpoint.

I understand your thoughts, John, about how historically, when we do pharmacovigilance studies, our track record isn't very good and, in particular, where that track record isn't good is if they are single arm studies, uncontrolled, and you have an immunosuppressive agent and MS or RA patients, and you are trying to find out if you are going to have an oncology risk, or you have a COX-2 inhibitor and you are wondering whether or not you are increasing cardiovascular, death, stroke, and MI, when you have a 1 percent rate in the population, and a 1.5 relative risk matters. Those studies have no hope in discerning what is the treatment effect versus what selection factors.

But this is different. This situation could be specifically a setting where not a passive or active surveillance pharmacovigilance plan but a prospectively designed study that would have an historical control to look for substantial effects could be a reliable indication, and this has the attraction that you are not randomizing people to some kind of untreated control.

You are providing the intervention, in this case the 200 L, to a select cohort of patients that you are following forward. A classic example--they aren't a lot--but a classic example would be in about 1982, post-cyclosporin, when we had primary biliary cirrhosis and primary sclerosing cholangitis and chronic active hepatitis, and we were looking at liver transplantation, and did it improve survival, it wasn't ethical to randomize at that point to liver transplantation, Yes versus No, and we were looking at very large differences, much like what you used when you approved this agent for the first time in the infantile setting.

So, my sense would be a way forward here would be not to do a pharmacovigilance passive collect what you can, but a very specific, as required by Subpart H, validation trial could, in fact, have two parts.

It could be an infantile-onset trial that essentially would be prospectively collecting data showing what we would all hope to be a very major effect on mortality and time to ventilator dependency.

For the adult onset, it is going to be a longer term to be able to see those events. But what we are hearing is a great deal of sense particularly if you include

a substantial representation of more advanced patients, that you are going to see by all indications may be improvement, but at least a stabilization and a delay of such magnitude that it would be discernibly different from an historical cohort by a major difference.

So, the limitation, the reason this isn't the right answer in most settings is that in most settings, you are not expecting a very large effect. But, if you are expecting a very large effect, then, the magnitude of that treatment effect exceeds the uncontrolled selection factors that you haven't controlled in the absence of randomization, so it seems like that could readily be the setting.

But this needs to be on clinical endpoints, this needs to be done in a proper and timely way. This can't be, well, we will take them as they come and, if we finish it in 9 years, that is fine. That is inconsistent with the intention of Subpart H with the validation.

It needs to be a prospective, aggressively conducted trial that could involve a wide collection, if not all the patients that would subsequently be treated both in the infantile-onset setting and separately, a separate study in the late-onset setting, to establish major benefits on these very important clinical efficacy measures that we have

heard a lot of testimony about, that are like to be seen.

DR. BURMAN: Thank you for putting that in context. I am sure we will have more comments after the vote. But I think we have to vote now, and the question is: Should additional studies be required as post-marketing commitments to assess efficacy with the caveats just mentioned? Vote Yes or No.

[Vote.]

DR. BURMAN: The vote for the record is 15 Yes and 2 No. We would like to go around the table quickly and again it's 4:30 just about. We have to end at 5:00 and we have one other question to vote on. But it is very important for the FDA to hear further discussion on the design of the studies and the record of your vote.

Dr. Schade.

DR. SCHADE: I will be very quick. I think Tom has said it wonderfully, and I will just say that in this case where you only have one treatment in town, so to speak, that the sponsor knows everybody who is getting therapy, and they won't be on any other therapy for this disease. So I think for those additional reasons, a good post-marketing study is feasible.

DR. HOLMES: I agree. These patients really need

to be followed very closely. The type of study is difficult because I don't think you can use placebo at this point, and, you know, high dose, low dose, some other dosing parameter maybe. But they definitely need to be followed closely.

DR. FOGGS: I voted Yes for the same reasons already articulated. I think the more we know about the therapeutic impact of the treatment of the disease, the better, and I think prospective longitudinal studies will help us do that.

DR. TEERLINK: I voted Yes. I agree with Tom it needs to be a very rigorous clinical study. I would also suggest to the sponsor that given that there is kind of a monopoly on the patients, I think it would be very disappointing to have you come back again and say, oh, now, we can't make the 2000 L anymore, and we have this new genetically engineered one, and we have stopped making the 2000 L, so now we just have to approve this new agent.

So, I think there is a line in the sand here today in terms of needing to show clinical efficacy.

DR. HANOVER: I voted Yes. My concern, of course, is designing a good rigorous study when you can't do a placebo. So I am going to defer to the practicing

physicians as opposed to the bench physicians for those concerns.

DR. PACKER: I voted Yes with significant concerns that since we have been all arguing about 0.04 versus 0.06, that these robust endpoints don't exist for the majority of patients.

I would again focus on the younger patients, that you might be able to see a robust endpoint. I also would like to make just a statement that I know we are going to spend a lot of time on some of these post-marketing things. I think the drug in general isn't that tremendous that we shouldn't be looking for new drugs and maybe spend more money on developing newer drugs that may be honed to the muscle rather than spending a tremendous amount of time proving that a drug that is okay is still okay.

DR. PROSCHAN: I voted No. That is a little bit misleading because the reason I voted No is because I believe that they have shown efficacy. I would be in favor of a post-marketing study for safety, though.

The question specifically said for efficacy.

DR. THOMAS: I voted that we should have some efficacy studies. And I just want to echo what everyone else has said, that they should be focused on the population

that wasn't studied, that we have essentially given approval to, which is the young age and potentially very high risk population.

DR. HENDERSON: I voted Yes and I agree with everything that was said before and also want to emphasize the younger population.

DR. FLEMING: I voted Yes and I have already given my comments.

DR. BURMAN: I voted Yes and I agree with Tom's discussion on what the study should be. It should be looking at juvenile patients, as well as adult patients, and looking at hard endpoints that you have mentioned. And I just wanted to clarify, Tom, you were proposing, given the problems with supply, et cetera, that it would be a 2000 liter trial versus historical controls.

DR. FLEMING: Yes.

DR. AOKI: I voted Yes for the reasons that you just articulated.

DR. JOAD: I voted Yes for reasons I had said before. I just wanted to emphasize that the study should go on for years because I don't think we can use an FVC change of 3 percent as a marker for the future. I think we need to know that it holds.

DR. FELNER: I voted Yes. I think again as mentioned before, to focus on the younger groups without cardiac disease.

MS. HOUSE: I voted No because I believe that efficacy was established in the trial.

DR. ROSEN: I voted Yes and I think the old traditional post-marketing survey on studies no longer should exist, that we need a rigorous evaluation of both efficacy and particularly of safety. And I agree that it should be younger individuals where you might get a more robust effect.

DR. FLEGAL: I also voted Yes and I concur, it should be a rigorous study and it should look predominantly at younger onset individuals.

DR. BURMAN: Okay. We will move on to the last question, which is: Should additional studies be required as post-marketing requirements to assess safety? We will vote Yes or No, and then we will go around the table and discuss the potential design.

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

[Vote.]

DR. BURMAN: The vote for the record is Yes 17, No zero, and zero abstains.

I would like to go around the table and discuss the design of any safety study that you think would be appropriate, that has or hasn't been discussed before.

Dr. Flegal.

DR. FLEGAL: I think it is important to have some assessment of safety. Hopefully, it can be also done rigorously and combined to some extent with the studies of efficacy. Beyond that, I don't have any innovative design suggestions, however.

DR. ROSEN: I would agree that we need a rigorous design. I am not sure I know exactly what endpoints other than the ones that have been outlined should be delineated. But I think we have to leave it up to both the FDA and the sponsors to come up with something that is pretty reasonable and that covers the full spectrum of what we are interested in.

MS. HOUSE: I voted Yes and my reason for that is that I think that with proper follow-up and care, that if there is some sort of reaction that it can be managed. I think that a post-marketing study should be done to ensure that patients who have some sort of reaction are managed

properly.

I am concerned for those patients that may have a physician that is not knowledgeable enough, sees a reaction and decides we should just stop therapy instead of trying to in some way manage it properly.

DR. FELNER: I voted Yes and I think that safety issues have at least come up with the anaphylaxis, and so, especially in the pediatric population, it should be evaluated.

DR. JOAD: I voted Yes and my particular concerns would be episodes of severe anaphylaxis that was not treatable, in good, well done clinics situation, and also long-term immune things, such as glomerulonephritis.

KINGMA: May I just--it may be important to know that--

DR. BURMAN: We really don't take any--

KINGMA: There is 12 out of 15 patients with anaphylaxis who have been retreated successfully.

DR. BURMAN: Thank you very much, but we really shouldn't be taking that.

DR. AOKI: I voted Yes for the reasons that have already been stated. I think we should be monitoring very carefully for patients who have untoward reactions like

anaphylaxis and to carefully monitor that throughout.

Thank you.

DR. BURMAN: I voted Yes and with emphasis on assessment of anaphylaxis and short-term infusion reactions, as well as long-term immunopathologies.

DR. FLEMING: I voted yes, and in the rigorous study that we talked about for efficacy, that would be the context for obtaining the safety information. We would surely want to ensure that we have high levels of sensitivity and specificity for key events, such as anaphylaxis so that, therefore, we would need to have reliable capture and adjudication of significant events as part of this rigorous efficacy and safety trial.

DR. HENDERSON: I voted Yes with particular concern to long-term possible effects, and so I would like to see the study be long term.

DR. THOMAS: I voted Yes and I think the emphasis should be on things like anaphylaxis, immunologic properties in the younger population which we didn't study, and there may be some combination of that in the older population, and long-term follow-up for untoward events.

DR. PROSCHAN: I voted Yes. I am not convinced based on the data that I have seen that there is a

difference in the anaphylaxis rates between the 160 and the 2000. But, of course, that doesn't mean that there isn't any. As Tom said, the absence of safety data doesn't mean that it's safe. So, I voted Yes.

DR. PACKER: I voted Yes, because I think you have to do this as part of this study in a very small patient population. But I do think we have to look very hard at the immunological things like vasculitis, as well as glomerulonephritis with long-term use of this.

The other thing that I guess I would stress is that I would like to see guidelines on how to manage potential anaphylactic reactions, who could be rechallenged, who shouldn't be rechallenged, and data concerning those who are rechallenged, what the likelihood of getting away with it is.

DR. HANOVER: I voted Yes. I view this as both an opportunity for the sponsor and the FDA to long term monitor the safety of a drug of this type, and I think every one of these that are approved provides unique challenges and unique opportunities. So I would follow that up, not only in terms of the severe reactions like anaphylaxis, but also more subtle effects, say, on the innate immune system.

DR. TEERLINK: I voted Yes with the idea of having

required clinical follow-up in every patient who receives this agent internationally and, in addition to that, there would be a subpopulation where you look at the usual enzymatic biomarkers, and things such as that.

DR. FOGGS: I voted Yes. I think there should be a global assessment of potential side effects and a post-marketing study especially comparing it with the world wide data that have already been collected.

In addition, I think it is important to look at any potential identifiable risk factors associated with anaphylaxis and hopefully attack those patients in advance so that precautionary measures can be implemented to decrease any expression of anaphylaxis in that subset of the population if they are identified.

DR. HOLMES: I voted Yes. Certainly, anaphylaxis will catch everyone's attention. But I am also concerned about the long-term effects of the compound in a chronic disorder like this.

DR. SCHADE: I voted Yes and I agree with what has been said. But, since we are now talking about treating the pediatric age group, I would certainly include growth development, going through puberty, some hormonal problems that may occur because we are giving so much foreign

protein. I think that maybe in the younger group, we would be monitoring things like that, that we might not think about for the older population.

DR. BURMAN: Thank you very much for all your comments. Are there any other comments from the committee members of the FDA before we close? Yes.

DR. JOAD: I don't think we ever said this, but many of us thought that under the infantile form, should still be treated with the 160. The way we voted that one time it wasn't clear that we ever made that statement. And maybe we don't agree. But that is a group that we haven't really discussed, should they be getting the 2000 or the 160.

I would say that you get the 160 because that was such an amazing effect, and it was a well done study and it is how it was approved.

DR. BURMAN: I think we did discuss that to some extent, but thank you very much for clarifying that, emphasizing that.

Does anybody have any other comments or questions?

[No response.]

DR. BURMAN: What I would like to do is thank, number one, the participants on the panel, number two, the

sponsor for an excellent presentation, the patient representatives with their compelling stories were really quite impressive.

I would like to thank the FDA for their work and getting everything ready and how easy they have made it for me to work with them, specifically, Paul Tran and Dr. Pariser. Thank you all very much.

Are there any other final comments?

DR. PARISER: The FDA would also like to thank everybody very much, the panel for coming today. I know everybody came from all over the country, and we really value your advice and your expertise and your time very much. We really appreciate it. Thank you.

DR. BURMAN: Thank you. This meeting is adjourned.

[The meeting adjourned at 4:45 p.m.]