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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC
ADVISORY COMMITTEE MEETING

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WEDNESDAY,
JANUARY 15, 2003

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

PRESENT:

THOMAS AOKI, M.D.	Acting Chairman
LAURA BARISONI, M.D.	Voting Consultant
THOMAS R. FLEMING, Ph.D.	Voting Consultant
DEAN FOLLMAN, Ph.D.	Voting Consultant
DEBORAH GRADY, M.D., M.P.H	Member
LAWRENCE HUNSICKER, M.D.	Voting Consultant
J. CHARLES JENNETTE, M.D.	Voting Consultant
ADAM J. JONAS, M.D.	Non-Voting Consultant
JESSE JOAD, M.D.	Voting Consultant
KATHERINE KNOWLES	Acting Consumer Representative

PRESENT: (CONT.)

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

FDA REPRESENTATIVES:

BLAIR FRASER, Ph.D.
ILAN IRONY, M.D.
MARC WALTON, M.D., Ph.D.
KAREN WEISS, M.D.

SPONSOR REPRESENTATIVES:

MATT PATTERSON
LORNE CLARKE, M.D., Ph.D.
GERALD COX, M.D.
EMIL KAKKIS, M.D.
WYSTKE KINGMA, M.D.
JOSEPH MUENZER, M.D., Ph.D.
GILLIAN SHEPHERD, M.D.
KAREN WALTON-BOWEN, Ph.D.

PUBLIC SPEAKERS:

MELISSA BRYANT
LINDA L. DAY
MARK A. DANT
DENISE DENGEL
STEPHEN E. HOLLAND
ERIC MERRELL
ABBEY S. MEYERS
STEVE SMITH
J.E. WRAITH, MB, ChB, FRCPHC

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

C-O-N-T-E-N-T-S (Continued)

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

(8:12 a.m.)

CHAIRMAN AOKI: Good morning. I'm Dr. Thomas Aoki, and I'm the Acting Chairman of this Committee.

I would like to start the activities for this morning, which is a discussion of the drug Aldurazyme from BioMarin Pharmaceutical Incorporated.

To begin with, I would like to ask the members of the Committee who are sitting at this table to introduce themselves, starting with my left.

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

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

MR. SWENSON: I'm Erik Swenson, Professor of Medicine at the University of Washington.

DR. SCHADE: I'm Dave Schade, an endocrinologist, University of New Mexico, School of Medicine.

DR. WOOLF: I'm Paul Woolf, endocrinologist at Crozer Chester Medical Center.

MS. KNOWLES: I'm Kathy Knowles from Health Information Network in Seattle, Consumer Representative.

DR. JOAD: I'm Jesse Joad. I'm a Professor of Pediatric Pulmonary and Allergy at University of California at Davis.

CHAIRMAN AOKI: I'm Dr. Thomas Aoki, Professor, University of California, Davis.

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

DR. WATTS: Nelson Watts, endocrinologist, University of Cincinnati.

DR. LEVITSKY: Lynne Levitsky, pediatric endocrinology, Massachusetts General Hospital.

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

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

DR. GRADY: Deborah Grady. I'm an internist and epidemiologist at the University of California in San Francisco.

DR. IRONY: Ilan Irony, clinical reviewer for the BLA, CBER.

DR. WALTON: Marc Walton, Food and Drug Administration.

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

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Centers for Drug Evaluation and Research and the Center for Biologics Evaluation and Research which have been reported by the participants present no potential for an appearance of conflict of interest at this meeting with the following exception:

Dr. Lynne Levitsky has been granted a waiver under 18 USC 208(b)(3). Her spouse is a member of

BioMarin Pharmaceutical's Data Safety Monitoring Board for a product unrelated to Aldurazyme. He receives less than $10,000 a year. Copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, at the Parklawn Building.

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

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and exclusion will be noted for the record.

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

Thank you.

CHAIRMAN AOKI: Thank you.

At this time I would like to ask Dr. Blair Fraser to provide the introduction for CBER.

DR. FRASER: Good morning. We are here to discuss BioMarin's Biologics License Application for Aldurazyme, recombinant human alpha-L-iduronidase, for the treatment of mucopolysaccharidosis I.

Filling in for Melanie Hartsough, Chair of the Committee, I am Blair Fraser, biochemist on this Review Committee. I will be presenting a brief overview of the CMC portion of BioMarin's application.

First, I would like to start my presentation by summarizing the review milestones for this application. CBER received BioMarin's application on July 29th, 2002. Since that time, there have been extensive interactions, discussions, and requests for clarification leading to this Advisory Committee meeting today. The first action due date for this BLA is January 28th, 2003.

Turning to the drug substance, Aldurazyme is a recombinant human alpha-L-iduronidase produced in a

continuous Chinese hamster ovary or CHO cell line. This protein has a molecular weight of 80 kilodaltons. The amino acid sequence for the recombinant protein is identical to the sequence for a natural polymorphism of the endogenous protein. This protein has six N-linked complex oligosaccharide sites and one disulfide bond. Review of the CMC portion of the BLA provided by BioMarin indicates that this is a well-characterized protein.

Turning to the drug product, the drug product is supplied as a sterilized isotonic intended for intravenous administration. Each single-use vial of drug product contains 2.9 milligrams of alpha-L-iduronidase, the active ingredient in 5 cc's.

There are no outstanding review issues concerning the drug product.

Finally, I would like to thank the FDA Review Committee for their thorough reviews.

CHAIRMAN AOKI: At this time I would like to ask Mr. Matt Patterson to oversee the sponsor's presentation.

MR. PATTERSON: Good morning, ladies and

gentlemen. My name is Matt Patterson. I'm the Vice President of Regulatory and Government Affairs for BioMarin Pharmaceutical, and it's my pleasure to give you a brief introduction to our presentation this morning.

As you know, we're here today to discuss a product called Aldurazyme, which is also known as laronidase, which has been developed for the treatment of a disease called mucopolysaccharidosis I, or MPS I. MPS I is an inherited metabolic disease or, more specifically, a lysosomal-storage disorder, which results from a deficiency in the enzyme alpha-L-iduronidase. The active ingredient in Aldurazyme is alpha-L-iduronidase manufactured by traditional recombinant technology.

The sponsor of the BLA is BioMarin, but I would like to note that Aldurazyme has been developed through a joint venture between BioMarin and Genzyme Corporation.

After my introductory remarks, I would like to ask Dr. Joe Muenzer to join us and give us a description of MPS I. Dr. Muenzer is an

internationally-recognized expert in the MPS diseases and was a principal investigator in both the Phase 1/2 and Phase 3 clinical studies.

After Dr. Muenzer, Dr. Gerry Cox will give us a review of the Aldurazyme clinical program. Dr. Cox has over ten years of experience in metabolic diseases and is a clinical geneticist affiliated with both Children's Hospital and Harvard Medical School. Dr. Cox was the medical monitor for the Phase 3 clinical study.

After Dr. Cox's presentation, Dr. Muenzer is going to join us again to briefly review for you his perspective on the results from the Aldurazyme clinical studies and, in particular, his perspective as a physician who sees MPS I patients on a regular basis and has seen them over the years during the clinical trials.

Finally, I'll return to give you some concluding remarks, including a brief review of our perspective on the questions you have been asked to discuss today as well as some final thoughts.

I would like to note that we have some

additional participants joining us here today. They are listed on this slide. As you can see, they bring a variety of areas of expertise which are related to the Aldurazyme clinical program. They're here today to help support the discussion as needed.

I would like to briefly review the Aldurazyme regulatory history for you. The program was designated an orphan drug product back in 1997, and I would like to note that the prevalence of MPS I is currently estimated at approximately 1,000 patients in the United States.

An IND filing followed shortly thereafter in October of 1997. The product was designated a fast-track product by FDA in September of 1998. The BLA was filed in July of last year and was granted a priority review by the FDA.

Finally, I would like to note that the development of Aldurazyme has involved frequent and detailed collaboration between the sponsor and the agency, including all the traditional meetings that you see listed on the slide here.

Briefly, on the development history of the

product, Aldurazyme development began with a series of pre-clinical pharmacology studies. These were performed in a naturally-occurring canine model of MPS I. The results of these studies demonstrated significant reduction of stored glycosaminoglycans, as measured in both the urine and the tissues.

The very encouraging results of these studies led to the filing of an IND and the commencement of the Phase 1/2 clinical study. This was an open-label study in ten patients, and the BLA contains 152 weeks of efficacy data and 235 weeks of safety data from this study.

The very promising results from the Phase 1/2 study led to the commencement of a Phase 3 double-blind study. This study included 45 patients and was 26 weeks in length. It was a randomized, placebo-controlled, multinational study.

At the conclusion of that study, all 45 patients were offered the opportunity to enroll in what we've termed an extension study. All 45 patients did choose to enroll in that extension study, and that study was an open-label study where all patients

received Aldurazyme, and the license application contains 36 weeks of data from the primary efficacy endpoints from that extension study.

Finally, I would like to note that 16 patients globally are receiving Aldurazyme as a part of a compassionate use program. This is a program that was initiated at the request of physicians and patients to treat seriously-ill individuals who are unable to participate in any ongoing clinical studies.

Aldurazyme is administrated at a dose of 100 units per kilogram of body weight once a week as an IV infusion.

Finally, I would like to end by reminding you of the proposed indication for the product. Aldurazyme is indicated as long-term enzyme replacement therapy in patients with MPS I to treat the non-central nervous system manifestations of the disease.

Thank you very much. I would like to ask Dr. Joe Muenzer to join us to give us a description of MPS I.

DR. MUENZER: Thank you, Matt. It's my

pleasure to be able to present the clinical description of MPS I. As you know, this is a lysosomal storage disorder due to the deficiency enzyme alpha-L-iduronidase. Deficiency of enzyme results in the progressive accumulation of glycosaminoglycans. This disorder is multisystemic, and it's a very heterogeneous presentation.

Due to this, we see severe morbidity and a very early mortality. Patients with MPS I can die as young as two or three years of age.

It's a very rare, autosomal recessive disorder. Its estimated incidence is 1 in 100,000. These patients, as I'll show you, have a significant unmet medical need.

MPS I is a typical metabolic disorder with a wide range of clinical involvement. Historically, we recognized the severe form as Hurler syndrome with profound mental retardation and progressive somatic disease, where the patients typically died before ten years of age and the average age of death was four to five.

As the biochemistry became evolved for this

disorder, we recognized that a mild form of MPS, initially called MPS V, was recognized to have the same enzyme deficiency as the severe form. These patients, even though they're mild and normal intellect in terms of CNS function, clearly have significant physical problems also.

The patients in the current trial are in the intermediate form called Hurler-Scheie syndrome. They have little or no intellectual impairment, but they have progressive somatic disease with death in the teenage years to early adulthood.

Even within the intermediate spectrum, the Hurler-Scheie syndrome, we see a wide variety of clinical involvement. The 17-year-old here has severe joint disease, had a tracheostomy at age 12 because of upper airway obstruction, leading to cor pulmonale, and has moderate liver enlargement.

In contrast, here's a 12-year-old who has also has severe joint disease but has minimal airway involvement at the same age the previous individual had a tracheostomy, and he has moderate hepatomegaly.

In contrast, an older individual who has

milder joint disease than those two, but clearly has sleep apnea requiring continuous positive airway pressure at night and has a massive hepatomegaly.

All these patients have virtually undetectable iduronidase activity. This enzyme cleaves a terminal iduronic acid from dermatan and heparan sulfate. Missing this enzyme results in the sequential breakdown in the sequential metabolism of glycosaminoglycans.

Missing the enzyme results in the accumulation of this storage material, and you can see here a liver section from an MPS I. We see very foamy, vacuolated liver cells and a very distorted liver architect due to that progressive accumulation.

MPS I is a multisystemic disease with a wide range of clinical involvement. I now want to spend the last part of my time talking about the different clinical manifestations of this disorder.

Pulmonary disease is a major manifestation due to storage in the lung, airway epithelial, and bone. The outcome is initially decreased pulmonary function. We see restrictive lung disease due to a

very small ribcage and very stiff joints.

This is exacerbated by decreased diaphragmatic excursion due to the very massive hepatosplenomegaly. These patients also have frequent infections with very thick secretions, and progressive involvement results in severe respiratory insufficiency.

In addition to their pulmonary disease, they also have upper airway obstruction caused by storage in the tongue. You can see a very prominent, enlarged tongue, lymphoid tissues, abnormal airway epithelii, and, probably most important, very redundant floppy tissue in their upper airway.

This upper airway obstruction clearly results in respiratory insufficiency and causes severe sleep apnea which untreated results in cor pulmonale. Down below is an example of a sleep apnea. Here's oxygen saturation over the course of the night, and what you see is dramatic dips. Thirteen percent of the night this individual experiences oxygen saturations less than 90 percent.

As a result of this, these patients clearly

need assistance in breathing. Continuous positive airway pressure is very beneficial, but many patients result to go on to having tracheostomies because CPAP is not effective.

This upper airway obstruction clearly contributes to the high anesthesia rates in these patients, and it is not uncommon for these patients to die in operating rooms around the country due to their high anesthesia risk and secondary to trying to improve some of their somatic disease with surgery.

We clearly see significant joint and skeletal involvement in these patients caused by progressive storage in their synovium. Instead of paper-thin synovium, they have synovium that's cardboard thickness, significant involvement of tissues around the joint, and clearly significant bone disease.

This results in joint stiffness, contractures. They have significant pain in their hips. Their skeletal deformities also contribute to the significant loss of mobility and the functional independence that's characterized by this disorder.

Here's an example of some of the joint problems we see in the disease. Here's a child in the typical bent hip posture. These patients have to bend all the time because they can't fully extend their hips; the same way as their knees. Here's a 12-year-old who's trying to raise her arms above her head, and clearly cannot do that because of shoulder restriction.

Hepatomegaly, as you saw, clearly occurs in this disorder due to storage in both the liver and the spleen. Restricted movement results from this with impaired breathing. They have difficulty eating, lots of discomfort, and the hernia you see here is very difficult to repair because a very protruding abdomen causes the breakdown to be very common.

Cardiac disease also occurs as part of the multisystemic portion. Storage occurs in heart valves, coronary arteries, and the aorta. The typical outcome is a valvular heart disease. Pulmonary hypertension clearly can exacerbate and pass to right heart failure that commonly occurs. Most patients, eventually, with time, will develop congestive heart

failure.

As you can see here, corneal clouding occurs in a major way. But, in addition to that, they have retinal disease, and glaucoma is very common in the young individual. Most patients with MPS I have decreased visual acuity, and blindness, unfortunately, is not an uncommon outcome.

CNS disease is clearly common in the severe form, where we see storage in neurons, macrophages, and meninges. Like the synovium, the meninges become 3-, 4-, 5-, and 6-millimeters thick, which clearly impacts CSF blood flow.

In its severe form, we see mental retardation, but even in the milder individuals, quote, "milder" from neurological disease but still have severe somatic disease, they develop communicating hydrocephalus with very common headaches. Even the older individuals have significant involvement in spinal cord compression, resulting in loss of mobility.

Our treatment for most of these patients is palliative at best, has limited effectiveness, and

because of the high anesthesia complication, it really limits surgery.

Bone marrow transplantation was first reported in this order in 1981. It clearly can improve some of the physical features and stabilize the CNS disease. Unfortunately, morbidity and mortality approaches 10 to 20 percent in the best of cases with a best donor. Because of this, we primarily use this bone marrow transplant to treat the severe MPS I patient, the Hurler syndrome, under two years of age.

In summary, MPS I is a multisystemic disorder due to lysosomal deficiency with progressive decline, with high morbidity and high mortality, and these patients have significant unmet medical needs.

I can now turn the podium over to Dr. Gerry Cox to present the clinical program.

DR. COX: Thank you, Dr. Muenzer. Good morning, everyone.

You've just heard from Dr. Muenzer that MPS I is a devastating disease of childhood. Patients have significant medical problems that lead to

disabilities, impairments, and reduced quality of life. Ultimately, these patients will die of their disease in either childhood to early adulthood.

What I would like to do now is present our clinical data demonstrating that Aldurazyme not only reverses the underlying pathophysiology of the disease by clearing glycosaminoglycans from the body, but that it provides meaningful clinical benefit to patients through improved functioning, and it does so in a safe manner.

This is an outline of my presentation this morning. I'll start with an initial review of the clinical program. I'll then present efficacy data from the Phase 1/2 and then the Phase 3 studies. I'll summarize our safety data, and then I'll close with concluding remarks.

The clinical program consists of a Phase 1/2 open-label study involving ten patients, now entering its fifth year. The program also includes a Phase 3 double-blind and extension study involving 45 patients, now entering its third year, and a compassionate use program involving 16 patients,

entering its second year. In total, 71 patients are being treated with Aldurazyme.

The Phase 1/2 study was the first study performed on humans. The objectives of this study were twofold: first, to demonstrate efficacy by reducing lysosomal GAG storage and, second, to demonstrate safety.

This was an open-label, ten-patient study in which patients ranged in age from 5 to 22 years of age, and eight of these patients had the intermediate form of MPS I, Hurler-Scheie syndrome.

Aldurazyme was dosed at 100 units per kilogram intravenously once weekly. This was a dose regimen that was found to be effective in pre-clinical studies. This study is now ongoing into its fifth year.

The primary efficacy endpoints were to demonstrate a reduction in urinary GAG level and a reduction of hepatosplenomegaly. These are both non-invasive measures of GAG storage. Urinary GAG levels had been shown in pre-clinical studies to correlate with tissue levels of GAG.

As you can see here, treatment with Aldurazyme led to an almost immediate reduction in the urinary GAG level in patients, and this reduction has been maintained with long-term treatment.

At week 52, it was a 63 percent reduction from baseline in the urinary GAG level, and this reduction was highly significant. With continued treatment, the urinary GAG levels have continued to decline slowly, such that by week 152 nearly all of the excess urinary GAG had been eliminated.

Similarly, these biochemical changes were, in turn, followed by physiologic changes with the reductions of both liver volume as well as spleen volume, such that by week 52 there was a 26 percent reduction in liver volume from baseline, which is highly significant, and a 21 percent reduction from baseline and spleen volume, which was also significant. These reductions have been maintained through a second year of treatment.

At baseline all of the patients had abnormally-enlarged liver volumes. After 52 weeks of treatment, nine of the ten patients had normal liver

volumes, indicating efficient clearance of GAG. I want to remind you to remember this later in my talk, as I discuss the maintenance of the long-term reductions in both urinary GAG levels as well as liver and spleen in the context of antibody formation.

In addition to these pharmacodynamic parameters, several clinical parameters are also evaluated. The New York Heart Association score is a functional status measure in which patients who are in Class 1 have no symptoms, patients in Class 4 have severe symptoms, even at rest. You can see that at baseline none of the patients were in Class 1, but with two years of treatment six patients had shifted over to Class 1.

Shoulder flexion is a measure of joint range of motion. A normal shoulder flexion value would be approximately 160 degrees. At baseline these patients were impaired, but with treatment they improved their shoulder flexion by approximately 28 degrees.

Dr. Muenzer had mentioned that many of the patients have sleep apnea, and this can be evaluated through a sleep study Apnea/Hypopnea Index. At

baseline the mean value of the AHI was twice the upper limit of normal, but with 26 weeks of treatment the level had come down into the normal range. Three of the patients who had very significant sleep apnea baseline showed very significant improvements.

Finally, in patients who had very severely-impaired vision these three patients all showed improvements with continued treatment.

Before I present the Phase 3 clinical results, I would like to take a moment just to share with you some of the thoughts that went into our choice of endpoints. We recognized that MPS I is a complex disease, and that it would be a challenge, frankly, to demonstrate efficacy in a clinical study.

MPS I is rare. It affects multiple systems, and it's slowly progressive. It exhibits significant patient-to-patient heterogeneity, and its symptoms have reversible as well irreversible components.

Study duration was also a major factor. When we discussed the study design with our investigators, they thought it would be difficult to recruit patients into a placebo-controlled study for

longer than six months. You have to understand that many of these patients are children who are chronically ill who have to receive infusions on a weekly basis, not only that, but also have to travel to receive infusions.

So, with these limitations in mind, our strategy to confirm the efficacy of Aldurazyme was to demonstrate reversal of the underlying pathophysiology now in a double-blind setting, to demonstrate clinical improvement in functional measures that we thought would show change over a relatively short study period, and to demonstrate a broad treatment effect across multiple organ systems with trends moving in the same direction.

No central nervous study endpoints were studied because of our pre-clinical data indicating that the enzyme does not efficiently cross the blood/brain barrier.

The Phase 3 study was designed, in consultation with the FDA, to be a pivotal study to confirm the safety and efficacy of Aldurazyme. This was a randomized, double-blind, placebo-controlled

study involving 45 patients at five sites in four countries.

Patients were randomized to receive either Aldurazyme or a placebo once weekly for 26 weeks. At the completion of the double-blind phase, all 45 patients chose to enroll into an open-label extension study, now entering its second year.

For entry into the study, patients had to have MPS I disease with iduronidase deficiency. They also had to be at least five years of age in order to perform the functional assessments.

The two co-primary endpoints of this study were a change in forced vital capacity and a change in the six-minute walk test. Thus, patients were required to have a force vital capacity less than 80 percent of predicted to maximize the chance of seeing a treatment effect.

Similarly, patients needed to be able to perform a six-minute walk test by standing for six minutes and walking at least five meters. However, no upper limit was placed on the six-minute walk test distance because of the rarity of the disease and the

fact it would be difficult to find patients who met eligibility criteria for both of these co-primary endpoints.

Patients were excluded if they had a tracheostomy or if they had had a prior bone marrow transplant.

The efficacy variables that we chose to study fell into four broad categories: the first, lysosomal storage of GAG, as measured by urinary GAG level and liver volume. These would now be confirmed in a double-blind, placebo-controlled setting.

As you heard from Dr. Muenzer, respiratory function is impaired in many children with MPS I. Patients develop a progressive restrictive lung disease as caused by a number of factors, including a small ribcage, limited diaphragmatic excursion from hepatomegaly, and spinal deformity.

Force vital capacity was chosen as the most relevant pulmonary function test to assess restrictive lung disease, and this became our co-primary endpoint. We chose percent predicted forced vital capacity because these patients were of markedly different ages

and sizes, and this was an attempt to normalize changes that we saw.

In addition to lung disease, we also looked at sleep apnea as a secondary endpoint, as measured by the Apnea/Hypopnea Index. This is a measure of functional airway obstruction during sleep.

We looked at functional capacity which is in patients. Patients have difficulty walking from a number of factors: their musculoskeletal disease, their respiratory disease, their cardiac disease.

The six-minute walk test is a widely-used, submaximal exercise tolerance test that relates to activities of daily living, walking. We chose this as a co-primary endpoint.

Shoulder flexion was chosen as a way of assessing upper extremity mobility and function.

Finally, there were several additional endpoints that were examined, including visual acuity and questionnaires relating to activities of daily living as well as quality of life.

Over the next few slides I would like to describe our patient population. There were 23

patients who were randomized to receive placebo and 22 who were randomized to receive Aldurazyme.

The mean ages of both groups were similar, approximately 15 years of age, but you'll note the wide age range from six to forty-three years. There were similar numbers of males and females. Patients were of similar sizes, and more than 80 percent of patients within each group had Hurler-Scheie syndrome.

These are the baseline characteristics of the co-primary endpoints. You can see that medians for both co-primary endpoints are similar between groups, and the ranges are similar as well.

As expected, all of the patients had less than 80 percent predicted FVC, as required for entering into the study. But you can see that, based on a median of approximately 50 percent of predicted, a large percentage of the patients had very severe to profound respiratory impairment.

Looking at the six-minute walk test, there's an enormous range of heterogeneity in the distance that patients walked. Some patients could barely complete the six-minute walk test, whereas others were

walking normal distances. As a reference, approximately 350 meters would be considered the lower limit of normal for adults.

I would like to describe some of the other features relating to the two co-primary endpoints. As expected for patients with severe respiratory disease, they experience a number of complications. At baseline they reported recurrent respiratory infections over the previous six months. Sleep apnea was prevalent, reactive airways, and asthma. Two-thirds of the patients had undergone tonsillectomy and adenoidectomy in an attempt to relieve upper airway obstruction, and a minority of patients were receiving respiratory support.

In terms of physical disease, patients complained of joint stiffness, contractures, pain, and a number had spinal deformity. A significant percentage of patients received physical therapy on a regular basis, and 30 percent used a wheelchair. These patients were not wheelchair-bound necessarily because they could complete a six-minute walk test, but, typically, with this disease children become very

tired after walking a few minutes and for extended periods of walking they will often use a wheelchair.

I would like to now describe our results on lysosomal storage of GAG as measured by urinary GAG level and liver volume in this placebo-controlled study. Just as we saw in the Phase 1/2 study, there was almost an immediate reduction in urinary GAG level followed by a stabilization.

The difference from placebo was highly significant. In the open-label extension phase, patients who continued on Aldurazyme maintained the reduction in urinary GAG levels, and the placebo-crossover patients who transitioned onto Aldurazyme showed a reduction very similar to what was seen in the double-blind phase and achieved levels similar to the patients receiving Aldurazyme.

Similarly, just as we saw in the Phase 1/2 study, there was a significant reduction of liver volume. The difference from placebo was 20 percent, and this was highly significant.

In the open-label extension phase, patients who continued on Aldurazyme maintained their liver

reductions, and now the placebo-crossover patients showed a reduction of liver volume.

At the start of the study, of the patients who had abnormal liver volumes who received Aldurazyme, 72 percent normalized their liver volumes after six months and 80 percent after twelve months. What I have just shown you now, then, is confirmation that, in fact, Aldurazyme does efficiently clear GAGs from the body.

Now I would like to move on to our clinical parameters, looking at respiratory function, as measured by the percent predicted force vital capacity and the sleep study Apnea/Hypopnea Index.

Treatment with Aldurazyme led to an increase in the percent predicted force vital capacity. The difference between groups was 5.6 percentage points, and this was significant to a p-value of .009 in our main analysis, the Wilcoxon Rank Sum Test. In a second, prospectively-defined analysis, an analysis of co-variants that takes into account baseline variables between groups, the p-value was .007.

Now in the FDA briefing packet they have

noted that between week 20 and 26 that appeared to be a large treatment effect. What I would now like to show you is additional data we have collected in open-label extension demonstrating that, in fact, this is a valid value, and we have confirmation of three additional time points of this increase in percent predicted FVC. In fact, the change from baseline after 62 weeks of treatment is highly significant.

Similarly, in the placebo-crossover patients we have seen an increase in the percent predicted FVC, albeit it took a little bit longer. This difference from initiation of treatment is approaching statistical significance.

Well, what is a clinically-significant change in FVC? On the last graph I have shown you changes in the percent predicted FVC of approximately 5.6 percentage points. On a baseline of 50 percentage points, that translates into approximately a 10 percent relative change from baseline.

In 1991, the American Thoracic Society published guidelines for interpreting pulmonary function testing. In these guidelines they state that

an 11 percent relative improvement from baseline in adults would be considered clinically significant. So the mean change that we saw in our group approached the 11 percent.

We can also ask, within each of the two treatment groups, what proportion of patients achieved a clinically-meaningful increase? In the Aldurazyme group, 41 percent of patients achieved an 11 percent relative increase in baseline compared to only 9 percent of the placebo patients. The difference in proportions was significant.

Now I would like to move on to our results and the effects of Aldurazyme on sleep apnea. When we looked at all the patients in both groups, we did see a trend towards improvement in patients receiving Aldurazyme, but it wasn't significant. We discussed the results with our blinded sleep study expert, Dr. Rapoport, who is with us today, and he noted that at baseline approximately half the patients had normal values. If you have a normal value, it's difficult to make it more normal, and we felt that this would be diluting out the treatment effect.

So, based on some guidelines published from recent papers, we chose thresholds of Apnea/Hypopnea Index of greater than 10 in children and greater than 15 in adults as reflective of sleep apnea. When we looked at the subgroup of patients above these thresholds, we saw a treatment effect that was significant. Patients receiving Aldurazyme showed a decrease of six events per hour compared to little change in the placebo group, and this result was significant. In the open-label extension phase, continued treatment with Aldurazyme led to a maintenance of this reduction in AHI, and now the placebo-crossover patients who received Aldurazyme showed a reduction.

I would now like to move on to functional capacity, as measured by the six-minute walk test and shoulder flexion. Treatment with Aldurazyme led to an improvement in the six-minute walk test, and relative to placebo, there was a 38-meter difference by 26 weeks. This value approached statistical significance with p-value of .066 in the main analysis, the Wilcoxon Rank Sum Test.

However, in a second prospectively-defined analysis, an analysis of co-variants which takes into account baseline variables known to affect a six-minute walk test, we did achieve statistical significance with a p-value of .039.

In the open-label extension study these results were confirmed. Patients who continued on Aldurazyme showed an improvement of similar magnitude as that experienced during the double-blind phase, and the change from baseline was significant.

Similarly, the placebo-crossover patients also showed an improvement similar to what was seen in Aldurazyme-treated patients in the double-blind phase, and this was a significant change from baseline.

I just want to point out that at week four there was a dip that occurred in both patient groups. We attribute this decrease to a loss of a training effect. At baseline patients were required to undergo three successive, six-minute walk tests on successive days, but at subsequent time points they underwent one test, and we believe that the decrease seen here at four weeks is related to that loss of training effect

in both groups.

Just as we asked for FVC, what's a clinically-significant change in a six-minute walk test? Well, in a study published in 1997 in adults with chronic obstructive lung disease, a 54-meter difference was considered a minimal clinically-important difference in this group.

So we looked at our patient population and asked, what proportion of patients within each group achieved a 54-meter increase? We found that 41 percent of the Aldurazyme-treated patients showed a clinically-meaningful increase in the six-minute walk test, compared to only 13 percent of placebo-treated patients, and this difference was significant.

We also looked at shoulder flexion in all patients. When all patients were considered, we saw no significant difference between Aldurazyme and placebo. However, there was tremendous heterogeneity in the degree of shoulder restriction among patients. So we looked at the patients who had the most severe shoulder restriction at baseline, and this is the group below the median of 90 degrees, which

approximates the horizontal.

Within this more severely-affected subgroup, we saw that Aldurazyme led to an improvement of nearly 10 degrees in shoulder flexion compared to a loss of 5 degrees in placebo-treated patients. When the patients went into the open-label extension study, the improvements in shoulder flexion were maintained in the Aldurazyme group, and they improved in those who crossed over from placebo to Aldurazyme.

I would now like to discuss the remaining efficacy variables: visual acuity and the questionnaires, the Child Health Assessment Questionnaire, and the adult version, the Health Assessment Questionnaire, which looks at activities of daily living, and the SF-36 and Child Health Questionnaire which looks at quality of life.

At baseline most patients had normal to near-normal corrected visual acuity. However, there were a few patients within each group who had severe visual impairment even with glasses. Among these patients, five of the six who received Aldurazyme showed a significant two-line improvement on a visual

acuity chart compared to none of the placebo patients.

We looked at disability and quality of life in these patients through questionnaires. After 24 to 26 weeks of treatment, either in the Aldurazyme patients in the double-blind phase or the placebo-crossover patients in the open-label extension, we saw no significant changes.

However, with continued treatment with Aldurazyme, after 50 weeks in the open-label extension, we began to see clinically-meaningful improvements in both instruments. We saw a decline in the CHAQ/HAQ Disability Index score and we saw improvements in the SF-36 and CHQ summary and subscale scores.

Many of the improvements that we saw related to physical functioning, and this would go along with the improvements that we saw in the six-minute walk test and shoulder flexion.

I should also just point out that these are questionnaires filled out by patients or their families, so the patients are telling us they're getting better through these questionnaires.

Now we didn't see changes over the first six months of treatment with either of these questionnaires, and we believe it's because these questionnaires are generic instruments that apply to many different diseases, but they're just not sensitive or specific enough to show change in a short time period in the MPS I population. In response to this, we're working with experts now to develop our own disease-specific instruments specifically for MPS I.

What I have just shown you are mean changes across groups in individual endpoints, but there are two key features of MPS I disease that are not really addressed through these types of analyses. The first is the patient-to-patient heterogeneity.

Because patients are so heterogeneous, there's a potential for both ceiling and floor effects when we look at mean group changes. Second, MPS I is a multisystem disorder, and if you look at individual endpoints, it's very difficult to know how a patient is really doing across their entire body.

In response to this, after completing of the

double-blind phase, we performed a post-hoc analysis through the development of a composite endpoint approach. This allowed us to assess change in individual patients across multiple organ systems. This type of analysis accommodates patient heterogeneity.

We chose several domains and established thresholds of the clinically-significant change. If there was a clinically-significant improvement, we assigned a score of plus one. If there was a clinically-significant decline, we assigned a score of minus one. And if there was no change or small changes in either direction, we assigned a score of zero.

The two endpoints of this type of analysis are responders who refer to the proportion of patients with overall net improvement -- so a patient who has more improvement than decline -- and the mean net change for the group, which would be the number of improvements minus the number of declines per patient for the group.

These are the different domains that went

into the composite endpoint, and you will recognize many of them from the Phase 3 study. The FVC and six-minute walk test were our co-primary endpoints. AHI and shoulder flexion were secondary endpoints, and visual acuity was a tertiary endpoint.

The clinically-significant thresholds listed on the right were taken either from the literature or in discussion with experts. This is a table that shows the Aldurazyme and the placebo-treated patients according to the composite endpoint.

Patients are listed in rows. The different domains of the composite endpoint are listed in the columns. Clinically-significant improvements are highlighted in red; clinically-significant declines in yellow, and no change in gray.

I think you can appreciate that in the Aldurazyme-treated group there's much more red than in the placebo-controlled group. In fact, 82 percent of the patients in the Aldurazyme-treated group showed improvement in at least one domain, and 41 percent of patients showed improvement in at least two domains. There is much more improvement than decline over here.

An opposite pattern is seen in the placebo-control group where there is relative more declines than improvements, and when improvements do occur, they occur generally in a single patient in no particular pattern.

To calculate a composite score, say, for example, Patient 30, we take the number of domains with improvement and subtract the number of domains with decline. So this Patient No. 30 would have a score of plus two.

On the next slide is a histogram showing the net change on a per-patient basis for both groups, and I think it's, again, easy to appreciate that there has been a shift to the right in patients treated with Aldurazyme, indicating overall net improvement relative to placebo.

If you look at patients who showed net improvement in at least one domain or higher, 59 percent of patients treated with Aldurazyme showed overall net improvement compared to 22 percent of the placebo patients, and this difference in proportions was statistically-significant.

The mean net change also differed between groups. Patients receiving Aldurazyme show on average an improvement of one domain per patient, and in the placebo patients there was a decline of .4 domains per patient.

Now I would like to take a moment just to synthesize and summarize the efficacy data I have just presented. Our Phase 3 clinical study has shown that Aldurazyme improves respiratory function. We met our co-primary endpoint of change in percent predicted FVC with a statistically-significant difference between groups that was also a clinically-meaningful difference when looked at a mean change. When we looked within the group, a much higher proportion of patients receiving Aldurazyme showed clinically-meaningful improvements compared to placebo.

As a supporting measure, we saw improvements in sleep apnea in patients who had symptoms at baseline, and the difference between the Aldurazyme and the placebo-treated patients in this subgroup was statistically-significant. These results were confirmed and maintained in the extension study.

Aldurazyme also improves functional capacity. The six-minute walk test was our second co-primary endpoint, and we showed a clinically-meaningful 38-meter difference between groups that approached statistical significance. When we took into account baseline variables in a second prospectively-defined analysis, we achieved statistical significance of analysis of co-variants. We also saw a much higher proportion of patients receiving Aldurazyme who showed a clinically-significant improvement of 54 meters than in the placebo group.

As a supporting measure, we saw improvements in shoulder flexion in the patients that were most severely impaired at baseline. Going back to the Phase 1/2 study, this correlates with changes that we saw in the New York Heart Association score shift to Class Zero. Again, these results that we saw in functional capacity have been confirmed and maintained in an open-label extension study.

In the additional measures, we saw improvements in visual acuity in the patients who were

most impaired at baseline. From these questionnaires, the patients are telling us that they have seen clinically-meaningful improvements and are reporting them in these questionnaires after 50 weeks, albeit this is an open-label setting.

We have also demonstrated in a placebo-controlled setting reduction of lysosomal storage, as measured by urinary GAG excretion and reduction of hepatomegaly. These pharmacodynamic results have been confirmed, as well as maintained, in the extension study.

As an alternative analysis, we developed a composite endpoint approach to look at change in individual patients, and what we saw is that Aldurazyme led to a broad treatment effect. The majority of patients receiving Aldurazyme were responders, and there was overall net improvement in patients receiving Aldurazyme compared to placebo.

Now I would like to move on to the safety and immunogenicity portion of my presentation. This slide summarizes our major findings. The overall adverse event profile of Aldurazyme was found to be

similar to placebo. Most of the adverse events that occurred were mild or moderate and were not related to treatment.

Similarly, infusion-associated reactions that occurred in Aldurazyme-treated patients were similar to those receiving placebo. Most were mild and no intervention was required.

The majority of serious adverse events that occurred during the study were considered unrelated by the investigators, and they occurred in a total of 14 patients. A single patient had two related serious adverse events, and I'll just take a moment regarding this patient. This was a very complicated patient who had severe respiratory impairment, and both of these serious adverse events involved respiratory distress, the second event requiring a tracheostomy.

Many of the patients in our study have profound respiratory impairment, as evidenced by the baseline percent predicted FVC. Many of these patients, including this one, who experienced these SAEs, have derived clinical benefit from Aldurazyme.

The other point I want to make is that these

two serious adverse events related to two infusions out of 2,600, and, importantly, there have been no treatment-related deaths associated with Aldurazyme.

Finally, most patients receiving Aldurazyme did develop low IgG antibody titers, but they had no apparent effect on either safety or efficacy.

This is the overall adverse event profile, the Phase 3 double-blind study. As would be expected for a disease like MPS 1, which is very chronic in nature, nearly every patient in the study experienced at least one adverse event, but, importantly, the types of adverse events and the numbers between groups were very similar between placebo and Aldurazyme-treated patients. Many of these adverse events are very common symptoms that are related to either infection or underlying disease.

When we look at the infusion-associated reactions, we see a similar pattern. Patients receiving Aldurazyme, 32 percent experience an infusion-associated reaction, but, again, importantly, 48 percent of the placebo patients also experience infusion-associated reactions.

In the open-label extension study, similar proportions, 30 to 36 percent in each group, experienced infusion-associated reactions. The most common ones were flushing, fever, headache, and rash, and they were similar between groups.

Ninety-one percent of patients who received Aldurazyme developed antibodies, but generally these were of low titer. The medium time to seroconversion was 50 days. Three patients underwent testing for IgE because of moderate infusion-associated reactions, and all were negative. One additional patient met the criteria for IgE testing, but was not tested, as per the investigator.

In the open-label extension phase, 89 percent of the patients had seroconverted by week 24 and, importantly, two patients who had been maintained on Aldurazyme throughout had tolerized, as evidenced by two negative antibody titers, confirmed by radioimmunoprecipitation.

Two patients underwent testing for IgE, and the results were generally inconsistent with both skin testing and serum tryptase results.

Well, we're interested in studying the effects of antibody formation on safety, pharmacokinetics, pharmacodynamics, and efficacy. In general, we found no clinically-meaningful impact. Nearly all patients who received Aldurazyme had seroconverted, and yet the incidence of infusion-associated reactions was similar to that of placebo.

Looking at the pharmacokinetics, we did see a decrease in the volume of distribution over time, but there was no impact on the clearance of Aldurazyme from the plasma. Importantly, we've seen sustained reductions in both liver volume and GAG levels in the setting of antibodies.

Finally, in terms of efficacy, patients receiving Aldurazyme have maintained improvements in both FVC and the six-minute walk test well after they seroconverted.

In conclusion, MPS I is a rare, progressive, life-threatening disorder that represents an unmet medical need. In an adequate and well-controlled clinical study, Aldurazyme has been demonstrated to rapidly decrease lysosomal storage of GAG, and this is

translated into meaningful clinical improvements in terms of both respiratory function and functional capacity.

Aldurazyme is well-tolerated with a safety profile comparable to placebo. The compliance of this study was amazingly high. Greater than 97 percent of infusions were received by patients in each group during the double-blind phase, and I just want to commend the patients for their participation in the study.

Finally, we believe that the totality of the data indicates that Aldurazyme has a favorable risk/benefit profile. Thank you very much.

I would like to now turn the podium back to Dr. Muenzer, who will share his clinical perspectives on the meaning of his clinical study results.

DR. MUENZER: In the next few minutes I want to share my personal perspective on the clinical benefit of Aldurazyme treatment in MPS I. I'm a pediatric biochemical geneticist with over 20 years of patient care experience. I have seen over 200 MPS patients, 50 which have MPS I.

As you consider the fate of Aldurazyme treatment, consider the following points since they have impact on the trial design and the interpretation of data:

MPS I is a rare disorder. The typical pediatrician in the U.S. may see one to two MPS patients in a lifetime of practice, may never see a patient with MPS I.

In the Phase 3 trial you just saw the data presented, the 24 patients studied in North America with Hurler-Scheie syndrome and MPS I represent 10 to 15 percent of the eligible patients for that trial.

MPS I is a progressive disorder with multisystemic involvement. The continued lysosomal storage results in cell dysfunction, cell death, tissue damage, and fibrosis in many tissues. With time, these changes become irreversible.

With that perspective, any reversible of clinical disease I believe is highly significant, and I'll be more than happy to accept stabilization or lack of progression as a very successful outcome. The multisystemic nature of disease also clearly impacts

many aspects of the disease.

As an example, as you saw, patients with MPS I have upper airway obstruction superimposed on severe restrictive lung disease in many patients. The deleterious effect of upper airway obstruction that's well-known is clearly exacerbated by the decreased airflow that occurs due to the restrictive lung disease.

There is no treatment for these disorders that is safe. Bone marrow transplantation has been used, but has significant mortality.

On a regular basis, when I see my patients in the clinic, I can offer them nothing but symptomatic care. I talked in the past that enzyme replacement clearly could have impact and I clearly believe the future is close.

Next slide. The improvements I have seen in the six-minute walk I believe reflect the functional improvement that I have observed in the patients, and that the patients and their parents report to me. These patients have increased mobility and endurance.

Treatment has resulted in less wheelchair

usage. They have increased endurance to carry out the normal activities of childhood. As an example, many of these patients after enzyme can now walk the length of the mall. You may say, "What does that mean?" Well, before they could never do that because of their disability. Either they used a wheelchair or they never did it at all because of the difficulty of doing that.

One of my patients, a 13-year-old, reported to me that he can now go to a friend's house on his own without assistance four or five blocks away, where before treatment he could never make it there because of joint stiffness and pain.

In addition to that, we've seen functional independence that's significantly improved. They have significant less need in terms of self-care. They don't need as much help. They don't need help to put on their clothes anymore, some of these patients. They don't need help for personal hygiene.

On Friday I saw one of my patients in clinic involved in the trial, and the mother reports to me, reminded me that, as a young child, prior to

kindergarten she learned to tie her shoes like most kids, but two or three years after that point she lost that ability due to her joints getting progressively stiff. With enzyme replacement, the mother reported she can tie her shoes once again. She's a 13-year-old teenager.

In my experience MPS I is always a progressive disorder. I've never seen improvements unless intervention has occurred. The sustained improvements that I've seen in this clinical trial have not before been experienced in this disorder.

More importantly for me and remarkable, these changes have occurred in as little as six months for some of these patients. The first patient involved in the MPS trial is a patient of mine I've known for 16 years. After six months of treatment, it appears that his clock was turned back, that his disease was turned back two to three years as a result of treatment.

One of the real benefits I believe of this drug will be we will no longer have to care for patients with the degree of physical disabilities that

you've seen as part of this trial. But what I really hope to be able to do is to prevent the progression of disease, to prevent the somatic disease, improve quality of life, and prevent the premature deaths that occur in this population.

In summary, physicians who care for patients with MPS I need to have Aldurazyme available to them as a treatment option. As a panel, I urge each of you, strongly urge each of you, to recommend approval. Thank you.

I will turn the microphone to Matt Patterson for concluding remarks.

MR. PATTERSON: Thank you, Dr. Muenzer. I would like to just conclude our presentation by giving you our perspective on the questions you have been asked to discuss at today's panel meeting.

The first question you've been asked relates to the impact of Aldurazyme on pulmonary function and your interpretation of that information; specifically, the value of the treatment effect demonstrated on percent predicted force vital capacity.

The Aldurazyme clinical data have

demonstrated a statistically-significant improvement in percent predicted force vital capacity. The primary endpoint was met and demonstrated a statistically-significant difference between groups in favor of Aldurazyme.

A statistically-significant treatment effect was also seen after controlling for baseline variables. This is the analysis of co-variants. I would like to highlight this because you may have noticed that in the question you were asked today the agency has highlighted a difference at baseline between the two groups and suggests that the treatment effect observed may have been caused by this difference between the groups at baseline. The ANCOVA result helps mitigate this concern.

The Aldurazyme clinical data have demonstrated a clinically-significant improvement in force vital capacity. As Dr. Cox noted earlier, 41 percent of patients treated with Aldurazyme had a clinically-meaningful 11 percent relative increase in FVC versus just 9 percent of patients treated with placebo. Again, I would like to point out that this

is an analysis demonstrating improvement in individual patients as opposed to group changes, and, thus, it also helps mitigate any concern that a difference at baseline was responsible for the observed treatment effect.

Finally, there's also additional support for the force vital capacity results. We have shown that the extension data are positive. Patients treated with Aldurazyme during the double-blind portion of the trial maintain their improvements. Patients treated with placebo during the double-blind portion of the trial improved after 36 weeks of the extension study.

It demonstrated an improvement in sleep apnea in patients with disease at baseline. Finally, it's important to remember the context of patient heterogeneity when interpreting these results. When we consider that, and you consider all the results as a whole, they become all the more impressive. Taken as a whole, the results related to function are both robust and meaningful.

I'm going to actually skip to the third question you've been asked because it's basically the

same question as force vital capacity I just covered, but this time for functional capacity and for six-minute walk, again, asking for your interpretation of these results.

The Aldurazyme clinical data have demonstrated strong statistical support for an improvement in the six-minute walk test. The primary endpoint approached a statistically-significant difference between groups in favor of Aldurazyme. A statistically-significant difference, treatment effect, after controlling for baseline variables was observed.

This is the analysis of co-variants. Again, similar to the FVC question, in this question to you they've asked, they've highlighted a difference of baseline between the groups and have suggested that this might be responsible for the observed treatment effect. The analysis of co-variants helps mitigate this concern.

The Aldurazyme clinical data have demonstrated a clinically-significant improvement in six-minute walk tests. Again, as Dr. Cox noted, 41

percent of Aldurazyme patients had a clinically-meaningful 54-meter increase in their six-minute walk test versus just 13 percent of placebo patients. Again, this is an analysis in individual patients showing improvement as opposed to group changes, and, therefore, again, helps mitigate concern that a difference at baseline is solely responsible for the observed treatment effect.

Finally, there's additional support for the results on the six-minute walk test. The extension study data are positive. Patients treated with Aldurazyme during the double-blind portion of the study maintained and continued to improve in the extension study, and patients treated with placebo in the double-blind portion of the study improved after rolling over to Aldurazyme treatment in a fashion very consistent with what we saw in Aldurazyme-treated patients from the beginning of the double-blind study.

It demonstrated an improvement in shoulder flexion in patients with restriction at baseline and an improvement in New York Heart Association scores in the Phase 1/2 study. Both of those help speak to an

improvement in overall functional capacity in these patients.

Finally, again, I ask you to consider that these patients are extremely heterogeneous at baseline. So when you interpret these data, they become more impressive when you consider the nature of the disease at baseline. Taken as a whole, the results related to functional capacity are both robust and meaningful.

I would like to actually now return back to Questions 2 and 4, which are both basically the same questions, except one is related to force vital capacity and one to the six-minute walk test, and they ask you about subset analyses.

Specifically, the agency has taken the Phase 3 double-blind data and has performed subset analyses according to traditional demographic subgroups like age and gender, and developed conclusions that there were differences in the treatment effect observed between these subgroups. We've done the same analysis and looked at the same data and have come to a different conclusion, and these points basically

summarize our perspective on this approach.

We believe that patient heterogeneity at baseline seriously limits the usefulness of these subset analyses, unless they're based on clinical manifestations of the disease at baseline. However, when you do these analyses, you actually see that the p-values for treatment effect are maintained for nearly all analyses after co-variant adjustment.

Nonetheless, the agency's conclusions have no effect in these demographic subsets that are based on small numbers, which they actually note in the question, and are not supported by improvements that we see in individual patients. Finally, it's important to note that from our perspective we see no biological plausibility for differences based on these demographic subsets.

The next question you have is Question 5 that asks for your interpretation of the effect of antibodies to Aldurazyme on the long-term efficacy of the treatment. It's important to point out the following couple of points:

As we've shown you, there's no data to

suggest any effect of antibodies on efficacy outcomes, and this conclusion is driven by one-year data from the force vital capacity and six-minute walk test results of the Phase 3 study and three-year data from the sensitive measures of urinary GAG levels and liver volume in the Phase 1 study.

But we would, of course, like to note that this is an important subject and we recognize that. So, therefore, we would like to note that we are, of course, open to working with the agency to determine the most appropriate means of continued data collection on this subject post-approval.

Looking at the next question, it is asking for your interpretation of the effect of antibodies to Aldurazyme, possibly cross-reacting with endogenous iduronidase, and thereby worsening the clinical course of these patients. There's really three basic points I would like to make on this subject.

The first is that endogenous iduronidase is intracellular in the lysosome and, therefore, is not accessible to circulating antibodies. There's over ten years of experience in treating Gaucher's disease

with enzyme-replacement therapy, and these data indicate no impact of antibodies to the drug product on the endogenous levels of the enzyme in those patients.

Finally, the most important point probably to remember, that all patients in the Aldurazyme clinical trials do have residual levels of iduronidase, and they've all developed antibodies, as you've seen, but yet we've also shown you that the data show that their efficacy improvements are maintained over time.

Finally, you have been asked to interpret the use of Aldurazyme in patients with profound respiratory impairment at baseline. As you can see in the question, this basically stems, in particular, from one particular result in a patient who received Aldurazyme during the extension study. This was a serious adverse event that Dr. Cox noted earlier.

But it is important to remember the context that Dr. Cox mentioned in his talk, which is that there are many patients' examples who have had a similar degree of respiratory impairment at baseline

who have not had serious adverse events after treatment with Aldurazyme. So it is important to remember that in context when considering that issue.

Nonetheless, we recognize it is an important question. So, clearly from our perspective, we believe patients with profound respiratory impairment can be treated with Aldurazyme as long as they're carefully managed by their treating physician.

You will also note that in your question today it was asked of you, "Should this be a specific warning in the labeling for Aldurazyme?" We don't think that's necessary, but we do fully support the thought, the idea that this become a precaution in the labeling to make sure that physicians have all the information they need related to treatment.

I would like to just conclude with a few big picture thoughts for you. You've heard today from Dr. Muenzer that MPS I is a heterogeneous, progressive, and clearly serious and life-threatening disease. The rationale for enzyme replacement therapy is very well-established.

The pre-clinical studies of Aldurazyme were

predictive of a successful outcome in patients, and the Aldurazyme clinical studies have demonstrated clinical benefit. Enzyme replacement therapy performed as expected. Lysosomal storage was cleared, and this translated into clinical benefit that was both meaningful and consistent with the nature of the disease in these patients at baseline.

We have demonstrated a good safety profile for the product and that infusion reactions, when they occur, are manageable. All this translates, from our perspective, into Aldurazyme having a favorable risk/benefit ratio.

I hope this presentation has been helpful to you. We're certainly very excited and pleased with the results of these clinical studies, and we hope they help convince you to support the approval of Aldurazyme for the treatment of MPS I and, thus, the opportunity to make it available to patients with MPS I.

That concludes our presentation. I would like to say that I was actually going to propose that I could stay at the podium to help manage any

questions you might have. We have a variety of people who are here and are willing and able to help answer questions. I'm happy to field those, point them to the right person, to ensure you get any answers that you might need to questions. So if that works, I'll stay up here.

Thank you very much.

CHAIRMAN AOKI: The sponsor is now open to questions from the Committee. Dr. Sampson?

DR. SAMPSON: I had a number of questions that relate to the questions that the agency has asked us. A lot of them are statistical, some of which you have touched upon. I would try to go through them quickly.

My first question is, why were both FVC and six-minute walk distance chosen as co-primary, given the difficulty in demonstrating significance in two co-primary variables? Could you briefly say the rationale for that?

MR. PATTERSON: Sure. I can ask Dr. Cox to help us with the rationale for the choice of both endpoints, if that works.

DR. COX: Initially, we had actually proposed having the six-minute walk test as a secondary endpoint, specifically because of the reasons of trying to enroll patients who would be at a given level of morbidity for both endpoints. However, there was some concern on the agency's part about FVC perhaps being a surrogate endpoint for improved respiratory function. It was really on their insistence that both co-primary endpoints were chosen. The agency did recommend limiting the distance walked as an entry criteria, but we felt that, because of the rarity of the disease, we really could not enroll enough patients.

DR. SAMPSON: Thank you. The next question I had was, there's a brief note in the agency's review about the sizing, sample size. I understand the difficulties in patient population, but could you say just a little bit, please, about the power on the sample sizing for FVC in the design of the trial?

MR. PATTERSON: Yes, we would be happy to. Can I ask Karen Walton-Bowen, the statistician for the study, to help us answer that question?

DR. WALTON-BOWEN: Yes. The sample size considerations for this trial were driven by both the force vital capacity and the six-minute walk test in terms of change from baseline to week 26 in the percent of predicted normal and the six-minute walk for the treatment group versus placebo.

The power is actually 80 percent, and the significance level for testing was 5 percent. This led to 21 evaluable patients in the treatment group, and there were 45 patients randomized into the study.

DR. SAMPSON: I'm sorry, perhaps I'm just not catching this quick enough, but are you saying that you powered this for -- each group changed in FVC from baseline and then you powered it for a difference in changes of 15 percent?

DR. WALTON-BOWEN: Yes. That was based upon some advice that we had at the time, and perhaps Gerry would like to talk about the clinical impact of those changes.

DR. COX: There were discussions held with experts regarding what might be an attainable change in percent predicted FVC, and 15 percentage points was

considered probably the most reasonable upper limit of change.

DR. SAMPSON: This is change from baseline?

DR. COX: No, this is percent predicted change, absolute change in percent predicted.

DR. SAMPSON: But within treatment group from baseline, are we looking at the difference across changes? I'm still not clear on that statement.

DR. WALTON-BOWEN: Yes, that's correct, Dr. Sampson.

DR. SAMPSON: Which is correct? I'm sorry?

DR. WALTON-BOWEN: Yes, it's the difference between the treatment and the placebo group.

DR. SAMPSON: In their changes?

DR. WALTON-BOWEN: In their changes from baseline to week 26.

DR. SAMPSON: Okay. The next question was, the Wilcoxon was designated as the primary analysis of the co-primary variables, is that correct?

DR. WALTON-BOWEN: That's correct.

DR. SAMPSON: Just two final questions: One was in terms of the analysis of co-variants --

DR. WALTON-BOWEN: Yes.

DR. SAMPSON: -- which has been raised as an issue by the analyses certainly that's been done by the agency. Could you say a little bit -- there was a statistical analysis plan finalized before the blind was broken.

DR. WALTON-BOWEN: Yes.

DR. SAMPSON: How did you handle the co-variants? And then I'm going to ask you specifically, did you look at the co-variants of gender and baseline severity individually without being put in a group? And when you examined those, did you look at the interaction of baseline severity with treatment and the interaction of gender with treatment?

DR. WALTON-BOWEN: Okay, could I have slide 14, please? This is giving details about the analysis of co-variants with the six-minute walk test. The week 26 six-minute walk was the dependent term in the model with main effect terms for treatment, center, gender, height, liver volume, and baseline walk. These were put into the model as a group. They weren't put in separately. Because of the small

numbers of patients, we kept it to main effects and we didn't have interactions in the model.

After controlling for these co-variants, we saw a significant treatment effect at p equals 0.039. As the previous speakers have alluded to, we believe this is a more appropriate analysis to adjust to the baseline variables because, six-minute walk, the main analysis was on the raw meter change. It's not normalized for factors which are known to affect the six-minute walk test.

DR. SAMPSON: But, specifically, you wouldn't have an analysis with just the change in FVC treatment and gender, and the interaction of those two, that might help some of us that are more analytically-inclined to answer some of the questions raised by the Food and Drug Administration?

DR. WALTON-BOWEN: We did not do that.

DR. SAMPSON: Okay. Finally, do you have confidence intervals, 95 percent confidence intervals, on the treatment effects for FVC and the six-minute walk that we could see exactly the variability in the treatment effects for both of those?

DR. WALTON-BOWEN: I don't have those right at this minute. It may be something we can get for you this afternoon. We did do that in response to one of the European agency questions, and we used Hodges-Lehmann estimates to put those confidence intervals also on the treatment effects.

DR. SAMPSON: It seems that would be helpful to allow some of the people here to assess the upper magnitude of the possible effect.

DR. WALTON-BOWEN: Uh-hum. Okay, we'll work on providing that for you for this afternoon's session.

DR. SAMPSON: And do you have any graphs of the --

DR. GRADY: Can I ask something?

DR. SAMPSON: Sure.

DR. GRADY: Can you tell us how you chose those co-variants? I mean you have infinite possibilities.

DR. WALTON-BOWEN: Yes. Those were pre-specified in the statistical analysis plan after discussions with the medical monitor as to which

baseline variables may influence the outcomes of the six-minute walk test.

DR. GRADY: So these weren't chosen based on differences -- you know, there were quite a few kind of surprising differences in the groups at baseline for a randomized trial, even though it was small. So it wasn't chosen based on differences between the groups?

DR. WALTON-BOWEN: No, it was chosen based upon what was medically thought to influence the outcome of that test.

DR. SAMPSON: And do you have any graphs of the change within patients of FVC versus change in liver size?

DR. WALTON-BOWEN: I do, and, Dr. Cox, would you like to speak to that?

(Pause.)

DR. GRADY: Could we just ask one more question? I'm sorry. The outcome of the previous analysis was still percent change from baseline, right? So, essentially, it was also adjusted for the baseline value? No?

DR. WALTON-BOWEN: For the FVC it was change in the percent predicted. It was an absolute change in the percent predicted FVC, and for the six-minute walk it was an absolute change.

DR. GRADY: No, no. So you're saying it was -- so, essentially, it was unadjusted for the baseline FVC?

DR. WALTON-BOWEN: The -- yes. Yes.

DR. GRADY: So it was absolute difference from the end of the study, from baseline to the end of the study, in predicted FVC?

DR. WALTON-BOWEN: In percent of predicted FVC, yes.

DR. GRADY: So it really isn't adjusted for that baseline difference in FVC between the two treatment groups?

DR. WALTON-BOWEN: The baseline difference is put into the model. We also did a stratified Wilcoxon that just had the co-variant of the baseline difference as well.

DR. GRADY: Well, you didn't have baseline value listed as a co-variant in the model? They did?

DR. WALTON-BOWEN: I put up the six-minute walk. We can go to the slide for FVC, which has the baseline in the model.

DR. GRADY: Okay. And for the six-minute walk?

DR. WALTON-BOWEN: The baseline was also in the model.

CHAIRMAN AOKI: Dr. Joad?

DR. JOAD: I just wanted to have been here while we're talking about the actual data. Is your data all done for FVC percent predicted based on the original height or based on the current height?

DR. WALTON-BOWEN: We did it both ways.

DR. JOAD: And all the data that we just saw --

DR. WALTON-BOWEN: Is baseline height.

DR. JOAD: Baseline height?

DR. WALTON-BOWEN: Yes.

CHAIRMAN AOKI: Dr. Follman?

DR. FOLLMAN: I had a few questions as well. First of all, you showed dramatic decrease in urinary GAG in both your Phase 1 and Phase 3 studies. Do you

know what the normal value is for urinary GAG?

MR. PATTERSON: I would like to ask Dr. Kakkis to help us address that question, please.

DR. KAKKIS: Urinary GAG excretion approached near normal in the studies. In the Phase 1/2 study, normalization was achieved by the three-year point for excess urinary GAG excretion based on adjusted-for-age ranges because individuals at different ages have different urinary GAG excretion. If you look at three years of treatment in the Phase 1/2 study, it showed 98.6 percent of the excess above the 95th percentile for age in urinary GAG excretion.

In the Phase 3 studies the urinary GAG excretion was near normal, but still was above the normal range. But because it is age-adjusted, because it's different for different ages, it's difficult to do the calculation without having made that adjustment.

DR. FOLLMAN: I also have some questions, building on what Dr. Sampson mentioned earlier. I think it was in the FDA's document they also did an analysis of co-variants on six-minute walk distance,

but in that analysis they only had one co-variable, which was the baseline value in six-minute walk distance. As I recall, it had a pretty small p-value, smaller than what you've presented here.

I was wondering, you know, that made me wonder, and I was wondering if you had plotted the change in six-minute walk distance for your Phase 3 studies baseline to end of study.

MR. PATTERSON: I would like to ask Dr. Cox or Karen Walton-Bowen to address that one, please.

DR. WALTON-BOWEN: Can I have slide 17, please? This is the change from baseline to week 26 in the six-minute walk. This is the change. On this axis is the baseline six-minute walk. The open circles represent the Aldurazyme group, and the filled circles represent the placebo treatment group.

You can see that across a wide variety of the baseline six-minute walks we have a different magnitude of changes across. We're not seeing the typical regression to the mean pattern that you would expect if the baseline differences were having an effect.

DR. FOLLMAN: Relatedly, do you have walk distance as a function of age, both for baseline and for the change, if you have a plot like that?

DR. WALTON-BOWEN: No, we didn't do that.

CHAIRMAN AOKI: Dr. Joad?

DR. JOAD: Yes, I have a couple of questions with regard to FVC. One is to have you explain again why you think you should use baseline height rather than current height, as is the typical.

MR. PATTERSON: I would like to ask Dr. Cox to address that question, please.

DR. COX: So in the clinical study we used the percent predicted FVC to normalize FVC volumes across patients of very different ages and sizes, and the percent predicted formulas that we used are dependent upon height. In fact, the one that we used for the majority of the patients from age eight onward was the Hankenson formula, which has height squared as part of the model.

When patients were receiving Aldurazyme, investigators told us that they noticed that patients were standing taller; their joints were releasing, and

that they were increasing in height, not due to necessarily linear growth, but just through the straightening of their posture.

The effect of this was really to systematically increase the predicted FVC and thereby decrease the percent predicted FVC of the lung volume changes that we were seeing in patients treated specifically with Aldurazyme.

Next slide. We have plotted out and calculated the percent predicted FVC using both current height as well as baseline height. You can see in the placebo group they show somewhat of a decline in percent predicted FVC using current height. The Aldurazyme group shows a modest increase, and the difference was 4.3 percentage points, which was significant.

Using the baseline height, which was in our presentation, you now see that the percentage predicted FVC is closer to zero change in the placebo group and a much higher change, 4.9 percentage points, in the Aldurazyme-treated patients, such that the difference between groups is 5.6 percentage points.

This was also statistically-significant in the Wilcoxon Rank Sum.

We also plotted out the changes in raw FVC volumes seen in this patient population, and in the placebo patients it actually declined by 17 cc's. The Aldurazyme-treated patients increased by 103, and the difference between groups was 120 cc's, again, statistically-significant.

This 120 cc's is on a baseline mean lung volume of approximately 1 liter. So it represents about 10 to 12 percent improvement from baseline.

And just to show you that, in fact, this was the explanation for the changes, if you look at the prepubertal patients in each group, the mean rate of height increase was 4.7 centimeters during the six-month time period, which is double the normal growth rate, and in the placebo-control patients it was 2.7 centimeters in six months. If you look at all the patients, you can see that the Aldurazyme-treated patients did go up in height more than the placebo-treated patients.

DR. JOAD: Did you do anything to try to

show that -- I mean, it doesn't seem to me you did show anything with contractures in the knees or anything that would go along with your hypothesis about that the increase in lung function was not related to -- that you didn't have to correct for growth as part of the increase in lung function.

DR. COX: Right. We found it very difficult to tease out what was true growth because the patients were also gaining weight. So we suspect there was some growth. But we also heard from investigators that just the patients were standing taller.

We did measure other joint range of motions. We looked at not only shoulder flexion, but also shoulder extension, knee extension, and this is a summary of some of that data here.

You can see that, with treatment -- let's see, I think you were asking specifically about the knee. This is right knee extension, left knee extension, right knee flexion and left knee flexion. You can see that there's variable increases in Aldurazyme-treated patients relative to placebo. Then in the open-label extension, the majority of these

joints are improving by several degrees in both the placebo-crossover patients as well as patients treated with Aldurazyme for 50 weeks.

DR. JOAD: I am assuming you would be talking about left knee extension and hip extension to get taller, right?

DR. COX: Yes. We didn't measure hip extension or flexion specifically.

DR. JOAD: So left knee extension was not very much? Am I right?

DR. COX: The difference in the left knee was not very much. The right knee was 5 degrees. In fact, in the patients who crossed over from placebo, after six months of treatment they showed approximately a 4- to 5-degree improvement, and those who continued on Aldurazyme for 50 weeks had nearly doubled that to an 11- to 13-degree improvement.

DR. JOAD: Then my last question has to do with your data about proportion of patients who had an 11 percent improvement in FVC. Was that an 11 percent improvement in the actual number of FVC or was it percent predicted? If it was percent predicted, was

it based on the original --

DR. COX: No, it was in the --

DR. JOAD: -- or on the current?

DR. COX: It was the raw lung volume.

DR. JOAD: So it was not corrected --

DR. COX: It was based on cc's.

DR. JOAD: -- for growth at all?

DR. COX: No.

DR. JOAD: Did you look at it? Did you do your proportions based on percent predicted based on current height, which would be corrected for growth and corrected for size of a patient?

DR. COX: The 11 percent improvement was based on the raw lung volumes, not on percent predicted. If you look at the change that we saw, the 5.6 percentage point difference, using the baseline height relative to the baseline of approximately 50 percent predicted, on average that was consistent with what we saw in the raw lung volumes, about a 10 to 12 percent improvement.

But the numbers I was showing you regarding the proportion of patients with 11 percent

improvement, those proportions were based on raw lung volume.

DR. JOAD: Over a six-month period?

DR. COX: Yes.

DR. JOAD: Yes.

DR. COX: Thank you.

CHAIRMAN AOKI: Any further questions? Dr. Woolf?

DR. WOOLF: Can you tell us something about the growth of the children who were prepubertal in the treated group? Did they grow better or not grow better? Did the pattern of bone abnormalities improve or not? And, lastly, I realize it is not in the application, but with spleens this big, were there signs of hypersplenism and did that improve?

MR. PATTERSON: There's a couple of questions there. I would like to ask Dr. Kakkis to help out with those, if possible.

DR. KAKKIS: When looking in the Phase 3 trial in terms of height growth or weight growth velocity, there wasn't sufficient height growth data pre-treatment to be able to compare the growth rates

in these patients. It was looked at, but there was not sufficient data to do that.

There were relatively few patients in the Phase 3 that were prepubertal. I can show you some data from the Phase 1/2 trial, if you would like to see that, on height growth velocity.

Can I have slide 113? In the Phase 1/2 study, we studied six patients of the group who were prepubertal based on Tanner scoring, and we looked at both height and weight growth. All patients were growth-deficient; many of them were less than 50 percentile.

If you compare, then, pre-study heights and weights, we looked at data from two years. These are data coming from their pediatricians for which the methodology was not well-established. However, during the study we measured heights using a statiometer and an appropriate mean of three independent measurements, as performed in our CRC.

The mean growth rates for these patients was 2.8 centimeters per year at pre-treatment and increased to 5.32 centimeters per year at week 52. It

was a mean nearly 100 percent increase in growth, and in weight we saw a similar increase, in fact, 135 percent increase in weight growth velocity concomitant with that height growth.

The next slide just shows a visual look at patients in the study. The dark line is their baseline growth rate based on pre-treatment values obtained from their pediatricians, and then the hashed is the first year and the other bar is the second year. You can see a fairly consistent increase in height growth velocity in these patients after treatment.

On the next slide it shows the weight growth velocity, also showing fairly consistent improvement in patients in weight growth after treatment. I think the data show that there is some improvement in growth height and weight in these patients after treatment, and in the Phase 3 trial there may be some improvement in height, but there's also clearly some improvement in joint function. So it's difficult to separate those two elements in that study, which is why we ended up using the baseline height.

DR. WOOLF: And hypersplenism?

MR. PATTERSON: Dr. Kakkis can also answer the second question. Maybe could you repeat the question just briefly for us? Thank you.

DR. WOOLF: All right. With spleens as large as in these children, certainly speaking as an internist, I would have expected to find hypersplenism, that is, decreased platelet counts, perhaps red cell turnover, increased red cell turnover as well.

DR. KAKKIS: There is significant splenomegaly in these patients, but it's several-fold normal. It's not the type of hypersplenism that you see in Gaucher's disease, where the spleen is maybe a hundred times normal. So those spleens that are enlarged, they're not having as great a hemologic impact as you might expect, for example, from Gaucher's disease or Neimann-Pick disease.

In the Phase 3 trial, when you looked at platelet counts, they weren't abnormal at baseline, but, clearly, after treatment there was a difference in the treated group of about 50,000 platelets

compared to the untreated group. So that there clearly was some impact of splenomegaly on platelet counts in these patients and that those improved with treatment.

CHAIRMAN AOKI: Dr. Levitsky?

DR. LEVITSKY: Dr. Sampson had asked a question a moment ago about the correlation between the change in liver volume and the FVC, and the slide got flashed up and then it got lost. So I would be interested to see that, if you could.

MR. PATTERSON: Sure. Dr. Cox, can you help us with that one, please?

DR. COX: This is a scatterplot of the two patient groups, placebo in black circles, the Aldurazyme in open circles. This is the percent change in liver volume on the X axis, percent change in predicted FVC on the Y axis. As expected, with treatment, patients receiving Aldurazyme show a shift to the left, indicating reduction in liver volume.

You can see that many of them have also shown improvements in the percent predicted FVC, but for a given level of reduction of liver volume there's

a wide range of changes in percent predicted FVC. What this indicates to us is that liver may be contributing somewhat to the improvement in the lung volume, but there are clearly other factors that are playing a role.

CHAIRMAN AOKI: Dr. Schneider? Dr. Schade?

DR. SCHADE: Yes, I'm having some difficulty understanding the mechanism between the treatment and the effect. In other words, I understand you have measured reduction in liver volume, but what I don't see, the outcomes you're measuring could be due to many changes in ribcage, liver volume, et cetera.

I understand you've measured a decrease in urine abnormal products, but what I don't see any, I haven't seen any histological data at all showing any tissue change in the abnormal lipids that accumulate or anything to indicate that your enzyme treatment is doing anything to the underlying pathophysiology.

MR. PATTERSON: Dr. Kakkis, can you help us answer that question, please?

DR. KAKKIS: If you would like, I can show you some data about urinary GAG excretion in the

canine model which relate to histopathology which --

DR. SCHADE: No, I'm not interested in the urinary data. I'm interested in the tissue data.

DR. KAKKIS: Right. What I'm saying is I could show you some data on urinary GAG and relate it to tissue GAG levels in the dog. We did not do biopsies in our trials with the children. There's certainly a number of anesthetic risks in doing that, and we opted not to do tissue biopsies.

With regard to liver --

DR. SCHADE: Well, do these lipids accumulate in the skin or any other tissue that's easily accessible that would show that, in fact, your treatment is actually doing anything to the underlying pathology?

DR. KAKKIS: Well, we feel that looking at liver volume is one way to look at storage, and the reason is that it is well-established that liver storage and the volume of liver is related to the storage of vacuoles within the liver. Now you could look at how many lysosomes are in livers or you can just weigh the whole liver and see how big it is. The

reality is that it's a better quantitative measure of liver storage just to look at the liver volume rather than to do a liver biopsy.

Secondly, doing a liver biopsy would be not a very rigorous test of whether an enzyme is treating these patients because there are so many other tissues that contribute to the disease that knowing that wouldn't help us.

Similarly, with a skin biopsy, we did skin biopsies but for other reasons, but these were not done -- only pre-treatment and not post-treatment. But if we showed improvement in the skin, I'm not sure how that would relate to the treatment of other aspects of the disease.

So, unlike some of these -- and I know you've heard two days of Fabry's disease and liver and renal disease. There's not any single tissue that we could access readily that would demonstrate to us that the disease would change. So we felt that clinical measures would be more to the point in demonstrating benefit in these patients.

DR. SCHADE: So are you saying that this

tissue doesn't accumulate in the skin or any other easily-accessible tissues, just in tissues that you can't reach?

DR. KAKKIS: No. What I'm saying is there's storage throughout the body in these patients, but the sites of storage that are critical to the clinical disease course and the clinical benefit in these disease are not as readily-accessible, things like synovium for the joint storage or, for example, other connective tissues or perhaps lung would be involved --

DR. SCHADE: Well, we heard about the breathing difficulties and the fact that there were redundant tissues in the breathing passages and the tongue was large, and so forth. It seems to me there are many tissues that are accessible. I just want any indication that you're actually decreasing the underlying pathophysiology. All I was really seeing is indirect evidence of liver size or something like that, and what you are measuring is complex clinical outcomes.

I'm actually very surprised that in the

short period of time you are seeing such a major clinical benefit because, as you were here the last two days, they had difficulty seeing clinical benefit. Yet, they were able to demonstrate an improvement in the underlying pathophysiology in the tissue accumulation of the abnormal compounds.

Here we are seeing just the opposite. We're seeing a number of clinical benefits without any evidence that the underlying pathophysiology is being corrected. Now liver volume is a very indirect measure. I'm very pleased the liver volume decreases, but there are things like glycogen, and so forth, that change liver volume that have nothing to do with this underlying disease.

So what I am saying is I'm very surprised that we're not seeing any mechanistic look/see at accessible tissues because all these tissues accumulate something. We don't even know, for example, in your walk test whether it's improvement in joint mobility, lung function, et cetera, that lets these patients walk farther, because it's such a complex actually endpoint that you're measuring.

I just wanted to see some human tissue that's improving at any level to indicate that systemically you're having a beneficial effect.

DR. KAKKIS: Let me address that by talking about the measures we did use and explain a little better why we used them.

CHAIRMAN AOKI: Let me stop you there. If you don't have the tissues that Dr. Schade is referring to, then I don't think you need to proceed any further.

I would like to go on to the final -- Dr. Watts?

DR. WATTS: I'm still trying to understand the six-minute walk test. I realize that your subjects were recruited based on reduced lung volumes and the ability to walk for six minutes, stand for six minutes, but there was no upper limit. Therefore, you had a lot of subjects or a number of subjects who seemed to be walking reasonable distances.

While there's a wide range of normal, and it's possible to go from normal to better, I really couldn't see the graph that was up there that looked

at the baseline versus the change. I was curious how much of a change you saw in the subjects who were most severely limited in their six-minute walk at baseline.

MR. PATTERSON: I could ask Dr. Cox to help us answer that question.

(Pause.)

DR. FOLLMAN: Would you just like to see that slide we saw earlier again?

DR. WATTS: I would need at least a two-line improvement in my visual acuity to be able to see that slide.

(Laughter.)

DR. COX: We did look at changes in the six-minute walk test distance according to severity. We performed a median analysis and looked at patients above and below the median. What we did see was relatively similar difference between groups in the six-minute walk test distance, 35 to 42 meters.

DR. WATTS: What was the median?

DR. COX: The median was 38 meters. Oh, sorry, the median six-minute walk test distance, the median was approximately 350. It varied a little bit

between groups. So that represents about a 10 percent improvement.

CHAIRMAN AOKI: At this time we'll take a very punctual 10-minute break because we will start in 10 minutes.

(Laughter.)

(Whereupon, the foregoing matter went off the record at 9:58 a.m. and went back on the record at 10:09 a.m.)

CHAIRMAN AOKI: Advisory Committee members, please take your seats.

(Pause.)

Okay, the Advisory Committee members are now present.

Dr. Irony is doing the FDA presentation. Dr. Irony?

DR. IRONY: Members of the Committee, good morning. My name is Ilan Irony, and I'm a medical officer at CBER. I'll be presenting today our review of the data obtained in clinical trials for the use of laronidase in the treatment of mucopolysaccharidosis Type I or MPS I.

BioMarin proposes the use of laronidase for the treatment of patients with MPS I. The proposed dose is 0.58 milligrams per kilo or 100 units per kilo, given intravenously once a week.

MPS I is one of a group of lysosomal storage diseases. It's due to a deficiency of iduronidase or IDU. Heparan sulfate and dermatan sulfate are lysosomal degradation products. IDU cleaves to terminal iduronic acid residues of these compounds. Deficiency of the enzyme leads to progressive accumulation of glycosaminoglycans. For the purpose of this presentation, I will abbreviate the glycosaminoglycans as GAG.

MPS I morbidity and mortality are related to complications of airway disease and pneumonias, cardiomyopathy, and heart valve disorders, and progression of hydrocephalus and neurologic decline. Hurler, Hurler-Scheie, and Scheie syndromes are three clinical categories of MPS I, defined on the basis of their overall severity, but these are arbitrary definitions in a continuum spectrum.

The diagnosis of MPS I is made by the assay

of the deficient or dysfunctional enzyme IDU. The assay is carried out in serum, leukocytes, or skin fibroblasts obtained from punch biopsies.

The only treatment available is supportive care, primarily to manage complications of MPS I. Allogeneic bone marrow transplantation has been tried as a means of replacing the enzyme, but this treatment is restricted to the most severe patients with Hurler. It can be effective, but usually only to patients younger than two years of age. There is significant morbidity and mortality associated with bone marrow transplantation, and it has not been shown to prevent or treat a neurologic decline that accompanies MPS I.

This table shows an overview of the clinical studies conducted. There is only one controlled study, which is Study 003, which we'll present in more detail later.

Certain subjects did not meet the entry criteria and are participating in an expanded access study, shown in the last row. All studies use a similar laronidase dose of 0.58 milligrams per kilo or 100 units per kilo, given intravenously once a week.

In the next five slides I will discuss the Phase 1 study, BIO7500. This Phase 1 study was designed as a single-arm, open-label study, initially to last 26 weeks. That study has been subsequently expanded. Ten subjects older than five years in both genders enrolled.

To meet the eligibility requirements, they had decreased IDU activity and hepatosplenomegaly as well as increased urinary GAG excretion. The dose was selected from pre-clinical studies in the canine model of MPS I. The weekly dosing regimen is based on in vitro data in fibroblasts derived from patients with MPS I.

The study investigated effects of laronidase in many tissues and organs during this study in an attempt to cover the spectrum of disease activity. The most notable are listed in this slide: liver and spleen volume assessed by MRI throughout the study; urinary GAG excretion as expressed per milligrams of creatinine; joint range of motion, particularly knees, elbows, and shoulders; cardiac assessments, including electrocardiogram, echocardiogram, and functional

evaluations through the New York Heart Association scoring; airway assessments, including sleep studies and MRI of the upper airways quantified as an index of upper airway obstruction; assessments of the central nervous system such as brain and cervical cord MRI.

This slide summarizes the results of study BIO7500. All subjects had reductions in liver volume of at least 20 percent by one year of treatment. All subjects also showed reductions of urinary GAG excretion of at least 50 percent as early as week six of the study. Most subjects had improvements of joint range of motion, New York Heart Association scores, and sleep apnea.

However, in some objective assessments, such as echocardiogram parameters, visual acuity, central nervous system, and anatomic abnormalities, and bone evaluations, no changes were seen. The non-controlled, open-label nature of this study precludes any conclusion about clinical efficacy.

This slide presents a summary of the safety data in BIO7500. Eight of the ten subjects had serious adverse events. Except for allergic

reactions, the serious adverse events were related to the background MPS I disorder.

Two of these serious adverse events were deaths. Subject 008 died at the end of her second year into the study of respiratory distress and arrest. The relevant pathologic findings were a viral lymphocytic myocarditis and bronchiolitis. This patient had high titers of anti-laronidase igG throughout the study and also complement activation early on, between weeks six and twelve. Subject 002 died after week 137 from complications of a surgical procedure.

All subjects developed anti-laronidase antibodies, as measured by an ELISA method. Of these, four remained positive using a more specific, Western Blot assay for antibody detection. The titers generally peaked at eight to twenty weeks of the study and declined over time.

In conclusion, weekly laronidase infusions have demonstrated bioactivity in areas of large accumulation of glycosaminoglycans, particularly liver and spleen, and on the excretion of urinary GAG.

There was no apparent correlation between anti-laronidase IgG titers or duration of seropositivity and the reductions observed in liver or spleen sizes or in urinary GAG.

Study BIO7500 has a non-controlled design with open-label use of laronidase which precludes demonstration of efficacy in the clinical endpoints proposed.

I will present now the design and the result of Study 003. Study 003 was the only double-blind, placebo-controlled, randomized study reported in this BLA submission. It was a 26-week, multi-center and multinational study. It enrolled subjects in both genders older than five years with IDU enzyme activity less than 10 percent of the lower limit of normal, symptoms and signs of MPS I, and the baseline of percent predicted FVC less than 80 percent. The laronidase dose used, as with other studies, was 0.58 milligrams per kilo IV given once a week.

The most notable evaluations, performed every four weeks during the study, are listed in this slide: pulmonary function tests, six-minute walk

distance, sleep study, liver volume, urinary GAG, joint range of motion, and electrocardiogram and echocardiogram.

The study had two co-primary endpoints. The first is the mean change from baseline to week 26 in the percent of predicted force vital capacity. This endpoint was chosen because of the permanent role of airway and pulmonary involvement in the morbidity and mortality of MPS I.

Subjects with MPS I were expected to have great variability in lung volumes. The percent of predicted force vital capacity is thought to reduce the variability due to the extra-pulmonary factors and enabling adequate examination of the pulmonary function.

Height is one of the variables, using the calculation of the percent FVC, and the protocol called for the calculation of the percent predicted FVC based on the height of the subject at each visit. For this presentation we will designate this as the percent FVC based on current height.

The second endpoint is the mean absolute

change from baseline to week 26 in the distance walked in six minutes. This test has been validated for assessment of certain conditions in a 30-meter platform that subjects being examined are required to walk. This endpoint can be relevant in MPS I, as it may reflect joint, cardiac, and pulmonary involvement, all affected by MPS I in a greater or smaller degree.

The six-minute walk test is also a measure of the important daily function. However, it has not been validated in MPS I. Furthermore, because of technical difficulties in certain sites, the test was performed for all subjects in a 15-meter platform.

The data extracted from this study cannot be compared to normative data external to the study or to observations made in other clinical entities. However, the data is valid for comparisons within the studies proposed, because all sites conducted the test in a similar walking platform.

The statistical analysis of these endpoints was performed with the Wilcoxon Rank Sum Test in the intend-to-treat population. The endpoints would be declared statistically-significant only if both had a

p-value of less than 0.05.

The study had four secondary endpoints listed in this slide: the Apnea/Hypopnea Index, liver volume, shoulder flexion, and the disability index from the Child Health Assessment Questionnaire or the Health Assessment Questionnaire. The study also explored multiple tertiary endpoints.

Forty-five subjects were randomized. Twenty-two subjects received laronidase at the 0.58 milligrams per kilo IV weekly dose, and 23 received IV placebo administrations. The study was conducted in five centers in four countries.

This table shows the demographic and baseline characteristics of the 45 subjects that took part in Study 003. There is an equal distribution across genders between the treatment groups. Most subjects were younger than 12 in both groups, and most fell in the clinical syndrome designation of Hurler-Scheie.

This slide continues to describe the baseline characteristics of the study participants. Both treatment groups were similar regarding the time

from onset of symptoms and the time from diagnosis. IDU enzyme activity was also similar between the groups and well below the 10 percent lower limit of normal required for eligibility. The subjects in both groups had similar weights and heights at baseline.

The percent predicted FVC and the distance walked in the six-minute test were the primary endpoints for the study. The laronidase group had lower values for both of these at baseline as compared to placebo. The baseline percent FVC and the six-minute walk distance will be presented with the results of the primary endpoints of Study 003.

This table shows the results of the percent FVC in Study 003. You can see that the laronidase group had a lower mean percent FVC at baseline, 48 percent in the laronidase group and 54 percent in the placebo group. After 26 weeks of the study, both were similar.

The statistical analysis was a comparison of the change from baseline to week 26 between the treatment groups by Wilcoxon Rank Sum, resulting in a p-value of 0.03. The difference between the groups is

4.5 percent.

The calculation of the percent FVC was based on the current height of each subject at the time of the study visits. After unblinding the study results, BioMarin proposed to analyze the percent FVC data using the baseline height rather than the height measured at each visit.

If true changes in joint stiffness and posture were to occur, there will be a change in percent FVC even without any changes in respiratory function. If this were a systematic change in posture, such as the lessening of posture abnormalities in the laronidase group, there will be a systematic effect to decrease the percent FVC.

Conversely, it was seen that the placebo-treated subjects had an apparent 3 percent decrease in the percent predicted FVC without any actual change in lung volumes. The actual change in respiratory function, which is a mean of zero, is better reflected in the percent FVC as calculated using baseline height.

If we compute the percent FVC calculated

based on baseline height, the mean percent FVC for the laronidase group increased 5 percent and showed virtually no change for the placebo group during the 26 weeks of Study 003. The difference between the changes in each group from baseline to week 26 would be 5.9 percent with a p-value of 0.02. For the presentation of the pulmonary results in Study 003, only the percent predicted FVC outcomes calculated on baseline height will be reported.

This figure shows the mean percent FVC in both treatment groups throughout the 26 weeks of Study 003. Placebo is represented in magenta, and laronidase is represented in green. The same plot in the briefing document was based on the percent FVC calculated on the basis of the current height but shows very similar trends.

As you can see, there is a small drop in the percent FVC from baseline to week four in the placebo group, occurring with a small rise in the laronidase group. After week four, the lines remain relatively stable, and a sharp rise in the percent FVC is seen between week 20 and week 26 in the laronidase group.

There was no clear explanation for the abruptness of this rise, but it accounts for much of the treatment effect seen in the percent predicted force vital capacity.

This slide shows the changes from baseline to week 26 in the mean absolute force vital capacity in the treatment groups. The laronidase group has a mean increase of 110 milliliters while the placebo group has a 20-milliliter decrease. The difference between the groups is statistically-significant.

This slide shows the changes in the percent predicted FVC observed in each treatment group by gender throughout the visits of Study 003. Females are represented by circles, and the males by triangles. As you can see, the drop in the percent FVC in the placebo group between baseline and week four occurs almost exclusively in the male placebo subset.

On the other hand, both males and females in the laronidase group contributed to the increase in percent FVC from week 20 to week 26. Females treated with laronidase had most of the effect, with a 7

percent increase compared to a 3 percent increase in males treated with laronidase. Male subjects on the placebo had a 4.6 percent decline in their mean percent FVC while female placebo subjects showed no change.

This figure presents the effects of laronidase in placebo on mean percent FVC at week zero and at week 26 in the different age categories. Each set of two columns represents mean week zero and mean week 26 percent FVC values. The two sets represented on the left side of this slide are the 7-to-12-years-of-age category. The middle two sets are the 13-to-18-years of age category, and the two sets of columns on the right are the 19-to-64-years category.

It is worth remembering that nearly half of the subjects are younger than 12. While there appears to be a larger increase in the younger subjects treated with laronidase, no clear pattern of differential in the between-group differences was apparent.

This figure shows the changes in percent FVC observed during Study 003 by levels of impairment in

pulmonary volume at baseline. Despite the high variation within the small subsets, a pattern of more change in the percent FVC in the least-impaired laronidase subjects emerges.

The distribution of subjects between the treatment groups resulted in an imbalance when we considered gender and degree of pulmonary impairment at baseline. Most laronidase males were in the two most impaired categories of the percent FVC range at baseline, and most females treated with laronidase were in the two least impaired percent FVC categories. This pattern of distribution suggests that the effects of gender cannot be distinguished from the effects of impairment of pulmonary volumes at baseline.

In the next few slides I will show the results obtained in the six-minute walk distance, the co-primary endpoint. This figure demonstrates the mean baseline in week 26 distances walked in the six-minute walk test for both treatment groups. The mean distance change in the laronidase group was a 20-meter increase while the placebo group had a decrease of 18

meters in their mean distance.

Please keep in mind that these changes occurred in subjects whose group baseline average distance walked was between 300 and 400 meters. The comparison of changes between the groups did not reach statistical significance.

This figure shows the changes in the six-minute walk distance over the 26 weeks of Study 003. Both groups had an initial reduction in distance walked between baseline and week four. In order to determine the baseline distance, subjects had to perform this test three times within a period of a week. The third distance measure was picked as the baseline value. The initial drop seen may possibly be attributed to a training effect of subjects during the baseline assessment that was lost after the interval of four weeks.

While placebo subjects remained constant, there is a slight and gradual increase in the mean distances walked by the laronidase subjects which did not reach statistical significance.

The figure on the left part of the slide

shows the mean distances walked during the Study 003 by male and female subjects of both treatment groups during the study visits. Males are again represented by triangles, and females by circles.

Female subjects treated with laronidase had a gradual increase in distance over the 26 weeks of the study, with a gain from baseline to week 26 of 68 meters, as shown in the table on the right. In contrast, laronidase-treated males had a decline similar to the placebo subsets.

This figure shows the changes that occurred in distance walked in both groups during Study 003 now divided by quartiles of impairment at baseline. The subsets least impaired at baseline had their mean distance change shown on the left and the degree of impairment in distance walked increases toward the right. No pattern can be distinguished between the treatment groups across the quartiles of mobility impairment at baseline.

This slide shows the mean distances walked at baseline at week 26 by subjects in both treatment groups now divided in age categories. The table on

the right side of the slide shows the differences between the changes in distance walked among the age category subsets. The difference in distance walked decreases as the age increases, so that most of the laronidase treatment is carried by the younger laronidase subjects.

Now we will present results of relevant secondary and tertiary endpoints of Study 003. This table shows the results of laronidase treatment during Study 003 in the Apnea/Hypopnea Index. An apnea episode is defined as cessation of airflow for 10 or more seconds, and hypopnea is defined as a 50 percent decrease in airflow per breath accompanied by arousal or desaturation.

The AHI, or Apnea/Hypopnea Index, is defined as the number of apnea and hypopnea events divided by the hours of sleep, reported as events per hour. Therefore, a decrease in the index is a favorable event.

The first data row shows the AHI results in the overall treatment groups with a slight decrease in the mean number of apnea and hypopnea events per hour

in the laronidase group. After unblinding of the results, the investigator responsible for interpretation of the data recommended to perform an exploratory analysis comparing the pediatric subjects with baseline AHI greater than 10 and adult subjects with AHI greater than 15 with those cutoffs for sleep apnea selected based on recent guidelines.

The exploratory analysis is seen in the second and third row of this slide. A mean decrease of six events per hour is seen in the most severely-affected laronidase subjects with no change seen in those with lower indices of apnea and hypopnea and baseline.

Liver volume was reduced by a mean 19 percent in the laronidase group while placebo subjects had no change in the 26 weeks of Study 003.

The other secondary endpoints, the disability index from the Children's Health Assessment Questionnaire, or Health Assessment Questionnaire in the adult patients, in shoulder flexion did not show a difference between groups with treatment during the study.

Similar to the Phase 1 data, a substantial decrease in urinary GAG was associated with laronidase treatment that started very early during the study period. Laronidase subjects had a mean decline of 108 micrograms per gram of creatinine in their urinary GAG excretion with a concomitant increase in urinary GAG in the placebo group.

The other tertiary endpoints were not supportive of laronidase effects on these endpoints.

BioMarin also became interested in a composite endpoint of five components to demonstrate the efficacy of laronidase. This exploratory analysis, however, was done post-hoc after unblinding of the data. No conclusions related to laronidase efficacy can be formed based on this data.

Pharmacokinetic studies were performed on 12 subjects treated with laronidase in two study sites. These studies were done at infusions 1, 12, and 26. A slight increase in the maximum laronidase concentration, or Cmax, was observed from week 1 to week 26. The volume of laronidase distribution decreased in half between the initial infusion and

week 12, from 0.6 to 0.3 liters per kilo, and remained the same until week 26.

The decrease in the volume of distribution can be affected by antibody formation. There was an inverse correlation between antibody titers and the volume of distribution observed. It isn't known if the distribution of antibody-bound laronidase is different than that of the unbound enzyme. It is also unknown if antibody formation results in a differential lysosomal uptake among organs and tissues.

This slide summarizes the safety data from Study 003. Most reported adverse events were related to the assigned study agent, with a similar prevalence in the placebo and laronidase groups. Approximately half of the placebo and one-third of laronidase subjects had infusion-associated reactions such as flushing, fever, headache, and rash. These reactions decreased with the use of pre-medications, mostly anti-inflammatory and antihistamines, and with slowing of the infusion rates.

The severe adverse events were most likely

related to the underlying condition of MPS I. The severe adverse events described in this slide were related to MPS I: abdominal pain from constipation resulting in hospital admission; worsening of cardiac valve disease that required surgery -- the surgery was complicated by cardiac arrest, sepsis, and renal failure -- and the partial obstruction of ventricular shunt.

This slide indicates the data on the immunogenicity of laronidase. Anti-laronidase IgG acid by radioimmunoprecipitation was detected from week 4 or week 8 to week 26 in 20 subjects randomized to laronidase. One subject treated with placebo had transiently-positive anti-laronidase IgG in only one visit. A protocol-mandated collection of serum for IgE and complement activation during fusion-associated reactions was performed three times, and they were all negative for IgE and complement activation.

The next two slides summarize the conclusions of Study 003, first, on the effects on the primary endpoints. Laronidase had a statistically-significant but small clinical effect size on the

percent FVC with an increase of 5 percent or 110 mL's of force vital capacity from baseline. The time course for observance of this effect was not uniform, with an unexplained, abrupt increase in the percent FVC in the laronidase group at the last visit in the study.

Part of the difference between groups also came from an unexplained decline in the percent FVC from baseline to week four in the placebo group. In addition, the effect was not uniform across the subsets analyzed. Females and subjects with moderate impairment of pulmonary restriction had shown the larger treatment effect.

The six-minute walk distance revealed a 38-meter mean absolute difference in the change from baseline to week 26 between laronidase and placebo which did not reach statistical significance with a p-value of 0.07. The effect was also not uniform across subsets, with larger effects seen in younger and female subjects.

The sleep studies in MPS I subjects treated with laronidase suggest the benefit in those subjects

more severely-affected at baseline. The pharmacodynamic effect of liver volume and urinary GAG reduction were noted in all subjects randomized to laronidase.

Frequent infusion-associated reactions were seen in both treatment groups, but these were generally mild to moderate and could be ameliorated with pre-medication and slowing the rate of the infusion.

Almost all subjects' anti-laronidase antibodies was positive. Over time there was a decrease in the volume of distribution with an increase in Cmax. It's unclear if these pharmacokinetic changes are related to formation of antibodies or what the long-term consequences are for laronidase safety and efficacy.

We will now turn to Study 006. This is an open-label, non-controlled extension to Study 003. All 45 subjects that completed Study 003 were enrolled. The study is presently ongoing. Data from the first 24 weeks were revealed for this presentation. BioMarin has submitted an update with

an additional 12 weeks of study, but these data have not been thoroughly reviewed and summarized.

As in previous studies, laronidase was infused at 0.58 milligrams per kilo every week. The infusions were conducted at the five original sites, but also at any of the thirteen regional subsites closer to the subjects' homes.

Most evaluations were performed at study entry, which was the last time point in Study 003 or week 26 in that study, and every 12 weeks thereafter. These evaluations were the same as those conducted in Study 003.

In the next nine slides I will show the results of Study 006 and compare them as appropriate with the results of Study 003. This figure shows the changes in the percent FVC during Study 003 and Study 006. The percent FVC in Study 003 is shown on the left part of the graph, corresponding to the first 26 weeks of the study. As we move to the non-controlled part of the figure, no additional increase in mean percent FVC was seen in the laronidase group, which continued to receive laronidase for an additional 24

weeks. The placebo group has shown no change in the mean percent FVC over these first 24 weeks of laronidase treatment, as shown.

These percent FVC changes were further analyzed by gender. The percent FVC changes shown on this slide were calculated with the current height of the subjects, as opposed to the baseline height that you have seen in the other slides. Again, this method of calculation of the percent FVC did not change the calculations on the data presented in this slide.

If you will recall from Study 003, females treated with laronidase had driven the treatment effect for the group with a 3 percent increase over 26 weeks. A comparable group would be of those female subjects randomized to placebo during Study 003 which now received laronidase for 24 weeks in this open-label extension. These female subjects exhibited a smaller mean improvement in the percent FVC. The male subjects in both groups did not show any changes in the percent FVC either during Study 006.

This table compares the effects of laronidase on the percent FVC changes calculated using

baseline height in the 26 weeks of Study 003 and during the first 24 weeks of Study 006 according to the age categories of the subjects at baseline. No changes can be seen in either group. If you'll recall from Study 003, the younger group had the highest increase in the percent FVC. When the comparable group, placebo subjects younger than 12 years of age, are treated with laronidase for almost the same duration, no change is seen.

The mean absolute lung volumes were minimal and similar in both treatment groups. Unlike Study 003 data showing greater effect in less-impaired laronidase subjects, no pattern can be seen during the 24 weeks of Study 006 between groups across the quartiles of baseline FVC impairment. This finding is not unexpected due to the absence of overall treatment effect.

We will now show the data on the six-minute walk distance during Study 006, also comparing as appropriate to the findings of Study 003. These figures show changes in the distance walked during both Study 003, on the left side of the graph, and

Study 006, on the right side.

During Study 003 a 20-meter increase was seen in the laronidase group. The same group had an additional 23-meter increase in distance walked during the first 24 weeks of Study 006. This increase was observed mostly between week 12 and week 24 of the extension study, shown here as week 38 to week 50 of the two studies combined.

Subjects randomized to placebo had a mean 18-meter decrease during Study 003. These same subjects had increased their mean distance by 24 meters compared to the end of Study 003, and most of this increase occurred in the first 12 weeks in the extension study, shown here as between week 26 and week 38.

Analysis of the six-minute walk distance by subset did not show differences across genders or across the three age categories or by the magnitude of mobility impairment at baseline. These findings are substantially different than the six-minute walk distance in the double-blind study, where females and younger subjects drove the treatment effect for the

laronidase group.

This slide shows the secondary endpoints of the sleep study data in Study 003 and Study 006. Concentrating on the left side of the table, we will see that, after a small decline of the Apnea/Hypopnea Index in the laronidase group during Study 003, no further improvement was seen during Study 006, and even possibly loss of half of the gain in Study 003.

Now on the right side of the table we see that subjects treated with placebo had shown no change during Study 003, but after they received laronidase in Study 006, they had a mean drop of 3.5 events per hour of sleep in the same magnitude as the laronidase group demonstrated in Study 003.

These slides present data in other secondary and tertiary endpoints of Study 006. The placebo laronidase group has a mean decrease in liver volume of 12.6 percent, comparable to the 19 percent mean decrease in the laronidase group during Study 003. The laronidase group had an additional 4 percent reduction in liver volume during Study 006.

Both treatment groups had a mean 6-degree

improvement in shoulder flexion during the first 24 weeks of Study 006. The disability index was unchanged in both groups during Study 006.

Finally, the urinary GAG excretion decreased by a mean of 69 percent in the placebo/laronidase group. Not shown in this slide, the laronidase group, which had a 54 percent reduction in urinary GAG excretion during Study 003, had an additional 20 percent mean reduction during Study 006.

This slide shows the safety data summarized for Study 006. The adverse events reported were similar to those seen in Study 003 and similar between the treatment groups during Study 006. One death was reported as a complication of an upper respiratory infection and bronchitis.

One notable serious adverse event has been a life-threatening anaphylactic infusion reaction that required an emergency tracheostomy. This subject had previously had a positive anti-laronidase IgE and complement activation and has had progressive worse episodes of urticaria and hypoxemia, controlled with the use of steroids.

This slide summarizes data on the immunogenicity of laronidase in Study 006. Forty of the 45 subjects in this study developed anti-laronidase IgG, as measured by the radioimmunoprecipitation assay. Of the 23 subjects treated with placebo in Study 003, 21 developed antibodies after being exposed to laronidase in Study 006, a proportion similar to those subjects randomized to laronidase in Study 003. Of the 22 subjects on the laronidase in Study 003, 20 were seropositive upon entry into Study 006. Another subject developed detectable anti-laronidase antibodies during Study 006.

On the other hand, two subjects that were seropositive during Study 003 became seronegative during the course of Study 006. No correlation could be established between the appearance or the persistence of these antibodies with the frequency of magnitude of adverse events during the study.

This slide will show the conclusions drawn from Study 006. No changes in the percent FVC were observed in either treatment group or in the subsets

of gender, age, and degree of impairment at baseline.

For the six-minute walk distance, a mean 20-meter increase was observed in Study 006 for both groups. For the placebo subjects, this increment reverses the decline seen in the double-blind study, and for the laronidase group this increase doubles what was seen in the double-blind Study 003.

For the six-minute walk test, exploratory analysis also did not show any differences among subsets of gender, age categories, and degree of mobility impairment.

Liver volume and urinary GAG were substantially reduced in both treatment groups.

Other secondary and tertiary endpoints did not lend support to the demonstration of efficacy of laronidase in the treatment of MPS I.

Now the last two slides will present the overall conclusions derived from the clinical studies submitted in this application. First, we will discuss the findings to support efficacy of laronidase in the treatment of subjects with MPS I. We will start with the primary endpoints, which were the same for both

controlled Study 003 and the non-controlled Study 006.

There was a small clinical effect on the percent FVC in six-minute walk distance reaching statistical significance only for the percent predicted force vital capacity. The effect observed was not consistent across subsets, usually higher in females and in less severely-affected subjects, and was not consistent over the time course of Study 003 for the percent predicted force vital capacity.

For the subjects randomized to placebo during the double-blind controlled study, 24 weeks of laronidase treatment were unable to change the percent FVC and resulted in minor gains in distance walked during the six-minute walk test.

Now for the secondary endpoints, the Apnea/Hypopnea Index declined in the most severely-affected subjects under laronidase treatment. The pharmacodynamic effect of liver volume in urinary GAG reductions indicate bioactivity of laronidase in tissues that accumulate large quantities of GAG.

The other secondary or tertiary endpoints were not supportive of a treatment effect.

This slide summarizes the safety of laronidase in this application. Frequent infusion-associated reactions were observed, but they could be managed without difficulty with rare exceptions. Most serious adverse events were likely related to the disease background. Almost all subjects developed anti-laronidase antibodies that persisted during the study period. No correlation was detected between formation of anti-laronidase antibodies and the frequency of adverse events or serious adverse events.

This concludes my presentation, and I thank you for your attention.

CHAIRMAN AOKI: Thank you. At this time we will take questions from the Committee for the CBER presentation. Dr. Follman?

DR. FOLLMAN: I would like to expand on a couple of questions that Dr. Sampson asked the sponsor a while ago. I would like to hear the FDA's perspective on why you had two primary endpoints for this study and why you required both to be less than p .052 to achieve significance.

DR. WALTON: In discussing this with the

company and what one might expect, I think actually the company gave a good sense of how those discussions went: that they were interested in examining the effect on FVC but, based upon our experience in a variety of other conditions, we had concerns about the ability to interpret a statistical change, a solely statistical change, in FVC and what would be the meaning for the patients.

So we asked them to examine endpoints that might be able to explain to us whether or not they were having any functional changes in their abilities. So they proposed, from within our discussions, they proposed the six-minute walking test as an evaluation of a functional capacity, and we've had certainly experience with this kind of test in other conditions and that that can be a very useful, informative endpoint about the functional capacity of patients. So that was how we came up with that.

And in the last part of your question, because we felt that the six-minute walking test was going to be so very important in supporting an effect on FVC as to its clinical meaningfulness of the effect

seen by, the effect conveyed by the enzyme, that it wound up being as co-primary endpoints.

DR. FOLLMAN: Was this an attempt in a way to do two studies simultaneously, to have both p-values less than .05 to be significant?

DR. WALTON: No, I think we looked at it as a single study. There's only a single set of patients randomized, but it is very true that these are two separate measures. I think that the information conveyed to you in our briefing document, as well as shown to you earlier, is that we're not convinced that, for instance, the effect on walking distance is solely an impact of FVC. So that there is an independence between the two measures, and to a reasonable degree they may be measuring very different effects.

So if your question is about the independence of, sort of the separateness of the benefits that might be examined, yes, we think that there is a degree of separateness.

DR. FOLLMAN: Well, it wasn't so much the separateness, I guess. Usually, you design a trial

where you have one primary endpoint. It's p .05, and then you're significant. Here you've got a much harsher threshold for the company to meet, which is you've got two endpoints; both have to be at .05. I was trying to understand why that was.

So the independence, or lack thereof, of the two endpoints doesn't really get to that, you know, get to why you have relatively -- why they have to show improvement on two endpoints for this study. Why was the bar set so high here?

DR. WALTON: It's also part of the -- the intention is that this single study was going to serve as the basis for making an approval decision. As you're well aware, the normal circumstance is to have two separate studies that both provide independent evidence, substantiation of the evidence in one case.

As has been explained in the prior days, the orphan drug status does not change how we examine evidence. So in light of that, there was a concern that we have ample evidence from a single study to be able to really evaluate a basis for approval.

DR. FOLLMAN: My next question has to do

with subgroups, which was a main theme in the questions that you have posed to us. Let me just say now I am wondering whether you did tests of interaction for, say, the two primary endpoints and some of the subgroups that you are interested in: gender, age, and baseline severity. Or were these observations of a differential treatment effect made more by looking at the numerical means and noticing that they were different or going in a particular pattern? So, shortly, briefly, did you do tests of interactions to supplement or buttress your observation about potential differential of a subgroup effect?

DR. WALTON: I would say that there were sort of two things that were playing into this. One is that it is standard practice within FDA reviews to examine subsets that might be informative about portions of the patient population that are gaining more or less benefit or safety from a product. So it is standard practice to examine subsets.

In addition, the information submitted to us from BioMarin, as I recall, did include their ANCOVA

analyses, and the co-variants were important in their analyses. So we didn't perform them independently. They provided that to us, and their analyses highlighted those as well. So we went on to further explore that.

DR. FOLLMAN: I wasn't really talking about the analysis co-variants actually. I was wondering whether the treatment effect, if you did a test of whether the treatment effect in men, say, was statistically different from the treatment effect in women, a test interaction like that.

DR. WALTON: Oh, no. Oh, I'm sorry. No, we did not perform that statistical test. I guess we were, given the sample size available, really not confident that that would really inform us.

DR. WEISS: Can I just expand on your first question, Dr. Follman, too? There's always a great deal of discussion in terms of formulating a primary endpoint, particularly when there is a new disease, for one where we don't have a lot of experience and don't have tried-and-true, tested outcome that we're very comfortable with.

I think Dr. Walton gave you a lot of discussions about our thinking into it. It is true this is a little bit different. There are times when there's two that are very important, one is considered or made the primary and one is considered like the key secondary endpoint. There are times when we try to put these together into a composite. Those have their limitations as well.

I think the fact, though, that we are here today discussing an application, when one test certainly was below .05 and one was above the .05, just shows that when we are talking about rare diseases, when we're talking about trying to look at just the totality of effects, we're not going to just look at whether or not something is just above or just below an 0.5 instead of, you know, you failed to make it; go back to the drawing board.

So there's a lot of thought, and it is not an easy -- you know, there were lots of intense discussions with the agency and with the companies, and sometimes with outside experts, to try to figure out what's the best outcome to really show a treatment

effect.

CHAIRMAN AOKI: Dr. Levitsky?

DR. LEVITSKY: I was convinced by the company, as they presented their data and looked at the patients more in terms of functional divisions rather than classical divisions like age and gender, and I was also convinced that, when you have two datasets, one of which looks a little bit unbalanced by happenstance, that it is more reasonable to look at co-variants than at standard ANOVA, as you seem to have done.

Would you convince me that I shouldn't do that? Tell me why I'm wrong to be convinced by the company's presentation?

DR. IRONY: No, I think it makes sense to look at both types of analysis, the company's analysis of their subsets as well as the analysis, the classic analysis, as we divide by gender and age and severity of disease at baseline or degree of impairment.

You have to realize that this is not a 5,000-subject trial. This is a 45-subject trial because it is a rare disease. Any conclusions that we

have in small subsets, in comparing small subsets, even if it's an informal comparison, not a formal testing of those, it's limited. It just shows some trends in one gender versus another and trends in different age groups as opposed to the totality of the laronidase-treated population.

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: Yes, I would like to ask the FDA, are you satisfied that the dose of the drug that is being used is appropriate? I ask that question because I can't find -- the only information I can find in the booklet here is it states that the dose was chosen from subclinical, from pre-clinical studies.

The reason I ask this is I don't see any endpoint being normalized. I worry about, even though the urinary GAG has decreased, to me that is not necessarily the optimal level. In other words, it's certainly possible that some individual who has an above-normal urinary GAG has just a more slowly-progressive disease. Certainly the reduction in liver volume, which is only 20 percent, could be explained

by an increase in fibrosis; it could be explained by a decrease in glycogen.

So I'm somewhat worried, in light of the discussions we have had in the last two days, about the dose. I am very worried that this is an inadequate dose because I see no indication, there's no data that the human tissue is decreasing its accumulation of lipid. There is no normalization of the urinary excretion, and the fact is the liver size only decreased by a fifth, which, if your liver is huge, may or may not make a clinical difference.

DR. WALTON: I think you're quite right about the question about, do we have an optimal dose? I don't think there is any data to truly address that question, whether we have an optimal dose.

Unfortunately, what we have are data on this single dose, and we're going to, I think, be deciding whether or not we have an adequate dose in the sense of are the evidence on this dose adequate, but I don't think that we or the company can really have any data that can address the question of optimal.

DR. SCHADE: Well, doesn't the FDA ever

request any type of dose response, even looking at just urinary excretion in a short-term, one-month trial? It seems to me that would be a rational thing to do, is to get a short-dose response curve in humans and then make some decision that it's rational.

DR. WALTON: Yes, the FDA does frequently request those kinds of studies, and we don't --

DR. SCHADE: But we don't have it in this case?

DR. WALTON: In this case we don't have that data.

DR. GRADY: But liver volumes were normalized in a lot of the patients treated? I mean, even though there's a 20 percent decrease, they were normalized in the majority of patients treated for a long time.

That actually brought up the same question to me. I wondered if there's some reason why there's a bigger, more dramatic effect in the liver perhaps than in other tissues. Is the drug concentrated in the liver? Is there some reason to think that --

DR. SCHADE: Well, excuse me. "Normalized,"

do you mean that they only started 20 percent bigger than normal or -- I'm a little --

DR. GRADY: Well, no, I think that --

DR. SCHADE: When we saw the pictures of gross hepatosplenomegaly or just hepatomegaly, a 20 percent decrease in that individual would not result in correction of the physical impairment. I didn't see any data that the liver is --

DR. GRADY: Well, in the Phase 1/2 it was only 10 patients, but after treatment for -- it was up to a couple of years -- nine of the ten participates had normal-sized liver. That's data from the company.

DR. WALTON: Well, it depends how big their liver was to start with.

DR. IRONY: Yes, the mean increase -- or the mean decrease in liver volume, it's only a mean group for the Phase 3 study or the Study 003. But Dr. Grady is right to point out that in the Phase 1 study, in which hepatosplenomegaly was a requirement for eligibility, there has been some gradual reduction in liver volume. In most cases the liver volume normalized.

Some of them required longer times than others, and up to two years of followup during treatment, but there was a gradual decline in liver volume, a normalization in most of them, which indicates that probably fibrosis or any reversible changes in liver structure were not playing a major role in this.

DR. GRADY: But is there any concentration of the drug in the liver that might actually indicate that the dose for other tissues could be too low?

MR. PATTERSON: We're happy to help answer that question, if you would like, Mr. Chairman. I would like to ask Dr. Kakkis to help us with that, please, both the liver question and further to the dose, if you wish.

DR. KAKKIS: In the studies we have done in the canine model, we've shown that the liver does take up more enzyme than other tissues, which may enhance its ability to be corrected. But we've also shown that other tissues do take up substantial and corrective amounts of enzyme, and that urinary GAG excretion reflects, for example, kidney storage, and

that reduction in kidney storage results in decreases in urinary GAG.

We do have data we could show you relating urinary GAG excretion to other tissue GAG reductions. But in the animal models we show that there is 60, 70, up to 80 percent reduction in tissue, in many different tissues, in those pre-clinical studies at the dose that we're currently using.

We have also shown that this dose at the enzyme levels you achieve are many-fold saturating for what would be the receptor uptake; affinity constant is present, indicating that we are maximally uptaking, providing enzyme for uptake at the dose that we currently use.

CHAIRMAN AOKI: Dr. Schneider?

DR. SCHNEIDER: Yes, I wonder why decrease in liver size wasn't taken as the primary endpoint. If my long-term memory isn't too bad, it seems to me that in bone marrow studies done, bone marrow transplant work done many years ago, when people thought they were seeing an effect, it was because of a decrease in liver size. It seems to me, it appears

to me that, because the Phase 1/Phase 2 showed this very dramatic decrease in liver size, you sort of took that as a given and looked for a more difficult endpoint.

CHAIRMAN AOKI: Dr. Walton?

DR. WALTON: The answer to this is exactly the point that Dr. Schade was bringing up, that the question is, how large is the liver to begin with? In many of these patients it was not so enlarged as to be a clear impairment in and of itself. So that a decrease in liver size, and even to a normalization, we felt would have an uncertain clinical impact on the patient.

CHAIRMAN AOKI: Dr. Zerbe?

DR. ZERBE: Yes. Could you provide some clarification? There is in the FDA presentation an anaphylactic reaction described, but I didn't actually see that presented in the sponsor's presentation. Could you clarify that case?

DR. IRONY: Yes. This was associated with an infusion in a patient that was initially assigned to placebo, and subsequently was treated during the

extension study with laronidase. That patient had urticaria and episodes of hypoxemia during previous infusions of laronidase. Initially, they were treated with a higher dose of antihistamines and inflammatory medications, including steroids. IgE was positive, as well as there was some evidence of complement activation in that particular subject.

But then in a subsequent infusion there was a development of severe hypoxemia that could not be controlled by intravenous steroids or antihistamines, and the patient had to be taken for an emergency tracheostomy, which was successful in establishing airway.

DR. ZERBE: And that's compatible with the assessment of the company? Okay. I just didn't see it in the company presentation.

CHAIRMAN AOKI: Dr. Watts?

DR. WATTS: I had questions about the dose in sort of two directions, and I don't think there's data to answer them, but I want to raise them.

One is the frequency. Is it necessary to dose this once a week? For a drug that will be

started in childhood and continued lifelong, every 10 days, every two weeks, if reasonably effective, would be a huge difference.

And the other question on the other end: Are there patients whose urinary GAG levels don't come to normal? Would it be possible to lower them by increasing the dose? Is this a one-dose-fits-all scenario?

I don't think the data answers either of those questions. There may be some data on the frequency that the company testified.

DR. WALTON: I would say, we, the FDA, has no data on alternative frequencies, and I would refer you to the company for any further insights they can offer to that.

As to whether or not this necessarily normalizes any particular parameter like urinary GAGs in all patients, I'm reluctant to offer that expectation.

CHAIRMAN AOKI: Very briefly.

MR. PATTERSON: Okay. I would like to ask Dr. Kakkis to briefly speak to both the once-a-week

infusion as well as any dose information that would be helpful to answer that question.

DR. KAKKIS: The original frequency was based on our studies in vitro looking at Hurler cells in culture, which demonstrated a half-life for the enzyme of about five days. So the choice of frequency was intended to provide a small amount of accumulation of enzyme, and given the five-day half-life, a two-week interval would potentially result in less increase, accumulation over time, which we felt was important in achieving optimal corrective enzyme concentrations.

The dose that we provide does saturate the receptors for uptake of this enzyme in the tissues. The serum levels in the patients in the Phase 3 trial were 20- to 30-fold times the uptake affinity half-maximal constant for uptake, which indicates that we are achieving a maximal uptake and reduction.

If you look at higher doses in the canine model, for example, a fourfold higher weekly dose, we can show that we do not get an increase in tissue GAG reduction by a fourfold higher dose.

We believe that the dose we are using and the regimen we are using is achieving the maximal reduction in tissue GAG that's achievable with this therapy on a weekly basis. That's not to say that other regimens might not be possible, but we believe this was the most reasonable regimen, based on the data we had in animal models.

CHAIRMAN AOKI: Thank you. Dr. Woolf?

DR. WOOLF: Getting back to Dr. Schade's question about hepatomegaly, on page 63 of the sponsor's briefing book, on the bottom, there's a statement that 12 out of 15 patients, or 80 percent, were evaluable who had abnormal liver function at the baseline, had normalization at the end of 24 weeks. But in the group that was treated in the subsequent crossover, or the non-blinded portion, in the folks who were treated with placebo first, five out of ten who had abnormal liver size to begin with normalized.

CHAIRMAN AOKI: Dr. Sampson?

DR. SAMPSON: I just had actually a concern. The issue was raised by the FDA about interpreting the 003 FVC data over the 26 weeks. The question, I

think, was the rise in these 20 to 24 and the decline in 0 to 4 in the baseline differences.

I am sure you're aware that the test was done on a non-parametric basis looking at medians. If one looks at the medians at baseline, they're not quadrants; there's a small difference.

I am wondering if you have the data over time that you presented not with means, but with medians by week, that might kind of ameliorate a little bit of the differences that you showed.

Also, I wanted to just make sure that I understood. The baseline height was used for all those weekly observations or were those the heights for each week? I was hoping they were the baseline heights and you could do the medians and have a graph of that.

DR. WALTON: Okay. What was in the presentation I believe is on the baseline height. I think what is in the briefing document is the current height.

DR. SAMPSON: Okay, that's my confusion, and then the medians --

DR. WALTON: So there was a small difference in that.

As to the question on a plot of the medians, no, we don't have that.

DR. SAMPSON: Because it looks like this data, it's small amounts of data, and there may be some aberrant values that have an effect on the mean that you might not have on a median. It would be helpful, if that issue is a real concern about the FVC over the 24 weeks, to look at that more carefully in terms of a more robust estimate of effect.

DR. WALTON: Yes, that's a very good suggestion. Thank you.

DR. SAMPSON: And I had just one other small kind of problem with my own curiosity, but I noticed that the FDA put a .016 p-value for the FVC Wilcoxon, and the company has a .009 p-value. I was wondering, was there a mistake by the company in doing theirs or was that because one used an exact calculation; one used a normal approximation?

DR. WALTON: I believe ours was just a simple Wilcoxon. Perhaps theirs was stratified.

MR. PATTERSON: I think the answer is that the .009 is using the baseline values, and the .016 value is using --

DR. WALTON-BOWEN: No, I think --

MR. PATTERSON: I'm sorry.

DR. WALTON-BOWEN: I can explain this.

MR. PATTERSON: I would like to defer to the statistician to help with that. I'm sorry.

(Laughter.)

DR. WALTON-BOWEN: Actually, we did get consistent results, but there was an FDA audit at one of the sites that highlighted that a few values from a pediatric-versus-an-adult lab had been recorded in the case report forms, and we went back to make that correction, whereas I don't believe the FDA has done that yet.

DR. WALTON: Yes, we've not gotten those -- it's only five values, and we have not gotten those values, and that's only a recent finding.

DR. SAMPSON: You have reflected the corrected values?

DR. WALTON-BOWEN: Yes, correct.

DR. SAMPSON: Thank you.

DR. WALTON-BOWEN: Yes.

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: I have a question about the infusion reactions. I may have misinterpreted this, but I'm reading here also in the handout. There were a large number of not serious but infusion reactions, but the company states that the same number were, or a similar number were, experienced in the placebo group. But I don't understand why the placebo group should have a high number of infusion reactions at all, unless there's something in the infusate that we don't know about and, therefore, maybe -- doesn't the FDA worry about the high level of infusion reactions in a placebo infusion?

DR. WALTON: Yes, I think we found that very, very unusual and very concerning to us as to what that means, but I don't think we have any explanation for that.

DR. SCHADE: Well, is there something in the placebo -- I don't know off the top of my head what's being infused in the placebo. Are they just getting

saline or they getting the whole vehicle, or is there something in the vehicle that's causing infusion reactions?

Because from a clinical point of view, from a physician's point of view, when somebody gets an infusion reaction, it mobilizes a lot of resources, including you start worrying about anaphylaxis that, to me, if it's in the vehicle that you're infusing, should be corrected early on during this phase of the development.

DR. WALTON: The placebo had all of the excipients in it except for the enzyme. That was the only difference. So all of the other components were present. It does suggest that some of the other components are contributing potentially, but I think that's not something that we can be certain about.

CHAIRMAN AOKI: Dr. Joad?

DR. JOAD: I noticed that in the protocol that for the infusions from the beginning in advance they were doing a lot of things worrying about infusion reactions, like they gave antihistamines and often gave steroids. So that this was sort of under

optimal conditions to prevent any sort of IgE-mediated response.

I'm curious, was there consideration of looking at IgE response to -- the one who had the anaphylaxis apparently did have positive IgE to the drug, but nobody else was looked at. Yet, it was a real prospectively-treated worry.

DR. IRONY: Well, the protocol mandated that for infusion-associated reactions there will be an IgE and complement activation, a collection of blood for that purpose. It was not prospectively done for all patients in infusions, but in three circumstances in which there were some infusion-associated reactions that triggered that protocol-mandated collection, the IgE was negative as well as complement activation.

DR. JOAD: So does that mean only three patients out of the treated group had infusion-related -- I don't think that's correct from your other data.

DR. IRONY: No, that's a good observation. I think the protocol mandated -- and I don't remember exactly; maybe the company can clarify this, but the criteria for the collection of IgE was like the

intensity of the reaction that would trigger that collection.

CHAIRMAN AOKI: Very briefly.

MR. PATTERSON: We're happy to help to add clarity. I would like to ask Dr. Kingma to help us, please.

DR. KINGMA: Yes. I would like to just point out that the infusion reactions, just to put it into perspective, we have had about 2,300 infusions, and the infusion reaction frequency is about 4.5 percent. All the other infusions have been well-tolerated.

The majority of the infusion reactions were actually three-quarters flushing in the treatment group and about half flushing in the placebo group, and they were related to one site-specific event that actually turned out to be equally distributed between placebo and treatment.

In addition, we have brought -- if you look at the other events, they are mostly fever, chills, and headache, which are more likely equally again distributed between placebo and treatment, and very

much correlating to the underlying disease.

With regards to the IgE matter, we have a very scrupulous, conservative measure that we put in place where every single infusion-associated reaction is defined as anything happening on the day of infusion. So it could have happened eight hours later, not per se with the time of infusion. Any moderate event, whether or not that was hypersensitivity-related, was mandated to be IgE tested.

We had three of those tested in the double-blind trial. Again, all of those were negative.

I also would like to clarify that, with regards to the Phase 3 trial, none of the patients actually were on corticosteroids, and only the one patient that was mentioned in the briefing document that the FDA turned up had a steroid treatment, the reaction type, before the event actually happened.

So we have actually management proposals with regards to how to manage these patients. We also have a consultant allergist here who helped us through the trial to discuss IgE.

CHAIRMAN AOKI: Dr. Swenson?

MR. SWENSON: Yes. To the FDA, we're seeing some new data here in a follow-on of the open-label. Is this new to you as well?

DR. WALTON: That data was only very recently submitted to us.

MR. SWENSON: Given the small number of subjects, obviously, given this disease, it would be expected that there might be considerable variability for duration of onset of improvements. In looking at those new data, it appears that a concern that I had initially, looking at just the open-label results, that is, that there appeared to be no gain in vital capacity and about equivalent gain in the six-minute walk test.

The next three months inclusion of data suggests that maybe those are real differences now developing, and in 45 subjects I could live with them failing to see something at, say, six months and then beginning to see it at nine. I just want your assessment at this point as to those data now appearing to be more concordant with the double-blind

study.

DR. WALTON: As I said, we've only received that relatively recently and really have not had the chance to do the normal thorough review. A very preliminary review of it, we have not seen anything anomalous in that data. So we have no basis for any particular concerns or doubts about that data. We just haven't had the chance to really thoroughly review it yet.

MR. SWENSON: And might I ask a question of the company then? With pulmonary function testing, clearly, when patients are ill to any degree, they'll probably not be able to give maximal efforts. Despite even their best efforts, they may just simply not be able to do it.

Was there any effort to assess whether any of these children or young adults had recently had viral infections before those numbers were obtained? Were they three to four weeks post any type of viral infection?

DR. COX: Well, my first point would be that these children are chronically ill, and there were

quite a number of infections during the study. In particular, in the middle of the double-blind phase there was a dip that occurred in both groups, more so in the Aldurazyme group than the placebo group. We did look to see if there were any particular events that might explain that variability.

There were a couple of patients who did have recent infections, and there was another patient who had just gotten over an asthma attack. That, in part, contributed to that variability.

CHAIRMAN AOKI: Last question is Dr. Grady.

DR. GRADY: Yes, I had sort of the same question, and that is that, you know, I think what we have here is a really nicely-done study with however small improvement in benefit, a small benefit on FVC and six-minute walk, both of which are effort-related tests. So it would really be nice to see that those improvements increase over time in the follow-up study.

The graphs shown us by the company and the FDA look quite different in that regard, and I think it's mainly because the company was showing us an

extra 12 weeks or so of followup, at which time we began to see quite a bit more improvement than the FDA graphs with the six months of followup.

So I think it would be very important for the FDA to look carefully at those data before making a final decision. That would be reassuring.

CHAIRMAN AOKI: Okay, at this time I would like to go to the open public hearing. The first speaker is Abbey Meyers. Please keep your comments to three minutes.

MS. MEYERS: Yes, I am Abbey Meyers, President of the National Organization for Rare Disorders. I have been here for all three days, and I want to say that I admire you all for all the very, very hard work that you have been doing.

We're looking today at another of the enzyme replacement therapies. As time goes on, we're going to see more and more and more of these, because of the Human Genome Project and because of the discovery of these genes and what types of enzymes and proteins they're not making or they're making them incorrectly.

So it just occurs to me, after listening to

all of this, that the FDA is having some problems in trying to catch up with the science of this whole thing. Back in the 1980s we had Ceridase, which I think was reviewed on evidence from about 15 people. There was very little evidence of safety or efficacy. All of the research, just about, was done by NIH, and they let it on the market.

It was a fatal disease, untreatable. It was okay. It reduced the size of the spleen and the liver, and nobody sat around saying, "Well, we really wonder whether that's going to have an effect on the disease." As you know, it saved many, many lives.

Then Prolastin for alpha-1 antitrypsin deficiency, and the evidence was so little on that, the effect of that product, that the FDA, in a way to solve this, required the company to set up a patient registry which they had to keep running to monitor these patients for five or six years, just to prove that the drug was effective. Because when you approved it, there really wasn't the substantial evidence of efficacy.

And then we had PEG-ADA for severe combined

immune deficiency. I think that was probably around 10 patients, something like that, when they reviewed that. The only evidence at that point was this is an enzyme deficiency. We're going to replace the enzyme. It probably works, and they approved it.

But today and the last couple of days, it just seems like nobody is willing to understand that, when you have an enzyme deficiency and replace the enzyme, it's probably effective, and that all you need is minimal evidence that it's helped in some way.

When you look at these endpoints -- I know the company sat down with the FDA, and you negotiate these endpoints. It boggles my mind to understand how anybody could have picked an endpoint involving a six-minute walk for kids who have these joint contractures. You don't have to be a brain surgeon to understand that probably you give the kids the enzyme for six months or eight months or a year, and their joints are not going to clear up overnight. So it is going to be pretty hard to see any kind of improvement in an endpoint like that.

I agree with what somebody asked before:

Why didn't you just say that reduction in the size of the liver, which you could see on an MRI, should have been enough?

The reason I am saying all of this is that this is among the first few enzyme replacement therapies. You're going to have a lot of these enzymes on your desk in the next few years, and you have to adjust the way you look at them and the measures that you're using for success.

We have patients here. We have parents who will be talking to you about how their children have taken the drug. To them, there's only one measure of success: Their children are better. Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Melissa Bryant.

MS. BRYANT: Good morning. My name is Melissa Bryant, and it's a real honor and a privilege to be here with you today.

My son, Bryant Graeber, was diagnosed with MPS I at age six by our pediatric ophthalmologist. I would like to share with you what has happened in the years following that diagnosis and his great success

with enzyme replacement therapy.

I had no idea the impact of the words I heard from our ophthalmologist. He said, "I believe Bryant has an enzyme deficiency." I had no idea what that meant.

But Bryant had all the symptoms of MPS. As he got older, life became more difficult, and his liver and spleen enlarged; his joints grew stiffer, and he had chronic respiratory issues. Bryant has had multiple surgeries which include carpal tunnel, six hernia repairs, eight sets of ear tubes, and three spinal fusions.

Bryant's eyes were incredibly sensitive. He constantly complained of floaters and always wore a hat. Anything bright was a distraction. He didn't like to wear a shirt with stripes, and an eye exam was a challenge.

Fatigue was an ongoing problem. His energy levels got lower and lower. We live less than two blocks from our church. To walk there, he had to stop at least twice to rest, and ascending the stairs in our two-stair home was a major ordeal.

Pneumonia, bronchitis, and other respiratory problems were an almost monthly occurrence 12 months a year. It was never confined to winter months. He had begun the slippery slope.

Almost five years ago we were privileged to be a part of the clinical trial for enzyme replacement therapy. What a difference treatment has made in Bryant's life. I am very committed to doing whatever I can to see that other MPS children have the same good fortune.

Today Bryant wears a hat, but only because it is cool.

(Laughter.)

He never complains of light sensitivity. His ophthalmologist is amazed at how easy his yearly exams have become, and he wears stripes and patterns.

We can hardly keep up with him walking to church. No grass grows under his feet. In fact, the last three summers Bryant has had a job at the Christian Life Center at church. He walked both ways and helped with programs they offered as well as with the maintenance and upkeep of the gym.

Incredibly, he is rarely sick. Bryant will get a cold from time to time, but the duration is short and doctor visits are almost never needed.

I consider my son a healthy young man whose life has changed in a positive way. We look forward to continued years of good fortune in other MPS children.

Finally, I have no financial interest or connection to Genzyme or BioMarin, and I thank you so much for your time.

CHAIRMAN AOKI: Thank you.

The next speaker is Stephen Holland.

MR. HOLLAND: Good morning. I want to take this opportunity to sincerely thank all the panel members for the time spent here today discussing this very important topic.

My name is Steve Holland, and I stand here today in my role as President of the National MPS Society, but, equally important, I stand here in my role as a father of three children with MPS I, here today with my wife Amy and our children, Spencer, 13; Madison, 11, and Laynie, 9.

The National MPS Society is a support group representing approximately 700 member families afflicted with mucopolysaccharidosis. As far as financial disclosures, the Society receives operating and conference support of the sponsors of less than $100,000 a year. I personally do not have any current or past financial interest in the companies, and our family's travel here was paid by the NORD's Patient Assistance Program.

The Society appreciates the safety objective of the FDA and how it helps protect children from the unintended negative side effects of therapy. We also appreciate the efficacy objective and the protection it provides to society's most vulnerable families from those who might want to fraudulently profit from our family's dire circumstances.

MPS is a particularly cruel disease, whereby a seemingly healthy child grows and gains skills, only to have those reversed and lose skills and health over time. It is degenerative. Therefore, time is the enemy for many MPS children. Without intervention, they will get sicker with each passing day. It is a

law of Nature.

However, enzyme therapy provides hope to our MPS I members and future sufferers of MPS I where none exists currently. It offers stabilization of many aspects of the disease and improvement in still others. It provides a reprieve from a death sentence that these children were handed on diagnosis. There are currently no safe alternative therapies to enzyme therapy.

My family has had the opportunity to experience enzyme therapy firsthand. We've also had the unique experience of seeing the difference between treated and untreated children just by looking at our own three children.

My son was in the first trial, and my daughters were not. This approximately three-year period provided many opportunities to see the stabilization and improvement in my son's condition while my daughters worsened.

My daughters were then accepted into the second trial with the placebo-controlled group. During the first six months of the study, I noticed

stabilization and improvement in one of my daughters while the other one worsened. Once the trial was unblinded, my observations were confirmed when I learned that my daughter that worsened was part of the placebo group.

For the past 18 months she has joined her brother and sister on enzyme therapy. During this period I have seen many of the same results with her that we saw with the other two children. At each step during this five-year period it was obvious to me as a parent who was receiving the drug and who was not.

Some improvements are easy to describe and explain, and some are not. The easy ones include actually making a basket when shooting at the goal; reaching the milk bottle from the top of the refrigerator; not taking an extended nap every day after school; walking around the block four times; not using a stroller for long walks, and staying awake until 10:00 p.m. on non-school nights.

(Laughter.)

Those less easy to describe and explain include feeling well enough to go to school most every

day; increased shine in hair; increased zest for life, and just feeling like a normal, healthy kid.

Their improvements are directly related to this therapy. There is no other explanation for them. But not only is the therapy validated by the improvements we have seen, an even larger validation is the lack of progression of certain aspects of their disease. This is where the true strength of the treatment shows brightest.

In closing, I appreciate the need for the FDA and the fine work it does. At this point I believe the drug has been proven safe and effective. This proof did not come from looking at samples in a lab, in data in graphs on paper. I cannot adequately debate surrogate versus clinical endpoints or why a particular trial design was chosen. I'm not educated in such matters.

My proof comes from living with three MPS I children 24/7 for the past 13 years, one nearly five years on therapy, and keeping tabs on the other families on therapy. I understand that the therapy is not a cure, but it helps, and it helps a lot.

I have seen that the benefits outweigh the risks firsthand. There is no alternative. MPS kids needs Aldurazyme until science progresses to the point that an ultimate cure is available.

Now is the time to allow therapy to be given to those who have been waiting so desperately for the opportunity to get better. All of us in this room owe them that opportunity. Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Linda Day.

MS. DAY: My name is Linda Day. My sons Scott and Greg were diagnosed with MPS I, Hurler-Scheie syndrome, at the ages of 3 and 4. We were suddenly faced with the reality that our two precious sons may not live past their teens but, defying their prognosis, they're here with us today. I'm proud to introduce you to my son Scott, 28; my son Greg, 27, and their older sister Danette.

By 1998, we had endured years of countless surgeries and illness due to the ravages of this disease. We increasingly felt like our boys were living on borrowed time. Then I received a life-

changing phone call from Amy Holland, a fellow MPS mom whose son Spencer was accepted into a clinical study using enzyme replacement therapy. All of a sudden, we were allowed hope again.

For many years the only medical treatment available was bone marrow transplant. The procedure was very risky, and there was significant chance that complications might prove fatal. Those were not good enough odds on the lives of our sons. So we decided to wait and pray for a time when a lower-risk treatment was developed.

Amy's call was the answer to our prayers. The results of enzyme replacement therapy on canines was very promising. Greg was accepted into the first clinical study, and we were privileged to have the opportunity to work with Dr. Emil Kakkis and his dedicated staff.

Besides this, our options were running out. Greg was in desperate condition. He was in his fourth year of college and his health had plummeted. He no longer had the energy to walk across campus, and his grades suffered. His heart was arrhythmic and

beginning to fail. His liver was grossly enlarged, and his liver enzymes were abnormally high, but my determined son was still unwilling to give up.

Because only one sibling per family could be accepted into the study, Scott chose not to apply. He relinquished his opportunity because it was apparent that Greg probably would not live long enough for FDA approval of the enzyme.

In our wildest imagination we never would have thought that enzyme would still be unavailable for Scott after five years. Yes, five years have passed since Greg began weekly infusions. He has flourished on enzyme. He graduated from college summa cum laude and has a great job in our County.

But while we've watched Greg thrive on enzyme, we have watched a dramatic deterioration in Scott's health. When we thought approval was imminent, we learned that a more extensive double-blind study was necessary. Scott was standing in line to be the first to sign up for this study. Even if he was on placebo for six months, it meant that he would be on enzyme at the end of that six months.

But fate would intervene when he had a serious complication during a cornea transplant. He was flown on life support to the University of Utah, where he received a tracheostomy. His cornea transplant failed. He got acute glaucoma in his other eye. They didn't know how much injury had been done to his vocal cords from the trauma. He developed cubidal tunnel syndrome from having his hands restrained. At one time we didn't know if he would have normal brain function again. At another time we didn't know if he would be able to see, speak, or write again.

But what we did know was that this ended his chances of being in the double-blind study because the protocol involved pulmonary function tests, and they weren't accepting participants with traechs.

Last year Scott's doctor was so worried for his life that he applied for a compassionate use, but Scott was denied compassionate use. Scott's probably not going to be able to have his traech removed until he's been on enzyme for a period of time.

He gets infections regularly and he deals

with the terrible pain of crushed disks. His liver enzymes are high, and we're continually worried about his eyes. He is plagued by chronic headaches and fatigue. The challenges of living continue to grow, but Scott never stops demonstrating his strength of character and his independence.

We've endured a quarter of a century of virtual hopelessness and then almost five years of holding our breaths for this chance. It feels like we're walking on eggshells waiting for the process of approval.

We have witnessed the miracle of enzyme replacement therapy that has given Greg his life back. It's obvious to us that enzyme has helped him greatly. Anyone who knows Greg knows that he would not go to the hospital once a week for an infusion if he didn't have to.

The option of enzyme replacement therapy has been the proverbial carrot on a stick for Scott. Approval is ever closer, but it continues to be out of reach.

Scott's life is completely dependent on you

and your recommendation. Please look at my family as I plead for you to recommend FDA approval for Aldurazyme. Life and quality of life is being lost every day that this treatment is not available.

I am confident that you will recommend approval if you look at the evidence and ask yourselves: Do the benefits exceed the risks? And I know that if you ask that question of the families, the answer will be, "Oh, yes, they do."

Greg is here with us today because he had the opportunity to be on enzyme. I'm here today to ask you to give Scott that opportunity.

I thank you very much for hearing us, and we welcome any questions that you might ask.

If you wondered who was in the back going like this all morning long (indicating), it was me.

CHAIRMAN AOKI: Thank you.

The next speaker is Mark Dant.

MR. DANT: We have a few PowerPoint pictures that we'll show during our brief discussion.

My name is Mark Dant. This is my wife Jeanne and my son Ryan. Ryan is 14-and-a-half years

old, and he's also an MPS I Hurler-Scheie patient.

My wife and I do own stock in BioMarin. The fair market value is less than $2200, and our trip here was sponsored by NORD's travel.

Although we see our son Ryan as normal, we realize he is not. He has MPS I, Hurler Scheie syndrome. At the age of three, Ryan's love for sports and team play had already began to shape his spirit, drive, and persona. At age three-and-a-half, Jeanne and I were told that Ryan's life would be shortened to young adulthood and as years passed his health would slowly deteriorate to a point where wheelchairs and the daily pain would be more part of his life than would balls, gloves, or the friends that could be found when one's accepted by the majority in our society as normal.

I have heard the passionate pleas from fellow MPS families and concur with how they have described the positive health experiences their children have gained since their lives were altered by the weekly infusions of Aldurazyme.

Ryan began his infusions on February 13th,

1998, eight weeks before his tenth birthday. I want to speak to you briefly about how Ryan's life has changed since Aldurazyme came into it, and not just his physical life, but, just as important, I want to try to relay to you how Aldurazyme has affected Ryan psychologically.

Seeing the reams of paper and the stacks of data-filled binders which have been gathered on our son as he moved through the Phase 2 trial, I know you have each reviewed the extremely accurate and objective data on Patient RCD 003. I wonder, though, how does one objectively measure quality of life, both physical and psychological? I also wonder where in the data does it say simply, "Patient RCD 003 feels better not only physically, but he feels better about life and how others will accept him."

It wasn't until Ryan was about eight that he began to realize that he was not able to run with the same balance, speed, or stamina as the other boys on his soccer team. By eight-and-a-half Ryan began showing signs of what we in the world of MPS call "toe walking," because his left heel would oftentimes not

touch the ground as he walked because his hips, knees, and ankles were beginning to stiffen.

Ryan's last soccer season was that year because he could not keep up and he knew it. The wheelchair was moving closer to the Dant home.

Ryan's last year in city league baseball was also that year. Physically, his shoulders, elbows, wrists, and hands had stiffened to the point that grasping a bat or throwing a ball was not the same for him as it was when he was three-and-a-half, and because he looked different when he was doing it, it was obvious to him he could not do it without looking like the other boys anymore, and that bothered him immensely. He began to realize he was not going to be the major league baseball player we all thought we were.

In December of 1997, Ryan played on a church league basketball team. Ryan's ability to stay on the court was severely limited compared to his peers because he was winded and needed to come out just after one trip down the court. He noticed this, too, but he also noticed the other boys staring at him as

he puffed and puffed, trying to catch his breath, which by that time was impossible because his liver and spleen had grown so large there was little space for his lungs to expand.

Ryan also noticed the boys staring at his funny tummy. By that time, he decided sports would not be in his future.

Ryan was also getting tired of his horrible headaches which would come without notice and cause him to miss game after game. While the normal boys were playing, Ryan would be home vomiting or trying to sleep off the pain. Many times our trips to or from the athletic fields would be interrupted by a stop on the side of the road for our son to vomit because of the onset of yet another headache.

By the age of nine, Ryan had decided that he was not like the other children. He also stopped talking about what he wanted to be when he grew up. When he was five or six, he would ask, he would often talk about growing up and going to high school and college, but by nine he began asking what it would be like in heaven. "What will it be like when I die?"

He knew that there was no future in his world. He had learned this not from mom and dad saying this, because we would not. He had learned this from watching his own body and by watching the others stare at him.

Four years, eleven months, and two days ago, Ryan began changing both physically and mentally. He has now grown over eight inches and put on over 50 pounds since his first infusion of Aldurazyme. The photos here you have just seen show a young man trying to pull off a squeeze bunt and beat the throw down to first base. That was last summer.

It also shows a little boy playing basketball. This game was last Sunday. With the basketball photos, you'll also see a little computer nerd who just really likes to work on the computer.

(Laughter.)

The basketball photos are from last Sunday's game where Ryan was the point guard for his eighth grade B team. The Mustangs took it on the chin, but Ryan competed. He shot the ball; he dribbled; he passed, and at the end of the game he posed for a

post-game team picture with his fellow teammates.

If you ask Ryan today, in closing, after nearly five years of changes brought about by Aldurazyme what he wants to be when he grows up, he once again will have an answer. The three of us know that Aldurazyme has not made Ryan's health perfect. We realize that there is no cure for MPS, but we also realize that Ryan has improved dramatically because of Aldurazyme.

We have been privy to watching the boys and girls in his classes and teams accept him as what he is today, and have continued to watch his outlook on life change because of that.

The pictures before you perhaps show things that cannot be measured by an MRI or a sleep study. They depict a happy young man getting to be what he wants to be most right now -- normal.

Thank you for your decision. It will change our world.

CHAIRMAN AOKI: Thank you.

The next speaker is J. E. Wraith.

DR. WRAITH: I would like to thank the

Committee for giving me the opportunity to speak with you this morning. My name is Ed Wraith. I'm a pediatrician from the United Kingdom. I'm Director of the Willink Biochemical Genetics Unit, and I'm here to represent the UK, families who have MPS disease.

As the principal investigator on the Aldurazyme 003 trial and extension study, my travel was paid for by the company to allow me to present my experience with this product in my patients.

It's been said many times this morning, and perhaps most eloquently by the parents, but I want to say it again: that it's important to remember that we're dealing with a progressive disease here. These children and young adults don't have time.

They have been robbed of normal childhood and normal adult life, and as each month goes by these children are deteriorating. We have in our hands the ability to alter this, and it's my view that we have to take that opportunity. We just don't have time not to.

My experience with Aldurazyme involves these patients here. You can see there's a very mixed bunch

of children and young adults in my center. I have a large experience in dealing with patients with MPS disease. In my clinic in Manchester over the last 10 or 15 years we have seen over 500 patients with various MPS disorders, including over a hundred children with MPS Type I. So we have a lot of experience in this disorder, and we know very clearly what this condition can do to you.

I want to use this just to illustrate some of the difficulties that the company has had in designing a trial to show efficacy. I think the hurdle at the company was set very high, and I don't care how you really address it in figures, I think they've cleared that hurdle.

Like many of the parents who have expressed their opinion this morning, if you had my parents here today, they would have said exactly the same. Within a very short period into this study, they knew whether their child was on placebo or drug. It was obvious to them because they could see the changes, irrespective of what the numbers or figures were showing.

I want to concentrate on a couple of

patients on this slide, in particular, this young lady here who is 20. I've looked after this woman since she was about five at diagnosis. Like many of the parents have expressed this morning, I have watched her struggle through a normal childhood, become depressed during adolescence, and then develop into a severely-disabled adult patient.

We need the computer person to come up again.

You know, this young lady has struggled with her disability, and it's important to remember that all of the patients that you are seeing here today don't have significant learning difficulties. This young lady's acutely aware of her disease and her disability.

It was ironic that just before the trial started she became very unwell, and I was slightly anxious that she wouldn't be able to meet the inclusion criteria for standing and walking. Fortunately, she had a recovery. She was included in the study, and, by chance, she was in the treatment arm of the study.

This picture was taken at week 26, so this is after the double-blind period. You can see we had a little party to celebrate the effect. Here you see, although at the start of the trial she was virtually unable to walk, here she is at the party in her high-heel, fashionable shoes and dancing with the other people who are at the party.

What's difficult for me to accept is this little girl here, who's nine, actually, she had very low expectations of the drug; she just wanted to be able to wear trousers that could fasten with a button properly at her waist rather than wearing elasticated trousers, so not a really high ideal.

But what was terrible for me was to realize that, actually, when I look back at pictures of this woman at nine, she looked very similar to this girl, and I didn't want to spend the next ten years watching the girl turn into this woman. Believe me, I think we have the ability and means to prevent that.

There's one other patient I want to talk about on this slide, this man here. He's 22 and had become reclusive because of his illness. Again, he is

a very intelligent young man; again, like many of these patients, highly computer-literate, certainly far better with computers than I am.

He became socially isolated because of loss of self-care skills. He couldn't go to the toilet on his own, for instance. To pass urine, he had to have someone with him. At the end of the 26-week period, he had regained those skills, and that was a tremendous improvement for him.

I think we have the abilities now to alter the outcome for all of these patients. We just have to accept it and realize that we have this ability.

Aldurazyme has made a tremendous difference to these patients. You've seen examples already from the parents and the children who have been up today and presented this far more eloquently than I have.

I realize the Committee will listen to all of the discussions and think very carefully about all of the presentations before they decide, but what I would urge you to do is to listen to the parents, listen to their desperation. See the children. These people have the same wishes and aspirations as all of

us, and they deserve a chance. Please make it possible for them. Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Denise Dengel.

MS. DENGEL: Hi. I want to thank you for being so generous with your time and your energy, sitting here all day today listening to all of us.

I have no financial connection to Genzyme or BioMarin.

My name is Denise Dengel, and I'm 38 years old and I have MPS I, Scheie syndrome.

I have not been a part of any of the ERT clinical trials. The last one I was not eligible because my pulmonary functioning was too good, which isn't a bad thing.

As you can tell by looking at me, I have a different stance than a lot of the people that you have seen pictures of and have seen. I'm skeletally pretty mild and, you know, just don't really have a basic look of an MPS person, but I am, however, quite severe in my symptoms now, and that's what I want to share with you.

I was diagnosed with Scheie syndrome when I was 10 years old. It was 1975. At that time the only symptoms that I had was stiff joints. I had adenoid problems, tonsil problems, and an umbilical hernia, had surgery for the adenoids and the tonsils and the umbilical hernia, and my stiff joints, and I went on my way.

I was unable to do some things as far as physical education went, but I just found other ways to be active and just kind of carried on in my life. I was considered a mild case.

When I was 25, I had carpal tunnel release. Four years later I had carpal tunnel release on the other hand, and I had the umbilical hernia removed yet again.

In 1988, I graduated from college and began my career as a social worker, working with homeless and street-involved youth in Seattle, and continued with my high activity level. When I say, "high activity level," I mean I was kind of one of those obnoxious people that got up at 6:00 and went to the gym, so I could go to work, so I could come home and

go biking or do something like that. I'm not talking a little bit. I was a little bit nutty about it and loved to go backpacking with my tent and hike, and it was a big part of my life. I had, of course, some things I couldn't do, but I definitely managed.

My neurological problems, beyond migraines, which I began to have when I was 11, began in 1995. I started to have symptoms of spinal cord compression. As it turned out, I did have spinal cord compression. At my C-1/C-2, brain stem area I had an MPS mass that completely surrounded my spinal cord and was squishing it. I went from being a person who was turbo active to being a person who could barely walk a block.

We then did surgery. They did a 12-hour surgery with three surgeons. It took them, like I said, 12 hours. They did an odontoidectomy, and they fused my C-1 and C-2 together.

I was not wheelchair-bound, but I was weak and I continue to work to keep what strength I have. They didn't get the whole mass, so I also continue to have spinal cord compression, although it's much more mild than what it used to be.

After that surgery, I thought I would get to feeling better, and I waited and I never did. My weakness, like I said, I got some strength back, but, all of a sudden, I was just sick. I was fatigued and I had headaches. If I got too tired, then my bowels got all whacked out. Nothing was well on me.

I ended up leaving my job and going on long-term disability in 1998. Since then, I have continued to have more neurological difficulties, although they're not really with what has to do with what's in my brain; it has more to do with what's on the outside of my brain, like with the mass. So it kind of affects how my brain works or how my body kind of works and connects with my brain. I say it's like I feel like I have a shortcircuit, kind of like the plug isn't plugged all the way in sometimes.

So, all of a sudden, a leg won't work or my speech won't work or I don't work. Times when my body completely shuts down, I become so fatigued that I am unable to function. I can't speak. I can barely walk. It takes all the concentration I can to call somebody to come to my house in case I have to go to

the hospital.

The first time it happened we thought I was having a stroke and went to the hospital, was monitored. The best guess that they have is that more than likely I have, amongst other things, limited blood flow to my brain caused by the MPS kind of surrounding the arteries and the veins going into my brain. So at times, if those things get constricted or whatnot, then it will shut off the blood going to my brain. I have TIAs.

I have been checked for seizures also. I also suffer from hydrocephalus-type symptoms and began taking medication for that just this last year. Again, it got so bad that nearly every day it was like a knife was being stuck in my head and I couldn't function. So those are a few of the problems that I have.

So really in the last six years I went from being a high-functioning, very active woman with stiff joints and some mild MPS problems to being somebody who, if I'm lucky, I have a couple of hours a day that I function. I never feel good. I mean that's done.

Some of the things I deal with daily, sometimes all at once; sometimes they kind of alternate. Sometimes they alternate through the day or within the minute, so you never really know what is going to come up: headaches, extreme fatigue, nausea, diarrhea, limbs falling asleep or going numb, dizziness, memory loss, pain and stiff joints, and that's to name a few. Anything else I've mentioned as far as like spinal cord compression or hydrocephalus, TIAs, you know, all of that is still there, too.

I have had two open heart surgeries. I had my aortic valve fixed three years ago, put a tissue valve in. I had it fixed again just this last August. I went in in April, had my yearly echogram. It was fine. My aortic valve was fine; measurement, the exact same.

Suddenly, in July I started having severe symptoms of cardiac problems, went in. It had clogged back up to the point that it was at when I had had surgery three years before, and this was with close monitoring. Why? We don't know.

My surgeon who had done my same surgery the

time before said that the MPS deposits were on the inside; they're on the outside. He's like, "I'm surprised the thing was working. It was like it attacked it."

So, anyway, enzyme replacement therapy, it's an option for me. I don't know whether it will reverse. I don't know what it will fix. I want to try it. I hear from people that it helps with the fatigue; it helps with the headaches. I see the data. I'm like, sign me; let me try that.

Right now I know what my path is. I know what's happened in the last year. I know what's happened in the last five years of my life. I was a very, very active woman, and now, like I said, I'm a woman who is going towards needing somebody to do everything for me. Right now I have people do my grocery shopping and a lot for me. That's a really short amount of time.

So I would really like to try it. So thank you very much.

CHAIRMAN AOKI: Thank you.

The next speaker is Eric Merrell.

MR. MERRELL: Good afternoon. I would like to thank the members of the panel for allowing us this time to talk to about our special children.

As was stated, my name is Eric Merrell. This lovely woman right here is my beautiful wife Vicki, and these are our two sons, Sean and Cody. We believe that we have a unique perspective to give you on this drug since Sean is in the trial and Cody is not.

When Vicki and I were first married and we discussed having children, I always wanted to have two boys. Since I grew up without a brother, I had always felt like I had missed out on something.

Although they do sometimes fight like cats and dogs, they're as close as I always dreamed that they would be. Hugs and kisses follow the punches and pushes just as much.

These children have been the best thing that's ever happened to Vicki and I. We feel like they're truly a gift from God. They and their little sister Amber have taught us more about unconditional love than we ever thought imaginable.

Unfortunately, however, Sean and Cody were diagnosed with MPS I in July of 2000, just a week before Sean's eighth birthday. We were devastated, but we were told that there was an experimental drug that could possibly help.

So, in January of 2001, we flew to New York University to try to enter our children in the Phase 3 clinical trial for Aldurazyme. We were thrilled that Sean was accepted into the trial, but our joy quickly turned to despair when we learned that Cody was not accepted into the trial. It had never crossed our mind that they both would not be accepted.

Before receiving the enzyme, Sean's abdomen was enlarged due to the deposits being formed in his spleen and liver. His range of motion was diminishing at an alarming rate. He was beginning to have some corneal clouding and deposits on his mitral valve.

But since Sean has been on the ERT his condition has stabilized. Almost immediately after beginning the ERT, his liver and spleen reduced to normal size. There has been no increase in the size of deposits on Sean's cornea and mitral valves. We

are thrilled and very grateful for these changes in Sean. We now believe that his dreams and aspirations in life may come to be.

However, every day that we awaken and watch Sean improve is another day that we watch Cody decline. Every day we watch this loving boy struggle more and more to complete simple tasks such as grooming himself, pulling on his favorite dragon T-shirt over his head, and bending over to tie the shoelaces on his sneakers.

Every day we watch as he squints his eyes to see the screen as he plays his PlayStation II that Santa brought for him. Every day that goes by we see him have less and less energy to chase his brother and sister around the back yard. Every day his abdomen grows more, as well as our fears for his future. It is very difficult to juggle the emotions of having one child in the trial and one who is not and watching him suffer more and more every day.

Every Monday we go to Children's Hospital in St. Louis and watch the enzyme as it goes into Sean's body, wishing we could just take and put a little bit

in a hidden bottle and take it home to Cody. That is why today is a very important day for our family. It didn't matter to us that we had to travel many miles or spend thousands of hours at the hospital to receive this drug.

If this drug is approved, Cody may have a chance to be a dragonslayer, a police officer, a comedian -- and if you know Cody, he is a comedian -- or whatever else he may wish to become, and so that other children afflicted with this horrible disease may have a chance to become whatever they wish to be, maybe even a doctor who one day works with MPS children or possibly even for the FDA.

(Laughter.)

Thank you for allowing us this time to talk about our children.

CHAIRMAN AOKI: The next speaker is Steve Smith.

MR. SMITH: I'm Steve Smith from Chicago. Thank you for letting me speak. I'm speaking to you as a father today of a boy with mucopolysaccharidosis Type IVA, which is called Morquio syndrome.

I want to also disclose that, starting a couple of years ago, I did get a consulting assignment from BioMarin; actually, two consulting assignments, and I haven't worked for them in quite a while, but those assignments were related to two things.

I was hired because I was a general management-type consultant and had computer background. I'm not a scientist, and I didn't know much about clinical trials at the time, but I was paying close attention because of my son. That's how we got into discussion.

The first project I did was to interview the patients in the trial and then write recommendations, much as any general consultant would do, on what would be the most compassionate way to distribute this kind of substance and work with patients on an ongoing basis, so that we can make life easy for them if enzyme replacement therapy becomes a reality.

So my real background for doing that project was my status as a parent, I think. The privilege I got was to meet many of the patients who are in the trial, not really the patients, but the whole family,

sitting in their living rooms, seeing how they live and talking about their lives.

The second project for BioMarin, by the way, was to use my computer background. I work for IBM now, by the way, so I'm out of the consulting business for the most part, IBM Life Sciences.

It was about putting together an epidemiological strategy for how would you collect patient data from around the world so that you could have a critical mass and begin to design better trials and prove things to the FDA. In my talks with a few members of the FDA and the NIH they said there is no such method right now which is really adequate for rare diseases, especially ultra-rare diseases like these.

So what I want to say to you, now that I've disclosed, you should know I have not worked for BioMarin in any way in the past, I think it's been, a year-and-a-half or two now. There's nothing in the future, and they have not paid for me to come here.

I came because of my son; also because many of the people in the MPS I community have become

really heroes to me as they have fought the way for my son and many others with mucopolysaccharidosis diseases, the other diseases in the mucopolysaccharide family to get what they're looking for.

On my own I have gone to MPS conferences in different parts of the world. Like many of us, I launched out as soon as my son was diagnosed in 1990. So I have seen MPS I kids over a 10-year period and how they progress, and I've seen many other kids with lysosomal storage disorders because I go to conferences.

My son, many of you, some of you may have seen. He was the star of a major motion picture called "Simon Birch" that came out. Disney's Hollywood Pictures put it out in 1998, and he played the title role of Simon Birch.

So if you saw that or if you rented it at Blockbuster now, you would see that he's very short. People with Morquio syndrome have dwarfism and very severe joint problems, and progressive problems also related to their respiratory systems and health risks.

If you knew him, you would know he's also

academically a very advanced student in high school. He's socially very well-integrated, and in eighth grade he passed the college entrance exam to get into any of the top universities in this country. So he's actually way above normal in his capabilities, but I'm very, very concerned about future potential.

When I went to speak at conferences in Europe, because the German MPS Society and the Austrian Society invited me on separate occasions to come speak, parents from all over the world are at those conferences. They come to where the conferences are from other countries to ask, what's happening with clinical trials in the United States? Where is the enzyme replacement therapy?

This is a very short list of their concerns, and then I'll conclude. They're concerned that this decision today or here with the MPS I trial impacts them, regardless of what their MPS disease is or their lysosomal storage disorder.

They're concerned that they're waiting for this approval to go well, so not just the scientific community goes on, but the investment community that

puts the money behind all this. They're watching not just the science and the medicine. They are watching that, but they're watching the process very carefully, and they're concerned that time and money and their children's chance is going to run out.

They know that they cannot provide a large number of patients. They can't prove things the way a cancer or an Alzheimer's group or an AIDS group would do because they just don't have those kind of statistics to compile, and you know it can't be done.

They hope the decisionmakers can also weigh in this case, because of that, the suffering that's going on and the lost opportunity they see going away from them right in their very living rooms. They are hoping that those who have the decision in their hands will not only improve the science that we have going on today and improve the medicine, but also improve the process and look at what's happened in this trial and make a decision to release this substance. Then let's move on to the other diseases. Thank you.

CHAIRMAN AOKI: Thank you.

This concludes this portion of the program.

I think we'll break for lunch. I want the Advisory Committee and the interested parties to return by 1:00. So go eat.

(Whereupon, the foregoing matter went off the record for lunch at 12:22 p.m. and went back on the record at 1:03 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:03 p.m.)

CHAIRMAN AOKI: Could the members please take their seats?

Dr. Sampson, you had a request of the company about the confidence intervals, and since all of our members aren't here, I thought we would just ask that now. The important people are here, the statisticians.

(Laughter.)

DR. SAMPSON: Tom, I'm glad you finally recognized that.

(Laughter.)

CHAIRMAN AOKI: It took a long time.

DR. WALTON-BOWEN: I don't actually have a slide of this, and we did just pull it from one of the responses to the European questions.

In terms of the percent predicted FVC, and you'll remember that the mean difference from placebo was 5.9, if we put a confidence interval on the median, which was what the test was on, using a Hodges-Lehmann estimator, the confidence interval, the

95 percent confidence interval for the percent predicted FVC is plus one to plus nine.

In terms of the six-minute walk, we also did the same thing. You'll remember that the mean difference from placebo was 38.1 meters. If we put a 95 percent interval on the median difference, also using the Hodges-Lehmann estimator, the confidence interval is minus two to plus seventy-nine, which is to be expected because our p-value was .066.

DR. SAMPSON: Say the upper one again, please, .79?

DR. WALTON-BOWEN: Yes, plus seventy-nine meters.

DR. SAMPSON: So that's one to nine for the FVC --

DR. WALTON-BOWEN: Yes.

DR. SAMPSON: -- on the Hodges-Lehmann and minus two to seventy-nine --

DR. WALTON-BOWEN: That's correct.

DR. SAMPSON: -- on the six-minute walk. Thank you.

DR. WALTON-BOWEN: Yes. I just want to

point out one more thing. The one for the percent predicted FVC work is before the audit of findings because we ran this a while ago. You'll remember that our results were slightly different in terms of the p-value.

DR. SAMPSON: Thank you.

DR. WALTON-BOWEN: Okay.

CHAIRMAN AOKI: In response to requests from the Advisory Committee members to speed up the process, I have asked a number of members of the Advisory Committee to specifically direct the focused discussion on specific questions.

The first question will be discussed by Dr. Joad.

DR. JOAD: Yes, I was asked to speak about the FVC.

CHAIRMAN AOKI: Why don't you read the whole thing?

DR. JOAD: Oh, read the whole thing?

CHAIRMAN AOKI: Yes.

DR. JOAD: Okay. "Study 003 was a six-month, randomized controlled study in 45 subjects.

FVC was one of the two co-primary endpoints. The overall treatment-associated difference in percent predicted FVC was a mean of 6 percentage points, from a baseline of approximately 50 percent predicted. The p-value was .02 for this difference. The groups were different in FVC at baseline, 48 versus 54 percent." That's treated versus control. "This baseline difference was similar in magnitude to the treatment-associated outcome difference. Examination of the time course of FVC during the study indicates that much of this treatment difference was due to an immediate FVC decline only in the placebo group that did not progress during subsequent months, and a last evaluation improvement in the laronidase-treated group.

"Please discuss the totality of the evidence regarding pulmonary function. Do the data support a meaningful laronidase-treatment effect in FVC?"

Well, the answer to this or my opinion on this would be, is that that's not an easy question to answer. Some points I would like to make about the data is that I would have to say that I do think it's

overstepping it a bit to have expressed the FVC based on previous baseline height rather than current height, because we don't really know why those patients are getting taller, whether it has to do with joint contractures or if they're just getting taller, and if they are, their lungs should increase -- the FVC should go along with their height. Otherwise, that represents a decrement in lung function.

But, as it turns out, the statistics go from .02 to .03. So it's still statistically-significant, even if you use the current high.

The other place where that I think comes in is when the company was presenting the percent of patients who had an 11 percent improvement in FVC. If that improvement in FVC was largely contributed by their increase in height, then it could just be a fancy way of measuring increased height.

So I think looking at the absolute increase in FVC from the percent of people who had that 11 percent increase in their absolute FVC over the six-month period is probably not useful.

So we have a statistically-significant

difference in the percent improvement between the placebo and the treated over the six-month trial. Then the question becomes, is it clinically-important? If you do it the way I think it should be done, which is with the current height, the difference is not 6; it's 4.5 percent difference.

Usually, I would consider that really marginal, a very marginal improvement, and not very clinically-significant or not at all, but I think in this context of a disease that's progressive over years and years and years and would be expected to get worse over time, that within a six-month period to be able to show a difference of 4.5 percent probably is clinically-important.

It's very difficult to say. What we really needed was a longer study to see what would happen in the next six months at least to be able to say that, but if I had to say, do I think 4.5 percent difference in six months' time is clinically-important, I would have to say very marginally so, but perhaps, yes.

CHAIRMAN AOKI: Okay, discussion? Dr. Weiss?

DR. WEISS: Could I just ask also, Dr. Joad, do you have any comments regarding the particular time course? We pointed out that there was this certain maybe anomalous pattern in the very last set of time points with respect to the FVC, particularly in the after-treated group. I was wondering if you had any comments.

DR. JOAD: Right. There's a lot, when you go back and look at all those data, the time course is very peculiar. The things that were pointed out in the paragraph are extremely peculiar, but, as the company pointed out, that last little surge didn't go away when they extended it for the six months.

So I can't say it didn't really happen. It's just unusual that it looked that way, and my overall opinion would be that, although these are all peculiar things when you look at them, they are not enough to say don't pay attention to the group data, because they can't really explain what happened.

What happened the first time to the FVC, the things that seemed to be important in what happened with the FVC in the double-blind, placebo-controlled

Study 003, when you went to the group that was originally treated with placebo and then treated with drug during the next study, you didn't see those same factors, particularly going into it.

So I just feel like it's trying to make too much out of some very interesting things that would be great to go back over with a bigger study and a longer time period. But, given the information we have, I think it's just people change, seasons change. As we say, the data are the data.

CHAIRMAN AOKI: Dr. Schneider?

DR. SCHNEIDER: Well, I would argue differently about which height to use. First of all, measuring height in children is extremely difficult, and most people don't appreciate this, but we all find who do research that, if you don't measure height in a clinical research center, you'll won't get close to it, and even then, if you measure the child when they first wake up versus a couple of hours later, you get a vastly different measurement.

And then on top of it, you have these children who are so difficult to get them to stand

straight the same twice in a row, let alone over a period of time, if there's any change in their joints.

I would think it's a much more accurate thing to take any one height and the same height all the way through, so that that's constant. Here the thing that you're using the height for, the FVC, which I know nothing about except that it's dependent on many factors, and I would simply say height is another factor. If this gets a little better because of increased height, that's just one of the factors that's gotten better, because actually you want to increase growth in these children.

So if I was asked a year ago what to base it on, I would have based it on one height and used the same height all the way through.

DR. JOAD: And just my response to the last comment you made would be FVC represents many things in this. It's kind of more than lung function, and it's the size of the diaphragm and the way the bones are put together in the skeleton, as well as intrinsic properties of the lung. If you want that to also include height, then you can put height in there. But

it just seems to me that's one of the things you would at least like it not to include if you're using FVC as a surrogate for lung function, respiratory problems.

CHAIRMAN AOKI: Dr. Swenson?

MR. SWENSON: Yes, I agree with those comments. I think you can look at it as a plus in either direction. Either they've really grown more than the other group, which anybody would probably put as a positive, or, in fact, they have just better lung volumes; they somehow have recruited a bit more alveolar space. I look at either interpretation as positive.

I think the difference is significant enough. This is a difficult variable with lots of changes, and we're looking at it over a very short period of time. Probably a longer look, if this were ever possible in an ideal world, would probably satisfy everyone.

CHAIRMAN AOKI: Dr. Follman?

DR. FOLLMAN: I would like to comment briefly about the time course of the effects of FVC in the two groups. When you do the primary analysis of a

significant effect, to try and cast dispersions on it you have to say there's perhaps an anomalous drop in the placebo group that happens quickly, and then perhaps an anomalous increase in the treatment group which happens near the end of the study. So it seems like it is making a lot of assumptions to try and cast dispersions on the primary results.

I am also encouraged by the fact that, when you do other analyses, including analysis of co-variants, this finding appears robust. So because we are looking at means in those trajectories and this is somewhat variable, the fact that there's maybe some glitches here and there is not enough to really overturn what I think is a significant effect here.

I am also encouraged by what was pointed out earlier. If you look at the open-label phase of the study, you see trends that are indicative of an improvement in FVC following open-label treatment with the compound. So I am not troubled by the time course of the disease, and I'm also not really so troubled about the imbalance in FVC at baseline, in particular, because we're looking at both changes and then in one

of the analyses we used analysis of co-variants, which in all cases we end up still being significant. So I am not that troubled, either, by the imbalance of FVC at baseline.

CHAIRMAN AOKI: Are you going to add something new?

DR. GRADY: No.

(Laughter.)

CHAIRMAN AOKI: This is the Boston-Yale-Harvard-California attitude.

(Laughter.)

I think at this point, then, we have been asked to vote on this issue. The issue is: "Do the data support a meaningful laronidase-treatment effect on FVC?"

So, starting on my left, Dr. Follman?

DR. FOLLMAN: Yes, I believe they show a meaningful clinical benefit in FVC.

CHAIRMAN AOKI: Dr. Swenson?

MR. SWENSON: I believe so.

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: Yes.

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: Yes.

MS. KNOWLES: Yes.

DR. JOAD: Yes.

CHAIRMAN AOKI: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes.

DR. SAMPSON: Yes.

DR. SCHNEIDER: Yes.

DR. GRADY: Yes.

CHAIRMAN AOKI: Are you guys sick?

(Laughter.)

Clinicians and statisticians don't agree.

(Laughter.)

DR. SAMPSON: When statisticians show truth, the decisions show judgment.

(Laughter.)

CHAIRMAN AOKI: It's 12-0.

Okay, Dr. Sampson is the discusser of Question 2. Would you like it read or would you like us to read it quietly?

DR. WEISS: Would it be too much trouble for

you to read it in, please?

DR. SAMPSON: That's fine.

DR. WEISS: Thank you.

DR. SAMPSON: "Subset analyses of the FVC data suggest that, while a treatment-associated difference was observed for both male and female patients, the effect was different for each gender. Laronidase-treated females had improvements in FVC; placebo-treated females had a stable FVC. Laronidase-treated males had a stable FVC; placebo-treated males showed a decline in FVC.

"Subset analyses also suggest that the treatment-associated outcome difference was more pronounced in patients who had the least amount of pulmonary impairment at baseline, with little difference between groups in the more advanced patients.

"However, in addition to these post-hoc subsets being quite small (4-7 patients), there is also an imbalanced distribution of gender and severity. In the laronidase group more female subjects are in the two lesser-impaired quartiles than

in the two more-impaired quartiles (7-to-4 ratio), while the reverse occurs for male laronidase subjects; fewer with less baseline impairment than with greater impairment" in a 3-to-8 ratio. "This limits the ability to separate gender from impairment as potential treatment effect interaction factors.

"a. In light of the caveats regarding the ability to draw meaningful conclusions from post-hoc analyses of subgroups, particularly in small databases, please discuss the exploratory analyses of FVC, and your interpretation of the data. If you have concluded (in #1) that laronidase has demonstrated a benefit on FVC, can one conclude that the benefit is applicable to all subgroups?"

The b question is, "Please comment on whether there is a biological plausibility to these disparate findings. Do these exploratory analyses raise enough concern to necessitate further investigation of subset-related interaction with treatment effect?"

And c, "If so, must this issue be clarified pre-marketing approval, or would" post-marketing (sic)

"exploration of the issue be suitable?"

I think that the question in some way answers itself in that the subsets in which the interesting effects are explored are small. It's a small dataset to begin with.

I think in regard to gender, and it would be very nice to have had more focused analysis of variants results on the specific co-variants of interest here with treatment interaction; it would have provided at least a small guideline to interpret this a little bit better, but it looks to me like there is a gender effect in kind of the change in the FVC over six months, but that's it not treatment-related, and that the treatment effect is roughly the same in the 003 for males and females.

The point that is made in the third paragraph that says that there's compounding of gender with the impairment quartiles makes it very difficult to interpret kind of the perceived differences that we're saying in the impairment quartiles in the treatment responses. Are those due to gender imbalances or is that really due to baseline

impairment differences?

Since I was one of the people that concluded in one that laronidase has demonstrated a benefit, the next statement is, can one conclude that the benefit is applicable to all subgroups? "All subgroups" is a strong statement.

I think, however, that the flip side to that is that one is not able to not conclude that the benefit is applicable to all subgroups, as there's been no strong evidence presented that there is a differential benefit to different subgroups. Until that somehow is more conclusively, if it were true, more conclusively established, I think one has to believe the benefit is applicable to all the subgroups.

With regard to biological plausibility, I am going to pass on that. There's only so much physician I'm willing to play.

(Laughter.)

It would be nice to see -- I think I expressed it this morning -- it would be nice to see a little bit more analyses in terms of interaction of

some of these noted co-variates with treatment, very focused analyses on those. Given the sparseness of the data, I don't know what they would specifically show, but it would certainly be nice to look at those.

Whether it has to be pre-approval or post-approval I'm not sure. I'm not sure if this is something that wouldn't be more appropriate maybe in a labeling discussion, if that were the case, as to guidelines that you might want to put in. But it doesn't seem to me to be critical in the approval process.

DR. WALTON: Just to clarify that portion of the item, that is really a question of whether or not we should be obtaining new clinical data, not attempts to re-analyze the existing clinical data, but whether or not you will be recommending that we try to explore this in new studies.

DR. SAMPSON: It doesn't seem to me to be a strong enough effect that it leads to necessitate new studies pre-approval.

CHAIRMAN AOKI: Dr. Grady?

DR. GRADY: Well, I just want to point out

that this is a small, randomized trial. It was done in a group of patients with a very heterogeneous disease, and their severity of disease was very different, very wide range at baseline. I think in that situation really you have to look at the overall findings of the trial.

While I think FDA has done just a great job today, and in the past couple of days, in making sure that the data are valid and in clarifying for us, I just think it's really fraught with danger in that kind of situation to begin going to look at patterns in the repeated measures or a subgroup analysis. I just think it is inappropriate.

CHAIRMAN AOKI: Okay, is there any further discussion on this question? Dr. Levitsky?

DR. LEVITSKY: Just a brief address to the biologic plausibility question: It seems to me that if it takes you a long time to get there, it's going to take you longer to get out of there. The people with the more severe symptomatology who didn't respond as much, it may well be a time issue.

If you're looking at FVC and the component

is not on the cage surrounding the lungs but the lungs as well, and whether the liver is enlarged or not, and you have someone who is so severely affected that their bones and joints or muscles are affected, in contrast to someone who may have decreased compliance because of lung function and because of a large liver, it is easy to see why there would be a biologic reason why the more severely-affected people would show less change in this short period of time.

CHAIRMAN AOKI: Dr. Schneider?

DR. SCHNEIDER: I agree, and it suggests to me that perhaps this means that treatment should be started at a younger age then.

CHAIRMAN AOKI: Thank you. Dr. Weiss?

DR. WEISS: There were a lot of questions and discussion this morning regarding dose and optimizing dose. I was wondering whether or not anybody on the Committee feels it might be helpful, even potentially in a post-marketing setting, to try to evaluate doses, particularly with people with perhaps more severe degrees of impairment.

CHAIRMAN AOKI: I'll bet you that Dr. Schade

would like to answer that one.

DR. SCHADE: Well, of course, you could do that. I think the company made actually a fairly valid response in receptor uptake and the fact that maybe, no matter how high you push the dose, the receptor does limit uptake. I think I would have to look at those studies much more carefully, but they may have a very valid point, that they're way above the critical receptor uptake level.

The fact is they suggested 10 times, whatever. Before one automatically jumps in, like maybe I did this morning, to suggest higher dosages, I think there are some valid biochemical measures that one would look at to make sure it's rational.

Without seeing that data or studying that data, I would be hesitant to recommend automatically. I think the FDA should look at the question and discuss the question with the company, but look at the in vitro data about receptor uptake. If you have totally saturated the receptor times ten, we'll see.

So I think the company really did make a very valid response to at least my question.

CHAIRMAN AOKI: Okay, then let's move on to Question No. 3. Dr. Levitsky?

DR. LEVITSKY: Well, I think that the FDA's point is that, using standard statistical approaches, we start off with two groups that are --

CHAIRMAN AOKI: Could you read? Do you want her to read the question?

DR. LEVITSKY: Oh, I'm sorry, should I read?

"The distance walked in six minutes was the other co-primary endpoint. There was a 39-meter difference between groups in the distance walked over the six-minute period, from a baseline of more than 300 meters in each group. The p-value for this difference was 0.07. The differences in six-minute walk between groups at baseline was 319 versus 267 meters in treatment and placebo groups, respectively. This baseline difference was more than the treatment-associated outcome difference. The net result was that by end of the randomized controlled portion of the study, the difference between groups present at baseline was largely absent.

"Please discuss the evidence regarding

walking distance. Do the data indicate that a meaningful treatment benefit has been demonstrated with laronidase treatment in walking capacity?"

And my response to this is that, using standard statistical techniques with this very heterogeneous group, as the FDA points out, the p-value for this difference is not significant. Part of that reason is because this was a heterogenous group in which the treatment group started out with lower walk capacity, apparently, than the non-treatment group and then somehow caught up.

On the other hand, I think the company presented some very compelling reasons why, because this group is so heterogenous, even though this was a random distribution, that use of an analysis of co-variants technique which took into account this lack of heterogeneity is a very important way to look at the data. When they do this, they did show significance, and that significance seems to stand up over the longer period of time when both groups are being treated with enzyme.

My response would be, when the agency

finishes reviewing the new data submitted out until week 62, if they feel that those data are reasonable, then I think we have very good data to support the fact that this primary endpoint was positive and there was a difference and that the drug made a difference in this population.

CHAIRMAN AOKI: We are being asked to vote on this question as well. Discussion?

DR. SAMPSON: I just want to add one small comment. Fixating on a .066 p-value and moving, as I think the analysis co-variance was .04, if I recall, something like that, the confidence intervals that were presented give you some idea of the magnitude in the walking difference. It is somewhere between minus two meters, which barely encompasses zero, and that's why you're getting the .066, and as much as 79 meters difference. This is the change from baseline and then the difference between two treatment groups at the end of the six months.

So I think that alone gives you a lot of confidence in just the amount of magnitude that you're looking at. I think to focus on p-values is to get

trapped in a little bit of kind of regulatory concern which is the FDA's best interpretative level of confidence.

(Laughter.)

DR. WALTON: May I comment? I think that we understand one has to interpret the data. If the p-value alone gave the answer, then we would not even bring the question to you.

So I simply want you to not misunderstand the manner in which we bring it. We feel it's important to bring you all of the facts. The fact that we are bringing this to you is an illustration of we are uncertain of how to interpret this and looking for your assistance.

We certainly agree that the interpretation of this information has to be based not on any single fact, but rather on the totality of all the information about this and the circumstance in which this study data is derived. That is why it is important for us to have this discussion and to understand how you are evaluating this, but it is certainly not a case where we feel the p-value tells

all.

CHAIRMAN AOKI: Okay. Dr. Swenson?

MR. SWENSON: I just wanted to make one comment on the six-minute walk test, to try to put it into some perspective. This has been largely developed more for adult populations with essential either single or combined cardiopulmonary disease, but oftentimes just in a homogeneous group like patients with COPD, adult patients with COPD.

The magnitude of effect I think that's being shown here is equivalent to what has been published in the respiratory literature for COPD. That is, now these are adults as opposed to young adults and children in this study, but the 38 meters or so difference is a difference in which adult patients routinely perceive that as an improvement in their lifestyle. So this is bordering on not only an objective improvement, but in another validated study at least something that suggests quality of life is also enhanced.

CHAIRMAN AOKI: Thank you. Are there any other comments?

(No response.)

Then at this time we are asked to vote on the question: "Do the data indicate that a meaningful treatment benefit has been demonstrated with laronidase treatment in walking capacity?"

Starting with Dr. Grady.

DR. GRADY: Yes.

DR. SCHNEIDER: Yes.

DR. SAMPSON: Yes.

DR. LEVITSKY: Yes.

DR. WATTS: Yes.

CHAIRMAN AOKI: Yes.

DR. JOAD: Yes.

MS. KNOWLES: Yes.

DR. WOOLF: Yes.

DR. SCHADE: Yes.

MR. SWENSON: Yes.

DR. FOLLMAN: Yes.

CHAIRMAN AOKI: Twelve-zero.

The next question will be discussed by Dr. Follman.

DR. FOLLMAN: I'll start by reading the

question.

"Exploratory analyses of the walking distance data showed that the treatment-associated difference was entirely restricted to the female patients...Baseline severity analyses did not suggest an interaction of severity with treatment, but analyses by age suggested that the overall treatment-associated difference was largely restricted to younger patients. In this overall small study, the age distribution is such that the older age tertiles are particularly small (3-8 patients).

"a. In light of the caveats regarding the ability to draw meaningful conclusions from post-hoc analyses of subgroups, particularly in small databases, please discuss the exploratory analyses of walking distance, and your interpretation of the data. If you have concluded (in #3) that laronidase has demonstrated a benefit on walking capacity, please discuss whether all subgroups are likely to benefit.

"b. Are there biologically-plausible reasons why the results might be discrepant? Do these exploratory analyses raise enough concern to

necessitate further investigation of subset-related interactions with treatment effect."

And, finally, "c. If so, must this issue be clarified pre-marketing approval, or would post-approval exploration of the issue be suitable?"

Well, before I answer that, I would like to sort of give the perspective I have on subgroups in general in clinical trials, and particularly I think they are important in these small studies.

Usually, you do a clinical trial in a population where you think the treatment is likely to be fairly homogeneous, and so you don't go looking for differential effects. You check them to make sure that your assumption was basically correct, but you need very strong evidence to go away from the supposition that you bring to the trial, which is that the overall treatment effect estimate is probably the best measure to guide therapy in all the subgroups.

Now having said that, it certainly does happen that occasionally there will be some subgroups for which the treatment may not work as well. In fact, that's probably what you expect, that the

treatment effect is not uniformly constant among every way you can classify the patients. That's to be expected, and I don't think that's very troubling. The overall treatment effect should be a good guide to therapy.

What you're concerned about really I think, when you do look at subgroups, is whether there is a subgroup that's harmed by the treatment. That's a serious issue, and that deserves special scrutiny. I haven't seen any evidence of that whatsoever in any of the subgroup analyses that we have done today. So that very scary spectre is not present, I think, in this study at all.

But to proceed to make something out of a subgroup, you have to have strong statistical evidence, I think, and you also need a strong biological rationale, both of which I think are absent in these studies. I don't see evidence of a qualitative interaction where it would be harmful in any group. So as a blanket statement, I am not concerned about subgroups in this trial.

Now to get to your specific question about

walking distance, you do see a numerical difference in the means between men and women at 26 weeks, where the delta in men is zero at 26 weeks. But if you look at 24 weeks, a little earlier, there is a delta in men, a numerical benefit of the treatment. Furthermore, if you look farther out with the open-label experience, you don't see evidence of a difference in effect by gender. So, for those reasons, I am not really concerned about that.

So there's some weak evidence -- it's very weak in my mind. We know these measures are fairly variable, and so to look at numerical differences in means without adjusting them for the uncertainty associated with them I think is problematic really. So I am not worried about a difference in treatment effect by gender, and similarly for age, I'm not worried about a treatment effect by age.

We see numerical differences in the means, but they don't seem consistent. There's no evidence of a qualitative interaction where it shows that it would be harmful for certain age groups. If you look at the open-label data, the concerns about

differential effect by age is not as marked. So I'm not worried about it.

Part b, "Are there biologically-plausible reasons why the results might be discrepant?" I can't really address that. I just think that what we see is consistent entirely with chance. So I don't think there needs to be post-marketing investigation of this issue.

If you're going to do post-marketing studies, I think it might be useful to consider what age you start this in, what dosing you use. You know, with long-term therapy, do you need to increase the dose? Does the product lose efficacy over time? These are important things that I think should properly be looked at in a post-marketing environment. I don't think they should be looked at now, because I think this compound seems to work to me.

CHAIRMAN AOKI: Any comments? Gee, it is the first time I've looked around.

(Laughter.)

Okay, we're now on Question 5. Dr. Watts?

DR. WATTS: Question 5 has three parts.

"Antibody formation was observed in nearly all laronidase-treated subjects. This occurred early in the treatment course, usually within two months. Thus, six-month findings on FVC and six-minute walk were observed in the face of at least four months of antibody presence.

"Please discuss your degree of concern with the potential for antibodies against laronidase to diminish or eliminate longer-term efficacy.

"Considering that this is a lifelong disease requiring lifelong treatment, please address to what extent data should be obtained on durability of effect.

"Specifically, if additional clinical study data must be provided, please discuss the requisite nature of these data, such as the duration of observation and the necessity for use of a concurrent control population not exposed to laronidase."

Well, antibodies form in almost everyone who receives this substance. The effect, the beneficial effect, seems to be demonstrated despite the presence of these antibodies, and the biochemical effect of

enzyme treatment persists despite the presence of these antibodies, at least over the course of the observation.

I think there is a theoretical concern that there might be a subset of patients who would have diminished activity of treatment as a result of antibody formation, and we touched yesterday and Monday on looking at the biochemical indicators of enzyme therapy. My guess is, since there's been no treatment for this disease, that nobody monitors urinary GAG levels, but my belief is, now that there is an effective treatment and the duration of that beneficial effect is unknown, that periodic monitoring of urinary GAG levels would be appropriate to assure that treatment effect is continuing.

I don't believe you need a control population untreated because I think that gives you adequate assurance, if the urinary GAG levels are low and stay down, that the enzyme is still effective.

CHAIRMAN AOKI: Are there any comments?

(No response.)

Hearing none, then -- oh, Dr. Schade?

DR. SCHADE: Yes, I guess I'm a little more cautious. All these studies are short-term, and we're talking about long-term therapy. Just from my experience, you're going to have patients who appear not to respond to therapy after five years, ten years, et cetera.

When that occurs, I think it's very important to have data to address there are non-responders, and we don't know what the percent of non-responders is going to be. I can just tell you there are going to be non-responders.

One of the possibilities is antibody formation. So I would really encourage in post-marketing studies to at least once a year, or at some frequency which is agreed upon, to simply bank blood or bank serum in which you can measure antibodies and anything else.

Because when we get this group of non-responders, they're going to say, "I need help," and I think we should be as smart as we can. We are going to need banked serum to do that. So I would really encourage the FDA in a post-marketing type of thing to

encourage the company to store serum for not only antibodies, but other factors that we're not smart enough today to know about.

CHAIRMAN AOKI: Thank you. I think we'll jump to Question 7 and then come back to 6.

MR. SWENSON: Question 7 reads, "The available clinical data suggest that the major safety concerns for laronidase relate to infusion reactions. In general, the incidence of infusion reactions during the controlled study appeared similar between the two study groups. However, one placebo-treated patient in the controlled study subsequently received laronidase in the extension study and experienced a life-threatening infusion reaction that required emergency tracheostomy. This patient had substantial respiratory impairment at baseline. The serious adverse experience was temporally related to the laronidase infusion and was cited as `definitely' related to laronidase by the site investigator."

The first question: "Please discuss the implications of this case in light of the potential use of laronidase among subjects with profound

respiratory impairment, including those with such profound impairment that they would not have qualified for enrollment into sponsor's major clinical studies.

"b. If licensed, should the label provide specific warnings about use in patients with profound respiratory impairment?

"c. Should additional studies be conducted in patients with substantial respiratory impairment?"

Clearly, it's always tough to deal with one single adverse reaction in a group of patients that are quite sick, particularly when it's one in some several thousand infusions, I think the company told us. However, it's still quite frightening that something like this should happen.

I think that in response to Question a, what are the implications for patients with profound respiratory impairment who would presumably begin this treatment once it's approved, what should be done, I think in part this is answered in b, is that this warning has to be provided in detail to practitioners that would be using this.

I think that Phase 4 or post-marketing

followup will be critical to establish what the incidence, the true incidence, of this problem would be.

I don't know that there should be additional studies conducted in patients with substantial respiratory impairment because this was a one-time serious-enough reaction to warrant just this question. I don't know that it would come up frequently enough. It might be a very difficult study to ask ahead of time, but I think clearly the followup on this question is going to be key, and that details about drug infusion might have to be altered on the basis of experience.

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: I think I would take a different tact on c. As a post-marketing study, I would definitely study patients with severe respiratory compromise before, during, and following of infusion to see whether there's some common denominator, and that this one individual was simply the tip of an iceberg that was otherwise there. Without doing any study, we'll never know whether this was idiosyncratic

or just a bad experience in people who have less bad experiences. So I would definitely do a study.

CHAIRMAN AOKI: Thank you. Dr. Joad?

DR. JOAD: And I would like, as part of that study, to look at IgE to the drug. We know it makes IgG. How do we know it doesn't make IgE? I was very impressed with the number of infusion-related events that happened.

I think the other thing that's very important is to go back and look at why were there so many in that placebo group. Is there something in the drug preparation that needs to be looked at?

I feel like this is a big concern, and I'm not sure it has anything to do with this underlying respiratory problem because anaphylaxis is usually an upper airway event, and he required a tracheostomy. We don't know why, but if it's because he couldn't move air through his vocal cords, it didn't much matter what was happening with his lower airways. It was really up here that the problem was, and that can be anybody.

So I concur that they have -- and then one

more point is that they used antihistamines for every infusion. So they were already treating for anaphylaxis sort of in anticipation of it. So it strikes me as the biggest worry about this drug, and one that has not been put to rest at all, especially with what happened to this patient. I was worried already before I read about this patient.

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: I have a very quick comment. I would suggest to the FDA that, when they look at infusion reactions, they have more than one definition of an infusion reaction, because I'm concerned that the definition was so broad by the company that you ended up with a lot of, quote, "non-infusion reactions" being labeled as such in the placebo group. That could mask serious infusion reactions that occurred in a very timely fashion with the infusion of this material.

In other words, we got so many in both that it obscured some real serious ones in the material infusion. So I would certainly look at a more restricted definition, ask the company to say, if we

restrict the definition, let's say, to the first five hours, and that we have to have hives or rash, or something, then are there differences between the placebo, et cetera?

So I think just having a huge, broad definition of infusion reaction, although I understand it, is not sufficient to judge infusion reaction numbers.

CHAIRMAN AOKI: She can't ask. No, go ahead.

(Laughter.)

DR. KINGMA: I would like to ask our expert, Dr. Gillian Shepherd. She actually has been part of the allergy monitoring board and has knowledge of the case that you have in your briefing document. She also has vast experience of IgG-mediated complications with recombinant therapies. So if I may ask her to come up?

DR. SHEPHERD: Thank you.

This reaction has been referred to as anaphylaxis, but in actual fact we really don't have much going for that. In the Phase 3 extension trial

this was the only patient who had a positive serum IgE, but subsequent to that being documented he received another 10 infusions relatively uneventfully.

With the infusion in question, it was three-and-a-half hours into the infusion. The patient was well enough to actually be asking for ice cream, although prior to that had a little drop in his oxygen saturation, but this is a patient who on sleep apnea studies, before any drug was infused, would drop his oxygen down to 60 percent and had significant upper airway impairment with flow volumes of 15 percent of predicted. So he was definitely on the more serious end.

At the three-and-a-half hour mark he was speaking, asking for the ice cream, and then abruptly could not speak. So, obviously, had immediate airway obstruction, which in his case his airway was really like a straw, which either it just could have bent; it could have been a ball-valve obstruction, or it might have been IgG inducing laryngeal edema and it was just so narrow that it reached a critical point. After that, he had apnea, and they were unable to intubate

him and had to do finally a tracheostomy.

However, coincident with this -- if it's IgE, normally, you put drug into a system. IgE is sitting there. It reacts instantly. Eighty-five percent of life-threatening anaphylactic reactions happen in an hour, almost all within two hours. This was three-and-a-half hours. It goes against IgE immunology to have a large amount of IgE look at the drug for that period of time and not react.

Secondly, it is often associated with other findings. He did have hives by the time that he went down to the emergency room on his trunk, but he also had complement activation, evidence of complement activation, which might suggest, too, that his IgG antibody was playing a role.

So we really don't have an answer, but previously with his positive serum IgE he also had negative tryptase determinations, which tells us that any other reaction that he has had wasn't consistent with release, IgE-mediated release of histamine from mast cells because that's a definite marker for that.

So I think it is very unclear that IgE

antibody was specifically involved in this patient. We don't know the mechanism, but I don't think that it necessarily -- we really are carrying it as more idiosyncratic to this patient and don't think that we have evidence that IgE antibody per se was a significant problem.

CHAIRMAN AOKI: Thank you.

We'll now turn to Question No. 6. Dr. Grady?

DR. GRADY: "Antibody formation was near universal in the subjects. Only a very few of the subjects in these studies approached the limit of eligibility, 10 percent of the lower limit of normal. More than half of the patients had levels below the limit of detection. Following marketing, laronidase may be more widely used among patients with the higher amounts of residual, intrinsic iduronidase enzyme activity.

"a. Please discuss any concerns you may have regarding the potential for antibody formation to worsen the clinical course in patients with residual, intrinsic iduronidase activity.

"b. Should the company be asked to specifically study such patients?

"c. If licensed, should labeling indicate that benefit has only been demonstrated in patients with low levels of intrinsic iduronidase activity and caution regarding use in those with higher amounts of residual activity?"

Well, I think in general we have been discussing this antibody response to the product, which is very common. I think we agree that post-marketing studies of this are in order. I think I would be inclined to leave exactly how those are done to a discussion between the agency and the company.

I think, however, these potential reactions need to clearly be described on the label. I think the company needs to think about, with the agency, whether or not pre-treatment is required for all infusions and what exactly that should consist of and, in addition, what sorts of facilities are required for the infusions, the facilities in which the infusions occur.

The case that we're most worried about, of

course, is this one patient who had a very serious reaction, required tracheostomy. That, of course, could have been deadly if it hadn't occurred in a setting with the ability to fairly immediate tracheostomy, and so on.

So I think with regard to a, I personally don't have any concerns that high antibody levels might worsen the course of the disease. My concern really is related only to side effects related to high antibody levels.

Part b of the question is, "Should the company be asked to specifically study such patients?" I think the answer to that is yes. Again, I think we should leave it to the company and the agency to decide exactly how that should be done.

The final question is, if licensed, should labeling indicate that benefit has only been demonstrated in patients with low levels of intrinsic enzyme activity? Again, while I think that's true and could be noted in labeling, I don't really see any reason at this point in time to caution use among those with higher levels of residual activity.

DR. WALTON: Dr. Aoki, I would just like to clarify the question to make sure that the Committee understands. This question was not solely related to the idea of adverse reactions, you know, acute reactions from the antibodies, but also the theoretical possibility that in patients who have some degree of intrinsic activity, the inducement of antibodies against the exogenous enzyme, they might also cross-react with the endogenous enzyme and the potential for an induced worsened deficiency, and whether or not that is felt to be of a concern.

DR. GRADY: Could the company tell us, do you know what the range of intrinsic enzyme activity was in the participants?

DR. KAKKIS: This is Dr. Kakkis.

In MPS I, if you use properly high-sensitivity assays, Scheie patients, even who have the highest levels, are still less than 1 percent of normal. Traditional laboratory assays are not all that sensitive. There isn't much iduronidase even in normal people. So the less than 10 percent is really a matter of sensitivity of the assays.

But even in the Phase 1/2 study, the Scheie patient there and all Scheie patients that have been studied with the proper sensitive assays had less than 1 percent of normal. So those tiny amounts of enzymes are sufficient to ameliorate the disease.

But the enzyme itself is lysosomal and it's trafficked intercellularly. It is not really exposed to the antibodies. It doesn't go out of the cell in order to go to its proper location.

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: It seems to me that the only way these patients are going to be picked up is symptomatically. No one is going to be doing the screening test for the lack of the enzyme. So if the patient is symptomatic enough to come to the attention of a physician because of the disease, they're symptomatic enough to be treated, and that would not be a concern of mine.

CHAIRMAN AOKI: Dr. Walton, do you have any questions?

DR. WALTON: I was just going to clarify the basis of the question is that the eligibility

criteria, as Dr. Kakkis said, had been for less than 10 percent of the lower limit of normal. As he said, most of the patients were considerably less than that. There were only very few that were at the higher end, but the eligibility had been for going up to 10 percent. So it's the potential for those patients who you really haven't studied in the future to be considered for treatment.

CHAIRMAN AOKI: Dr. Levitsky?

DR. LEVITSKY: Dr. Walton, just as the company representative just clarified, this is an enzyme which spends its life in the lysosome. Could you give me the biologic reason why a circulating antibody would interfere with its action, why you would worry about interfering with endogenous enzyme activity? I don't know how that would happen, actually.

DR. WALTON: I'm certainly not an expert in the disease, and I think we recognize this well, that it's an intracellular enzyme; however, felt the need to bring the question to the Committee for a discussion of whether or not there was anything that

they could bring that would pose a cause for concern.

CHAIRMAN AOKI: Are there any other questions for this question?

(No response.)

Dr. Walton?

DR. WALTON: I take it, then, that the Committee has concluded discussing this question. Then, since this was the last question that we had listed, and we have been able to get through this before running out of time today, I would like to ask the Committee to give us some further advice on another question.

(Laughter.)

CHAIRMAN AOKI: I'm sorry, but we're adjourning.

(Laughter.)

But you're right, it's better than coming up again.

DR. WALTON: This may be a more difficult question because it involves envisioning how the course of events in the future will be, and it ties into a couple of the comments that we have heard about

the areas of use that we don't have knowledge about and questions like, you know, when might be the proper time or optimal time to begin treatment, things like that.

But the question I would like to ask and hear comments and advice on what to do in the future and how much we should try to be concerned about is: By and large, the patients we have studied have been those of the Hurler-Scheie form, although it's a broad continuum, general in that class, patients who have been fairly markedly affected at a fairly young age.

But I think that we have concerns that, as a treatment is available, I think we have seen in many cases as a treatment becomes available, and physicians are more aware, that we find out there are more people with the disorder than had been recognized before, when there was no treatment. That has occurred in many diseases.

I think that, given that we may have a treatment available, that the patients who have the more prominent manifestations will come to diagnosis. That will lead to the evaluation of the remainder of

the family, and I think that we are very liable to find patients for whom, on a genetic and biochemical basis, there would be great concern that they will develop symptoms in the future.

But, as we have heard, based on enzyme activity level alone, one really can't predict, at a very early age on enzyme activity alone, one can't predict. The Scheie form of patients can have very low levels as well.

So physicians will be faced with people who are in a family where there is an affected member, and they have a person who, on a genetic and biochemical basis, is suggestive that they may develop symptoms in the future, but at the present time do not have. How should the agency go about thinking about this circumstance? How can we recommend in determining who should be an appropriate candidate for this therapy?

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: It sort of gets back to my comments this morning, that I think it's very important, if in fact these whole series of diseases is due to abnormal accumulation in tissues, I think

it's very important to have some sense of what tissues accumulate and whether, quote, "a relatively non-invasive biopsy" of the skin or something will give really information as to when the disease will progress.

For example, in the types of patients that you suggest in which they don't have symptoms yet but they're worried about getting the disease, if they had a negative skin biopsy once a year, once every five years, and if we were pretty sure that real symptoms and signs do not develop without some infiltration of tissue, of abnormal lipids, or whatever we're measuring, I think that's what we really need.

That's why I said this morning that I really think the histology of a non-invasive biopsy could be very important for determining who gets treated when. Because the fact is, if you have a negative biopsy, then I think you really have to look elsewhere for other diseases such as lupus or anything else that cause symptoms that are very general in nature. In other words, just because you have a generic marker does not mean that you cannot have a different

disease.

So I really think the agency should in some way insist post-marketing or other applications, or whatever, that in these kind of unifocal diseases in which you have a one-enzyme hit and the lack of the enzyme does cause accumulation of abnormal lipids, or whatever, that that ought to be part of the developmental process, which I didn't see this morning, because I think it is ultimately very important for addressing your question: Who do you treat who doesn't yet have any symptoms that are obviously related to the disease?

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: It seems to me that we have an autosomal recessive disease which sounds like very high penetrance. So the parents are obligative carriers. We have at least 60 families whose children have participated in this study. We ought to be able to ask the parents if they wish to participate in a very simple study, and I would propose looking at urinary GAG levels perhaps as a way to start, to see what they're like, and also find out whether they

suffer any of the symptoms suggested of the disease.

Now I'll grant you that the phenotype may not represent the genotype, but at least we have a cadre of people who I would think would be interested in providing that kind of information. A urinary GAG would be something very easy to do and use that information to decide how to proceed.

CHAIRMAN AOKI: Who was first? There's three of you. Dr. Levitsky?

DR. LEVITSKY: Many years ago Dr. Schade tried to teach me what he knew about Scheie disease, and I think that that's changed a bit since he tried to teach me and I didn't learn too well. I think that most of the people at this table are very educated and intelligent amateurs when it comes to this disorder. There are few who are not.

At least I think I'm the wrong person to be asked this question. I think that there are very competent biochemical geneticists who have devoted their life to this disorder who could be sat down with, and families who could be sat down with, and who could give you the information about what GAG

excretion looks like in heterozygotes, what family members look like, what the degree of penetrance is in families, et cetera, et cetera.

I think that is probably more known than most of us at this table know and perhaps should not be asked that question somehow. I think you need other people who have the data.

DR. WALTON: I'm not thinking of only the -- really I wasn't even thinking primarily of the heterozygotes. I was thinking of the homozygote patient who perhaps at age 13 or 15 is found to be homozygote, to have the biochemical markers but not to have the symptoms, but that may in the future become a mild case, perhaps when they are 30.

DR. LEVITSKY: Are the natural history data known, so that that question could be answered? If every 15-year-old who has the biochemical disorder is going to have problems at 40 that could be prevented, then you have to decide how to set up a study to see how early they need to be treated to be prevented and what the earliest signs of the disorder are.

I'm, once again, not the one to know the

answer to that question. I think there are a couple of people here who do know the answer to that.

CHAIRMAN AOKI: Hold it. Does the company have some wonderful information about this issue?

(Laughter.)

DR. CLARKE: Well, we definitely would like to respond to this. I'm Lorne Clarke. I'm a clinical geneticist from Vancouver. I look after MPS patients and also do research in MPS I.

To address your question of the complexity of the patients and how many pre-symptomatic patients are out there, I think that is a very hypothetical and theoretical question.

I would basically answer that -- let me be a physician. We look after these patients. We have taken a vow to do no harm. Our intent here is to improve the life of these patients. I don't think you can dictate a cautionary use of a product based on a hypothetical patient that may be out there that may have a lesser disease. Let us be clinicians and treat our patients appropriately.

CHAIRMAN AOKI: Okay.

DR. MUENZER: Can I respond to the biochemistry? This disorder is due to the missing enzyme iduronidase. Parents with this disorder, to my knowledge, have never reported any convincing symptoms related to the disease, and they do not have abnormal glycosaminoglycans in their urine.

In general, people who get diagnosed with this disorder present because of symptoms, whether it's relatively mild joint stiffness or whether it's overt airway or other problems. So, in general, I'm not concerned at all about treating patients who have no disease.

This is a slowly progressive disorder where there is no treatment. Current status, we have probably not missed very many patients. I say that only because in the pediatric range the combination of this neurological problem and the severe physical disease bring these patients to attention, sometimes later than they should, but they come to attention.

The very mild adult who may have Scheie syndrome who has virtually no symptoms, that patient may or may not benefit from treatment. But given some

of the things you have heard and the things I observed, these patients feel better. I don't know what that's due to, but there's something about this disease that affects the whole body. Clearly, until we try this in patients who do have mild disease, we won't know.

In the current study we excluded all those patients, for obvious reasons. Those patients clearly are virtually normal and to see reversal of disease is impossible. So, therefore, I think we need to treat patients before we can make any decision on how effective or not effective it is.

CHAIRMAN AOKI: Dr. Follman?

DR. FOLLMAN: I just wanted to think about this a little more generically and amplify the comments yesterday by Dr. Fleming. You know, as a generic issue, it seems like in this area of correction of metabolic disorders, there will be compounds made that will affect and improve the lives of the sickest patients initially, and then there could be a spectrum of a disability associated with the disease.

You're going to have the issue of maybe writing the labeling for the product rather narrowly, so that it is focused on the sickest patients, and when it's out there, presumably, it's going to be used more widely.

So you really like to have some information to guide you in whether it is appropriate for less sick patients, but I think the way to approach that may be to, once something is licensed and its use is being expanded, find a group that's probably the least diseased or the least severely restricted, and do a randomized study on those people, where you would have equipoise, that there would be legitimate question as to whether 40-50 years of therapy, or 30, would be really worth initiating in a young child.

So you're going to be approving these compounds. They will be used in a group. It will expand, and then I think the way to study this would be in the least severely restricted.

CHAIRMAN AOKI: Dr. Grady?

DR. GRADY: Well, I guess I am less worried about this issue in this situation than in many

others. I mean, in some ways the diagnosis of this disease is way more straightforward than the diagnosis of coronary heart disease, for example.

I think that it is currently treated by a small number of experts who are expert. So I think, particularly if there are some restrictions on the facilities that have to be available in order to give it, I mean I guess I kind of agree; I think right now we need to rely on the expertise of the small number of physicians who treat people with this illness. Maybe at some point in time -- I just somehow find it hard to imagine that a weekly infusion of a therapy is going to become widespread in the general population.

(Laughter.)

CHAIRMAN AOKI: Dr. Swenson?

MR. SWENSON: I just want to ask somewhat of a philosophical question. Does the FDA wish to begin to -- I don't want to use the word "dictate" because that sounds too harsh, but strongly advise treatments under certain conditions? That may be the purview of subspecialty groups to come together within that field to begin to provide consensus statements as to its

appropriate use outside the initial testing, particularly for minimally-symptomatic or totally-asymptomatic persons.

DR. WALTON: Actually, it is within the requirements of the FDA that, in writing the labeling, that we do our best to assure that the labeling provides adequate directions for use. It's not uncommon to provide guidance in the labeling about the patient populations in which it has been studied and in which it has not been studied, to provide guidance about patient populations in which there may well be doubt about the utility of the product. So it is actually common practice to provide this kind of guidance.

It is also important for us to understand this. Dr. Follman's advice was to have somewhat narrowed labeling and to seek to have this done, this question evaluated as a post-marketing study. That kind of advice is very valuable to us in determining whether or not we should be pursing that.

MR. SWENSON: Well, I agree with everything that you have said, but what I heard, or thought I

heard, was that you might be moving to say that asymptomatic people would not be suitable for treatment. I just want to get a sense for how firm you wish to be or what type of guidance you would want from us on those very fine points.

DR. WALTON: I think we are asking for guidance on how firm you feel perhaps we should be. Obviously, there is a concern that in the patients we've studied, as I can't remember who but one of the other people on the Committee has expressed, that we study the patients who were at least moderately affected. Clearly, if we can take these patients that have been studied and turn them into mildly-affected patients, then we'll have done a grand thing. There's no doubts about that.

But it is a separate question that, having done that, can we be sure that this same treatment, dose regimen of this product, can take a patient who is mild and turn them into and alleviate their mild symptoms? And how concerned should we be about that and, as a consequence, how should the agency pursue that concern, is the kind of advice that we are asking

for.

CHAIRMAN AOKI: Dr. Schneider?

DR. SCHNEIDER: Yes, my advice to you would be to list on the label things that it has been approved for and not to go into other things. I agree with Dr. Swenson that I think this is something that should be addressed. In this case it would be one of those genetic groups of people who are really expert in the field. I am sure that they will look on this as a very important problem, that the people really involved in this will come up with a consensus statement that will be widely circulated.

I think that makes more sense. I think the FDA has enough to do without getting involved in this type of the fine points. I agree with the physician from Canada who said let the physicians decide. No physician is going to become rich treating too many patients. As Dr. Grady said, not many patients are going to come fighting for this weekly injection.

I think you are getting too involved in it. I think just approve it for this disease for patients who have now been studied, and just not get into the

question of what other patients. These are very important, difficult questions that will be thought about and discussed and worked out over many years.

DR. WALTON: I'm sorry, Dr. Schneider, I ask you to clarify, approved for the patients who have been studied or just for the disease in general?

DR. SCHNEIDER: Just for patients with Hurler and Hurler-Scheie disease. In other words, for patients who are symptomatic with deficiency of this enzyme.

DR. WALTON: Okay, that's very important. That is very clear advice, and that is what we are looking to hear.

CHAIRMAN AOKI: Ms. Knowles?

MS. KNOWLES: It is really important for FDA to really, I think, get our opinions on this issue for third-party reimbursement issues because that's going to be really needed to take care of the patients.

CHAIRMAN AOKI: Although I suspect that just an FDA-approved treatment ensures probably they will have to fall in line.

DR. WOOLF: "Mild" is a very subjective

term. What is mild to one person may be devastating to another. I would never use that in any labeling at all.

Then, if you are going to get into parameters where you can only use the drug if this, that, or the other thing, it will be a morass. So I would stay away from any of those qualitative symptoms at all. If you've got the enzyme deficiency and you have some symptoms, to me that's indication for treatment.

If you put any caveats on there, our third-party payers will find all sorts of ways not to pay for it. So I would be very, very clear, an enzyme level below a certain amount, and leave it up to the docs.

CHAIRMAN AOKI: Here's your chance. Dr. Walton, do you have any other questions?

DR. JOAD: I just have one more comment, which is that I so much would have liked this to have been a one-year study. You know, the fact that we all voted 12-0 for both of the primary endpoints, I think we were -- hopefully, if anybody was going on my

advice, I was really putting a whole bunch of things together to be able to say I thought it was clinically, the FVC, clinically-important and statistically-significant -- well, clinically-important.

So we have a chronic disease that very slowly deteriorates. I just think six months was way too short, and that as advisors to you and as people who have to make the decision yourselves, making the decision on inadequate information -- you know, this is barely adequate information -- it's a mistake.

One year would have given so much better information. They collected the data anyway. I just wish that it had all been double-blind, placebo-controlled.

DR. WEISS: Thank you for the comments. Certainly, with chronic diseases there is always a question about how long a duration, particularly of a control period, is important because you're going to extrapolate from that information to a longer duration.

We have had experience with a number of

chronic diseases where some of the treatments go on for two or three years, multiple sclerosis being one example. But, of course, this is even a much rarer disease.

And there are issues we discuss with all companies, concerns about duration of a placebo-controlled period, that come up every time in these types of discussions, and concerns particularly when you're talking about children and putting children on trials, and keeping a placebo control with IV infusions, in particular.

Those are the kinds of things, I mean we wrestle and try to balance the need for knowing and getting enough proof, and in a chronic disease how long is it going to take before you're going to potentially see something that is convincing versus some of the other difficulties in terms of conducting trials.

DR. WALTON: Could I ask that -- I think that your comments are very, very valuable, very important, and we feel much the same way about the one-year duration as opposed to the six months. I

think it would be helpful to the agency, in thinking about the other disorders that are going to be coming before the agency, if we could hear some other comments.

Specifically, do you believe that a one-year, randomized study would be feasible and should be the preferred development program for these sorts of studies?

CHAIRMAN AOKI: Dr. Watts?

DR. WATTS: I'm glad you raised the question because I'm more inclined to go the other way. That is, if you can show in six months that there is some benefit, clinical benefit, having seen shrinkage of liver size and something tangible, I would be inclined in similar diseases to accept the surrogate for a clinical endpoint. That is, if you can shrink liver size, you don't need to do a long-term, randomized, placebo-controlled trial with a clinical endpoint.

CHAIRMAN AOKI: Dr. Schade?

DR. SCHADE: I would agree. If you do the calculation, if you go an extra six months and there are a thousand patients in the United States, you are

talking about 500 man-years or patient-years of continuing with this disease without adequate treatment.

I think that if you reach an endpoint that the Committee can accept as either a surrogate or as an endpoint, then that is what post-marketing studies do. I agree a hundred percent that we need to get these drugs out to the people that need them and not delay another 500 man-years before we do that.

So I strongly would support not -- or I would strongly oppose instituting any rule that said, well, we need a one-year, double-blind, randomized trial. Even though I totally appreciate the statistical aspect of it and I would like that data, I think there is a patient care issue here that is so overwhelming that we need to really be very careful about mandating any strict guidelines relative to duration of studies.

CHAIRMAN AOKI: Dr. Woolf?

DR. WOOLF: Well, I would like to follow up on a comment made by the first speaker this morning from the audience about the need for the FDA to really

seriously think about procedures for orphan drugs that are going to be coming down the pike, just like the two we have heard this week. The problem is only going get more severe, and it is going to be more difficult.

A lot of us are voting on some data and a lot of hope. I would like to see the effort put in very early on what is the appropriate surrogate. I would spend the extra time getting the surrogate that both the agency and the sponsor feel, and perhaps even with input from the groups who are affected, that what is likely to be a beneficial effect that can be observed relatively easily, reproducibly, and quickly.

Shrinkage of liver for MPS I is an obvious one. The ones from earlier in the week are less obvious. But someone who knows the disease, what is likely to respond quickly and be used as a surrogate, and then do a very, very careful post-approval or post-marketing survey.

So I agree with my esteemed colleague to the left.

(Laughter.)

CHAIRMAN AOKI: Dr. Follman?

DR. FOLLMAN: I don't think one-year studies are what we should mandate. You know, it is going to depend, obviously, on the disease and how quickly you expect the treatment to manifest a benefit, et cetera, et cetera. So one-size-fits-all I don't think is appropriate.

In this particular case, you know, would I like to have a year of data? Well, I suppose that would have been better, but I think we all felt pretty comfortable making a decision on six months of data.

The objective of a trial is to not use up too many resources or take too much time or too many patients, and also not to do too few patients or follow them for too short a period of time. So I think in this case, you know, maybe we would have felt a little more comfortable if we had a little more data, but I think we made a decision we can all live with. So I think this is probably properly calibrated in terms of length of followup.

CHAIRMAN AOKI: Ms. Knowles?

MS. KNOWLES: Well, I think the really

important factor here is a well-designed study, and I think another really important variable is the medical condition of the patient population. I think we really have to take that into consideration in terms of how life-threatening that condition might be.

And then the last point I will make is I think we have seen a real wide variation in the last three days of study design. I think that is something for sponsors to think about and for maybe the upfront discussions between FDA and the sponsors to really get together with to make sure that they make use of their resources and are doing a good study to benefit the patient.

CHAIRMAN AOKI: Dr. Joad?

DR. JOAD: I don't want to repeat myself too much, but 4.5 percent difference in FVC is not clinically important. If that's all that there's ever going to be, then it is a disservice for us to say that that was an important change in FVC. It is really in the context that I thought it was.

Once something is post-marketed, you want everybody to get it. You're never ever going to get a

placebo control again. So it has to be done right the first time in a way that you feel confident that you are, indeed, helping someone, when there are going to be side effects and expense and trouble to the people to get the treatment.

CHAIRMAN AOKI: Dr. Grady?

DR. GRADY: You know, this is a hard problem, and I think you can't answer it with one-size-fits-all. But I guess the other thing I would like to recommend that you think about is sometimes I think what we do is we pick out outcomes that can be measured precisely, but often don't have as much clinical meaning. We do that because we are aiming at this .05, which is some sort of, you know, "the holy grail of statistics."

So, for example, we are sitting here talking about whether the walk time was statistically different in the groups because seven out of a hundred times it might have occurred by chance compared to five out of a hundred times that it might have occurred by chance.

So in some ways I think the agency might

also consider negotiating with sponsors to perhaps use a more clinically-meaningful outcome at a lower alpha, with a lower p-value. To me, that would be more persuasive perhaps oftentimes.

Certainly you don't want to do that for all studies. Generally, you want to have a very low -- we want to have a very high confidence that we haven't made a type 1 error.

But in this kind of situation where the real limitation for an orphan drug is the number of patients you can get into a study, then using a more liberal p-value seems to me to be only reasonable.

DR. WEISS: We would totally agree with that. I think there has been a fair amount of flexibility in certain types of settings where it is just very difficult.

I don't think anybody here -- I think you've heard several people from the FDA say several times today that .05 is just what it is, and it's nothing -- you don't hang your hat on that. Not everything is based on that, but it is a target that people shoot for in terms of designing the trials, in terms of

sample size, but of course you look at everything. You look at consistencies. You don't look at just value.

DR. GRADY: On the other hand, I think it does really strongly drive the choice of outcome, and often drives that outcome to something that is less clinically meaningful because there is a continuous variable measurement or it is a more precise measurement.

CHAIRMAN AOKI: Dr. Levitsky?

DR. LEVITSKY: One of the things that I have noticed, as I have looked at the three studies that we have watched, is that I haven't always been sure that there was a clear understanding of the disorder, that it takes a long time to cause problems. It is also going to have a long time before you can show effect.

So that using a marker which is obviously not clinically-significant but may point to the longer problem, like using hemoglobin A1C in diabetes, for instance, may be very necessary in all sorts of disorders.

For instance, I was very happy with the

shrinking of the liver in this disorder and didn't really need to see the rest. I was happy with that as a surrogate marker.

If you have a child with a urea-cycle defect and you have the cure for it, you may need a six-week study to prove that the urea-cycle defect medication is appropriate.

With something that is going to manifest itself in full blossom when someone is 20, I think it is hard to expect that a six-month trial looking for a real clinical endpoint is necessarily going to show up with something.

So it seems to me that one has to go prospectively into these studies with a very good surrogate marker in these disorders which have outcomes which take a long time to manifest themselves. We don't always guess right. I think maybe there were some guesses that were a little bit off in the past three days, and that is very important to think about, to make sure that guess is appropriate.

CHAIRMAN AOKI: Dr. Zerbe?

DR. ZERBE: Yes, I think it is fair to actually commend all three companies in the three days for taking on a real difficult clinical problem. I think that, though you can always make the system work better, in reality, as you look at it and you step away from it, the system has actually worked pretty well to deliver these really lifesaving medications for patients, done in a balanced way, so that the risks are thoroughly evaluated and presented.

I think that the debate and the argument shouldn't be misinterpreted as a system broken. I think it is really a system that is working pretty well.

CHAIRMAN AOKI: Hearing nothing further, the meeting is adjourned.

(Whereupon, the Committee was adjourned at 2:35 p.m.)