FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

8:33 a.m

Wednesday, June 25, 2003

Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

ATTENDEES

COMMITTEE MEMBERS:

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School of Public Health and Cancer Institute
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ATTENDEES (Continued)

SPECIAL GOVERNMENT EMPLOYEES: (Voting)

JOSE CARA, M.D.
Henry Ford Hospital
Detroit, Michigan

ALLEN MANGEL, M.D., PH.D.
Research Triangle Institute
Research Triangle Park, North Carolina

STEPHEN SWENSEN, PH.D., Patient Representative

ACTING INDUSTRY REPRESENTATIVE: (Non-voting)

GEORGE S. GOLDSTEIN, M.D.
White Plains, New York

FOOD AND DRUG ADMINISTRATION STAFF:

HUGO GALLO-TORRES, M.D.
FLORENCE HOUN, M.D., M.P.H.
ROBERT JUSTICE, M.D.

SERONO, INC. REPRESENTATIVES:

THERESA A. BYRNE, D.SC.
JOSEPH GERTNER, M.B., M.R.C.P.
SUSAN KENLEY, PH.D.
GARY KOCH, PH.D.
PAMELA WILLIAMSON JOYCE, RAC
DOUGLAS W. WILMORE, M.D., FACS

ALSO PRESENT:

BRENDA BOBLITT
THOMAS ZIEGLER, M.D.

C O N T E N T S

NDA 21-597, Serostim (somatropin), Serono, Inc.
For the treatment of short bowel syndrome
in patients receiving specialized nutritional support.
Serostim therapy should be used in conjunction with
optimal management of short bowel syndrome.

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P R O C E E D I N G S

(8:33 a.m.)

DR. WOLFE: Good morning everyone. I'd like to get the meeting started.

I'm Michael Wolfe. I'm Chair of the Advisory Committee for Gastrointestinal Drugs.

Before we get started with the opening statement by Mr. Perez, we'll start with the introductions of the table.

DR. GOLDSTEIN: George Goldstein, industry representative.

DR. MANGEL: Allen Mangel, Research Triangle Institute.

MS. COHEN: Susan Cohen. I'm a consumer member, and I should disclose that I grew up near Rockland. I don't know if that's going to make a problem or not.

DR. WOLFE: I think you're conflicted out.

MS. COHEN: Yes, don't you think so?

(Laughter.)

DR. SHIH: Weichung Joe Shih. I'm a biostatistician and an FDA advisory committee member.

DR. WOLFE: Again, I'm Michael Wolfe.

I ask the people at the table, when you're not speaking turn your microphone off.

MR. PEREZ: Tom Perez, Executive Secretary to

this meeting.

DR. LEVINE: I'm Bob Levine, SUNY Upstate Medical Center, Syracuse, New York.

DR. LaMONT: Tom LaMont. I'm a member of the GI Advisory committee. I'm from Beth Israel Deaconess in Boston.

DR. SWENSEN: Steve Swensen. I'm the patient representative. I have a son who has short bowel syndrome.

DR. CAMILLERI: Michael Camilleri, Mayo Clinic, Rochester, Minnesota. I'm a member of the advisory committee.

DR. GALLO-TORRES: Hugo Gallo-Torres, medical team leader, GI drugs.

DR. JUSTICE: Robert Justice, Director, Division of Gastrointestinal and Coagulation Drug Products.

DR. HOUN: Florence Houn, Office Director, Drug Evaluation III.

DR. WOLFE: I will add. I forgot to mention I am from Boston University, Boston, Massachusetts.

And now Mr. Perez will read the meeting statement.

MR. PEREZ: Thank you and good morning.

The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at

this meeting.

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

Susan Cohen has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4), amendment of section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor to Serostim. The stock is valued between $25,000 and $50,000.

Steven Swensen has been granted a waiver under 21 U.S.C. 355(n)(4) of the Food and Drug Administration Modernization Act for ownership of stock in a competitor. The stock is valued at less than $5,001. Because 5 C.F.R. 2640, section 202(a)(2) de minimis exemption applies, Dr. Swensen does not require a waiver under 18 U.S.C. 208(b)(3).

We would also like to note for the record that Dr. George Goldstein is participating in this meeting as a non-voting industry representative.

In the event that the discussions involve any

other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their 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 product they may wish to comment upon.

Thank you.

DR. WOLFE: I'd like to call now on Dr. Justice to read the opening comments.

DR. JUSTICE: Good morning. I'd like to thank members of the committee and consultants for participating in today's meeting.

Serostim, or somatropin of recombinant DNA origin for injection, is approved for the treatment of AIDS wasting or cachexia.

Today we're considering an application for the treatment of short bowel syndrome in patients receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome.

As you will hear, the application is supported by a single study, IMP 20317, in patients with short bowel syndrome. The study is a randomized, controlled,

multicenter trial. The primary endpoint was change in total intravenous parenteral nutrition volume.

This application poses several issues that we'd like the committee to consider during their presentations and following discussion.

First, only one trial in 41 patients was conducted. Are the results sufficiently robust that a replication is not required?

Second, the trial was conducted primarily at a single center. Can the results be generalized to the entire population of patients with short bowel syndrome?

The primary endpoint is change in total intravenous parenteral nutrition volume, or IPN, from week 2 to week 6. Given the study results, is this endpoint clinically meaningful?

Fourth, a change in total IPN calories and change in IPN or lipid frequency were secondary endpoints. Again, given the study results, are these endpoints clinically meaningful?

Treatment was administered for 1 month and follow-up for efficacy was limited to evaluation of IPN volume change at 18 weeks. Is the duration of therapy and follow-up for efficacy adequate?

Finally, safety of long-term administration was not established in this trial. Is this a concern?

We look forward to receiving the committee's advice on these issues, and with that brief introduction, I'll turn it back over to the chair. Thank you.

DR. WOLFE: Thank you, Dr. Justice.

At this point, I would like to call on Pamela Williamson Joyce, who is Vice President of Regulatory Affairs and Quality Assurance at Serono, Incorporated, to begin Serono's presentation.

MS. JOYCE: Good morning. My name is Pamela Williamson Joyce, VP of Regulatory Affairs and Quality Assurance at Serono. I would like to thank Dr. Wolfe and the members of the advisory committee, as well as the members of the Food and Drug Administration, for the opportunity to be here today and to share the results of our clinical study of Serostim, Serono's brand of recombinant growth hormone, in treatment of patients with short bowel syndrome.

The proposed indication for Serostim is as follows. Serostim, somatropin (rDNA origin) for injection, is indicated for the treatment of short bowel syndrome in patients receiving specialized nutritional support. Serostim therapy should be used in conjunction with the optimal management in short bowel syndrome.

The agenda for our presentation is as follows. I will open with a brief introduction and a brief

regulatory history, and then Dr. Douglas Wilmore from the Brigham & Women's Hospital in Boston will come up and he'll share the clinician's perspective on the unmet medical need of patients with short bowel syndrome. Following Dr. Wilmore, we will hear from Dr. Joseph Gertner, Vice President and head of the Clinical Development Unit at Serono, and he will share with you the efficacy and safety results of our pivotal trial. And then following the presentation by Dr. Gertner, I'll close with some concluding remarks.

Serostim is a growth hormone produced by recombinant technology and is currently available in lyophilized vials of 4, 5, 6, and 8.8 milligrams. Serostim is administered by subcutaneous injection.

Serostim is not a new molecular entity. Other sponsors have their recombinant growth hormones approved for a variety of indications, both within the United States and worldwide. For Serono's product, Serono's product Serostim is currently approved to treat patients with AIDS wasting or cachexia.

It's of note because it will become apparent, as Dr. Gertner presents the results of the clinical trial, that Serostim has received orphan drug designation from the Office of Orphan Drug Product Development. The orphan drug regulation does provide incentives for the development of

drugs to treat rare diseases or conditions. The rare disease or condition needs to have a prevalence of less than 200,000 patients in the United States, and in the case of short bowel syndrome, the actual prevalence is closer to 10,000 to 20,000 U.S. adults dependent on parenteral nutrition due to short bowel syndrome.

There is currently no approved drug treatment for the treatment of patients with short bowel syndrome.

I'm going to just take a couple of extra minutes to talk about the regulatory history of the file, and the reason I'm going to do that is because the clinical development program has actually spanned the course of a period of about 8 years. During that period of time, people come and go. The original IND was transferred from one sponsor to another, and then most recently, the NDA was transferred from the Division of Metabolic and Endocrine Drug Products to the Division of Gastrointestinal Drug Products.

Back in 1994, there was a pre-IND meeting with the Division of Metabolic and Endocrine Drug Products and that meeting was to review the data available at the time and to discuss some ongoing studies and specifically to discuss what the requirements would be to approve a recombinant growth hormone for treatment of patients with short bowel syndrome. There was a series of discussions

back and forth, and then in August of 1995, the Food and Drug Administration provided guidance in response to the seeking of the advice for a study design that would be required in order to support approval.

Specifically -- and this could be in quotes -- the agency suggested that a study with the following design be incorporated to help answer the necessary questions required for approval of the indication. The recommendation was to conduct a 3-arm, randomized, double-blind study. The recommendation was to have 5 patients on growth hormone alone, 5 patients on glutamine only, and 15 patients on the combination therapy. This was all in the context as well of all patients receiving a specialized oral diet across all the treatment arms. The recommendation was to have a 2-week, in-house control period, followed by treatment of at least 3 weeks with patients being followed for at least 3 months in order to establish a database for safety. Additionally, it was recommended that we ensure that there was adequate statistical power to meet the objectives of the study.

Following several different discussions back and forth about the possible options for design of the study, in June of 1997, agreement was reached with the FDA on the protocol design. This agreement included the dose to be included in the study of 0.1 milligram per kilogram

per day, as well as the primary and secondary endpoints, the primary endpoint being the reduction in total parenteral nutrition.

In October of '97, the agency confirmed that this one study would suffice as the pivotal study. And I'd like to make note that that is not unusual for indications being studied in rare orphan conditions.

Serono wanted to ensure that there was no ambiguity on our part as far as what the requirements would be for registration of this indication. So, again, we went back to the agency. We wanted to make sure that this study, conducted properly of course, would suffice. And indeed, we received correspondence back from the agency. I want to make sure you understand I'm not capitalizing these. This is exactly how it was written in the correspondence. The agency did agree with Cato, who was the CRO for the original sponsor at the time, that one study, the May 1997 protocol, inclusive of the comments from the medical reviewer at the time, would suffice as the pivotal study for the short bowel syndrome treatment with somatropin and glutamine indication.

Following that, the IND was actually transferred then to Serono who became the sponsor and conducted the study.

After the study was initiated in August of

2000, we requested a meeting which was held by teleconference with the agency to discuss some of the challenges that we were encountering in the conduct of the study. Specifically, we were having difficulty in identifying a second site due to the residential treatment period of the initial 6 weeks. FDA strongly recommended the addition of a clinical site, and in July of 2001, we were successful in identifying another clinical site. At that point in time, the study was very well underway and a significant proportion of the patients required for study were already enrolled. The agency did point out to us that with a single study, the NDA could be filed, but the hurdles for approvability would be high.

In September of 2002, after we had completed the study, we had a pre-NDA meeting with the Division of Metabolic and Endocrine Drug Products and a series of dialogues, and the FDA agreed that based on the safety and efficacy data that we presented, that the NDA would be fileable. And they also indicated that additional information would be required, such as to quantify the intake in diet to determine whether there was an imbalance or a potential imbalance amongst treatment groups.

So very shortly after that meeting, we filed the NDA and then subsequent to that, the Division of Metabolic and Endocrine Drug Products, who had reviewed and

approved the previous growth hormone indications, determined that the review of the application would be best done by the Division of Gastrointestinal Drug Products due to the nature of the condition and the indication that was being sought. So since that time, we've initiated some dialogue with the division and have been responding to questions that have arisen during the course of the review of the application.

As I conclude this part of the agenda, I would like to take note of some additional people that we have with us here today. In addition to the presenters that you will see, we have some additional external consultants that we may ask to respond to some of the questions that come up, so I would like to briefly introduce them to you at this time.

With us today is Dr. Kareem Abu-Elmagd. He is Professor of Surgery and Director of Intestinal Transplant Services at the Thomas Starzl Transplantation Institute in Pittsburgh. Dr. Theresa Byrne. Dr. Byrne is the Director of Research and Clinical Services at the Nutritional Restart Center and Instructor in the Department of Surgery at Harvard Medical School. Dr. Gary Koch, statistical consultant. Dr. Donald Kotler. Dr. Kotler is Professor of Medicine at Columbia University and Chief of GI at St. Luke's-Roosevelt Hospital in New York City. Dr. Bert

Spilker, co-founder and former President of Orphan Medical. And Dr. Douglas Wilmore, who I mentioned earlier, Frank Sawyer Professor of Surgery at the Brigham and Harvard Medical School in Boston.

And from here I would like to invite Dr. Douglas Wilmore to the podium to share with you the clinician's perspective on patients with short bowel syndrome.

DR. WILMORE: Mr. Chairman, members of the committee, members of the FDA, ladies and gentlemen, good morning.

I cared for the first patient with a short bowel syndrome back in 1964. It was an infant that lost 90 percent of its intestinal tract, and amazingly this child, taking oral formula, adapted its intestinal tract and had normal growth and development.

In the next several years during my training period, I saw a number of other patients who had massive bowel resections, and most of those individuals succumbed to their disease process because no method of care or support was available to them.

Because of my interest in intestinal failure, I joined a group at the University of Pennsylvania to develop total parenteral nutrition which is a method of caring for patients who have intestinal failure in the short bowel

syndrome.

In 1975, I had the opportunity to work with derived human growth hormone in adult patients with catabolic conditions and examine the body compositional changes that occurred with that treatment.

So in 1985, when recombinant growth hormone became available, I was able to continue those studies and focused on growth hormone and the gastrointestinal tract with my colleague, Dr. Theresa Byrne, who is here with us today. Most of this work over the last 15 years or so forms the foundation for the studies that will be discussed today.

What is a short bowel syndrome? Well, the healthy intestinal tract is about 600 or 650 centimeters in length, about 21 feet, if you will. And the short bowel syndrome is loss of approximately two-thirds of this intestinal tract.

There are a variety of causes. The major categories are impaired blood flow to the GI tract, inflammatory bowel disease, and then a host of other types of illnesses. Impaired blood flow can be caused by thrombosis or embolization of the mid-superior mesenteric vessels, trauma, malrotation, volvulus usually in patients that have had previous abdominal surgery. Inflammatory bowel disease does not cause an acute response, but rather

is related to progressive resections of the bowel over a period of time so that eventually the patient malabsorbs and cannot support themselves. Then there are a host of other causes, including radiation enteritis, a variety of metabolic diseases, and a variety of immunological diseases.

As has been pointed out to you, it's thought that about 10,000 to 20,000 adult patients are dependent upon parenteral nutrition because of loss of large segments of their intestinal tract.

What are the characteristics of the short bowel syndrome? Well, the loss of absorptive surface area results in impaired absorption of nutrients and that results in diarrhea, dehydration, macro and micro nutrient deficiencies, resulting in progressive weight loss and a variety of nutritional symptomatology.

This is a life-threatening condition and I think that's particularly important for you all to realize. The two references shown here, one from Europe and one from the United States, concur that if one takes the whole population of nonmalignant causes of short bowel syndrome, the life expectancy is about 75 percent at the end of 5 years. However, there are subgroups in this population, and particularly the elderly have a much increased mortality rate, and those individuals with 0 to 49

centimeters of small bowel have a survival rate of only 50 percent. So we're looking at a disease that has lethality, a disease that somewhat can be compared to patients with cancer who do have a mortality rate somewhere between 25 to 50 percent at the end of 5 years.

Now, in the 1960s, there were really no therapies for this disease, and at the end of the 1960s, total parenteral nutrition was developed. This was applied to patients with the short bowel syndrome in the early 1970s. Dr. Jeejeebuoy at the University of Toronto had a patient, a young mother, who had a newborn infant, had infarcted her intestinal tract, and he sent her home on parenteral nutrition. This really demonstrated for the first time that patients could be cared for at home and set up a whole home care industry around total parenteral nutrition and then other drug administration.

Throughout the '70s and early '80s a whole cohort of patients were then cared for at home with long-term parenteral nutrition, but it became apparent that there were serious complications related to this therapy, and in the 1980s, a variety of attempts were made to use other therapeutic approaches. One was bowel rehabilitation which we initiated in the mid-1980s and I'll talk more about that in a few minutes. The other was intestinal transplantation which was really stimulated because of the

success of, first, kidney, then liver, and pancreas transplantation so that the transplantation surgeons then started to focus on the opportunities to transplant intestinal tracts in patients who needed it.

But there are problems with this current approach, and one of the first problems is that parenteral nutrition does not enhance bowel function. It supports the patient. It keeps the patients alive, but it does not enhance the improved function of the gastrointestinal tract.

Secondly, long-term parenteral nutrition is associated with serious complications. These patients have one to two hospital admissions per year. About half of the hospital admissions are related to complications associated with the parenteral nutrition.

Now, the most common complication is catheter sepsis; that is, these patients have an indwelling plastic or silastic catheter placed in a large vessel in their chest and infection forms around the catheter. These rates are about one infection per every 18 months or so, but there's wide variation between patient groups. Steve O'Keefe looked at the Mayo Clinic series several years ago. In the 41 patients on long-term parenteral nutrition, 7 had no catheter infection and 7 had recurrent catheter infection at such a rate as to do away or obliterate any

potential advantage of the parenteral nutrition.

Catheter sepsis is the most common complication. Then hepatic dysfunction is the most serious complication. This paper by Cavicchi in the Annals of Internal Medicine is really the definitive work on that complication. This the Paris Group who looked at 91 patients over a period of 11 years doing liver functions and liver biopsies in their group, and they pointed out that 42 percent of home PN patients had complex liver disease by 17 months and, more importantly, 20 percent of their entire group died of liver failure during this period of study.

Finally, parenteral nutrition is not normal nutrition in humans, and a variety of studies both in the 1980s and the 1990s from Europe and the United States show that micro nutrient deficiency occurs in at least two-thirds of the patient population. That is deficiencies of vitamins, minerals, trace elements, and fatty acids that are pretty universal in this group of patients.

Now, intestinal transplantation would be a possible option, but it is evolving therapy. It's not for everyone. There's a moderately high mortality rate still associated with it, and the immunologic problems are fairly formidable because the transplantation involves moving of a large mass of immunologic tissue to the host.

Finally, the cost of caring for these patients receiving parenteral nutrition is greater than $100,000. In Lynn Howard's report in Gastroenterology in 1995, she estimates parenteral nutrition costs at $109,000 per year.

So let's talk about the limitations of the current standard of care, that is, parenteral nutrition.

First, there's a decrease in quality of life. There now are a variety of testing methodologies that assess quality of life, and using the scale of 0 to 100, with 100 being normal life quality, these patients score between 60 and 70. That's somewhat comparable to patients on chronic hemodialysis if you will. There's diminished life quality in this patient group.

Secondly, this therapy restricts patients' lifestyle. As I pointed out before, these individuals have an indwelling catheter. They infuse for 10 to 12 hours a night for 5 to 6 nights a week, so that every night by 6 or 7 or 8 o'clock, they're tethered to their pump to infuse overnight. They stay close to home. Granted, they can travel, but it's quite a difficult achievement to take their pump and their solutions on the road, and they're at home infusing.

You'll see later in the morning data that shows that these patients that have infused 5 or 6 days a week can infuse only 1 day a week, which is a tremendous change

in their lifestyle.

Let's look at this another way. Each liter of parenteral nutrition infused takes about 6 or 8 hours out of a patient's life, so that if we save 4 liters of infusion, we have given a person 24 to 32 hours of new life. It's as if your boss came to you and said, look, you're such a good employee, I'm going to give you a 3-day weekend every week the rest of your life. I think almost everybody in the room would take that as a suggestion.

So this is very restrictive to a patient's lifestyle.

Finally, it depletes patient's economic resources. Patients on private insurance generally have a cap of $1 million, and in general, this private insurance is exhausted by 5 or 6 years in these patients so that they've used $1 million, generally for their initial disease, $100,000 or more a year for their TPN, $50,000 or so for each hospitalization, and their insurance is gone. These patients then move over to public health insurance, Medicaid or Medicare, which we all pay for. We know that those particular insurance systems are clearly stretched in terms of providing health resources for our nation. So this depletes the economic resources. It's a high economic use disease.

What would be the attributes of new therapy?

Well, ideally we'd like to take the residual bowel and have it function better, and if we had it function better, we could reduce or eliminate the need for parenteral infusions, in terms of the volume infused, the calories infused, and the frequency infused. As I pointed out, because of the relationship between volume and time, these things are all intimately related, volume, calories, and frequency, so that once we can reduce one of these points, we can reduce all of them.

Three years ago or so, we did a quality of life study in a group of patients coming through this rehabilitation program. 18 patients had SF-36 quality of life assessment before and after in a serial manner for a year after rehabilitation therapy. Of the 12 patients, that came off parenteral nutrition totally or partially, quality of life greatly improved, and even the patients that came off 1 night had an improvement in life quality. Of the 5 patients that did not change in their response, there was no change in quality of life. In the 1 patient that required additional parenteral infusion, there was a fall in quality of life. So quality of life is totally tied to the infusion of this fluid over 12 hours a night for 5 or 6 nights a week.

Secondly, we'd like such a therapy to allow patients to maintain a near-normal nutritional state

primarily by an acceptable oral diet. This isn't tube feeding. This isn't liquid diet. This isn't something that's unpalatable. These are dietary nutrients that you can purchase at as reasonable price at a grocery store. So that's another one of the things we want to achieve.

We'd like to have an appropriate benefit/risk profile. We'd like the therapy to be tolerated and accepted by the patients without undue burden, and then finally, we'd like it to be cost effective.

So what is intestinal rehabilitation? Well, it's well known that following intestinal resection, adaptation or increased absorptive function of the residual intestine occurs. That is, with time, particularly in the first 6 months after resection, the intestine absorbs more nutrients per unit length. And intestinal rehabilitation is simply trying to capture this response, and it is a program to optimize diet and to provide appropriate nutrients and growth factors to allow an increase in the adaptive response.

Starting in the 1980s in my laboratory, we did both laboratory and clinical investigations to examine the effects of available substances to enhance function of the bowel. Now, we particularly chose things that we could use in the human condition, and one of the items that we evaluated was growth hormone. Growth hormone increases

mucosal mass and villi proliferation in animals. It enhances transport of water, electrolytes, and nutrients in both animals and humans, and data is available to show that it does this with amino acid metabolism by up-regulating those transporters. And finally, it increases insulin-like growth factor-1 generation in the intestinal mucosa. This factor is one of a number of factors which is thought to be key in the regulation of the health of the mucosa.

You'll also hear this morning some about the amino acid, glutamine. Glutamine is the most important nutrient for the enterocyte in the lining of the small bowel and the second most important nutrient for the colon. It's necessary for cell proliferation. It enhances the adaptive response to resection in animal models, and finally, by key work by Dr. Rhodes, when he was at North Carolina, it is a specific cell regulatory co-factor that is necessary for response of growth factors in the intestinal tract. You can't give growth factors to enterocytes without having glutamine in the mix to aid self-signaling.

Now, we've done a variety of pilot studies with growth hormone. Both experimental and clinical data has been done on the effect of growth hormone in enhancing function of the residual bowel. We've had 15 years of experience at the Brigham & Women's with growth hormone

treatment of the short bowel syndrome and have written a variety of publications on this. I'd like to introduce just two or three of these in the literature.

The paper at the bottom is the first report of a consecutive series of 45 patients receiving this treatment. The response rate was about 80 percent in this group of people. The complete response rate, which means we could take patients on parenteral nutrition off their infusions totally, was 60 percent, and at the end of 1 year, the duration of this complete response was 40 percent.

The details of those patients who were freed of parenteral nutrition is shown in the paper in the middle. In that paper, there are a variety of hepatic, renal function tests, quality of life scores, and dietary intake data which is provided.

Finally, the paper at the top of the slide is a recent paper presented to the transplantation group. This really helps determine a paradigm by which we can say which patients can be successfully treated by bowel rehabilitation and which patients cannot be successfully treated by bowel rehabilitation programs. These latter patients should then be considered for transplantation. And in that paper particularly, we've demonstrated that patients with jejunostomies and ostomies in very short

segments less than 50 centimeters of bowel were not responsive to this particular program and probably then should be considered or at least evaluated for intestinal transplant.

Again, in this paper, there was about a 60 percent complete response rate, and at the end of the year that slid down to about 40 percent for a complete response. So this therapy is not for everyone, but it is for a large number of the patients. The response rates are high and the duration is there and good.

So in conclusion then, the short bowel syndrome is a life-threatening condition in a limited and difficult-to-study population. These are chronically ill patients that consume a wide variety of the hospital and medical resources in our communities. Parenteral nutrition is the standard of care, but it does not enhance intestinal function. We do not have a therapy for this disease.

Finally, growth hormone and an optimized nutritional support support the concept that bowel rehabilitation is possible. This really means that a well-controlled, double-blind study was needed to confirm these preliminary findings.

So the hypothesis which emerged for this pivotal study is simply this. From the evidence in the prior work and other publications, treatment with growth

hormone and optimal diet supplemented with glutamine may allow patients with a short bowel syndrome to be nutritionally maintained on oral feeding. This is the hypothesis which was tested by the pivotal study which will be presented to you today by Dr. Joe Gertner.

Joe?

DR. GERTNER: Thank you, Dr. Wilmore. Thank you to the chairman and members of the committee for giving me the opportunity to present our work. I work for Serono in Rockland, Massachusetts, but I have to admit that unlike committee member Ms. Cohen, I wasn't born there, but I will try to give you the full background and data from the clinical study.

What I'm going to do today is to talk about what this clinical trial consisted of, how we derived the idea of doing it, the concepts behind the endpoint, behind the clinical trial design and strategy. Then I'll show you want kind of patients were enrolled into the study, the clinical efficacy and benefit from the study. I'll review with you the safety, and then will draw some conclusions from the clinical trial.

I'd like to point out that the formal title of the trial is given right here on the slide, randomized, double-blind, controlled, parallel-group evaluation of the relative safety and efficacy -- I don't need to read the

whole thing, but I would like to emphasize that this was a randomized, double-blind, controlled study. The investigators did not know what injected material the patients were receiving.

The concept of this trial, of course, arose from the antecedent publications which were largely discussed just now by Dr. Wilmore. I'd like to point out a couple of the highlights of these studies. First of all, from Byrne, et al. in 1995 from JPEN, they used as a growth hormone, Protropin, from Genentech in a dose of .14 milligram per kilo per day, and they found increased absorption of energy, protein, and carbohydrate and a decreased stool output in a controlled clinical trial of 10 patients.

At about the same time, they reported a larger case series, an uncontrolled case series, also using Protropin in a dose of 0.14 milligram per kilo per day, and here they found that 40 percent of the patients had been able to come off parenteral nutrition on follow-up for an average of 1 year, and 45 patients participated in this series trial.

More recently, as has already been mentioned, there's a publication in Transplant Proceedings. Patients were treated with different growth hormones, this time Humatrope from Eli Lilly, and our own growth hormone from

Serono, 0.1 milligram per kilo per day. This was a prospective case series. 49 of the patients in the series were dependent on parenteral nutrition, and the study provided further evidence of improved intestinal function. In fact, 20 out of the 49 were completely weaned and remained off for an observation period of up to 1 year.

Now, I'd like to review with you also some of the background of other publications that have been conducted in this field. What I've done here on the slide is -- let me highlight, first of all, this column which shows you whether these were double-blind, controlled clinical trials, and as you can see, most of them were. They're more or less in chronologic order of publication.

The first one is from Bengtsson's group, Ellegard, et al. from Goteborg in Sweden, and they used Genotropin from Pharmacia in a somewhat lower dose than most of the other studies reported today. These workers found that lean body mass did increase in the patient population studied. However, there was no gain in the absorption reported in water, protein, or energy.

Then we come to the study from the Mayo Clinic, reported in terms of its functional efficacy by Scolapio in 1997, and then in terms of the intestinal morphology, largely in 1999. They used Humatrope growth hormone from Eli Lilly in a dose of 0.14 milligram per kilo per day.

This was a double-blind, controlled clinical trial, rather small, with 8 patients participating in the study. They found that there was no -- when I've got negative here, that means not statistically significant. So there was no statistically significant improvement in fat or nitrogen balance or in d-xylose absorption, but there was a statistically significant increase in electrolyte balance. There were no noteworthy changes in intestinal morphology.

One can point out in this study that the patient population was somewhat restricted in that 6 out of the 8 patients had no colon. 7 out of the 8 patients had Crohn's disease. The duration from the time of resection of the gut until the clinical study that they performed was quite long, 12.9 years, and many of the patients had rather short, particularly short, segments of intestine remaining when the study was conducted.

About the same time the paper was published from Denmark in the group of Mortensen, and these workers used Norditropin in a dose of .14 milligram per kilo per day. They did not find any significant improvement in energy, carbohydrate, fat, or electrolyte balance, again in a rather small study of 8 patients. Of note is that they deliberately made no attempt to optimize the nutrition or to give any kind of a specialized diet. Once again, the proportion of patients with Crohn's disease is quite high

in their study, 6 out of 8.

In 2002, last year, a larger study but uncontrolled was reported from the group of Li in Nanjing, China by Zhu, et al. These workers used Serono growth hormone in a dose of 0.05 milligram per kilo per day, and they reported a significant reduction in stool frequency, stool nitrogen, and a significant improvement in d-xylose absorption. They also were able to follow 8 of the patients that were in the series for up to 2 years and over 2 years, and of the 8 patients who were completely off TPN at the end of their study, 4 of those 8 remained off TPN throughout the 2-year follow-up period.

Finally, there's a study from Paris from the group of Messing with the first author Seguy, and that was just published earlier this year. They used Genotropin, a growth hormone from Pharmacia, in a dose of 0.05 milligram per kilo per day, in a well-controlled, crossover design study, and they found that energy, nitrogen, carbohydrate, fat, and electrolyte balances were all statistically significantly improved in the group receiving growth hormone during the active treatment period of their clinical study.

So encouraged by the background data and struck by the medical need for some kind of help for these patients, we decided to undertake a clinical trial and to

draw some conclusions for what kind of clinical trial it should be. We bore in mind that this was a serious and rare condition with a limited patient population. We recognized that you needed an adequately powered clinical trial that had to be double-blind and that had to be representative and generalizable in the group of patients with short bowel syndrome.

We felt that in order to get well-controlled and good results, the study had to be done on a residential basis. This ensures rigorous control and it ensures very careful and meticulous observation of the response. Then we gave due consideration to the practical and ethical considerations of the endpoint, and I'll come back a bit later to explain what I mean by the practicalities of the endpoint and also the ethics of how we do this.

So let me now describe how the clinical trial was put together and what choices we made based on these original considerations.

Patients were referred from a variety of referring physicians who performed the screening at the home area from which the patients were referred, and I'll show you how wide this area indeed was. When the patients were deemed suitable for the study, they came to one of our two study centers and signed an informed consent form and were then stabilized for 2 weeks to make sure that their

condition was stable as a baseline for observations of the effects of the clinical trial.

After 2 weeks, the patients were randomized and they were placed into the three treatment groups that you can see here. Sometimes I'll refer to these groups just by the shorthand of the initials of the treatment arms. I hope you'll forgive me. The first is the specialized oral diet supplemented with glutamine, which we can call SOD (GLN). Then we have a treatment group who received growth hormone and the specialized oral diet, and finally, those who received growth hormone and the specialized oral diet, supplemented with glutamine, growth hormone plus SOD (GLN).

These treatments were administered, let me emphasize again, in a blinded fashion. These patients received placebo injections which were dummy injections as placebo for growth hormone. The treatments were administered for 4 weeks and the observations made, and at that time, the patients left the clinic and went back to the management of their referring physicians. The referring physicians then attempted to ensure that the patients were being optimally managed during 12 weeks, at which time they attended those referring physicians for a post-treatment evaluation, which was mentioned earlier by Pamela Williamson as being originally proposed as a safety evaluation.

The patients who were treated with glutamine during the residential treatment period had glutamine given to them continuously through the follow-up period of 12 weeks. Those patients in this group here who did not receive glutamine in the in-patient phase also did not receive glutamine in the out-patient phase, in the phase which was managed by their referring physicians.

Now, how did we come to the dose that was used in the study? First of all, we knew that antecedent experience, which you've already seen represented quotes of, showed good efficacy and tolerability at 0.1 milligram per kilo per day. Nevertheless, the sponsors of the study, as we developed the clinical trial design with the agency, proposed doses over a range of doses from 0.03 to 0.14 milligram per kilo per day. The agency's response to this was that given the small size of the clinical trial, it would be difficult to interpret results from a large range of doses because there would be cells in which there would only be a very few patients in each treatment group for each dose.

So we came back with the counter-proposal that we would, in fact, treat with .1 milligram per kilo per day. Everybody would receive one dose and that we would allow, for safety reasons, a 50 percent reduction in dose if any kind of toxicity occurred. This proposal was made

to the agency, and the agency agreed that that was a sensible proposal.

I should point out that that dose, 0.1 milligram per kilo per day, is also the indicated and labeled dose for some other uses for growth hormone both from Serostim, which is the drug we're talking about now, and other manufacturers' growth hormones.

Now, as part of the clinical study and applied universally across the three treatment groups, people were taking a specialized oral diet, which has been explained to some extent by Dr. Wilmore. The objective of this diet was to ensure that each patient was able to maintain through oral feeding an adequate nutritional status. It's important to state that the diet consists of readily available foods and was constructed in such a manner that patients could go out and go home and buy this diet from their local store and cook it for themselves, or their family members could, in order to provide them with a continuation of this diet when they were back home.

The diet consisted of complex carbohydrates providing 50 to 55 percent of calories. 20 percent of the calories came from protein, 25 to 30 percent from fat, and there was also rehydration fluids and dietary supplements which consisted of multivitamins and minerals.

Now, the endpoints which I alluded to earlier

-- really the considerations that we took into mind on this were that we wanted something that could be directly quantified and that was related to the patient's need for intravenous nutrition. We felt that the reduction in IPN, intravenous parenteral nutrition, volume was something that represented a direct clinical benefit to the patient, and I'll go into that a little bit later. But it's pretty clear that having less infusate is a direct benefit.

We also considered alternate endpoints and we decided not to use them. One would have been to do complex absorption and balance studies which are more appropriate for small physiological studies but not for a therapeutic trial of the scope that we were undertaking here.

And the second approach would have been to actually look at nutritional measures during the trial. But this is where I come to some of the ethical considerations that I mentioned. In order to look at the nutritional stages of patients, we would have had to put some patients in a treatment arm such that their nutrition would be deliberately suboptimal, and since these patients are marginally nourished to start with -- or many of them are -- we really didn't feel that this was ethical or acceptable. So we didn't apply a study in which we tried to look at nutritional values. On the contrary, we tried to keep everybody as well nourished as we possibly could

throughout the clinical trial.

The eligibility for the trial, quite straightforward. Men and women were eligible. The body mass index covered a wide range from 17 to 28. All patients had to have short bowel syndrome with less than 200 centimeters of bowel in continuity. They had to be able to eat some solid food regularly, but they needed to require at least 3,000 calories per week of intravenous parenteral nutrition for nutritional support. And the time of bowel surgery had to be at least 6 months prior to entry into the study. The stomach and duodenum had to be intact, and we stipulated, regarding the presence of a colon, that if more than 30 percent of the colon was functional, then they would need to have more than 15 centimeters of jejunum or ileum also existing, and if less than 30 percent of the colon was functional, they would have to have more than 90 percent of small intestine remaining intact. Finally, as an eligibility criterion -- 90 centimeters. Did I say percent? 90 centimeters of jejunum/ileum remaining intact. And finally, regarding stool volume, the patients had to be producing less than 3 liters of stool per day to be eligible for the study.

Now, this shows how the patients flowed through the clinical trial. 47 patients enrolled into the study. 41 of them were randomized, and there were 6

discontinuations between the time of enrollment and randomization. 5 had various intercurrent illnesses, which I can go into if you like, but they were conditions that were considered serious enough for them not to be able to participate. And 1 patient decided to change their mind and to withdraw consent to the trial.

In the three groups that patients were then randomized to, there was actually quite good continuity of patients throughout the clinical trial. Here you can see that in the SOD (GLN) group, 9 patients started, 9 patients got to the end of the in-patient period, and 9 patients completed the follow-up period.

Here 16 patients were randomized. 15 completed the in-patient period and 15 came to the follow-up evaluation. 1 patient had to discontinue during the in-patient clinical trial due to a serious adverse event not related to the administration of growth hormone. It was actually a vascular event related to the catheter, thrombosis followed by a localized hemorrhage near the thrombosis.

Finally, in this group, the group receiving growth hormone plus the specialized diet, there were 16 patients randomized to that group. All 16 completed both the residential treatment period and the follow-up period under the care of their referring physicians.

Demographics of the trial. I won't spend too long on this. You can see that the mean age is in the 40s and 50s, that the balance of male to female is approximately between three-quarters and two-thirds in favor of females, and that the mean body weight was in the low 60s of kilograms of body weight in all three treatment groups.

I think it's important to point out that the patients that came into the study in the two sites, one in Massachusetts and one in Nebraska, came from a wide background of geographical residence and some other aspects of their demographic description was also quite widespread. So in this slide, you can see colored in red or orange or tan here the States in the United States from which these patients were referred to the clinical trial. You can see that it covers a wide geographical area of the country. And in fact, of the 41 referring physicians that referred patients in for this trial, no referring physician had referred more than 1 patient. So they came from 41 doctors living all over the United States and there were 2 from overseas, 1 from India and 1 from Israel, all participating in this trial.

The etiology of short bowel syndrome was just as diverse as the geographic origin of the patients. There were people with intestinal obstruction, Crohn's disease,

vascular insufficiency, volvulus, and acute trauma, as well as some less common conditions.

The time from resection is shown here on this slide, as is the proportion of patients who had no colon. You can see that the time varied between 3 and 5 years on average in the three groups and that relatively few people had no colon.

I would just like to go back to the etiologies of short bowel syndrome in these patients to show you how this stacks up with the literature on the subject, and the recent technical document published by the American Gastroenterological Association in Gastroenterology two months ago gives a very good summary of this whole field. Among the items mentioned in this Buchman paper are that the most common causes of short bowel syndrome are Crohn's disease, vascular conditions of the gut, volvulus, all kinds of trauma, and cancer. We did not study cancer patients in this trial. However, all the other conditions here are well represented and without being overwhelming towards the one or the other. So Crohn's is this green group here. Vascular are shown in tan. Trauma is the light blue, and intestinal obstruction are shown there in yellow. So we had a good representation and a broad representation of etiologies in the clinical trial for short bowel syndrome.

So this really is to summarize the fact that the trial can be considered to be a generalizable one. The underlying causes cover a spectrum of recognized etiologies of short bowel syndrome. The referring physicians constitute a professionally diverse group who are responsible not only for the decision to refer but also for management of the patients over the 12-week follow-up period after the discharge at week 6. There was a wide geographic referral base for patients. The components of the nutritional therapy that they received in the residential centers are widely available and can be maintained at home. And the standard of care that they received in the residential centers, with regard to the nurse helping them with the TPN and the general conditions there, were more typical of usual practice.

So I'm coming now to the actual description of what happened in the trial and how we did it and what the results were. The endpoint of the clinical trial was a reduction in the total volume of intravenous parenteral nutrition, or IPN -- that was the primary endpoint -- a reduction in total IPN calories, and in the frequency of administration of parenteral nutrition or supplemental lipid emulsion which was needed by 1 or 2 patients for essential fatty acid deficiency. So those two, the calories and the frequency, formed secondary endpoints.

The definition of the endpoint we should pay attention to, please. The total IPN that was used as the primary endpoint is defined as the sum of parenteral nutrition as normally understood, plus IV hydration, plus the supplemental lipid emulsion that I just described. So it was the sum of those things that formed the primary endpoint and will form the basis for some of the efficacy data slides that I'm going to show you.

The idea of the study was to apply across the three treatment groups uniform weaning criteria to reduce the IPN prescription, the prescription for intravenous parenteral nutrition, when the patient shows the ability to maintain hydration, to maintain serum electrolytes, and to sustain an appropriate body weight. This was applied across all three treatment groups, of course, in a blinded manner since everybody was receiving injections.

Now, what do the results look like? First, we can see here the primary endpoint, and this slide shows the changes from the baseline at 2 weeks, the 6-week changes in total IPN volume, and you can see that in the SOD (GLN) group, which served as a control, the reduction was 3.8 liters per week, and progressively across the chart here to the growth hormone plus SOD (GLN) group, the reduction was 7.7 liters per week.

In terms of kilocalorie administration, we see

the same progression across the three treatment groups, with a reduction of 2,600 calories in the SOD (GLN) group, going up to 5,700 calories per week in the glutamine supplemented growth hormone-treated group.

For looking at the frequency of administration of parenteral nutrition or supplemental lipid emulsion, I've shown you the actual numbers rather than the change. You can see here that these folks had a reduction in the frequency of administration of IPN from 5.89 to 3.89 treatments per week on average. In this group, it fell from 5 to 2.11, and in this group, from 5.44 to 1.25. These look like cold numbers, but obviously for someone who has to receive parenteral nutrition from a machine all these nights, taking up many hours in each night, this is a clinically important benefit. These are people who have 5.5, on average, infusions per week, 5.5 nights per week that they're hooked to the machine, and here they're down to 1.25 nights per week on average requiring the treatment.

This can be looked at another way in the table provided to you by the agency. This table looks at the total numbers rather than just showing graphically the changes. What you can see at the bottom in groups A, B, and C -- the order of groups is changed here in the table compared with what I've shown you, so please note that the group given growth hormone and glutamine supplemented diet

is labeled group B here. So group B started with 10.5 liters per week. They reduced by 7.7 liters per week. So that's a really big reduction, and the reduction corresponding to the control group, the SOD (GLN), was somewhat less than half of that total reduction in the growth hormone plus glutamine supplemented diet group. So not only is the change versus controls highly significant at the p is less than .001 level, as shown on this slide, but also more than half the benefit actually comes to those patients who are receiving growth hormone, almost 4 liters, remembering that each liter represents approximately 6 hours of infusion for the patient overnight.

Similarly, we see the data here for the caloric reduction laid out by the FDA for the benefit of the committee, and at the bottom of the slide, the change in the infusion frequency. You can see that the reduction in frequency was 4.2 treatments per week for the patients who got the growth hormone with glutamine supplemented treatment, and that this was more than twice as great in the treated group as in the control group. Once again, the statistical significance of that is p is less than .001. Once again, the clinical significance is really there, less than half the number of infusions on average for these patients in the group treated with growth hormone and the supplemented diet.

Now, some of the data I'd like to show you relate not to the total IPN but to the PN itself, what really most people and especially the people on the committee who are gastroenterologists would normally regard as parenteral nutrition, not counting hydration, not counting supplements that have to be given for fatty acid, but just parenteral nutrition. We can look at that and we can look across the groups. This shows reduction per week in liters, kilocalories, and frequency. The reduction is greater in the people on the growth hormone and unsupplemented diet than it is on the SOD (GLN) group with significance levels shown here, .001, .002, and .006, and greatest yet for the group on the glutamine supplemented diet plus growth hormone where we have a significance level versus the controls of 0.001 for all three parameters.

Looking at the follow-up period, remember that during the follow-up period, patients were maintained in good shape by their referring physicians. They were, of course, not being treated with growth hormone at this time. It was after they had gone home. We can see that in terms of volume, in terms of kilocalories, and in terms of frequency of administration, the gap between 2 weeks on admission to the centers and follow-up at 18 weeks progressively gets bigger. In other words, the benefit progressively get bigger as you go across the three groups

from the control group to the growth hormone plus diet group to the growth hormone plus glutamine supplemented diet group. That's also true for kilocalories and it's also true for frequency.

The statistical significance of this is that in the tan group here, which is the group receiving growth hormone plus glutamine supplemented oral diet, all these differences remain statistically significant relative to the control group at the 18-week follow-up time point.

Now, as mentioned earlier by Ms. Williamson, we were asked, subsequent to completion of the clinical trial, to comment on the diet, and you can see here that the baseline diets that the patients were receiving at the start of the study -- that is to say, at 2 weeks inter-optimization at the time of randomization -- were very similar in all three patient groups. These relate to fluids, kilocalories, protein, carbohydrate and fat. Very little difference between the groups. At the end of 6 weeks, we can see that again there are very sparse intergroup differences with regard to what was being taken in the diet. So I hope that will allay some concerns about the fact that diet could have had a large effect on the outcome of the study.

At the 18-week time point, we looked at nutritional factors to see whether in fact it was correct

to assume that these patients were in reasonably good nutritional status having been weaned and sent home and being managed by their referring physicians. Here we see some data first related to hydration, serum sodium at week 2 and week 18 in the three treatment groups, very little change in serum sodium, very little change in BUN, very little change in creatinine or in the BUN-to-creatinine ratio, all of which can be regarded as measures of hydration.

Magnesium could be regarded as a nutritional factor because it's specifically something that's lost when there's excessive intestinal fluid loss. Once again, there was no evidence of substantial change in serum magnesium in any of the three groups between the 2-week admission and the end of the 18-week follow-up period.

A good marker for nutritional status is serum albumin, and here again we see essentially no change in serum albumin between the time of entry into the clinical trial and the time of follow-up at 18 weeks.

Body weight did go down slightly in all patient groups. As you can see here at the bottom of the slide, most of the patients remained very close to their ideal body weight, and there were changes in all three clinical groups in body weight, none of which were statistically significantly different from each other.

We did have the opportunity to get some follow-up data beyond the 18-week time point. Serono is currently conducting a survey, at the request of the agency, of all the patients who participated in the study, and we're obtaining data from them at the 6-month, 1-year, and 2-year time points. This data will be made available to the agency as soon as we get it. We're in the process of obtaining it right now.

We were able to follow 7 of the 9 patients who were off TPN. All 9 patients who were completely off TPN, at the time of discharge from the center remained completely off TPN at the time of the 18-week follow-up visit. And of those 9, we have longer follow-up data on 7 patients. 2 of them are back on TPN and 5 remain completely off. You can see the dates of discharge. This is quite current. So we're in 2003 now. So this is 5 years, 4 years, 4 years, 4 years, and 3 years that these 5 patients have been completely off.

We will have the opportunity to make this database much more complete and to provide the agency with the data for follow-up not only of the patients who were completely weaned, but for the whole patient population in the clinical trial.

Now, let's ask ourselves is this primary endpoint that we chose really clinically relevant. I think

what you need to bear in mind is that after 2 years of parenteral nutrition, 94 percent of individuals with short bowel syndrome are said to have permanent intestinal failure and they will not return spontaneously to usable intestinal function.

The reduction in parenteral nutrition that can be provided to patients and that has been demonstrated by the use of growth hormone in this clinical trial could be considered to be useful, very useful, for a reduction in line sepsis and a reduction in catheter occlusion. We can focus on liver disease where we know that the liver disease seen in patients with short bowel syndrome maintained on chronic parenteral nutrition is proportional to the amount of parenteral nutrition that they receive. The data that I have in the parentheses here regarding end stage liver disease in 15 percent of patients receiving chronic parenteral nutrition comes from Bistrian's group in Boston.

We believe -- well, it's clear actually -- that the reduction in parenteral nutrition of a large extent is associated with an increase in oral feeding and assimilation of oral food, the lack of which is believed to contribute to biliary disease. So this can contribute to an improvement in biliary disease in the patients.

It's already been discussed that the reduction of the need for having to be hooked up to pumps and

parenteral nutrition can greatly enhance well-being and autonomy. So we have a reduction in line sepsis, a reduction in liver disease, a reduction in biliary disease, and improved well-being and autonomy. You might say that an additional benefit and a pretty important additional benefit, both from the patient's point of view and the societal point of view, is the reduction in cost, the tremendous cost of parenteral nutrition and its associated therapy.

The safety data regarding the use of growth hormone in this clinical trial are presented in the next few slides. I'm going to show you the adverse events that occurred. We know that growth hormone administration to adults is associated with tissue turgor and limb pains. You can clearly see that in the slides here under the heading of "body as a whole: general." Peripheral edema and facial edema occurred in the growth hormone-treated groups and it did not occur in the group that did not receive growth hormone. These are well-known and expected adverse events associated with the use of growth hormone.

Similarly limb pains and joint pains occur quite a lot when you give adults growth hormone, and we code here arthralgia and myalgia with incidences that are either 0 or very low in the control group, but the incidence is up to 44 percent in the groups who received

growth hormone. Again, that's what you would expect from the administration of growth hormone.

By contrast, if you look in the middle of the slide at the gastrointestinal system, the adverse events attributable to the gastrointestinal system are the adverse events which occur as a result of having short bowel syndrome, things like flatulence, abdominal pain, nausea, and tenesmus. These were evenly distributed, more or less, between the three treatment groups because they were not growth hormone related adverse events. They were adverse events related to the patient's underlying condition.

I'm showing you next the serious adverse events that occurred during the clinical trial. None of these are considered to be related to growth hormone. There were 5 patients with serious adverse events during the active phase of the clinical trial: chest pain, hemorrhoids, purpura, fungal infection, and pharyngitis. You might ask why was pharyngitis a serious adverse event. But, of course, this is a matter of good clinical practice, regulated clinical trial. If a patient is hospitalized, it's regarded as a serious adverse event. If a patient with an indwelling line has a fever, they have to go to the hospital, they have to have bloods drawn, et cetera, a sepsis workup. So that's how these patients got to be coded as serious adverse events.

During the follow-up period, the patients were not receiving growth hormone or placebo injections. There were 11 adverse events to that patient population, and you can see here what they were. This patient had a viral illness which led to dehydration and hypokalemia. There were several cases of line sepsis and two occurrences of pancreatitis, all of which are known to be associated with TPN therapy for short bowel syndrome.

So in summary of our clinical trial, we performed a 4-week, double-blind, randomized clinical trial of growth hormone in patients receiving a specialized diet with or without glutamine supplementation. There were 41 patients dependent on intravenous parenteral nutrition in the trial, and the patients who received the specialized diet with glutamine supplementation served as the control group. Patients were evaluated by their referring physician 12 weeks after discharge.

Growth hormone achieved a significantly greater reduction in parenteral nutrition than the glutamine-supplemented diet alone. The extent of that improvement was highly statistically significant and highly clinically significant in terms of the benefit that can be expected to be gained by the patients from the reduction of IPN requirements. The response was maintained for 12 weeks after the end of growth hormone therapy, and as I've just

said, because I'm enthusiastic about the results of the study, the reduction in volume and frequency of the infusions constitute a major clinical benefit to this parenteral nutrition-dependent patient population.

As far as safety is concerned, the growth hormone treatment was generally well tolerated. The growth hormone-related adverse events were expected. They were well characterized and they were transient. Only 1 patient withdrew during the trial, and as I mentioned, that was not due to a side effect of growth hormone. And none of the serious adverse events logged for the trial were considered to be related to growth hormone.

With that, I've really come to the end of my presentation of the clinical trial. I'd like to hand back over to Ms. Williamson Joyce for the conclusion.

MS. JOYCE: Thank you, Dr. Gertner.

As we prepare to conclude our presentation, I wanted to share with you an excerpt from a recent publication in Gastroenterology. This is from 2003, and it is the AGA technical review on short bowel syndrome and intestinal transplant. As I read this, I was struck with how remarkably consistent this statement is with both the attributes of the new therapy that have been shared with you during Dr. Wilmore's presentation and the design and conduct of our clinical study. Specifically the statement

reads: "The goal of medical therapy is for the patient to resume work and a normal lifestyle, or as normal of one as possible. This is undertaken via the use of specific measures to gradually decrease the requirements for TPN, and at best, to eliminate its need."

Serono has sponsored the largest double-blind, controlled clinical trial conducted in patients with this rare and life-threatening condition. And in terms of size, the 41 patients in this rare condition can be considered a large trial. I believe that we've demonstrated that growth hormone reduces the needed quantity, calories, and frequency of IPN and that the dose of 0.1 milligram per kilogram per day was both safe and effective in treatment of these patients. The results and the treatment of these patients is generalizable and can be accessible upon approval to patients with short bowel syndrome. And there is enhanced well-being and autonomy through administration of this treatment. There's the potential for considerable cost reduction. And as I mentioned earlier, there are no other currently approved drug treatments available to patients with short bowel syndrome. So in conclusion, I'd like to state that we believe that there is a very positive benefit-risk profile for growth hormone treatment of patients with short bowel syndrome.

With that, I hope that we've been able to share

and answer some of the questions that have arisen during the course of the review of our application and some of the questions that you have been asked today by the Food and Drug Administration to comment on. I'd like to thank you again for having the opportunity to present these data, and we would be very happy to take your questions at the appropriate time.

DR. WOLFE: Thank you, Ms. Joyce. I'd like to thank Drs. Wilmore and Gertner as well for their presentations.

I'd also like to welcome to the panel Dr. Jose Cara, an endocrinologist from Henry Ford Hospital in Detroit, Michigan.

Now, Dr. Cara is a classical endocrinologist. The reason I mention that is because the original endocrinologists are gastroenterologists. So it seemed apologetic that we were being asked to evaluate growth hormone, but in reality the first two hormones discovered were secretin in 1902 and gastrin in 1905. Insulin came next. So we are the original endocrinologists.

(Laughter.)

DR. WOLFE: Additionally, the largest endocrine organ in the entire body is the GI tract. So please keep that in mind. I've spent my entire career looking at gastrointestinal hormones and examining their regulation,

their physiology, and other actions as well. So we can provide, I think, a very good evaluation not only from the gastrointestinal pathophysiology point of view, but also from the effects of growth hormone itself.

We're right on schedule. We will take a break until 10:15. My watch is correct to the second. So we have 19 minutes for a break. We will resume at exactly 10:15 at which time the panel can address questions to Serono. Thank you.

(Recess.)

DR. WOLFE: The time is 10:15 and we will now continue the meeting with questions from the panel on the presentation. So I'd like again to remind all the panelists, all the members of the FDA advisory board, that when you ask your question to turn your microphone on, and when you're don't, turn it off.

Do we have any questions?

DR. LEVINE: A couple of points of background interest I wanted to know relating a little bit to the design. I'm not sure if it was actually back in the '90s when you mentioned the FDA insisted or that you suggested that glutamine be considered in all arms of the trial.

As a background to that, I would have to say your presentation today and this slide on role of glutamine implies that there are definite advantages of glutamine.

It's highly controversial. The surgical literature is certainly in favor of it. Some of the medical literature is and some is not. I'd like the answer to that question first.

MS. JOYCE: Well, first I would like to clarify I didn't mean to infer that the FDA insisted that we include glutamine in the treatment arms. Glutamine was one of the components that was under discussion in options for the clinical design of this study and that was proposed and agreed. So following all of the discussions, the recommendation was, by FDA, to have a growth hormone alone arm, a glutamine alone arm, and a combination arm. That was one of the recommendations.

Perhaps Dr. Wilmore --

DR. LEVINE: What's the genesis of the glutamine inclusion? I just wondered. On the basis of past experience with the investigator and with your company or other reasons?

MS. JOYCE: Yes, and I think Dr. Wilmore could speak to that.

DR. WILMORE: Yes. The original therapy was combinations of glutamine and growth hormone, and that preliminary data was taken to the FDA, and they looked at that data and agreed that glutamine be included in the dietary component.

DR. LEVINE: Well, I only ask the question because it is controversial and things could have been simplified based on some of the statistical analysis here. In my own work back in the early '90s and mid-'90s and even later, we looked at various models of inflammatory bowel disease and DSS-induced colitis and gave intravenous nucleosides and nucleotides and arginine, and even though we saw an improvement and it was published, it's still controversial. I would have to say I still think the role of glutamine is highly controversial as a beneficial factor in the nutrition of small bowel patients or in any patient.

DR. WOLFE: Dr. LaMont?

DR. LaMONT: Thank you.

I have a number of questions. I guess the simplest one would be, how does this compound work? You told us you couldn't measure absorption, and I agree. In a big study like this, that would be an incredible job. But we're told that you reduced intravenous nutrition, IPN, and we're told -- I think slide 60 or 61 -- that oral fluid increases. So does treatment with growth hormone improve diarrhea and is this how the physicians who are adjusting fluid intake by mouth or by vein were making changes, or was it body weight? I also didn't find any information about body weight. So I wonder if you could tell us how it works.

MS. JOYCE: Dr. Gertner?

DR. GERTNER: Yes. The underlying mechanisms whereby growth hormone is effective appear to include a stimulation of transport properties, and that's been seen in a number of direct studies looking at transport, as well as at balance studies. I think what you're asking is actually how we decided to wean the patients based on their weight. Is that correct?

DR. LaMONT: I have several questions, but that would be a good place to start.

DR. GERTNER: Yes. I think maybe the best way to address that would be for actually Dr. Byrne to tell you about that because that was largely her area. If we could have the slide of the weaning criteria up, please.

DR. BYRNE: To address the question about body weight and its role in the weaning of parenteral nutrition, we never looked at body weight alone. We really looked at three criteria that Dr. Gertner emphasized. First, the patient had to demonstrate an ability to hydrate themselves, and this was assessed by a number of different parameters which we'll also show on a subsequent slide. They had to show an ability to maintain serum electrolytes and sustain an appropriate body weight.

For each of these categories, however, there was additional information that we utilized. The serum

electrolytes being the easiest, we just looked at blood parameters.

To demonstrate their ability to hydrate themselves, they had to have a positive enteral balance which was a measurement of all their oral fluid intake, minus their liquid stool output, and that had to be greater than a 500 ml per day to assist in covering for their insensible fluid losses and/or they needed to have adequate urine volume, as shown on the middle part of the slide, or a minimum urine volume prior to their nighttime infusion. So that would give us an indication if the patient was going to be able to hydrate themselves without IV support.

In terms of maintaining their normal electrolytes, we looked at all electrolytes to make sure that they stayed within normal parameters, as shown on this slide.

In terms of body weight, we never, again, looked at only at body weight. We used the measurement of bioelectrical impedance to help us differentiate out fluid gain from weight gain since weight could be influenced by a number of factors, not only growth hormone but improved caloric absorption or excess caloric infusion, increased sodium intake. So the measurement of bioelectrical impedance, particularly the resistance measurement, allowed us to differentiate out why the weight was increasing and

therefore to be able to judge if the patient was maintaining weight or gaining true weight. Therefore, we were able to more appropriately make decisions about weaning.

In addition, all patients had to consume 80 to 100 percent of what we would calculate to be caloric requirements to maintain or sustain an appropriate body weight, and these calculations included a factor for malabsorption as well.

DR. LaMONT: Well, if you look at figures 60 and 61, it looks like the major difference between baseline and week 6 is an increase in fluid by mouth. It doesn't look like, at least to my eye here -- and there's no statistical analysis of these data -- the big difference is in fluid intake by mouth. So I guess I'm trying to ask is, is that how growth hormone works? Does it allow you to absorb more fluid? Is that's what's happening here? Because it doesn't look like calories, protein grams or carbohydrates or fat went up in any group.

DR. GERTNER: Yes. I could try to address two aspects of your question, if I may.

First of all, there are data to show that growth hormone does produce an increase in water and electrolyte transport across the gut, and some of those were quoted in the papers that I showed. I guess Dr.

Wilmore could also comment on that maybe.

With regard to the dietary components, there was not, as you mentioned, a big change. Apart from the increased oral fluid, there wasn't a big change in dietary consumption during the study. And yet, the ability to wean and hydrate was present. So one implication that could be drawn is that the patients were assimilating the diet that they were taking more efficiently. I think, as I say again, that maybe Dr. Wilmore could comment on that.

DR. WILMORE: Dr. LaMont, if we look at enteral fluid balance, oral intake versus output, enteral fluid balance became more positive in the group where there was a positive treatment response. That's consistent with earlier studies by ourselves and the studies from Paris that show improved absorption of nutrients in fluid and electrolytes.

MS. JOYCE: Dr. Susan Kenley, the Director of Worldwide Biometrics, can speak to the question with regard to the statistical analyses.

DR. KENLEY: Good morning. Yes, we did analyze the diet parameters, all the components of the diet, and if you're interested in seeing them, I could show you all the analyses. There were no differences between either the growth hormone group or the glutamine group in any of these components.

DR. LaMONT: (Inaudible.)

DR. KENLEY: No, it's not. Let's bring that up. EF80.

DR. WOLFE: Actually I want to ask a question related before you go on to statistics again and come back to that mechanism. Growth hormone is mitotic. It's not mitotic, but it's a growth factor obviously. That's what it is. It's growth hormone. So were there any morphologic changes seen or have there been studies looking at morphology? There presumably would be an increase in the villus:crypt ratio. Anything like that seen? And what remaining test there is? There may have been damage in other patients?

DR. GERTNER: This again comes under, I think, the rubric of not being able to conduct complex physiological examinations during a therapeutic clinical trial of this proportion. So we didn't biopsy or look at morphological changes during the study.

DR. WOLFE: Do you have data in other studies, though?

DR. GERTNER: Oh, yes, they have done. Again, I think Dr. Wilmore is far more expert than I am on this topic.

DR. WILMORE: These have been done and no changes have been observed. There have been more subtle

changes, however, in IgF-1 generation, in up-regulation of amino acid transporters and things of that sort, but in terms of gross morphology in the human situation for the short term, there have not been changes observed.

DR. WOLFE: I'm still a little confused. This is again a mitogenic hormone. There are no changes. So you're saying the main changes are in transport? That's the mechanism?

DR. WILMORE: Within the context of the time given for the hormone, the changes have been seen in transporters and other cellular components, and within the 4-week period of time of the administration, people have not observed morphologic changes.

DR. WOLFE: One second. Dr. LaMont, have you completed? We'll come back later on if you want.

DR. LaMONT: Yes. I have some more.

DR. WOLFE: I'd actually like to keep the questions in a theme. If someone else has some more questions, let's keep that questioning going rather than coming back to it. So we'll come back to Dr. LaMont later.

Dr. Camilleri?

DR. CAMILLERI: Thank you.

One very brief question. I saw you had an unbalanced randomization, and perhaps you could tell us the reason for that. That's the first question.

But I'd like you to also address a second question, if I may. I refer really to your slide number 62 and that's the slide that looks at nutritional changes because I think there's an important message here. If you look at body weight, at week 2, the body weight is, say, in the active treatment arm, 63.9 kilograms. Now, that group had a body weight to start off with of 62.1 at day 0. At week 18 when these people presumably were weaned off and whatever, their body weight is 58.7. That's like a 10 percent or so reduction in body weight. It suggests to me that the edema that was observed in the study could have been quite significant and that much of this weight may have been perhaps related to the uptake of water and electrolytes being more efficient, partly related therefore to edema rather than body mass.

It also suggests to me that because 69 to 81 percent of the people on growth hormone had edema, I wonder whether there was a possibility that the people deciding on the nutritional status may have been unblinded.

Therefore, I'm concerned about those two aspects of the experimental design, one being the unbalanced randomization and, second, the possibility for unblinding of the individuals that ultimately determined how to assess the primary study endpoint. And I'd be interested in your comments. Thank you.

DR. KENLEY: I'll address the unequal randomization. The rationale behind that was to have more patients exposed to growth hormone treatment compared to the control arm of just glutamine. Just for a bit of information, an equal randomization will require less patients to have the same power compared to an unequal randomization. So we actually enrolled more patients in this trial to have them exposed on growth hormone. That was the rationale.

DR. WOLFE: Dr. Shih actually has a related question, as does Dr. Cara.

DR. SHIH: My question actually goes back first to the generalizability, which is a major question, as the chairman has alluded to. In your slide 47, that was your generalizability of the clinical trial. And then based on your slide 43, you showed the geographical distribution of the study patients. However, I would like to see your slide, if you have one, to indicate the clinical centers or investigators that are involved in the study. You can have many patients from this nation to be referred to the study, and that's usually done in clinical trials. However, the generalizability also relies on how the investigator conducted the study. As you can see, there are many measurements that involve how the investigator treated patients as a center. So can you comment on the

generalizability in light of how many centers in the study as a comparison to how many centers that can treat as a center those kind of patients?

MS. JOYCE: Yes. With respect to the generalizability, as you've indicated, the patients did come from all over the country. There were two centers. One was located in Boston, Massachusetts, and the second center was located in Nebraska.

As far as the total number of centers around, very much I would like to have Dr. Byrne speak to the types of care in these centers and the generalizability, and then we can come back also to the further generalizability after she's addressed your question on the types of centers and where they might be located.

DR. SHIH: And also when you do that, can you comment on how many patients in the two centers in the study?

MS. JOYCE: Yes. With respect to the two centers, there were 38 patients in the first center and 3 patients in the second center.

DR. BYRNE: Both centers were designed to be a home-like environment, with the real intent to make it applicable elsewhere. The staffing was based more similar to a home care company where patients who are on this type of nighttime support often receive services that way. So

really the uniqueness of the center is that it was intended to make it applicable elsewhere because of the home setting that was provided.

The types of care that were instigated at the center, in terms of the diet, are definitely available in the public domain. We've published papers trying to describe and clarify the diet so it is applicable to other clinicians who follow these sorts of patients.

And the weaning criteria that was previously described, we have also tried to codify so that those things are applicable to clinicians who are well trained in the care of this sort of patient population.

So for those reasons, the setting itself we didn't feel minimized how this type of therapy could be applicable to a broader spectrum of patients in different centers and different physicians. The care that was actually provided is well codified, and therefore we felt also generalizable to all of the patient population who have this problem, as well as the clinicians who care for them.

MS. JOYCE: I would just like to comment further that with respect to the number of patients per center, it took a bit of time due to the fact that we were looking for a center that could accommodate prospectively the residential 6-week period of time. At the point where

we did enroll the second center, the enrollment of the patients was substantially far along, and that is why the second center had a limited number of patients. At that point we had reached the total number of patients needing to be enrolled for the results, and that's why there is a disparity in those two centers.

I also would like to point out that if the results were marginal in terms of statistics, I could understand -- certainly understand even stronger -- the concern, but I just would like to mention again that the results were highly statistically significant with p values of less than .001.

DR. WOLFE: I'd like to hold off discussing any further the question of multicenter versus single-center study until the afternoon.

Dr. Cara, you have a comment and question?

DR. CARA: Yes. Getting back to the fluid status in these patients, given the well-recognized effects of growth hormone on fluid retention and edema, I wonder whether there was a creation of a false sense of security in some of these patients in terms of their fluid status as it was interpreted as weight status. What particularly concerns me is the loss of weight on the week 18 follow-up that at least both groups of growth hormone-treated patients had.

Did you look at either water-free weight through bioelectrical impedance in these patients? Or do you have any sense of what their actual body weight did during the course of the study and then on week 18 follow-up?

DR. GERTNER: Yes. I can answer those questions. We did look at bioelectrical impedance. In fact, that was used to calculate extracellular fluid volume and deduct that from any observed weight gain as just explained by Dr. Byrne. So the weight that was used to judge whether weaning was appropriate was a weight from which wet weight or water weight had been deducted so as deliberately to exclude the possibility that growth hormone-induced water retention could influence the weaning criteria.

I'd like to, if I may, show the weight change between the start and the end of the study in another way. Would that be acceptable? Because that was asked by Dr. Camilleri also. If we could have the slide on, please.

These bars show the weight changes from the screening by the admitting doctors to the 18-week follow-up period, and one of the things that we observed was that there was a brisk rise in weight in all the patients when they came into the clinical center before the institution of any therapy at all. This might have been due to

increased sodium intake or any one of a number of dietary and nutritional factors. So I think it's more balanced, as it were, to take a look at how the weights moved from just prior to admission to the 18-week follow-up period, measured by the same practice and on the same scales.

What you can see here, the white line on each pair of bars represents the calculated ideal body weight for the patients, and you can see that in all three groups the weight just prior to entering into the center was a little bit above the ideal body weight, and in all three groups it was a little bit below ideal body weight at 18 weeks. The gap is somewhat larger for the growth hormone-treated patients, but they still remain very close to their ideal body weight.

It has to be borne in mind that these patients had quite a big reduction in IPN volume and that IPN itself can lead to weight gains, the fluid that's given, the electrolyte content that's given, the hydration. So I think that that in itself explains these relatively small changes in body weight that we see between week 0 and week 18.

DR. WOLFE: Yes.

DR. MANGEL: I have two questions related to your responders, with the responders being individuals who were able to remove themselves from parenteral nutrition.

The first question is that we saw the same individuals who were off TPN at week 6 also being off at week 18, and would you have any information from other studies in which individuals received a retreatment with growth hormone when they would require going back on TPN?

DR. GERTNER: Well, the question is, if I'm right, what are the characteristics of the patients who responded. Is that correct? Is that what you're asking?

DR. MANGEL: No. The individuals who were able to terminate parenteral nutrition, from other studies would you have any information of individuals who needed to go back on and then were retreated with growth hormone, if the agent was efficacious, with a second bout of treatment?

DR. GERTNER: I'll leave that to Dr. Wilmore because it was, in fact, not within the scope of our study to retreat anybody.

DR. WILMORE: This is anecdotal information. We've retreated 10 or 12 individuals. Generally it's after an intercurrent illness. It's at an interval of 1 or 2 years following the initial weaning, and several of these people have had intercurrent illnesses and weight loss and they simply can't regain their weight. And we've retreated them and they've come back up to where their desirable weight was and did quite well. So we've treated them at least at year intervals and some at 2- and 3-year

intervals. One woman that we retreated actually called up and said she's now gaining too much weight and can't fit into her clothes and wanted to be able to reduce her diet. So that was a very positive kind of response.

DR. MANGEL: And in this study for those, once again, responders able to stop parenteral nutrition, could you tell us what the weights were in that cohort?

DR. GERTNER: I can give you the prescreening weights for those patients. I'd have to look up the later weights, but the prescreening weights were quite varied. There was 1 patient in the glutamine alone group who weighed 65.9 kilos. There were 4 patients in the growth hormone and unsupplemented diet group and their mean weight was 70.8 kilos. And there were 4 patients in the growth hormone plus glutamine group and their mean weight was 53.1 kilos.

So it doesn't seem to be a characteristic of pretreatment body weight because in the growth hormone alone group, the complete weaners actually were heavier than average, and in the growth hormone plus glutamine-supplemented group, the complete weaners were below average in starting weight. We can look up the follow-up weights on these for sure.

DR. WOLFE: Dr. LaMont, then Dr. Cara.

DR. GERTNER: I would like to add. Sorry. I'm

not sure if this was absolutely clear, but none of these patients were retreated as part of the study or, as far as we know, outside the study.

DR. WOLFE: Dr. LaMont, then Dr. Cara, then Dr. Camilleri, then I have a couple of questions.

DR. LaMONT: I'm sorry to beat this to death, but I'm still struggling with the body weight and fluid because this seems to me to be a critical thing here.

I can't find, but I think it's in here somewhere, the weights at week, I guess it would be, 6. You showed us 0, 2, and 18 on the last slide, but what do they look like after they've had 4 weeks of growth hormone?

MS. JOYCE: Excuse me one second.

DR. GERTNER: Yes, we're just finding the slide for you, if we can. There's a slide of body weights by week.

But the answer to your question is the weights go up during growth hormone treatment. Every patient that receives growth hormone increases their body weight. I'm not speaking specifically of this trial, but generally speaking, when you give growth hormone to people, their body weights go up. This has a very brief duration. After the end of treatment with growth hormone, then the weights go down again. That's why we adopted this measure of using BIA to exclude excess hydration in the weaning.

Have we got that slide? Yes, we're getting the slide of the weights. It will be up in a moment. If we could have the slide on please.

I just have to orient myself. Let's look at the growth hormone plus glutamine group. At week 2, 63.9 was the mean weight; at week 3, 66.3; at week 4, 66.3 again.

Slide off and the next slide on, which has the following weeks. Week 5, 66.1. Week 6, it's gone down a little to 65.6, and here you see there's a difference between the weights now in these patients. In the SOD (GLN) group, it's 61.8 kilos. Here's it's 64 kilos, and here it's 65 kilos. So the weights did go up in the growth hormone-treated patients, just as I mentioned earlier.

We anticipated this. We built BIA into the evaluation of the capability for weaning, and that is a well-known phenomenon of the administration of growth hormone.

DR. LaMONT: So is the weight gain salutary or is it mostly edema?

DR. GERTNER: The weight gain, to some extent, is extracellular fluid. So you can characterize that as largely edema. That would be manifested in terms of BIA as a reduction in resistivity. So you could read that off and deduct that from the body weight and use the corrected body

weight as a criterion for making the dietary and weaning adjustments.

DR. LaMONT: But physicians in practice that didn't have impedance measurements wouldn't use weight as an outcome measure.

DR. GERTNER: I think the use of BIA in clinical practice is not at all difficult, and the physicians who manage this could certainly become aware of the techniques, if they're not aware already, and adopt them.

But, as just pointed out to me, the weight is not the only weaning criteria at all. The weaning criteria are also based on hydration capabilities and maintaining electrolytes and other factors.

DR. CARA: Do you actually have the BIA data, the impedance data?

DR. GERTNER: Yes, we do.

DR. CARA: While you're looking that up, is all short bowel syndrome the same? In other words, were some patients more likely to have water retention than others? And did you look at any subgroups of more optimal versus less optimal responders?

DR. GERTNER: Yes. You asked about the subgroup analyses, and we did do this for all the etiological subgroups and also for the presence of a colon

versus no colon, the presence of Crohn's disease versus no Crohn's disease, and we really didn't see -- the way this was done was by using a covariate model where you, first of all, looked to see whether that factor was important in the model, and generally it wasn't. When you factored out that particular covariate, something like has the patient got Crohn's disease or not, for example, it was quite clear that the efficacy was maintained across the three treatment groups in the same order, less for the SOD (GLN) group, more for the growth hormone and unsupplemented diet, and still more for the growth hormone and supplemented diet. That pattern, with very significant results, in the growth hormone and supplemented diet was maintained, whichever of these covariates you tried to factor out.

DR. CARA: Yes, but if you look at the SDs, they're quite broad.

DR. GERTNER: Well, yes. I mean, they're small studies.

DR. CARA: And I guess the question is, how much of the response was determined by a select number of individuals versus the group as a whole? And it would be nice to see either individual data or some other source of information that would give us an idea of whether this was a very common response or if it was more selective in nature.

DR. GERTNER: Could you just repeat that question? Because I was looking for the BIA for you and I found it.

DR. CARA: Okay. Well, the bottom line is that -- I'm trying to think of how I worded this. I don't know that I can remember.

DR. GERTNER: I'm sorry. I do apologize.

DR. CARA: The standard deviations were very large in all your groups, which means that the individual response was very variable. It would still be nice to know whether there was a common response of all individuals in response to growth hormone or whether there were some individuals that responded better than others or, for that matter, swayed the group, if you will, in terms of showing of a positive response.

DR. GERTNER: Do you mean whether there were particular outliers, the presence of which sort of forced the results to --

DR. CARA: Exactly.

DR. GERTNER: I actually don't think that was the case, but I could ask Dr. Kenley maybe to comment on that.

DR. WILMORE: The statistical group has looked at a variety of variables including age, weight, gender, Crohn's disease, no Crohn's disease, time of infusion since

resection, jejunal length, IPN volume, IPN calories, frequency, and the like, and none of those variables are significant. That doesn't exactly address your question, but it points out the fact that we can't find differences in subsets within the group. We're happy to provide the whole data set for you.

DR. CARA: A simple way to look at this is just to compare each individual to their baseline status. Did you do that?

DR. WILMORE: Well, we've done that in terms of the outcome.

DR. CARA: You've done that in terms of the groups, but you haven't done that in terms of the individual patients. Do you follow?

DR. GERTNER: I think I know what you're getting at, but to me as a clinical investigator, what counts is the statistical integrity of the group analysis according to the statistical analysis plan. We asked ourselves the question if you measured these changes before and after in this group, was it statistically significantly different from the corresponding changes in the control group, and it was. And actually it was in both growth hormone-treated groups, although one obviously more marked than the other. So there may have been 1 or 2 people who responded hardly at all or didn't respond and there may

have been 1 or 2 people who responded a lot. That's what you see in every clinical trial, and the overall statistics, by using all the correct methods of adjustment and allowance, gave a high value of significance for efficacy.

DR. WOLFE: Lest I be accused of cutting off people, this is the main topic of discussion this afternoon looking at the first two questions specifically looking at the study parameters and whether they are clinically significant with regard to patient care. Unless there are specific questions regarding design, I'd really like to try to table this discussion because we will continue. We're way behind schedule. That doesn't bother me, but I think we'll have a lot of time to discuss these questions.

DR. GERTNER: Dr. Wolfe, may I quickly show the BIA data which were requested by Dr. Cara?

DR. WOLFE: Sure.

DR. GERTNER: Because I think they illustrate the point very well.

Here you see the BIA values at the baseline and at 6 weeks in the three treatment groups, and I'd like you, please, to focus on the bottom line, the mean and standard deviation of BIA resistivity change from week 2 to week 6. You can see that the change in the control group, SOD (GLN), was 6 units. Ohms actually are the units. The

change in the growth hormone alone group was 72 and the change in the hGH plus GLN was 89. So there was a substantial change in BIA, and observable change and one which we had planned to take into account in assessing that one of the weaning criteria which relates to body weight. So we did do a clinical test to look for growth hormone-induced fluid. The test was positive and the necessary adjustments were made.

DR. WOLFE: Dr. Camilleri?

DR. CAMILLERI: Yes. It's a design question, Mr. Chairman.

I look at slide number 55, and I'm sure that you have it in the materials that you presented. But group C, which was your control arm, your diet only arm, had an IPN requirement of 13.5 liters per week, whereas the active treatment arm only required 10.5 liters per week. And the question I have is does that not suggest to you that the severity of the problem of the short bowel syndrome was greater and you were unfortunate enough in your randomization process to end up with the more severe patients in the control arm? And how does that influence the interpretation that you can give to the efficacy of treatment? Thank you.

DR. KENLEY: I would like to address that from a couple of statistical angles. The first is that those

baseline values of 10.3 through 13.5 certainly were not statistically different across the treatment groups. So that's number one.

Number two, I would also like to say that we did take into account this most important covariate in our primary analysis. It was the dominant covariate, that is, the patients' baseline status with regard to total IPN volume. When we took into account this covariate, we found that depending on where the patient was at baseline, their response was different. If you would like to see that, I could show you that as well.

DR. CAMILLERI: It's what I predicted.

DR. KENLEY: Do you want to see it?

DR. CAMILLERI: I mean, quite honestly, the fact that they're not statistically different doesn't tell me anything. It just tells me that the variance was too large. But clinically a 3 liter per week difference constitutes a different clinical scenario, and perhaps the thing that would convince me would be to show us how much residual small bowel and how much colon there was in each of the three groups. I know that when you did your covariate analysis, you didn't see a difference, but biologically when I'm a clinician looking after the patients, I know that those are the two most important factors that determine whether I can rehydrate these

patients without TPN, whether I can use enteral rehydration solutions, et cetera. So I was actually quite impressed or disappointed that that sort of information was not provided during the presentation.

DR. KOCH: Gary Koch, statistical consultant.

The analysis of covariance basically provides a comparison of like with like. So when you adjust for the covariate, you're basically producing a comparison of individuals at essentially the same value at baseline across the range of baseline. The differences that you see presented are differences that apply at the average of the baseline.

Now, the sponsor also did an analysis in which they allowed different slopes on the covariate and they found in that analysis that differences are bigger when the baseline is higher and differences are smaller when the baseline is lower.

Your concern seems to be whether they should have included some additional covariates, and their previous discussion seems to indicate that relative to the range of things they looked at, they didn't seem to find those other covariates doing anything. But the two that you mentioned they could consider further.

DR. CAMILLERI: Can I come back? The reason why I raise this point is that the patients in the control

group seem to have the worst disease, and the whole question here is whether the statistical maneuvers with a covariate analysis actually obviates the biological variation that occurs with that variation at baseline.

DR. GERTNER: Can I see EF013, please?

DR. WOLFE: While you're getting the slide up, that was my question exactly because there is a significant difference in biological variability, most extreme among humans. And what we often do to correct that is use percent change rather than absolute differences. Do you have that data looking at percent change among the different groups, and are they different? Is that what you're asking, Mike?

DR. KENLEY: I would like to respond to that. We did not look at percent change from baseline and the reason for that is because we felt that that was not the clinically meaningful parameter. We felt that by reducing a liter per week was the meaningful parameter, that is, reducing a patient's infusion time, and not the percentage change from baseline.

Additionally, if we did look at the percentage change from baseline, we would expect that variable to be a skewed variable. It wasn't planned and so we would have to do a nonparametric analysis. Now, if you would be interested in seeing that, we could provide it to the

agency, but again, we did not feel that was the clinically meaningful efficacy endpoint.

DR. GERTNER: All right. This is fine and then I'll follow up with EF12. Slide on, please.

If you look at the percent colon intact, because you were asking for some gastrointestinal variables with regard to the baseline state. Is that correct?

DR. CAMILLERI: Yes.

DR. GERTNER: So here you can see that actually the mean of percent of colon intact is less in the combo group of 52.6 in growth hormone plus glutamine-supplemented diet, least in the growth hormone alone group, and intermediate in the control group at 61.8 percent of colon intact.

If we can have that slide off and have the next slide on, we can see length of residual jejunum-ileum, and here there is a difference in the mean values. It's 62.3 centimeters in the control group, 84.2 in the growth hormone alone group, and 68.4 in the growth hormone plus glutamine group. So what I could point out is that there's a 6 centimeter difference in length of jejunum and ileum which represents about 1 percent of the normal length of small intestine, a difference between the control group and the group that performed best on efficacy. As we said earlier, all these factors were brought in as covariates

into the model and didn't make a difference to the robustness of the result.

DR. KENLEY: One further just elaboration to address what Dr. Koch said, that when we do account for these baseline covariates in the analysis, it's an overall response by treatment. In other words, that is then taken care of in the analysis.

Also, if requested, we can show you the patients' response depending on their baseline etiology status or any of the disease history characteristics.

DR. WILMORE: I join the parade to the microphone. Slide up, please.

Again, to remind you of the distribution of diseases, the large number of Crohn's disease patients are in the combo group, not in the control group, and in general, mucosal disease would be considered a more severe disease.

Next slide, please. And then again to remind you the groups of people with no colon had been considered in the past as more difficult patients, and they're also in the combo group. I interpret that as loading us with the sicker patients over in that group.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: That's very helpful and I thank you for adding this additional data.

So the proportion with colon resection and the amount of residual small bowel is effectively the same in the three groups. Is that fair?

DR. GERTNER: Yes, I think it is fair.

DR. CAMILLERI: And the amount of residual Crohn's disease in the diet alone group is minimal, in fact, probably 0 because there's only 1 patient. So the amount of mucosal disease cannot explain the difference.

So have you got any explanation for why there's a 3 liter per week greater requirement in the control group?

DR. GERTNER: The simple answer to your question is no. There are a lot of variables, obviously, that go into the optimal treatment. Remember that all these patients were optimized before randomization. So while not knowing exactly which factor in which individual led to them requiring more TPN, we do know -- not only in a blinded way but before they were even randomized, so they had to be blinded -- the TPN was optimized for each patient. It just happened to be that the people that were randomized into the control group, despite the fact that they didn't necessarily have these worst diagnoses, required more TPN.

DR. WOLFE: Dr. Gertner, I have a few questions and some require very short answers.

DR. GERTNER: Okay.

DR. WOLFE: What period of time are you requesting or are you looking for approval, what period of time of treatment? Is it indefinitely or is it a definite period of time?

DR. GERTNER: I'm sorry.

DR. WOLFE: How long approval? How long are you looking for? For 6 weeks, 6 months, 5 years?

DR. GERTNER: Oh, we're looking for 4 weeks treatment as a course of treatment.

DR. WOLFE: Then, in other words, on slide 63, you indicated that there were some permanent adaption which took place in these patients. They were off TPN entirely. Is that correct?

DR. GERTNER: It's correct to say that they were off TPN for the period of observation which was up to 3 or 4 years for some of the patients. I would not be so rash as to say it was permanent.

DR. WOLFE: And those are different among the groups?

DR. GERTNER: Well, the numbers are really small.

DR. WOLFE: They are small.

DR. GERTNER: We do know that at 12 weeks after the end of treatment, 25 percent of the patients in each of

the growth hormone groups and 1 patient, which translates to 11 percent, in the control group were completely off treatment. I guess the necessary approach to this would be to see whether, at some future stage, some of them need to be retreated.

DR. WOLFE: Maybe I'm missing it, but on slide 63, I see 5 patients off --

DR. GERTNER: Can we have the slide on, please?

DR. WOLFE: A total of 5.

DR. GERTNER: Yes. There were 9 patients --

MS. JOYCE: I just wanted to clarify because you had asked about the treatment period. The treatment period that we are recommending, based on these study results, is a treatment period of 4 weeks. Then what we did was a follow-up period, 12 weeks afterward, and we're in the process of doing an up-to-2-year follow-up on the patients to determine for all 41 patients those who reduced and stayed reduced or changed and those who stayed off. These are the data that we have to date for the patients that were off.

DR. GERTNER: Well, yes. The follow-up data that we have obtained to date on the 9 patients who were completely off treatment cover 7 patients whose data are available beyond the 12-week time point, and these are the 7 that I'm showing you here. The other 2 we know were off

treatment at the follow-up, but we don't have yet their survey results in, so we don't know what their current condition is. Of the 7 from whom we have data, 5 remain off treatment and 2 had to return onto treatment.

DR. WOLFE: Well, if you look at these data then, 1 of the 9 in the control group is off treatment.

DR. GERTNER: Correct.

DR. WOLFE: That's one-ninth. And 4 of 32 receiving growth hormone are off treatment. That's one-eighth. That doesn't seem very different to me.

DR. GERTNER: These data are not related to the primary endpoint of the study. The primary endpoint of the study was the reduction in volume of IPN which was highly statistically significantly better in the growth hormone plus glutamine diet treatment group.

DR. WOLFE: I'll move on. Do you have any questions related to this?

DR. SHIH: This is actually a carryover of my question about clinical relevance of IPN volume. In your slide 64, you talk about clinical relevance of the primary endpoint, and one item was to enhance the patient's well-being and autonomy and that carried to your conclusions. I was wondering -- this is an induction. It's not a direct measure, is it? Have you really measured in your pivotal study and shown this enhancement of patient well-being and

autonomy?

Also, you mentioned that the reduction of PN reduces line sepsis and catheter occlusion and so on and so forth. I believe those are inductions. Do you have in your data that directly measured this kind of reduction induction?

MS. JOYCE: With respect to this particular study, we did not prospectively build in a standardized quality of life tool. So in terms of patient well-being and benefit, we're not per se making a quality of life claim based on that type of data from the study.

That being said, I do believe we have information, data, from Dr. Wilmore and also I think we have some additional information that Dr. Kareem Abu-Elmagd could provide.

DR. WILMORE: There are two reports using quality of life end assessments. We've done one with 18 patients, as I mentioned before. 12 of the patients had either reduced or came off parenteral nutrition. Their SF-36 scores rose. 5 patients had no change. Their SF-36 stayed the same over a period of a year. 1 patient received more TPN fluid. Their quality of life score fell.

DR. HOUN: I'm wondering if we could ask the committee and the company to focus in on the data in the studies and the claims you're going to make for your

product. You've clearly said that that's not going to be a claim. I don't think we should discuss it.

The other question Dr. Shih had was are you going to be claiming reduction in line sepsis, catheter occlusion, liver disease, and do you have the data to support that.

MS. JOYCE: We're not anticipating to make labeling claims. And of course, we've not had an opportunity yet to have any discussions with you on the label itself. But we did not design the study in order to indicate a statistically significant difference in line sepsis or that sort of thing. What we've done is provided information from the relevant experts about their clinical experience and what they've observed in patients that they've treated with short bowel syndrome.

DR. WOLFE: Dr. Mangel?

DR. MANGEL: I would like a little clarification on the number of individuals who were able to be removed from parenteral nutrition. I believe in your presentation you said there was a total of 9, 1 in the control group and 8 between the other two groups. In one of the briefing documents, it actually lists 13 to 14: 1 on the control group; 7 to 8, depending if you're including hydration, in the combo group; and 5 in the rh group. In your primary presentation, you also said all of those off

of parenteral nutrition at 6 weeks were also off at 18 weeks. Is that the number 9 or is that the number 13 to 14?

DR. KENLEY: I just would like to address the one issue about the people that are off that Dr. Gertner showed. Slide on, please. These people that have been off after they left the study. Just one comment. This is a sample of what we could obtain at this point. It is not all patients. So just a point to say that 1 out of the 9 glutamine patients versus 4 out of the 32 and those percentages being equal is not really fair because those denominators -- we don't have follow-up on all of the 32 patients on growth hormone or the 9 patients on glutamine. These are all the data that we have, so we can't make that comparison at this point.

DR. MANGEL: But is it correct that at the 6-week time point you had about 11 percent of your control group who were able to terminate TPN, about 50 percent of your combo group, and about a third of your growth hormone only group?

DR. GERTNER: I'm sorry. I'll have to calculate these percentages. Could you repeat the question please?

DR. MANGEL: Sure. Is it correct at 6 weeks there was 1 individual out of 9, so about 11 percent, in

the control group who was off TPN; 7 or 8 out of 16, depending whether or not you include hydration, or about 50 percent of the people at 6 weeks were able to terminate TPN; and 5 out of 16, so about 30 percent, in the growth hormone group only was able to terminate TPN?

DR. GERTNER: Yes, that's correct. And the difference between the numbers of the 9 and the 13 that you're asking us about is exactly the difference in hydration fluid. So the 9 patients that I described as coming off what we defined as total IPN are the patients who also did not require any hydration fluid. In addition, there were 4 patients who came off what would normally be regarded as parenteral nutrition and only required peripheral hydration to a total of 13, and those numbers were also maintained to 12-week follow-up period.

If I can have the slide on please, you can see how much hydration fluid was actually required at the 6-week time point by the patients as a whole. And you can see that the mean value in the growth hormone plus glutamine-supplemented diet group was less than 700 ml per week or less than 100 ml per day, and the median value was 0, which means that most of the patients did not require any extra hydration fluid. So the amount of hydration fluid per patient as an average, if you like, was quite small, but it was that small amount of hydration fluid that

made us be conservative and presenting to you the conservative data made us say that the number of patients who were completely off all treatment was only 9; whereas actually if you disallow these 100 mls average per day of hydration fluid and look at the patients who did not completely come off hydration fluid but did completely come off PN, we increased the number of responder patients to 13.

Does that make it clear? Thank you.

DR. WOLFE: Dr. LaMont?

DR. LaMONT: Can you just clarify the slide you just shut off? I'm sorry. I just don't understand the week 2 data. This is before they received anything. Is that right?

DR. GERTNER: Yes.

DR. LaMONT: This is at the end of the --

DR. GERTNER: Yes. I don't know if you've noticed that the volume of hydration fluid required by the patients who were going to go into, at week 2 before they had had anything, was 687.5 ml per week, and this volume is also 687.5 ml per week. But we've checked these numbers numerous times, and it is exactly correct.

DR. LaMONT: I didn't spot that, but I'm trying to figure out -- I wish I had.

(Laughter.)

DR. LaMONT: I don't understand the difference in the groups. For example, the mean in the glutamine alone group is 1722, and then in the other two, they're far less. It seems like they're unbalanced. What's going on here?

DR. SHIH: Well, I suggest that you don't pay too much attention to this table because you compared the mean to median. It's so different. That suggests that your distribution is skewed. Therefore, you don't want to look at just the mean. Look at the median. They're all 0's. So don't pay much attention to this table at all.

(Laughter.)

DR. GERTNER: I would also point out, of course, that the 12-week data was not the primary endpoint, and this is just a small component of what the primary endpoint was which was total parenteral nutrition plus hydration fluid per week.

DR. WOLFE: Dr. Cara.

DR. CARA: But this sort of data gets back to the concept that looking at percent change for an individual patient might be an additional way to get information about actual fluid requirements. Granted, it may not be the primary efficacy variable that you want to look at, but it's an important piece of information.

The other thing that I think that we're sort of

on the fringes of that I'm having some difficulty with is whether or not -- well, there are really two issues, and maybe we'll discuss that this afternoon. I don't know. One is nutritional status. The other is hydration status. We'll do that this afternoon?

DR. WOLFE: Because that's really what we're talking about in the afternoon, are the endpoints what we're looking for? Are they meaningful endpoints? I really want to table those discussions, if we can.

I have a couple safety questions. They should be very short answers. I understand as a gastroenterologist that hepatotoxicity can occur in the absence of any changes in liver enzymes, very commonly. However, did you measure liver enzymes and were there any changes in the different groups?

DR. GERTNER: We did and there were no significant changes in liver enzymes.

DR. WOLFE: Good, okay.

The other question may be a little bit longer one. You did exclude people with cancer. Again, this is a mitogenic hormone. So if you're contemplating the possibility of long-term therapy, what are your expectations or what do you expect to do with regard to exclusion of certain patients' potential for having malignancies elsewhere? Because this conceivably could

make occult malignancies grow faster.

DR. GERTNER: First of all, we don't necessarily propose long-term therapy. That's not what is currently being suggested.

I would think that with regard to cancer patients, the label for growth hormone that currently we and other companies have is that growth hormone should not be used in patients with active malignancy, and I think that that would be a very wise precaution to take also for this indication. I could give you further information, if you want, about this issue.

DR. CARA: As a follow-up question to that, we've generally looked at IgF response as a way of looking at potential risk of tumorigenesis in patients receiving growth hormone therapy and have ideally tried to keep IgF within the upper 50th percentile but not above the normal range. Do you have any IgF data in these patients in terms of the values that they got up to?

DR. GERTNER: We did not measure IgF-1 during this study, and so we don't have any data. The study was brief. It was a 4-week study, and we did not anticipate that this kind of consideration of long-term use needed to be assessed considering that we're not requesting long-term use. Therefore, IgF-1 would be a reflection of patient adherence maybe, which is not relevant in a residential

study such as the one we conducted. It would be a question of whether the dose of growth hormone was correct, but that already is fixed by the study. So this is not the kind of treatment paradigm equivalent to growth hormone replacement where I agree completely you would be giving growth hormone for a long period of time and you would want to check the IgF-1 over that long time to make sure you didn't go too high.

If you have the slide on, I could point out also that we have recently convened an advisory board for the specific purpose of looking at long-term safety of the administration of growth hormone from the point of view of the potential tumorigenicity of IgF-1. And what this board have told us is that the risks of cancer in IgF-1 -- and I think that's the general opinion -- is quite theoretical, that clearly there has to be a risk-benefit analysis. You wouldn't be giving growth hormone if there wasn't a benefit, and that has to be weighed against these potentially theoretical risks, and that the chance of getting tumors really relates to these epidemiological work with regard to the fact that people with high IgF-1 are somewhat more likely to get various cancers. This is people who have had the high IgF-1 over a life-long basis, not 4 weeks. So it's quite reassuring that short-term administration of growth hormone does not fit us into any

of these risk categories.

DR. CARA: But if you were to consider repeated treatments, that would be an issue that would be of concern.

DR. GERTNER: Yes. I'm not sure, even with repeated treatments, that we would have -- we would have obviously the surveillance. If I can have the slide about the surveillance.

Obviously, we would apply post-marketing surveillance, and one would look for occurrences of serious adverse events such as cancer. I can point out, as you well know, Dr. Cara, that growth hormone is extremely well studied in the pediatric population and has been used safely. Post-marketing surveillance would, undoubtedly, be conducted by our company. As I just said, the duration of treatment proposed at present is only 4 weeks.

DR. WOLFE: I've done an informal check of the panel. There are no more questions at this point. We can always ask questions in the afternoon, and we really need to move on. Thank you very much.

I'd like to move on to the FDA presentation by Dr. Hugo Gallo-Torres.

DR. GALLO-TORRES: Good morning. As an introduction, I should say that a few of the slides I'm going to present have already been presented by the

sponsor. So we will be reiterating some of these things, but that means I don't have to spend a lot of time on some of the slides.

The topic of today's presentation is Serostim for the treatment of short bowel syndrome reviewed under NDA 21-597. I'm Dr. Hugo Gallo-Torres. I am a medical team leader at the Division of Gastrointestinal and Coagulation Drug Products.

This is an outline of what I will be summarizing for you this morning. After a brief introduction, I will refer to some data in the medical literature that has already been mentioned by the sponsor and the members of the advisory committee. Then I will move to significant findings in the study IMP 20317, and I will finish my presentation listing what we call outstanding issues, outstanding in the sense of unresolved issues, which we hope will be resolved by the end of the session today.

The proposed indication is for the treatment of short bowel syndrome in patients receiving a specialized nutritional support. The medication, the drug, growth hormone is to be given in conjunction with optimal management of short bowel syndrome, and I believe there is need to define what do we mean by optimal management of short bowel syndrome.

I just would like to reiterate a couple of things here, that the short bowel syndrome treatment includes nutritional management and replacement of fluid, as well as electrolyte losses. The intravenous parenteral nutritional requirements vary. They change depending on a number of factors, but ileocecal valve, presence or absence of jejunum, functional colon, and the length of the residual bowel are very important. This explains the questions that we and you have asked already about whether these factors are influencing results.

Another statement can be made: that patients with residual bowel of 100 centimeters or less frequently require chronic administration of intravenous parenteral nutrition and also to reiterate that the bulk of the patients in study IMP 20317 have less than 100 centimeters of bowel left.

Also, to help you in your deliberations, we have listed here the complications of long-term parenteral nutrition. These are not arranged in any special rank, but as you know, the complications include cholelithiasis, catheter sepsis, liver dysfunction, macro and micro nutrient deficiencies, bone demineralization, central vein thrombosis, glucose metabolism disorders, progressive renal insufficiency, and so on.

Also, even though safety I believe is not an

issue in this study -- very few adverse events were reported -- the complications associated with growth hormone are very well known. The sponsor said it and at least two members of the committee repeated that, and it is true. Again, these complications include edema. Fluid retention is very well known associated with growth hormone. Arthralgia, headache, hypothyroidism, antibody formation, glucose metabolism disorders, possible association with leukemia, and intracranial hypertension with papilledema. Most of these occur, of course, after long-term administration with the hormone, and as I said, very few of these have been observed in the actual clinical trial. We have to be clear about that.

We now move to we call controversial findings in the medical literature. In essence, what we have here is listed the clinical outcome measures that other investigators from other studies have published. We have here what in the literature is called high, low, and low dose growth hormone. What do we mean by this? This is a study by Jeppesen. This is a study by Seguy, and this is a study by Ellegard. The title of the paper says high-dose growth hormone. This is low-dose growth hormone, and this is also low-dose growth hormone.

For example, in the study by Jeppesen, who used another form of growth hormone, from Novo-Nordisk, these

outcomes did not change. The "NC" means no change. In other words, in that study by Jeppesen, body weight, lean body mass, fat mass, absorption of fatty acids, and 24-hour creatinine excretion did not change.

In the study by Seguy very recently reported, there was a change in body weight and a change in lean body mass and an increase in the absorption of fat.

And in the last study, there was an increase in body weight, an increase in lean body mass.

Both of these studies showed an increase in the insulin-like growth factor-1 or insulin-like growth factor binding protein 3.

This dose, the first column, which was labeled or called high-dose growth hormone is 0.14 milligram per kilo per day. This dose, the second column, is 0.05 milligram per kilo per day, and thi, the third column, is 0.024 milligram per kilo per day. Another way of saying this is this is 24 micrograms per kilo per day, which is about half of this, which is 50 micrograms per kilo per day, which is about half of this, which is 140 micrograms per kilo per day.

So there seems to be no consensus on what we are calling high or low dose recombinant human growth hormone, and this is one of the questions of the committee. That type of data invites the question, is low-dose

hormone more effective than high-dose hormone? It's one of the questions that we are going to ask you today. It is important that we realize that there is no pharmaceutical bioequivalence between these preparations.

You have seen a description of the design and the results of this study, IMP 20317. It consisted of the evaluation of recombinant human growth hormone and glutamine singly and as co-therapy in the improvement of residual gut absorptive function in patients with short bowel syndrome. This was a phase III study testing the dose of 0.1 milligram per kilo, as we said, administered subcutaneously for 4 weeks. The length of the study is 4 weeks. It was a randomized, double-blind, controlled, parallel-group, 3-arm trial.

There were three treatment arms. I think it is of interest to characterize these three groups, to understand better the results, group A, B, and C. Group A was the active growth hormone and glutamine placebo. Group B consisted of the co-therapy of active growth hormone plus active glutamine. Group C we believe is an adequate control. Why? Because it contains growth hormone placebo plus active glutamine. So we are going to see in a minute pairwise comparisons between A versus C and B versus C. All patients received a specialized oral diet which consisted of oral fluids, oral calories, and macro

nutrients that we all know.

The primary endpoint, again, consisted of the change in total intravenous parenteral nutrition volume, and I think it's important to reiterate this because there has been a little confusion about the wean off IPN. I hope we will later clarify this. There are three components to the main endpoint: component one, IPN volume; component two, supplemental lipid emulsion that is abbreviated as SLE; component three, intravenous hydration. I like to remind you that the intravenous hydration may also contain calories and that the total IPN volume requirements were captured on a daily basis within those 6 weeks that the patients remained in hospital.

The secondary endpoints, already mentioned are two: the mean change in total IPN calories due to the macro nutrients, carbohydrate, protein, and fat; and the mean change in IPN or lipid frequency, the number of days per week of IPN or lipids if greater than 200 kilocalories, or intravenous hydration.

The sponsor and we also did what we call an exploratory analysis. I see that you were discussing a lot about the wean off IPN, and I repeat, I hope this information helps.

These patients were labeled as complete responders at week 6. The definition of complete

responders was two ways. One, complete wean from IPN, lipids and wean from intravenous hydration, that this patient does not need the catheter any longer. The other definition, though, is complete wean from IPN and lipids, but intravenous hydration is allowed. There are two different groups in here, two different number of patients that we will see a little later.

Why do we call these exploratory? Actually I call these hypothesis-generating data because the results of these study populations were summarized only descriptively. There were no statistics. There were very few patients per cell.

This is to reiterate a point about the number of randomized patients, the number of randomized patients for group A are here, group B here, group C here. There were two sites involved. Site number one enrolled a total of 38 patients. Site number two enrolled a total of 3 patients, 1 patient each per treatment group. What is the bottom line here? The bottom line here is that the study consisted of 41 patients, but the bulk of the patients were enrolled by site one. So, in essence, this is a one-center study.

The study population, again, consisted, as we said, of 41 randomized patients that were of the age of 20 to 75 years. Most of the patients were less than 65 years,

caucasian, and female. As the sponsor has said already, the baseline characteristics were similar between the treatment groups, and these included length of residual bowel, IPN requirements history, and duration of therapy.

This slide you saw before, and it gives the results of the primary efficacy analysis which was the change in total IPN volume. There are two sets of data here.

On this side of the slide, we have the actual results, the mean change in total IPN volume at week 6 in comparison to baseline, at the end of week 2.

And over here we have the pairwise comparisons. You saw this also, the IPN requirements at baseline among the three treatment groups. There was a decrease of 5.9 liters per week in group A; 7.7 in group B, which is the recombinant human growth hormone with glutamine in co-therapy; and 3.8 liters for the control group C. The pairwise comparison, group B versus C, the dual co-therapy, growth hormone plus glutamine, gives a difference or a therapeutic gain of 3.9 liters per week. The growth hormone by itself without the glutamine versus the control gives a therapeutic gain or a difference of 2.1 liters per week. Both of these differences, as you can see, are statistically significant. The question for the committee is, are these differences also clinically significant?

That's probably the main question today.

We heard discussions about follow-up data, and we feel strongly that there are limitations of the follow-up data. In summary, the growth hormone was discontinued after 4 weeks of treatment, at week 6. There were no data collected between weeks 6 and 18. There were only IPN data recorded at week 18, but not throughout the 6th to the 18th week. In other words, there are no data on total lipid volume calories and there are no data on intravenous hydration volume calories. So I feel that these data have many limitations, such as the number of patients, which is very small. I don't think we should spend too much time discussing this.

Similarly for the secondary efficacy endpoints -- similarly meaning as the primary -- here we have the actual change from baseline to week 6 in the total IPN calories and the change in IPN of lipid frequency, and here the pairwise comparisons. You have seen these figures before, so I'm not going to repeat those other than to say that the comparison of the group containing the growth hormone plus glutamine versus the control gave a difference of 3,100 kilocalories per week, that of the growth hormone alone versus the control gave a difference of 1,700 per week. There were 2.2 days less from this comparison and 1 day less from this comparison. So again, the question to

the committee is that these comparisons are, as you can see, statistically significant. Are these comparisons clinically significant? That's another question we have for you.

There was also already discussion about the covariates of the primary endpoint. The FDA statisticians were very interested in knowing whether weight, residual bowel, volume history, and so on have an influence on the results. Here is the summary of these evaluations.

The total intravenous parenteral nutrition volume was significantly influenced by patients' weight. Why? Because the higher the body weight, the greater the reductions in IPN volume. I do not know if that contributes to answering Dr. LaMont's questions about the effect of weight.

Length of residual bowel. Why? Because the longer the residual bowel, the greater the reduction in IPN volume.

IPN volume history. The findings were that the higher the IPN volume requirements, the greater the decrease in IPN volume during the treatment period.

And finally, in this particular study under these experimental circumstances, caucasians responded to treatment better than non-caucasians.

The significance of treatment effect after

adjusting for covariates is summarized here. The pairwise comparison of group B to C, again this is the hormone plus glutamine, maintained significant difference in total IPN volume after adjusting for covariates. However, the pairwise comparison of group A, the growth hormone alone without the glutamine, to the control only reached a significant difference in total IPN volume when weight was used as a covariate.

The effects of covariates on secondary endpoints are summarized here. The total IPN calories for the ITT population were not influenced by any of the covariates that we have listed. And only weight influenced the treatment results for frequency of administration of IPN or lipids. Covariate analyses for the evaluable efficacy population yield similar results to those mentioned about the ITT population.

A couple of words about the changes in specialized oral diet. The greater the reduction in total IPN, the greater the increase in oral diet. With the exception of oral fluids, a larger increase in oral intake occurred in those groups containing growth hormone compared to the control. Another way of saying this is that as nutritional status improved, subjects' appetite increased.

Here are the results of what we are calling exploratory analyses. As we said, complete responders are

defined two ways, which I'm not going to repeat. But these results are only in terms of numbers. I do not feel that we should put percentages here because the number of patients is very small. Using that definition, as we said, there were 9 patients. Using this definition of complete responders, there were 13 patients.

All I can say from this is perhaps two things. Yes, numerically these numbers are higher than these, and these numbers are from the groups that contained growth hormone. But the other thing that we should not forget is that there was a randomization of 2 to 2 to 1. So what we are saying is that these, again, are hypothesis-generating data that need to be expanded.

In terms of adverse events, we agree that in this particular trial safety is not really an issue. There were one or more adverse events in groups containing the growth hormone, and in all these groups all of the patients experienced adverse events compared to the control, 89 percent, but these differences were not statistically significant. Once again, the most frequently observed adverse events were fluid retention, edema, fatigue, and of course, gastrointestinal disorders, but we are talking about short bowel syndrome where the GI manifestations are many. There were no deaths in this study.

I think it's fair to say that there were no

serious adverse events that were considered related to the test medication, and I think it's also fair to agree with the sponsor that the safety profile in this population under these experimental conditions is similar to the rates reported in the package insert for the drug. And there were no clinically significant differences in laboratory values for the three treatment groups.

What are the conclusions from study IMP 20317? The conclusions are that a single 41-patient study demonstrated that subcutaneously administered recombinant human growth hormone at the dose of .1 milligram per kilo per day in co-therapy with glutamine and specialized oral diet reduces the total IPN volume requirement in patients with SBS. However, the clinical relevance of the primary endpoint, that is, the reduction in total IPN requirement per week, is uncertain, and we hope you clarify that for us.

I'd actually like to end my presentation by listing the four unresolved, up to this point I hope, issues. One is replicability; the next, generalizability; the validity of the primary endpoint of efficacy; further exploration of dosing.

Replicability ,because essentially this is a one-center, single study randomizing 41 patients. But it's important to reiterate, because the sponsor mentioned this,

that this is indeed the largest, the biggest study ever carried out in short bowel patients that has been published. There may be others which are the same number of patients or more, but from the published literature, this is the biggest.

Generalizability. The question is can one center be representative of the United States' short bowel syndrome population?

The validity of the primary efficacy endpoint. Again, this was the reduction in total IPN requirements? Should the primary endpoint be complete wean off IPN and lipid and hydration, or is this asking too much of the drug? Again, durability of response which can really not be assessed based on the data we have.

And the final question, is a low dose of growth hormone more effective based on the literature?

And that's all I have to say. Thank you very much.

DR. WOLFE: Thank you, Dr. Gallo-Torres.

Are there any questions from the panel of Dr. Gallo-Torres at this time? Dr. Cara.

DR. CARA: Can you comment on the 18-week follow-up data as it relates to sustained efficacy?

DR. GALLO-TORRES: Yes. At 18 weeks, only IPN requirements were measured, but these measurements were not

done throughout. This is only one point to one point. At the end of week 6, you have data. There's nothing in between, and then at week 18 you have that. What is missing is any assessment either at that point or throughout the 6 to the 18 weeks of SLE, the lipid requirements. The hydration data is also missing. Again, there were no hydration data collected from week 6 to 18. It was only IPN requirements at that particular point. So we feel that there are significant limitations to interpretation with these data. We don't feel these data are very useful.

DR. WOLFE: Ms. Cohen?

MS. COHEN: Yes. How important is the increase in body weight, lean body mass, fat mass, and bone mass in all of this study?

And since each diet is tailored apparently to each individual, in the real world how will the physician be able to do this in conjunction with medication?

DR. GALLO-TORRES: Well, I think this is a difficult question to answer in that the sponsor is presenting data using a set of endpoints which we are asking you to determine whether they are clinically significant or not.

The data in the literature have used nutritional endpoints, nutritional means. So you have

already heard that weight could be interpreted at least two ways. If the SBS patient is malnourished, therefore underweight, and maybe having marginal nutritional deficiencies, it might be important for that patient to gain weight. But the weight that should be gained should consist of lean body mass and some fat. So if that weight gain is due to fluid retention, that's probably not a good thing to do, and it is misleading.

It's a difficult answer for me because nutritionally the clinician is looking at the patient, and weight was mentioned before as one of the factors but not the only factor that the clinician uses to determine the progress of these patients.

So yes, one should look into the nutritional status of the patient, meaning there will not be vitamin deficiencies, the classical vitamin deficiencies, and so on. One should actually look also into quality of life for the patient and so on. Are these data in total IPN requirements, a reduction of that not because there's no complete wean from these data -- there are too few patients and the data are just preliminary. Are these data enough to make up for the nutritional requirements? I think that's one of the things we are asking you to discuss.

DR. WOLFE: That's what I was going to say. That's our discussion for the afternoon.

Dr. LaMont, you have a question.

DR. LaMONT: Yes. I wonder, since we're going to talk about generalizability and applicability, if we could hear some description of the study site, the main one. Is it a general hospital? Is it a CRC? Is it a nutritional center? Are patients in overnight and so forth?

DR. HOUN: The company can answer that one.

DR. GALLO-TORRES: Yes, right.

DR. LaMONT: That's what I thought, yes.

MS. JOYCE: Yes. We'll have Dr. Byrne answer that.

DR. BYRNE: The Nutritional Research Center is located in an assisted living facility so that patients had rooms that were not necessarily similar to a hospital base. So it was not a CRC setting. They had access to a kitchen and a home-like environment, again trying to make it applicable for them when they returned back to their home, wherever they were from throughout the United States. So the setting was assisted living, comfortable, not hospital-based, located outside of the greater Boston area in Hopkinton. There were very few nursing staff available. So it wasn't like what you would picture in a clinical research center or a hospital-based environment.

DR. LaMONT: And who determined the volume of

fluid? Was it the patient or somebody else?

DR. BYRNE: The volume of fluid that the patient --

DR. LaMONT: Intravenous fluid, yes, IPN. Was that determined by staff?

DR. BYRNE: The clinical team.

DR. LaMONT: So a nurse or a physician or a nutritionist?

DR. BYRNE: Physician, dietician, and nursing all involved.

DR. LaMONT: On a daily basis.

DR. BYRNE: On a daily basis we looked at the measurements.

DR. WOLFE: Dr. Shih.

DR. SHIH: Here we're discussing the primary endpoint for the efficacy. Now, just to be fair to the sponsor, I heard they were saying that in June 1997, FDA did agree on the protocol design, including dose and primary endpoint. So I would like to understand the rationale for that agreement between FDA.

DR. JUSTICE: Well, unfortunately, none of us were there at the time, so it's difficult to answer the question.

DR. HOUN: I think the Division of Metabolic and Endocrine and the CRO and previous sponsor discussed

that this endpoint was feasible. What we're looking for now is your advice on that. Sponsors and FDA come into agreement, but the reason why we have public airing is we also are looking for scientific expertise on what do you think about how we're doing this or what we've recommended. So we want your advice on that.

DR. SHIH: I understand. I'm not bound by the agreement. I will render my judgment on that.

But I would like to hear the rationale. There must be something on the FDA side that you thought that's agreeable.

DR. HOUN: I think some of it dealt with we are looking at a very difficult to study population. It's hard to recruit. It's hard to follow these patients in a controlled setting. If we wanted reliability in measurements, we felt that they had to be institutionalized, and to keep people institutionalized for how many weeks, how long for follow-up, those are things that lent to some of the practical considerations. I think the sponsor, if there are other issues that were limiting, can contribute too.

DR. WILMORE: I was there and we presented preliminary data to the Endocrine Division, and the Endocrine Division looked at the data and looked at the number of patients that would need to be studied and said

5, 5, and 15.

They also said they wanted a 2-week control period to bring the patients in to assure that they were stable before any sort of change was done, and that required some sort of an in-patient sort of care. We chose a residential facility. This particular facility has a nurse present to take care of all the patients. It's a 350-bed facility. We had 8 apartments. The patients hooked up their own IV infusions. They had a cafeteria-like kitchen to select food from and the like. That was agreeable and acceptable to the FDA.

And we also were told by the Endocrine Division that one study site was acceptable. After a year or so and, in fact, after the study was started, we received a letter that a second site would be necessary.

We came back, as has been previously mentioned, to the agency asking for this particular design that you have seen which increased the number of patients from 25 to 41.

DR. WOLFE: Doug, was the population and the study center at Nebraska similar to the one that you utilized?

DR. WILMORE: It's similar. It's an assisted living facility that the State of Nebraska has built next to their university hospital. It's probably one of the

nicest facilities in the country. So families and chronic care patients or post-operative patients stay there so they have in this facility a nutritionist and a nurse to be on call for the patients to deliver therapy. Our particular nurse gave growth hormone and drew bloods. That's primarily what her function was. And the University of Nebraska is the same.

DR. WOLFE: Are there any similar such -- there have to be other centers like this throughout the United States. I realize you have a very sophisticated one. These are very difficult studies. But there must be other centers to call upon to do these types of studies.

DR. WILMORE: Well, we don't envision these studies being done in this kind of setting. Recall that when growth hormone was approved by the FDA for short-stature children, that the home care services were really employed for the delivery of the drug and the monitoring of patients. And that's a very nice scenario for how this could be woven out to the countryside.

DR. WOLFE: That was actually my next question. Why didn't you do it that way?

DR. WILMORE: Simply because of the monitoring that was requested by the FDA. We can't have it both ways. We can't --

DR. WOLFE: Yes.

DR. GOLDSTEIN: I think it's necessary to remind everyone that this was an orphan drug, an orphan indication. Dr. Houn mentioned it and Dr. Gallo-Torres asked an important question, the rest of the population. I think to repeat a study like this is going to be extraordinarily complex.

Two weeks ago, I attended, by request because I am a pediatrician, a previous growth hormone presentation. The safety issue was easily, I think, disposed of, as indeed you have here. But I think it's important for everyone to remember -- and I'd like to hear if the company has further information on the description of the U.S. population. But it is by definition a rare disorder and I think everyone has to keep that in mind in terms of replicability and other things that have been mentioned.

DR. WOLFE: Do you have a question of Dr. Gallo-Torres?

DR. GOLDSTEIN: Actually it's a request for a further description of the population at large which, of necessity, this committee and the agency will have to address in their considerations. Just how large, Dr. Spilker or others, is the population?

MS. JOYCE: I think what we did earlier in the presentation was indicate -- and we've had a couple of references. We did do a reference check and a prevalence

check when we originally submitted the application for orphan designation and we did some subsequent follow-up. I could find that reference for you. But certainly around the magnitude of 10,000 patients in the entire country, perhaps slightly more than that, that are on PN for short bowel syndrome.

DR. JUSTICE: Can I just ask a question? Over here.

DR. WOLFE: Yes. I'm sorry.

DR. JUSTICE: I think the question about the discussions over the endpoint wasn't addressed. Perhaps the company could talk about what the discussions with the Division of Metabolic and Endocrine were about the primary endpoint. Why was it chosen as opposed to other alternatives?

MS. JOYCE: Well, given the fact that I personally wasn't at the meeting, I'm going to have Dr. Wilmore comment on that. I can tell you that I've done an exhaustive search of all the documentation and, in fact, when we had our pre-NDA meeting with the Division of Metabolic and Endocrine Drug Products, they also said what additional information might you have on file that could fill in some of the discussions.

With respect to the primary endpoint, there was no indication at all in any of the documents that we have

from the agency that the clinical relevance of the primary endpoint was in question. But I can certainly have Dr. Wilmore speak to that more specifically.

DR. WOLFE: Actually this is so important. I'd rather, Dr. Wilmore, have you give it right before we discuss this because I want it to be fresh in our minds when we discuss because, again, I think the points you make about moving targets are very, very important. So I want you to have every benefit that you can have in this discussion later on.

We have a question over here.

DR. SWENSEN: Yes. I had a question about the patient population or a comment actually. I don't think anybody really knows the figures and they vary rather broadly.

But one of the characteristics that's often omitted when considering patient population is what percentage of the patient population has access to a really high standard of nutrition support. In light of that, I'm wondering from where you recruited the patients who participated in your study, and did they come from major centers that had established nutrition support programs and were subsequently returned to those centers for follow-up?

DR. WILMORE: In our country, in the United States, the figure is that about 55 percent of patients on

long-term parenteral nutrition are on Medicare/Medicaid insurance and the rest are privately insured. If you look at home care companies in this country, you'll find that almost all the patients are cared for by a single different physician. To say it another way, each doc only has one or possibly two patients. There are centers of excellence, Cleveland Clinic, Pittsburgh, Mayo Clinic, and the like. But throughout the country, there are only one or two patients cared for by a single physician. And that was characteristic of this study. 41 different physicians referred in 41 patients for this study. So they came not from big centers but from practicing physicians out across the country.

Now, the standards of care with these particular patients are really predominantly through a home care company and companies have particular standards and they're professional standards. So we can have some assurance that these patients were followed and cared for by a home care company who also has dieticians and nurses under their employ.

So that's the best information I can give you. These are not patients that came a quarter of them from the Cleveland Clinic and a quarter of them from some other place. They came from individual referring physicians.

MS. JOYCE: And in fact, if I could just add to

that, one of the objectives here, of course, in wanting to gain approval for this indication is to try to make this treatment more widely available.

DR. WOLFE: Dr. Cara?

DR. CARA: Which time point do you consider the study endpoint? Week 6 or week 18?

MS. JOYCE: Is that for us or is that for the agency?

DR. CARA: Either you or the FDA.

DR. GALLO-TORRES: Week 6. The first 2 weeks are a baseline, and the 2nd week to the 6th week is the experimental period. So it is a 4-week, 28-day treatment period. Is that your question?

DR. CARA: That's my question, but if the company is seeking a 4-week treatment period, what's the rationale for only a 4-week treatment period? If you're analyzing your data at 6 weeks, what you're doing is looking at efficacy of ongoing therapy. If you're looking at it at 18 weeks, then you're looking at short course of therapy and its longer-term effect. So it's a critical issue.

DR. GALLO-TORRES: I absolutely agree with you. It's a critical issue. Number one, most of the studies published in the literature are 3 to 4 weeks. Those were randomized, maybe crossover, well-designed studies. There

are other studies which are open-label which are maybe a little longer. But the question of durability, absolutely we agree with you. It has not been answered and needs to be addressed.

DR. CARA: Does the sponsor have a response to that?

DR. WOLFE: Does the sponsor want to respond to that?

DR. WILMORE: Please realize the first 2 weeks were a control period.

DR. CARA: Right.

DR. WILMORE: So from week 2 to week 6 is 4 weeks, and that's the period that we're requesting. It wasn't evaluated at week 6 if you start week 1 for treatment. It was evaluated at the end of the growth hormone treatment.

DR. CARA: Then why are you proposing a 4-week treatment period?

DR. WILMORE: Because we gave 4 weeks. That was the protocol.

DR. WOLFE: Do we have any more questions?

DR. SHIH: I have a question. In the morning, the company gave us some presentation of the review of relevant publications and also other experience. I'm referring to the slide 33 and 27 and so on. Has FDA or the

company done any meta-analysis in collecting the literature? That may help you to do some generalizability assessment.

DR. WOLFE: This time period really should be questions directed at Dr. Gallo-Torres about his presentation. If we want any further clarification during our discussion, we can always ask the sponsor. I guarantee you they're going to be here.

(Laughter.)

MS. JOYCE: Should we answer that now or later?

DR. WOLFE: Why don't you wait unless Dr. Gallo-Torres has something he wants to say about that.

DR. GALLO-TORRES: No. There were no data for that.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: Dr. Gallo-Torres, I'm going to ask you either for interpretation or some further feedback on the number of days of infusion because the delta for groups B and C, which is the active treatment and the control treatment arm, in your presentation was 3.9 days difference. In the sponsor's assessment where they looked at parenteral nutrition or lipid emulsion infusion, the difference is much larger.

The question I have in my mind is it would seem to me that if the number of days of infusion is only 1 day

for the lipid emulsion and parenteral nutrition rather than fluids, it's conceivable, is it not, that with more careful rehydration, perhaps with oral rehydration solution, one might be able to achieve an even greater response to treatment with the growth hormone combination treatment?

In other words, I guess I'm asking you perhaps to put in perspective for us whether the difference that we're seeing with parenteral nutrition overall, as you have assessed it, kind of devalues the important change which the company presented this morning in slide 54 which was like a 4-day difference or 4.5 days. So do you have any comments on that?

DR. GALLO-TORRES: Yes, I have a couple of comments, but I'm also going to ask Dr. Price to comment on that.

Comment number one, even though we are talking about a week, the mean number of days that the patients were getting IPN was already less than 7. It was anywhere from 5 to 6 days.

Number two is that what you're referring to are the results of the co-therapy -- that is, growth hormone plus glutamine -- versus the control. With growth hormone alone, there is only a 1-day difference. Only 1 day less. I'm going to stop there and see if Dr. Price would like to add something.

Do you have additional questions? Okay.

DR. WOLFE: If there are no other questions, we'll break now. It's 12:15. We're a little behind schedule. That's okay. There are only two speakers in the open forum. They don't take an hour. They take about 10-15 minutes. So I'm changing lunch to lunch and a rest room break as well. So we'll do about an hour and 5 minutes. How is that? So we'll come back here at 1:20 and resume the afternoon session. Thank you.

(Whereupon, at 12:15 p.m., the committee was recessed, to reconvene at 1:20 p.m., the same day.)

AFTERNOON SESSION

(1:25 p.m.)

DR. WOLFE: Good afternoon, everybody. We'll start the afternoon session, and we will start with the open public hearing. We have two speakers. And again, in fairness to everybody else and the panel members included, we ask that you mention any previous or current financial interest which may be considered a possible conflict of interest. So we'll start with Ms. Brenda Boblitt.

MS. BOBLITT: My name is Brenda Boblitt and I'm here to represent myself. I have no compensation from anyone else. I'm here to represent myself and other people with short bowel syndrome.

I've had short bowel syndrome for 3 years and 8 months, after having a car accident where a seat belt cut me completely in two except the skin and the spine, and other multiple injuries. I have 75 centimeters of small intestine and two-thirds of my large intestine.

Prior to receiving treatment, I was infusing TPN 7 days a week. I was told I would be on TPN the rest of my life by four pieces of paper because once I came off of morphine after about 2 months, I realized that I wasn't quite what I used to be. A doctor handed me four pieces of paper. In reading that, it told me that I would be on TPN the rest of my life, gradually I would lose my job, my

friends, my kidneys, my bones, and everything else. And I was like totally shocked. So I realized that I had to do something because I wasn't ready to accept that.

The reason that it stood out is because it said if you had 100 centimeters, you can do it, but if you had less than 100, there was no way possible that you would be off of TPN.

This was a book that he was treating me with. I'm not blaming the doctor because this is all he knew. He had photocopied this from a text that was printed in 1994 which indicated to me right then that this is old news because I know how long it takes to do research and to get to press.

So I started to call friends. I had a friend that is a doctor in San Francisco who is a surgeon and she said glutamine. That's the first time I had heard the word glutamine. Start doing glutamine. So I talked to the doctor about that and he says, no, just people that are dying take that. And I thought, well, I'm almost dying from what you just handed me on these four pieces of paper. Then they thought I was crazy to see a psychiatrist.

So I proceeded to go outside the system. I was with an HMO, which is Kaiser, which is very, very good. I'm very thankful to be with Kaiser. It's because they were not knowledgeable how to handle my situation of short

bowel syndrome.

So I went to another doctor at USF, and he suggested that he had a patient with short bowel syndrome and that a diet was very important and that growth hormone would help me also. I said okay, but I had no direction, no one to really tell me how much to do or how much did I beg for it from Kaiser or how I should handle the situation.

Then the next magic word was Nutritional Restart Center. So at that time -- and this is when I was dragging my tubes and all the other tubes was in me to San Francisco knocking on doors there outside, paying out of my pocket for services, trying to find help for short bowel syndrome.

So on March of 2000, 5 months after resection, I was treated at the Nutritional Restart Center where I received growth hormone, glutamine, and a diet therapy for 24 days. When I was admitted to the NRC, I was on it 7 days a week. When I left, I was totally, completely off TPN. I lost 8 pounds after I left, but that was fine because I thought I was a little heavy anyway, and I always wanted to be 118 and that's what I have managed to be ever since that I have left. I've never been back in the hospital. I have not been back on TPN. I've not been hydrated with therapy.

The program was very, very successful for me. I work. I dance. I do everything everybody else does except I get to eat a little bit more than you do, but certain stuff. It's not easy living with short bowel syndrome, but it's a lot easier without TPN living with short bowel syndrome.

I eat approximately four meals a day. If I want five, if I want six, I can eat. I take approximately 37 vitamins a day. I do about 30 grams of glutamine. I do a D shot every month. Every other month I do a B12 shot. I have a glass of wine with dinner every night and sometimes two. And protein, complex carbohydrates, and unsaturated fats is my diet. Today for lunch I had a steak sandwich and about five pieces of bread. Of course, I had to take off the lettuce and the tomato and leave the French fries there.

But what I am here for, we need more centers. We need more help for people with short bowel syndrome because a lot of people do not have a determination that I have. I have met these people. I've been with them, and they just even talk different with short bowel syndrome. And there's no need because if they get the help which -- what worked for me is therapy and diet. Diet is very important, and the other things that go with it, glutamine and growth hormone.

After I left the Nutritional Restart Center, I had only one other treatment of growth hormone. I chose to have it because I wanted to build muscles. I was at the gym and I wasn't get any muscles. So I took a few shots of that.

I want to thank you all for allowing me to speak.

DR. WOLFE: Can I ask a quick question? You said you paid out of pocket.

MS. BOBLITT: No. What I did was when Kaiser was going to release me to go to home care and have a nurse to come to see me, I said, no, just send me to a rest home. I went to the rest home and I laid there for 11 weeks begging to go. I said you're going to save money if you get me off TPN. You're not showing me how to eat because the first thing they told me to eat when they pulled my tubes out and all this is have anything you want. I had a turkey sandwich and I almost died in pain. Actually I thought, God, if you want me to live, I can't live like this. But I went to the rest home and I stayed there 11 weeks and pretended it was my hotel and that I would get off of TPN.

So finally, they paid for me. Kaiser -- I don't know if you all are familiar with Kaiser -- paid for me to go to Nutritional Restart Center. The other places

that I went to see the other doctors I paid for out of my pocket.

DR. WOLFE: It was the physicians you paid for, not the drug.

MS. BOBLITT: The physicians, yes. But like all of my stuff now, Kaiser doesn't pay for like glutamine or any vitamins, none of my nutrients. I do no drugs. I take no drugs, no Prozac, nothing except vitamins. I eat mainly organic, not that everybody can do that, because you can eat other things.

But Kaiser pays for nothing except my blood draws. I have a major blood draw once a year. It was, when I first got out, about every 3 months, but once a year I check everything out. Kaiser is glad to do that because I'm low maintenance. I mean, I'm no expense to them. I want to be well. Then if I'm down a little bit, then I boost up my D. And that's the way you find out because with short bowel syndrome, you have to measure yourself at all times, your blood.

DR. WOLFE: Are they doing bone densitometry on you?

MS. BOBLITT: Excuse me?

DR. WOLFE: Are they doing bone densitometry?

MS. BOBLITT: I don't understand the question.

DR. WOLFE: Bone densitometry.

MS. BOBLITT: Oh, yes. I have bone density. I have had some loss of bone. Let's see. I've had it checked twice and it's gradually deteriorating, yes. But that comes with short bowel syndrome. I know that.

And I'll be glad to answer any questions you have about short bowel syndrome.

DR. SHIH: Can I ask you, were you 1 of the 41 patients in the study they reported here?

MS. BOBLITT: I'm not sure, but I saw someone that was dismissed at a certain date. So I could be. I don't know. When I went there, I didn't know basically anything was going on. I trusted the people because I had nobody else to trust, and it never dawned on me -- no. No, I'm not in the study.

(Laughter.)

MS. BOBLITT: I don't know.

But if there are any questions about short bowel syndrome. It's 24-hour maintenance. It is not easy. It's not easy.

MS. COHEN: I'm a consumer member, so I'm very curious to know where you got your growth hormone.

MS. BOBLITT: I don't know. Kaiser got it for me. I got on my knees.

MS. COHEN: They provided it for you.

MS. BOBLITT: They paid for it, yes.

MS. COHEN: What was your experience, though, as a consumer trying to get help for your syndrome? What happened and could you get help? Was there understanding? Were people able to tell you diet?

MS. BOBLITT: They don't know, no. Nobody knows and they still don't know. My doctor -- I go in now. I call him my PR person and he knows. He says, Brenda, I know nothing about short bowel syndrome. You're the only patient I got. You're the only one in Kaiser. You're the only one in this facility in the Napa Valley which is where I live. He doesn't know. He has to do what I tell him to do or what I ask the Nutritional Restart Center. If I call and ask, they will answer any question I have and make recommendations.

MS. COHEN: Now, did you figure out your diet yourself?

MS. BOBLITT: No. The Nutritional Restart Center.

MS. COHEN: What kind of diet are you on?

MS. BOBLITT: Complex carbohydrates, protein, and unsaturated fat, polyunsaturated, mono-unsaturated, and complex carbohydrates. That's bread, rice, pasta. No simple carbohydrates.

MS. COHEN: Do you think that's an essential part of your --

MS. BOBLITT: Absolutely. Believe me. I was up all night last night because I cheated yesterday.

MS. COHEN: I do all the time.

MS. BOBLITT: And I didn't cheat today at lunch. I took that tomato and I took that lettuce. I took everything off because I paid for it all day because if you cheat, you stay in the bathroom and it can be very painful. You get things called fissures. I mean, it's very painful. So you don't want to cheat.

MS. COHEN: Other than talking about growth hormone, what would you wish for consumers if they have this? What would you want us to do to educate consumers about what they should do?

MS. BOBLITT: Well, first of all, they don't know where to go and the doctor doesn't know either. So no one tells them, so they just keep on TPN. The knowledge has to get filtered down because not everybody has computers or access to computers. Not everybody has money to go and do some of the things that I did. But that's why I'm here. There needs to be a facility for that, but if there are only 10,000 that have the situation, it will probably be a slow process.

MS. COHEN: What did they tell you about growth hormones? What did they tell you what you can anticipate? Did they know anything about it? Did they know if there

could be future problems?

MS. BOBLITT: Before I got -- I read the literature there. I don't remember what it said because I knew whatever they were going to do was -- there's always pros and cons in taking an aspirin, taking --

MS. COHEN: But did they discuss it with you?

MS. BOBLITT: Yes.

MS. COHEN: And what did they tell you? Can you remember?

MS. BOBLITT: I don't remember. No.

MS. COHEN: Okay, thank you very much.

DR. WOLFE: Did they tell you to drink wine?

MS. BOBLITT: No, but you know what? I'm in the wine business, and when I went there --

(Laughter.)

MS. BOBLITT: -- every day I walked to the wine shop and bought a bottle of wine and put it on the table. And all these short bowel syndrome people would look at me going, I can't believe she's doing this. But every night I drank wine and I still do.

DR. WOLFE: Well, Serono should consider getting wine as part of the diet with glutamine added to it.

(Laughter.)

DR. WOLFE: We have one more. Does anybody

have any questions? I'm sorry.

Okay. Dr. Thomas Ziegler.

DR. ZIEGLER: Thank you. I'm here as an interested citizen, investigator, and clinician. And let me just give you some background real briefly. I just have a few brief comments. I'm Associate Professor of Medicine at Emory University. I also direct the GCRC at Emory University Hospital. And just by way of disclosure, Serono did support my trip to come down here, my travel arrangements.

And I have an RO1 from NIDDK to study mechanistic aspects of growth hormone in humans and animal models. It is supported partially by Serono. As you know, research in recombinant drugs is impossible without the cooperation of industry. So these types of studies are not possible without industry support.

I'm also involved in studies, have been involved in studies with KGF and GLP-2.

I really just want to reiterate a few comments I think Dr. Wilmore brought up very succinctly. There really is no good therapy for this disease and these patients have, as we just heard, significant morbidity, and there's actually very, very high mortality in these individuals, in part as a function of how much bowel they have, et cetera, and the etiology of the bowel disease.

Those of us who have been doing specialized nutrition support -- and I've been doing this for 17, 18 years where I really focus on nutrition support and bowel rehabilitation -- know that even a small decrease in the length of time the patients have to infuse, particularly the number of days they have to infuse, is really clinically significant, particularly for the patient, but also because there are lots of data that do show that the significant side effects that we heard about and those of us do nutritional support for a living have to deal with all the time are directly related to the amount of days the patients have to infuse.

I wasn't involved in the design of the study or in the interpretation of the data, et cetera, but what impresses me the most about the data for me is really the number of days of infusion. I don't think that was their primary endpoint. I think it was the infusion volume, but even the reduction of a day or 2 to me as a clinician I would consider extremely highly significant.

Again, there are data on the quality of life. Clearly, the cost we've heard about and all these horrible complications that seem to be related to the TPN burden. So my argument would be that that seems to be a clinically important endpoint.

Dr. Wolfe, do you have a question?

DR. WOLFE: Yes, I have a question for you. Do you have the means to do these kinds of studies yourself?

DR. ZIEGLER: I'm sorry?

DR. WOLFE: Do you have the means and the ability to do these kinds of studies in your CRC?

DR. ZIEGLER: I have an RO1 basically that has animal and human models of short bowel syndrome. And you can do these studies in the GCRC setting, obviously.

DR. WOLFE: But do you have an out-patient facility in Atlanta analogous to the one in Hopkinton?

DR. ZIEGLER: I'm sorry. In terms of what they had, it was more or less the Nutritional Restart Center. I believe that's a very unique type of center. I don't know if they could speak to that. That and the center in Omaha I believe are the only centers of that type. Of course, a GCRC setting, of which there are 75 or 80 GCRCs, is another potential setting for these.

DR. WOLFE: These questions I'm asking very specifically because of the generalizability of the results because you have a very controlled setting versus a non-controlled setting. That's why I'm asking these questions. Could you do these kinds of studies? You have patients with short bowel syndrome. Could you do these kinds of studies by having your patients as out-patients and then having them come in periodically for testing?

DR. ZIEGLER: Yes.

DR. WOLFE: Do you have that capacity?

DR. ZIEGLER: I believe so.

DR. WOLFE: Do your colleagues in nutrition have the capacity to do that?

DR. ZIEGLER: I believe so. I mean, as was pointed out by Brenda, a modicum of dietary instruction is important in my opinion as a clinician and researcher. But those are relatively straightforward recommendations that could be made. So I believe that these studies could be done in an out-patient setting.

DR. WOLFE: Any questions for Dr. Ziegler? Ms. Cohen?

MS. COHEN: The funding that you receive from the company -- what do you do with that funding? What kind of research?

DR. ZIEGLER: Well, the funding that I have received from Serono -- the history of it is that when I was a young faculty member at Emory, I applied for a CAP Award, which at that time was an award given for junior faculty who were interested in doing GCRC based research and I was very interested in looking at mechanistic aspects of growth hormone in people with short gut. So I received study drug and a modicum of funding to allow the study to get going. My salary in part was paid for by the CAP, but

then when I got my RO1, again that provides the bulk of the funding for the current study that I have going on.

MS. COHEN: Is it with growth hormone?

DR. ZIEGLER: It is.

MS. COHEN: And DDK?

DR. ZIEGLER: NIDDK funds that. But again, I do receive study drug and I did receive a modicum of funding from industry which is quite usual I think in these types of studies.

MS. COHEN: Thank you.

DR. ZIEGLER: With regard to maybe Dr. Wolfe's question, can these types of studies be done on an out-patient basis? Yes, but again what they did and what some of us are doing with growth hormone and other agents -- I mean, clearly in a GCRC setting, when you have the ability to control the diet -- and I think the nice thing about their design was that people come from all walks of life into the center, and they made sure that the patients were not malnourished because in part patients may not respond if they're malnourished. So they had this 2-week lead-in period which I think is sort of an in-patient setting that was an advantage I would say.

DR. WOLFE: Dr. Camilleri, then Dr. Cara.

DR. CAMILLERI: Dr. Ziegler, perhaps you could give us some more information about clinical relevance here

because I think you made the excellent point that the number of days of infusion may determine the risk-benefit of total parenteral nutrition. I'm wondering, with your expertise, could you draw on some of the data from either Lynn Howard's work or the Oley Foundation to put in perspective for the advisory committee or to translate perhaps what does a 2-day less of infusion per week translate to? What might you anticipate would be lower complications so that we can understand the clinical relevance.

DR. ZIEGLER: That's a great question and I'm glad you brought up the Oley Foundation. I was invited to speak there actually last week, and it was the first time I was there. It's a foundation for adults and children with short gut basically and other forms of intestinal failure, but it's primarily short gut. I found that very moving in a way to really talk to all these patients and talk to them about their quality of life and what works for them. They were peppering me with questions. This is a group with a significant burden on their life in terms of their morbidity and just what they have to go through.

For them, every time they access that port, there's a risk. As Dr. Wilmore pointed out, catheter sepsis is a risk. The overall intake of TPN seems to be a risk factor for liver dysfunction associated with TPN. So

the total TPN burden. The ability to increase your oral intake, as I believe they showed in this study, seems to be associated with decreased infectious complications but particularly liver dysfunction in part.

So I look at it as kind of just a proportional thing. If you're on 7 days a week and you're cut down to 6 days a week, I don't think there's any amazingly super strong data on the complications as a function of 1 day versus 1.5 days versus 2, but there's a lot of data that suggests that the overall TPN burden and the number of days does relate to complications. So if you're able to reduce your complications by one-seventh, when you have this significant incidence of complications, to me that is a very clinically relevant factor.

In talking to patients throughout my career and in talking to the patients at Oley, et cetera, it makes a big difference to be able to go from Monday, Wednesday, and Friday and be able to take Saturday night off, for example, in terms of quality of life and ability to do things with family, et cetera. As a clinician, I would say that it's proportional to the degree, but even 1 day to me would be significant improvement.

DR. CARA: As a pediatric endocrinologist, my own experience is that when we see a youngster who we think that clinically would benefit from growth hormone therapy,

even though it may not be specifically approved for that indication, we find ways of getting that patient growth hormone.

How available is growth hormone for individuals with short bowel syndrome?

DR. ZIEGLER: At present? It's approved for a number of indications, as you've heard, including catabolic states, other catabolic states. Physicians can prescribe it off label. But it's not free. And so some of us have occasionally written to insurance companies in a non-study situation where we thought we would try it in somebody, and rarely do they approve it. And if they do, they might approve it for 2 weeks. But I haven't done that particular attempt in about 10 years personally, but in the past as a clinician I have occasionally written letters to insurance companies. But most of the time they have said no. And if they say yes, it's like for -- I think I had two patients where they agreed to let me do it for a couple of weeks or something like that. I don't know if that answers your question.

DR. WOLFE: Dr. Levine, then Mr. Swensen.

DR. LEVINE: I have a leading question. First, you seem to have a great deal of experience over a decade. Approximately how many patients have you treated with TPN alone without necessarily growth hormone?

DR. ZIEGLER: How many patients have I cared for --

DR. LEVINE: Yes, because most of the gastroenterologists I would guess around the table, like myself, have treated a handful a year or less. But I wonder what your experience is.

DR. ZIEGLER: I mean, I run the nutrition support service at Emory and we have 40 home patients, some of which are on tube feeding. But I cared for hundreds of patients in the course of my career.

DR. LEVINE: And of that number, how many have you treated under experimental means or otherwise with growth hormone over the years?

DR. ZIEGLER: That's a good question. In the context of my current study, it's currently blinded. It's still blinded, and I've treated about 24 patients in a double-blind, randomized trial.

DR. LEVINE: So this is recent. You don't have any previous treatment years ago with --

DR. ZIEGLER: I have previous experience working with Dr. Wilmore's group. I did my fellowship at the Brigham with Doug and was involved in the early studies. I believe on the references, you see my name on some of those. So I have a significant amount of experience --

DR. LEVINE: If it's blinded, you can't answer the question.

DR. ZIEGLER: -- not nearly as much as they have with the Nutritional Restart Center.

DR. LEVINE: How often have you been able to -- if never is the answer -- how often have you ever been able to stop a patient on TPN who's had indications to be on TPN with short bowel? Have you ever been able to spontaneously stop them over time?

DR. ZIEGLER: That's very difficult. Again, you might consider me biased because I have been involved in the pilot studies that were unblinded and I have a current NIH-funded blinded study going on. But it's very, very difficult to wean these patients off of TPN. You try your best with diet. Again, my bias is that additional factors are needed to help facilitate what you can potentially do with diet.

DR. SWENSEN: Dr. Ziegler, I'd like to ask you a question about the availability of clinical expertise to home parenteral nutrition patients.

You mentioned Oley. I'm also affiliated with Oley. I've been with Oley for approximately 12 years and I'm presently the president of it. The good thing about that is that it has enabled to meet quite a few hundred people who have short bowel syndrome and to talk with many

of them.

My distinct impression is, certainly I'd say it's universally accepted within that community, that clinical support, especially for new patients, is often very inadequate. They don't have access to the kinds of resources that they need to have a reasonable hope of a good, smooth transition to TPN. I think Ms. Boblitt's comments suggest as much as well.

If growth hormone were generally available for use throughout the country on a broad basis, do you think short bowel syndrome patients would have adequate clinical backup by people with expertise in nutrition support?

DR. ZIEGLER: I think that all the home TPN patients are covered by what, by and large, are extremely competent home health care companies. They have expertise in monitoring the patients and stuff. So the basic safety issues with regard to monitoring the potential side effects -- I'm sorry -- monitoring the patients -- you know, when they have a fever, they send them into the hospital, et cetera. Those are covered.

It's definitely true, as all you physicians probably know, that we don't get wonderful training in nutrition in medical school. So there's definitely a disparity among knowledge of physicians in the general community.

However, I think increasingly clearly GI physicians and surgeons are aware of this bowel rehabilitation concept that basically has begun by the Boston group. Gastroenterology, as you saw, just published a big review on short bowel syndrome. I think that the overall community of gastroenterologists and specialists who tend to care for these patients could use this agent effectively. Specialists exist in all fields and there are specialists obviously in nutrition support. So, I mean, I don't know if that really answers your question.

DR. SWENSEN: Just a quick follow-up. I think both you and -- earlier the suggestion was made -- Dr. Wilmore I think made it -- that it's the home care company that actually would provide a significant measure of this expertise. I infer from that that you do have some reservation about the availability of the top quality clinical support at the hospital level.

DR. ZIEGLER: I think that in clinical care throughout the country in any discipline there's variability. So I don't know that for any agent -- I mean, I think growth hormone was just approved for short children a couple of weeks ago or something like that. I mean, I don't know that every pediatrician, for example, would refer their patient into a pediatric endocrinologist for that in that regard. So I think that's a tough question.

If your question is, is there an equal playing field among physicians about knowledge in nutritional expertise? The answer is no.

But I think that it's increasingly disseminated out there to physicians, particularly gastroenterologists and surgeons who do nutrition support, how to feed these individuals. And there's lots of data in the literature. There's lots of data presented at Oley, for example, and on the web as far as that goes. I'm not sure if that answers your question.

DR. WOLFE: One last quick question, Ms. Cohen.

MS. COHEN: Do you use glutamine or do you use it in conjunction with GH? And do you study the lean muscle mass and the body mass of those patients that you have?

DR. ZIEGLER: I don't use glutamine in my current trial because my trial is focusing primarily on the efficacy of growth hormone in combination with a modified diet. I mean, I was involved in studies with growth hormone and glutamine earlier, and setting on a new career path, I'm interested in underlying mechanisms. So in my particular study, we're not asking the question of the combination of glutamine and growth hormone. We're asking simply the question of mechanisms of growth hormone in animal and human short gut. And we are doing DEXA and BIA.

So we're looking at lean body mass.

Again, that's very well established in the literature that growth hormone enhances lean body mass in a number of settings, including a number of studies in short gut. That would not be a surprise.

DR. WOLFE: That's why it's called growth hormone.

(Laughter.)

DR. WOLFE: Thank you, Dr. Ziegler.

We'll now move on to the rest of the afternoon, and Dr. Robert Justice will lay out to us our charge for the rest of the day.

DR. JUSTICE: What I'd like to do actually is briefly go through the questions prior to the committee's discussion to orient you to the issues that we have raised.

Before I do that, I'd just like to say in response to the discussion prior to lunch that we acknowledge that the company was given advice by another FDA division, and years later we have raised the question about the primary endpoint. But I'd like to emphasize that we've not reached a conclusion about the endpoint. Our intent is to seek the committee's best advice based on the science.

If I could have the first question. The first question is that the primary endpoint of the study was

change in total IPN volume from week 2 to week 6. Pairwise comparisons of the results of the primary endpoint yielded statistically significant differences between the recombinant human growth hormone-containing arms and the control group. Are the findings in the table in the next slide clinically meaningful? In your response consider the definition of primary endpoint and the duration of the study treatment.

You've all seen this slide twice, so I think we can skip to the next slide.

The second question is that the secondary endpoints were change in total IPN calories and change in IPN or lipid frequency. Pairwise comparisons of the results of these secondary endpoints yielded statistically significant differences between the recombinant growth hormone-containing arms and the control group. Are the findings in the table on the next slide clinically meaningful?

And again you've seen this slide twice, so I think we can go to the next slide.

The third question is changed a little bit from the handout just for clarity. The primary endpoint was change in total IPN volume. Only one of the three components, the IPN volume, was recorded at week 18. Is this measurement of IPN volume alone adequate to

demonstrate durability of effect? If not, what do you recommend as a minimum follow-up period?

The fourth question is that the data were primarily derived from a single nutritional support tertiary care center. Are these data generalizable to the population of short bowel syndrome patients? And there's already been a lot of discussion of that issue.

The fifth question is, are there specific safety concerns considering the potential for long-term use of recombinant growth hormone in the treatment of short bowel syndrome patients?

And finally, do the data support the safety and effectiveness of recombinant growth hormone alone or in co-therapy with glutamine in patients with short bowel syndrome? Are there additional studies that you would recommend, such as dose-finding? And I would add this could be either pre-approval or post-approval.

Thank you.

DR. WOLFE: Thank you, Dr. Justice.

For those of you who have been to these meetings, a lot of times I change the order of the questions, but I'm not going to this time because I think the order is perfect and really addresses the issues, at least in my view, and how they should be addressed. So in this case, I'm not going to do much speaking. I'm going to

sit back and listen to you. I'll speak last.

But we're going to start with the first question at that end of the table. We'll go around. The next time we'll start at this end of the table and go down. So we'll start with Dr. Goldstein. Would you like to say something to start off?

DR. GOLDSTEIN: Yes. The issue in one sense can be framed in the following way. Growth hormone has been approved for long-term use in children recently and, indeed before that, in other ways as well. What the sponsor is requesting here is a 4-week course of therapy which may not have to be repeated. Indeed, I think one needs to look at it that way.

Now, I happen to have a daughter with Crohn's disease who has lost part of her bowel and who, in fact, was on total parenteral nutrition for a year with a couple of near misses with hospitalizations for a variety of reasons. And I think any reduction in the daily burden of that therapy at small risk, as demonstrated both by the previous advisory committee and as was demonstrated here, should be seriously considered.

Thank you.

DR. WOLFE: Thank you.

Dr. Mangel?

DR. MANGEL: Looking at the data in the slide

that Dr. Justice put up and taking into account the comment of Dr. Camilleri in which at baseline there was an imbalance between the groups with, at one level at least, group C being unfairly prejudiced at baseline or perhaps the individuals appearing a bit sicker, however, my understanding of the various statisticians, their comments were that when that is corrected for, the treatment effect still remains. I do consider the magnitude of the difference, considering the statistical input, at least my understanding of what was said, clinically significant.

When I look at that endpoint, as well as the percent of individuals which were able to come off of TPN, and recognizing, once again, it's a very small number, as Dr. Gallo-Torres pointed out, and looking at it in conjunction with several of the other endpoints, I do consider it clinically relevant.

DR. WOLFE: Thank you.

Dr. Cara.

DR. CARA: I think this is a very complicated question actually. I guess maybe I'm reading too much into it, but it gets back to the whole issue of what is significant weight gain as it relates to nutritional status versus fluid status and are they necessarily different, are they the same, and how can we gauge one or the other. And I don't know that I know all the answers to those. I

haven't, at least, seen enough data to make any conclusions about what happens to water weight gain versus body weight gain versus lean body mass. I know that growth hormone does increase lean body mass. I'm not sure that increasing lean body mass is necessarily our goal in treatment of short gut syndrome. Maybe one of you can answer that better than I can. But my concern is that fat loss might be fairly significant.

In terms of the total IPN volume from week 2 to week 6, I think that that is a clinically significant difference. My only concern is what happens subsequent to that and whether or not the total IPN volume that initially dropped is a reflection of water weight versus body weight. What concerned me especially was the weight loss after stopping therapy, which I don't think is trivial, by the way.

So I think if I answer this question the way that you posed it, my answer is yes, I think that it's statistically significant. I think it's clinically meaningful from what I've heard of people in the field and individuals that have either short bowel syndrome or have worked with individuals with short bowel syndrome.

But there are other issues inherent in the question that you haven't asked but I think need to be addressed somehow, and I don't know that we've gotten a

good sense of how to handle those other issues.

DR. WOLFE: Thank you.

Ms. Cohen.

MS. COHEN: Dr. Cara said some of it better than I possibly could, and I think they're on the right road. But I find the study inadequate. I find the study is not long enough. It was in an ideal setting. That isn't the real world and that isn't where the patients are going to be. So I think there has to be more study on nutritional status, and I'd like to know about glutamine and a better diet. I notice when they reduce the growth hormone, sometimes the patient reacted better. So I think that it's on its way, but I wouldn't be satisfied as a patient because I don't think they could answer enough questions for me. Thank you.

DR. WOLFE: Dr. Shih.

DR. SHIH: I really think that in terms of statistical analysis, they did a very good job in terms of a small number of patients and that's all you can do.

But considering the clinical importance of the primary endpoint, in many places we heard that, yes, it is clinically relevant, but I think that's all induction of possible benefit, for example, a decrease in mobility because of the total IPN volume. So you reduce the total IPN volume, you can increase your mobility. But we don't

see that kind of quality of life data. It doesn't have to be primary, but you've got to collect those data to associate what you're trying to make as clinically relevant. Can we find from the literature support for your induction that reduction of PN really gives you quality of life better?

DR. WOLFE: So when we talk about future studies, I guess you have one in mind.

Dr. Levine. There are no votes right here.

DR. LEVINE: My concern is in translating exactly what other people have said, the volume into clinical outcome. Clearly in this experimental ideal situation over a 4-week period of treatment, there's a difference. Does that, indeed, translate into year after year someone receiving growth hormone? I don't know. I would be cautious. I think you're pretty much at the level that we are with glutamine. When we get to that question, we can discuss it, but I think we're in a very unknown area as to clarity as to outcomes. Outcomes were not looked at in the distance, so that makes it even harder when you look to approve a drug that might be something in a microcosm, in a small area that you can't know who's going to be treating it outside of a clinical ideal research unit, what's going to happen. As pointed out by the sponsor, many individual doctors will get educated, but are they

going to be able to properly interpret improvement and are we going to have good data in the end? So I'm cautious mainly about the outcome based on this small area. I think there's some more work to do and I think it needs to be looked at.

DR. WOLFE: Dr. LaMont.

DR. LaMONT: I think this is precisely the right outcome that they measured and the results are clinically significant. In fact, if the sponsors came to us with improvement in quality of life and improvement in lean body mass but no change in TPN volume or frequency, I'd be unimpressed. I think this is what doctors and patients want. When I have patients on TPN -- I don't manage them myself, but I send them to somebody to help me manage -- I want to see them get off or get on less. I'd liken this to what happens to patients on home peritoneal dialysis or even patients on hemodialysis that have to come to the hospital three times a week. If they had to do it one day less a week, that would be a big plus for every single one of those patients.

So I think to focus just on this question, I think this is clinically meaningful. I have all the other concerns have already been raised and a whole bunch more, but on this question, I think this is the right endpoint and it's clinically meaningful.

DR. WOLFE: Thank you for mentioning focus because we are focusing on this question right now. Other questions will be answered later on. Thank you.

Mr. Swensen, on this question.

DR. SWENSEN: Focusing just on this question, I read the question on the issue of clinical significance here from two points of view. In the first instance, a reduction in total infused volumes is to me an objective and unquestionable advantage. On the flip side of that, there must be some corresponding increase in oral nutrition. Notwithstanding nuances of the weight question, I presume there must be some meaningful increase in oral nutrition. That being the case, I don't think you need a study to establish at least certain basic quality of life issues. The more normal a person's oral diet is on face, the higher the quality of life he or she will experience. So in my opinion, yes, the endpoint is clinically significant.

DR. WOLFE: Thank you.

Dr. Camilleri.

DR. CAMILLERI: Well, I think it's gone in the right direction. We've heard that the requirement of less intravenous nutrition days is probably important to the patients in terms of mobility, but I'm still stuck with the ultimate desire to reduce the mobility in these patients

down to 0 from parenteral nutrition. When you look at those data with 4 versus 4 versus 1, which we reviewed this morning, and the 1 being the control group in a much smaller sample size, I still am not convinced that the data from this study demonstrates the clinical significance that I would expect from an additional therapy.

DR. WOLFE: I just want from Ms. Joyce or Dr. Gertner either a nod or a shaking the head no. No big explanation. Was your endpoint that you discussed with the FDA before this endpoint?

MS. JOYCE: Yes.

DR. WOLFE: Okay. Then I'll start by saying just specifically on this question -- and I had mentioned this before, and I talk about other studies too -- when clinical researchers or any kind of researcher has a hypothesis they place forth, the endpoint that they are trying to achieve is discussed and established in advance. If the endpoint is achieved, is it proper for us to come back and say, well, it was the wrong endpoint that you should have gone for? In my view, the answer is no.

Also, in listening to Mr. Swensen -- I'm not going to violate HIPAA rules because his son is not my patient. He mentioned this. His son has short bowel syndrome. We also listened to Ms. Boblitt who mentioned also from their own experience a decrease in time spent

hooked up to an IV is very important to them.

So for those reasons and also -- again, I agree what Dr. LaMont said. You want to diminish the possibility as much, even if it's only part of the way, of being hooked up to TPN, being hooked up to anything, dialysis or anything else. So I think these endpoints are indeed significant.

Just one last comment I want to make is that just remember, for those of you who aren't gastroenterologists or people involved in digestive diseases, you are what you eat.

(Laughter.)

DR. WOLFE: The goal is in these patients to let them eat, let them assume a normal life as much as possible.

With regard to what Dr. Ziegler said, we are seeing more of a shift back to understanding -- gastroenterology fellowships now do require nutrition as a part of the fellowship training. So you will be seeing one of my fellows at Emory who is nutritionally trained, completely trained, and will be helping you out in that division.

So again, in my view I don't like moving targets. That was the preset goal and it was achieved, and therefore it's significant.

Any more discussion?

DR. SWENSEN: Can I just add one thing to that? Certainly it's important to decrease the amount of time you're hooked up to a machine, but the actual volume of the things you're infusing are themselves harmful. The more lipids you're infusing, presumably the greater the risk. The more calories you're infusing, the greater the risk of some sort of TPN-associated liver complication. It's not just a mobility issue. Certainly reducing the infusion volume is intrinsically beneficial.

DR. WOLFE: Any more discussion?

(No response.)

DR. WOLFE: We don't have to necessarily vote on every single question, but on this one, I would like to get a vote. And I can vote. I'm a member of this committee. So again, the question is are the findings in the table below clinically meaningful? If you think they are, please raise your hand.

(A show of hands.)

DR. WOLFE: If you don't think they are, please your hand now.

(A show of hands.)

DR. WOLFE: And I don't think there are any abstentions. It's 6 to 3 that the primary endpoint has been achieved, and it is clinically significant and

clinically relevant, as well as statistically significant.

Let's move to the next question, question number 2. I'll read it again in case some of you are suffering from a little bit of senior moments. Secondary endpoints were change in total IPN calories and change in IPN or lipid frequency. Pairwise comparisons of the results of these secondary endpoints yielded statistically significant differences between the recombinant growth hormone-containing arms and the control group. Are the findings in the table below clinically meaningful?

We will start this time on the other side with Dr. Camilleri.

DR. CAMILLERI: Well, to me this is in many respects a flip side, expanding upon question number 1. So I'm going to be just as consistent and say no.

DR. SWENSEN: I ditto that. It's the flip side, and I'm saying yes.

DR. LaMONT: Ditto, yes.

DR. LEVINE: No.

DR. SHIH: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: No.

DR. WOLFE: Dr. Cara.

DR. CARA: Can I ask for a clarification? You're talking about at the 6-week time point.

DR. JUSTICE: That's correct.

DR. CARA: Yes.

DR. MANGEL: Yes.

DR. WOLFE: And I say yes also, so we have a 6 to 3 vote on this one too. Because this is, in essence, the same thing, the same idea, same type of question.

We have to leave time for discussion. Do we want to discuss this question or did we discuss it in the first question? Do you want to move on to the third question?

The third question is different from what we have written, so I'll read it from the screen. The primary endpoint was change in total IPN volume. Only one of the three components, IPN volume, was recorded at week 18. Is this measure of IPN volume alone adequate to demonstrate durability of effect? If not, what do you recommend as a minimum follow-up period?

Dr. Goldstein.

DR. GOLDSTEIN: I'm sorry. I wasn't prepared for the question. Could you repeat it please?

DR. WOLFE: It's up there. I don't want to read it again. You can pass and we'll come back to you.

DR. GOLDSTEIN: I'll pass and come back. Thank you.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: If I could get a clarification. In the sponsor's briefing document on table 10, page 31, I at least certainly get the impression that at week 18 IPN volume, IPN calories, as well as frequency, were all monitored or measured, not just IPN volume. Could I find out if that is correct?

DR. WOLFE: Could you hold on one second? Could we get the slide back up there possibly? Is that possible?

DR. MANGEL: This is in the briefing document. I did not see a slide this morning. But in their briefing document, it suggests that more than the one parameter was measured.

DR. WOLFE: They do have a slide.

DR. JUSTICE: I think we have an answer while they're looking for the slide. I think they're not measuring total IPN volume which consisted of three components. They're just measuring IPN fluids. They're not measuring IV hydration or lipids at week 18.

DR. GERTNER: With your permission, Mr. Chairman, I'd like to try and clarify this point because I don't think we were successfully making it clear before.

DR. WOLFE: Can you be succinct?

DR. GERTNER: I'll be very succinct.

The contribution of SLE, or supplemental lipid

emulsion, to the final volume of fluid infused both at 6 weeks and at 18 weeks is very trivial. Only 2 patients were on it, and they were taking about 100 cc's per week of this product. So it's virtually not necessary to consider it.

With reference to hydration, there was a minority, approximately a quarter, of patients who were receiving hydration fluid at the end of the study, and the clinical burden of hydration fluid is far less and far less important than the clinical burden of parenteral nutrition fluid. Therefore, I believe that the described test point at the 18-week time point, which is TPN, parenteral nutrition as understood by gastroenterologists and nutritionists, is the endpoint which far and away conveys the clinical treatment and burden that these patients were undergoing, and that it's not really correct to say that we only presented one aspect of their treatment. We presented the main, predominant aspect of their treatment, and that's what you see in the chart.

DR. WOLFE: Thank you.

Dr. Cara, does that answer your question? Does that clarify things now for you?

Dr. LaMont has a question for you.

DR. LaMONT: I'm sorry. I don't understand the parameter in the slide. Could you put it up again?

DR. GERTNER: Slide on, please.

DR. LaMONT: Table 10. What does 0 mean? Does that mean no change? It means 0 change.

DR. KENLEY: Let me just tell you that the data during this period was very skewed. So what you're seeing up on the screen are medians.

DR. LaMONT: Oh, those are medians.

DR. KENLEY: They're medians, as well as the p values to detect them.

So just as a clarification, week 18, PN calories, volume, and frequency were collected at week 18. The only component of the primary parameter that was not collected was SLE and hydration fluid. As Dr. Gertner said, only 2 patients during week 6 had SLE. One of them had .2 liter during that week -- no, sorry -- .8 liter, and one of them had .02 liter. So that was basically negligible.

DR. LaMONT: I'm still a little lost. So the 0 there under SOD glutamine, n equals 9, means no change between week 6 and week 18. Is that what that means?

DR. KENLEY: Yes.

DR. LaMONT: So nothing changed. It was completely durable in each of the groups because they're all 0.

DR. GERTNER: Sir, there were changes, but what

we're showing here in this slide are the median changes, and if less than half the people have any change at all, the median is 0 because the change, which is equivalent, greater than that number or less than that number, was 0. There were changes in fluid volume. They were small and we do have a slide, which is unfortunately not in your briefing document, which we can show you if you wish to see it, which would take a minute or two to pull up.

DR. LaMONT: I'm sorry. I don't understand what this means.

DR. HOUN: If you saw the individual patient data, would that help you?

DR. LaMONT: Yes.

DR. HOUN: Do you have that?

DR. KOCH: This is Gary Koch, the statistical consultant. This display is addressing the change between week 6 and week 18 over which the claim would be there's little or no change. Previously you saw displays that compared week 18 to week 2, in which case you would have seen an effect still present at week 18 in comparison to the baseline at week 2. This is the difference between 6 and 18, and it's simply addressing the preservation of the effect that was shown between week 2 and week 6.

DR. HOUN: Do you have the individual patient data?

DR. CARA: That would be very helpful because if what you're showing here are the medians, that really doesn't give us a good perspective of what's going on.

DR. WOLFE: This is means.

DR. SHIH: No. They're medians but you can interpret it as means if you want to. It's the average, a way of measuring the average. But the essence of this, as I understand, as Dr. Koch explained, is that this is the maintenance effect.

DR. WOLFE: Can I have a clarification also? Are you even asking for a maintenance? This is a 4-week study. Basically these are extra data, aren't they?

MS. JOYCE: That's correct.

DR. WOLFE: Anyway, could you show the individual data? That would be very helpful.

DR. KENLEY: What you see here in the left-hand side are by treatment group. The first treatment group is the glutamine group. You have your 9 patients listed there in your glutamine group. The first three columns are their IPN volume.

DR. WOLFE: Can you use a pointer?

DR. KENLEY: Oh, sorry. I'm not very good with pointers, but I'll do my best.

This is the glutamine group, and then we have the 9 patients in the glutamine group. Then the next

columns are the week 2 values of IPN, SLE, and then the hydration volume. Then we have the week 6 values of those three parameters, IPN volume, SLE volume, and the hydration volume. And then we have the week 18 values over here, again SLE and hydration were not collected during that week.

But what you can see and what I was trying to say is that this slide just shows glutamine and growth hormone. The next slide -- but I don't want to go there yet -- shows growth hormone plus glutamine. But what you can see is that during week 2 there is no SLE. There is no SLE during week 6 for either of these treatment groups.

I guess you can show the next slide. There's no SLE at week 2. No SLE at week 6. I skipped one. There was 1 patient with .8.

DR. KOCH: All you really want to do is put your finger on the fourth column and the seventh column in each row and then let your finger go from the first row to the second row to the third row, all the way down the rows, holding the fourth column and the seventh column constant, and that will give you your profile of individual patient change between week 6 and 18.

DR. WOLFE: Could you give us the percentage real quickly of durability? It looks like the vast majority had a durable effect. If you compare column 4

with column 7, that would show you durability.

DR. KENLEY: Correct.

DR. HOUN: Can you explain why no one receives SLE? Is that standard of care?

DR. BYRNE: Supplemental lipid emulsion by itself is given just to treat an essential fatty acid deficiency. So it was only given to those patients who demonstrated an essential fatty acid deficiency.

The IPN, just regular total parenteral nutrition, the first column in each of the blocks, typically includes lipid emulsion in that infusion. So additional supplemental lipid is given only in the setting of a documented essential fatty acid deficiency, and that's why there are so few patients actually receiving it.

DR. WOLFE: Is it fair to say that out of the 14 patients here, only 2 didn't have a durable effect? Is it fair to say or ask out of the 14 patients in this group, this latter group, only 2 did not have a durable effect?

DR. GERTNER: That's correct.

MS. JOYCE: Yes.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: Can I ask whether you have these data in your document and where I can find them? And if not, would you be able to print them and let us take a look at them?

MS. JOYCE: The answer is that they're not in your document, and the answer is yes, we can print them and provide you with a copy.

DR. CAMILLERI: I have a question. If you can put the slide back on, the last slide we saw. One hasn't had time to study this very much, but can you help me determine in the clinical trial what characteristics led the investigators, for instance, in patient number 3, patient number 108, you list there, for instance, a 3-liter hydration volume but not an IPN volume. But your characteristics for determining fluid were predominantly based on hydration. Right? Your determination of how much parenteral volume you needed to give the patients were determined by the state of hydration of the patient, how much urine did they pass, et cetera.

So what determined in the course of the study whether somebody would get just hydration, which I would believe is just crystalloid, versus IPN which I would assume has nitrogenous compounds and carbohydrates? Can you help us with that?

Because you see, the same applies, for instance, with patient number 123, who is taking 8.7 plus 6 and then has only taken 4 later. So one questions the interpretation of this information in terms of the impact of the therapy.

DR. BYRNE: By week 6 of the study, we were locked into what we felt to be the patient's needs. So no additional weaning of parenteral nutrition went on during week 6. That went on during week 3, 4, and 5 based upon the pre-established weaning criteria.

The administration of hydration fluid that you see there was more typically related to something that may be occurring with the patient unexpectedly. They had a viral incident or they had some sort of incident that we felt that they were presenting with symptoms that made them more dehydrated and therefore temporarily required additional supplemental hydration.

DR. CAMILLERI: But did you standardize when and how the IPN volume would be reduced? Because intrinsic there is a fluid load.

DR. BYRNE: Did we standardize how we would reduce parenteral nutrition volume? Yes. We used very specific weaning criteria and the patients had to maintain that, and we looked not only at one day but at the trend week to week, again week 3, 4, and 5.

DR. WOLFE: So you had very strict criteria. Let me see if I can interpret this myself. Let me try. We'll go to 108. 108 right there needed 15.8 liters and that included the TPN solution and all the hydration they needed. They were getting so much, they didn't need extra

hydration, I assume, through a peripheral vein.

Now, over here, you have the situation at 6 weeks. They're getting no nutritional support through TPN, but they still need a little hydration.

Is this correct? Is that fair? I don't do this very often.

And over here, looking down here now, there's still no nutritional support. Is this a correct interpretation?

DR. WILMORE: Correct. The hydration fluid also includes fluid used to deliver drug. So if the patient needed magnesium, for example, there would be --

DR. WOLFE: The peripheral vein.

DR. WILMORE: Yes.

DR. WOLFE: It's not central. Line sepsis is diminished. Expense is diminished.

DR. WILMORE: You got it.

DR. CAMILLERI: Can I ask for another clarification, though? I'm sorry. So when you did your analysis, which volumes did you include as your primary endpoint?

DR. KENLEY: The primary analysis, the week 2 to week 6, were the sum of the three components at week 2 and at week 6, although we also did a supplemental analysis, as Dr. Gertner showed you during his

presentation, that was just the PN volume alone at week 2 and week 6. But then when we analyzed week 2 to week 18, it was PN volume alone.

DR. CAMILLERI: Can I ask a question then? I'm sorry. But if you look at this group given the diet and growth hormone and you look at week 18, the volumes are much higher, aren't they, than on the next page? Is that fair? Than on the next slide?

DR. GERTNER: The mean volume at week 18 was less in the growth hormone plus glutamine combination group than in the growth hormone alone group, if that's your question. So clearly the components of that mean would also be different.

DR. WOLFE: Any more clarification needed or can we continue on this question? Ms. Cohen, if you have a question, please ask.

MS. COHEN: I'm trying to figure out the nutritional standards that they determined. What were the nutritional standards?

DR. WOLFE: Didn't you talk about that before earlier in the morning? Didn't you mention the criteria you used?

MS. COHEN: It would be nice to repeat them.

DR. WOLFE: Do you want to reiterate again briefly what they were?

DR. BYRNE: All patients had to be well nourished to enter into this trial, and then in terms of weaning the patient and making decisions regarding weaning, they had to stay well nourished. They had to stay well hydrated, and they had to maintain stable electrolytes.

DR. CARA: How did you assess nourishment or nutrition status?

DR. BYRNE: At baseline upon admission, we had to make sure the patients had not been losing weight and they were within an appropriate body weight range for their height. Their albumins also had to be normal. When they entered into the study and began treatment, we looked at those same parameters, following albumin on a weekly basis, although it's not a good indicator of short-term change.

In terms of weaning them and judging were they going to be able to tolerate a reduction in TPN, we asked really three questions. Could they hydrate themselves? Because the first thing we're removing is volume, and if we remove volume, if they can't hydrate themselves, they will become dehydrated. And so they had to meet one of these three criteria to demonstrate that they were able to hydrate themselves.

They also had to, throughout the treatment period, maintain normal electrolytes, these as well as others.

And they had to sustain an appropriate body weight, but that weight was corrected for using bioelectrical impedance which helped us to differentiate water gain and fat gain, and they also had to be consuming a number of calories that would allow them to maintain a stable body weight. It was based upon standardized equations and accounted for malabsorption.

We also looked at the patient's nutritional status in terms of their vitamin and trace element levels prior to treatment to make sure that they were not having nutrient deficiencies, and they were supplemented with their oral diet to receive appropriate vitamin supplementation if they did have a deficiency.

DR. CARA: So every one of the patients at week 18 had a body weight with impedance studies done to calculate nutritional status?

DR. BYRNE: No, not at week 18. The real rationale behind bioelectrical impedance was anticipating that there could be -- with fluctuations in sodium intake with growth hormone administration, that it would aid us in interpreting what was really truly happening with their weight. Once the drug was removed, we didn't anticipate those sorts of things to be occurring.

DR. LaMONT: Can you tell us, were the patients in the center between week 6 and 18, or did they just come

back at week 18 for a follow-up? I think I know the answer.

DR. GERTNER: They did not come back for a follow-up. There was communication throughout the follow-up period between one or other of the study centers and their referring physicians, but the management of the patient and the evaluation at week 18 was made by the referring physicians. If you want expanded details on that --

DR. LaMONT: You mean you telephoned and asked them how much they were getting?

DR. GERTNER: Could Dr. Byrne address that one, please?

DR. BYRNE: We had frequent communication with the patient and his or her local physician, but because they were the physician actually being able to examine the patient, they were able to make the final judgment related to any changes in parenteral nutrition or any other adjustments that they might need. But we were in frequent communication with them, and there's documentation in all the patients' medical records to that effect.

DR. LaMONT: I have another question, if I could, Mike, about this body weight and how you decide who gets what kind of fluids. If we find patients have edema, we often change sodium and water intake in that patient and

give diuretics, which of course influence urine volume. So I wonder what sort of edema these patients had and how did you respond to it?

DR. BYRNE: Some of the patients did receive diuretics and we anticipated that to influence their urine output, but that is why we used enteral balance to help us judge if a patient was adequately absorbing because, again, that measurement is an indicator of their total fluid intake by mouth minus their stool output, and it's not affected by diuretic use. It helped us to judge their ability to cover their insensible losses.

DR. WOLFE: Dr. Camilleri?

DR. CAMILLERI: Can you tell us the limits of acceptability of the bioimpedance measurements and how close you were able to maintain patients within that? The second parameter there for nutrition on the last slide. Can you tell us how you used that information?

DR. BYRNE: Right. We did it actually on a daily basis to make sure we were actually looking at a true trend as opposed to a daily fluctuation. The measurement itself is that we particularly paid attention to was the measurement of resistance, which is inversely related to total body water. What we found was that approximately a 45-ohm change, for instance, in resistance would correspond with a 1 kilogram weight gain. If there was a greater

change in resistance but a corresponding comparable change in weight, such as 1 kilogram, that that could actually reflect the patient's losing weight. We would say there would be a disproportionate gain in fluid under those circumstances. If there's a less change of resistance, in the 30-ohm to 0-ohm change, there would be no change in fluid, but if the patient's weight was increasing, that could suggest fat gain since fat is anhydrous.

DR. CAMILLERI: So as I recall from this morning, there were one or two groups that had a 70- to 80-ohm change mean. So to come back to Dr. LaMont's question, bearing in mind that at least 50 percent of the patients had more than 40 ohms, how did you interpret that information and did that lead you to use diuretics? It's still not clear to me whether this was just fluid that was brought on board, and certainly the way in which the weights went from 67.6 kilograms at week 6 down to 59 at week 18 suggests to me that this was entirely fluid.

Because I'm still concerned that ultimately the primary endpoint of the study was determined on the interpretation of the medical and nursing team that was using these data. So there's some circularity in the definition of the endpoint, and this is what I'm struggling with. And I'm sorry if I keep bringing it up, Mr. Chairman.

DR. WOLFE: It's okay. And it's very important. But that may actually be part of the next question. That's the reason I'd rather not discuss that any further at this point. I don't think in my view there's any question that part of the weight gain was due to edema, but that's not an endpoint. And the weight was lost. That brings up also the question on number 5. So these are questions that we will be discussing as we go on, unless you think there's more to discuss specifically with this.

Remember, the question at hand here, the question we're discussing now, do the data at week 18 indicate a durable effect? Is that correct? So let's, if we can, maybe try -- I understand there are other questions we have. We have several questions. If we can try to sort of stick to this one because other issues that you're all bringing up, which are very, very important issues, will come out in the discussion of the specific questions.

Dr. Levine.

DR. LEVINE: Well, while we're talking about these measurements, I'm a little confused. You say that you communicated at week 18. The other measurements like the ohm measurements that you did, were they done by one individual, circulating individuals, doctors, or nurses? How much variation was there in that measurement?

DR. GERTNER: Yes. The bioimpedance analysis was done during the growth hormone treatment phase in the residential facility during the double-blind treatment phase of the study. It was done so that weight changes observed on growth hormone therapy or on placebo injections could be correctly interpreted as changes in relatively dry weight, and therefore weaning decisions would not be inappropriately made based on accumulations of water weight.

Following discharge, the patients were not receiving growth hormone and therefore there was no need to do BIA to look at any kind of inappropriate fluid shifts.

DR. LEVINE: My question was, was this done by digital computer analysis? No. How did you measure the impedance? Who measured it?

DR. LEVINE: The impedance was measured -- Dr. Byrne might correct me, but my understanding is that the impedance was measured by the dieticians at the in-patient residential center using the readout from the standardized, conventional bioimpedance apparatus, which are widely available in clinical practice.

DR. WOLFE: Dr. Cara.

DR. CARA: Sorry. But you showed data this morning looking at week 6 in relationship to week 18 showing weights, if I'm not mistaken.

DR. GERTNER: Yes.

DR. CARA: Those were actual body weights. Can you give an estimate of what the non-water weight was --

DR. GERTNER: No.

DR. CARA: -- based on the impedance studies?

DR. GERTNER: Yes, I understand your question I think. Do we have the components of the body weight, say, by using a BIA or other type of body composition analysis at week 18?

DR. CARA: No, no, no. At week 6. If you have the impedance data and you have the actual weight, you can get an estimate. It's not perfect, but it's an estimate of what the body weight was and then look at that versus week 18.

DR. GERTNER: I would just like to clarify that the endpoint of the study was actually the ability to wean from TPN. Weight was not the purpose of the study. We were not trying to assess any kind of nutritional or other status based on weight. We were trying to see, by weighing the patient and applying these corrections with BIA, whether weaning could take place, and we thought that corrections were appropriate and weaning did take place. The study was blinded, so the right doses --

DR. CARA: And I can appreciate that, and I'm sure you may not have expected this or may not have, for

whatever reason, taken this into consideration. But again, the concern is the weight loss that occurs after stopping growth hormone therapy relative to where patients were at the end of week 6 and where they were relative to week 2.

DR. GERTNER: Yes. I could show you, if you wanted to -- I don't know how --

MS. JOYCE: I'd like to have Susan address that.

DR. GERTNER: Sure.

DR. KENLEY: I just wanted to say we did analyze the change from week 6 to week 18, as well as the change from baseline to week 18, in weight, and there was no difference between the treatment groups. I mentioned that earlier.

DR. CARA: Was that the estimated weight after the impedance studies were done?

DR. KENLEY: No. That was their body weight.

DR. CARA: Their actual weight.

DR. KENLEY: Their body weight.

DR. WOLFE: Any more clarification? This is very, very helpful. It helps us to really answer this question appropriately. Any more questions from the panel?

DR. SHIH: Yes. Now, you mentioned that the other two components, the SLE and the intravenous hydration, was not measured at week 18. Was that a

decision in the protocol or something happened that you did not measure?

DR. GERTNER: Yes. There was no provision in the protocol for BIA measurements to be made at week 18.

DR. SHIH: My question was, was that in the original protocol design or it happened during the operation of the trial?

DR. GERTNER: I'm sorry. I wonder if you could repeat the whole question, please. I do apologize.

DR. SHIH: You have two components that you didn't measure at week 18. Right? The SLE and intravenous hydration.

DR. GERTNER: Yes.

DR. SHIH: Now, my question was whether that was a design or due to operation issues after the design in the protocol.

DR. GERTNER: It was in the design of the protocol and written that way.

DR. WOLFE: Any more points of clarification?

(No response.)

DR. WOLFE: If not, actually we'll go back to Dr. Goldstein to see if he is ready to comment, and then we'll go in proper order.

DR. GOLDSTEIN: The question number 3 raises a couple of questions in my mind. What really is meant by

durability of effect? 18 weeks? Is it more? If it's more, how much more would one need to judge durability? Could it be less?

We have information that was presented to us that in fact in a number of patients in this cohort, a year of durability was achieved. That being the case, if one looks at the patient population at large, I would suspect that a significant chunk, if you will, of the patients would achieve durable results, durable enough to be clinically meaningful, durable enough to save them and society a great deal of pain and money to boot.

I'm not sure what's meant in that question by minimum follow-up period, but in this case we have 4-and-a-half months. One can argue which way one wants to go.

But I think the answer to the question that I see before me is that the effect was, in fact, durable and, in a significant enough percentage of the patients, would continue to be durable. And I'll have more to say in the same context when we reach question 5.

DR. WOLFE: Dr. Mangel?

DR. MANGEL: I also see the results at week 6 not being substantially different from the results at week 18.

Returning to one endpoint, which I know we're not adequately powered to speak on, that of individuals who

were able to wean off of TPN and remain off of TPN, it's still striking to me that the number of responders of no TPN at week 6 was the same as at week 18. If we're comfortable with accepting a study with the active treatment group of n equals 16, it's also notable that 50 percent of those individuals are off of TPN at both week 6 and week 18.

I think the evidence is that for a 4-week treatment it is durable to week 18. I also feel that additional studies will need to be done to look at durability of effect, but perhaps we'll discuss it in question number 5. And I'm not convinced in my mind that that cannot occur post-approval.

DR. WOLFE: Dr. Cara, you're on.

DR. CARA: If I limit my response to the primary endpoint, which is total IPN volume, and looking at IPN volume specifically, is that adequate to demonstrate durability of effect? I think it is. The question remains, though -- well, there are still issues related to other questions that I've addressed previously. So I'll just limit my response to what I've already said. Thanks.

DR. WOLFE: Thank you.

Ms. Cohen?

MS. COHEN: I'm struggling, if you want to know the truth. I'm not sure that the IPN volume is adequate to

demonstrate the durability of effect. I think there are still some questions in my mind.

DR. WOLFE: Dr. Shih.

DR. SHIH: I don't have an answer. I pass this. And I'll tell you the reason. In the previous questions, you can see that the p values are significant. Here you are judging a maintenance effect. Essentially you want to see no change, which means maintenance. But the no change there can be due to small sample size. So I don't think this data can answer this question.

DR. WOLFE: Dr. Levine.

DR. LEVINE: Again, I think because of the small size of the study, a single-center study essentially, we need as much information on durability as possible, so I would not be happy with a relatively short-term of 4-and-a-half months. I'd like to see it longer.

DR. WOLFE: Dr. LaMont.

DR. LaMONT: Yes. I don't think the data they showed us here is adequate to demonstrate durability of effect because there are too many other questions about what else was going on, including weight loss. If I understand it correctly, these data on IPN volume were collected from remote sites in part. And it seems to me that, however, what they did collect is promising. It looks like there is some durability, but we weren't given

the complete data set to look at and I think it's too hard to look at in a complex of busy slides. So I would say the recommended minimum follow-up period would be 6 months.

MS. JOYCE: Excuse me just one second. If it's helpful beyond seeing it on the slide, we have printed the data to the extent that you may want that now or later.

DR. WOLFE: Let's hold off. Really, in fairness to everybody else, we'll go around one time. We'll come back for people to make comments and ask questions, unless you have a point of clarification.

DR. CARA: I have a point of clarification.

DR. WOLFE: A clarification.

DR. CARA: An issue of clarification regarding the question. If I interpreted this question correctly, what you're asking is durability of effect until 18 weeks. You're not looking beyond 18 weeks.

DR. WOLFE: No. The question is if you feel 18 weeks is enough to show durability. That's the question. Is that correct, Hugo?

DR. GALLO-TORRES: Yes.

There's another important clarification because you keep mentioning the word "maintenance." I don't believe we are talking about maintenance in the usual, customary way. Maintenance you talk about when you continue administering the medication. This is not the

case.

The question we're asking is, after discontinuation of the medication, after week 6 -- that is 4 weeks after the treatment period -- is there still an effect? And what I presented was there were no data to see what was going on in between. As an endpoint of efficacy at the end, some collection was made, but it was incomplete with respect to the primary endpoint. So that's the question.

DR. WOLFE: So aren't you still asking is it adequate? Is time point adequate to demonstrate durability? Is that the question you're asking?

DR. GALLO-TORRES: Yes, I believe so.

DR. CARA: What you just said was that that's not the case. You were asking whether there was durability of an effect until 18 weeks. What you just said was that you are looking to see if there's durability of an effect until 18 weeks, not is 18 weeks sufficient to evaluate durability of effect.

DR. GALLO-TORRES: I'm sorry. That's the third issue which I did not address. The third issue is how long should the study last. That's all. Three issues. Maintenance versus durability. The second one -- yes, you're right.

DR. WOLFE: At the end -- I'm going to vote on

this too -- if the answer is no, I'm going to ask you what period of time you would recommend, and Tom will record it.

DR. SHIH: Can I just ask that during that 6 to 18 weeks, it was no longer double-blind? Right?

DR. KOCH: Yes. The patients, as I understand, returned from the study site to their home.

Now, on the durability, there are actually two points. One is the point that at week 18 there are significant differences between glutamine plus growth factor and the control group alone. So the statistical significance was preserved at week 18.

The sponsor, of course, really doesn't have week 18 as a primary endpoint, and also the main reason why the week 18 information was collected was to shed light on whether the benefit at week 6 had totally disappeared by week 18. And the data show that it hasn't totally disappeared by week 18. It is reasonably evident at week 18. There are significant differences in favor of the combination against the control at week 18, and there appears to be little change between week 6 and 18.

DR. WOLFE: In a way I think what Dr. Gallo-Torres is doing was saying if the data does, indeed, show in your mind that there is a durability effect shown at week 18, do you feel that is sufficient to conclude that there's durability. Is that fair? Is that what you're

saying?

DR. GALLO-TORRES: That's exactly one part of the question.

DR. WOLFE: Let's try to stick to this question because there's a lot more to discuss.

MS. JOYCE: And may I make a correction to one of our statements?

DR. WOLFE: We can start over, yes.

MS. JOYCE: The study was blinded through week 18, to answer your question.

DR. WOLFE: It was.

MS. JOYCE: Yes, it was. I realize you're trying to determine today's --

DR. SHIH: That's very important. In Dr. Koch's answer to that, you still see the changes from week 2 to week 18, and that comparison has to be valid, and it only can be valid if it's double-blind, if you maintain that.

MS. JOYCE: Yes, it was. Again, the 3-month follow-up period was originally recommended in order to gather safety data, and that was the time period that had been recommended.

DR. WOLFE: There's really no need to start over. What I'd like to do is continue the discussion phase. The way we're going to do this is a roll call vote.

You then will say yes or no, and then if it's no, you'll be able to say how long you recommend. You'll have a second chance to speak. You'll have as many chances to speak as you want.

DR. LaMONT: Mr. Chairman, can I ask for a clarification? Is abstention a possible vote?

DR. WOLFE: Abstention is one vote you can absolutely give. No question. Actually Tom was whispering that to me before. Some of you sound like you want to abstain. Abstaining is fine.

DR. GALLO-TORRES: Mr. Chairman, we have a quick question too. There were no observations between 6 and 18 weeks. We are talking about one point at the end of 6 weeks and one point at the end of 18 weeks. Should you consider that in your deliberations?

DR. WOLFE: Exactly. Consider that point. There were no interval time points. You may have gotten the person on a good day. Who knows? Consider all these in your answer when you give your final vote on this question. And again, if you say no, I encourage you at that point to recommend what you feel would be an adequate time period.

DR. SWENSEN: I think I'm up.

DR. WOLFE: You're up.

DR. SWENSEN: Well, that's confusing because if

the question is simply one of durability, I say to myself you've got a person here, someone who has had a net reduction in the amount of IPN they've infused over an 18-week period. Is that durable? Sure. You'd want that for a person that you were close to.

But if I say, is it adequate to just take measurements at 6 and 18 weeks, no. The variability from day to day with these kinds of things is pretty substantial. So I wouldn't think that's a great way to determine it, but yes, it's durable.

DR. WOLFE: Dr. Camilleri, at this point what we're going to do -- oh, no. Actually I'm the last person. So you're second-to-last.

DR. CAMILLERI: I look at this as two questions. Is the measurement of TPN volume adequate to demonstrate durability of effect? Effect to me isn't just for this endpoint. It's effect of the treatment. So in my opinion, the answer is no. This measurement is not adequate to assess the effect of this treatment on the patient.

What is the recommended follow-up period? I have no idea, but I think that it's up for grabs. Maybe 6 months.

DR. WOLFE: Actually I want to say something. Then what we'll do is we'll go around the room one more

time. At that point you'll give your vote unless you want more clarification, and we can do that as well.

But if I can just say a couple things. Again, I'm going to be consistent with my comments before. This was not a stipulated endpoint. So the question is in a way moot because no one is really trying to at this point -- I think this was additional data the sponsor wanted to provide. As far as I'm concerned, it's inadequate. It's one time point only. It's 12 weeks after cessation of therapy, and if you want to see durable effect, I would want to go out to a year with intervals in between. That would be my choice.

I always point out to my lab that it's very important to express your data in a way which is honest but brings home the point you're trying to make. I would have expressed my data a little differently than you did. I would have shown the percentage of patients with a durable effect. I think that really helps. I would show the individuals as well because to me I was actually more impressed with the table, after seeing it, than the way you described it.

In any event, are there any more clarifications or questions or comments? Dr. Goldstein.

DR. GOLDSTEIN: This may serve a useful purpose. I hope it does. In case perhaps people may not

be aware -- and the FDA can confirm this -- I think the purpose of this discussion is to allow them, along with the sponsor, to develop appropriate labeling in terms of the duration, the frequency or lack of frequency with which repeat doses can be given, and certain very, very practical issues like that. I think that's where -- you're shaking your head, so I assume you agree, Hugo or Dr. Justice.

DR. HOUN: I think there seems to be a lot of confusion on this question. One aspect of it is that we are wanting to make sure we are studying a clinically relevant endpoint, and if people are saying yes, it is clinically relevant at 4 weeks, the other question is what does 4 weeks mean. Is that clinically relevant that we have a measurement at 4 weeks? And do we have enough data to say -- the data that we do have is this 18-week data. It has some limitations. It's not the primary endpoint measured again. It's a little bit different. We want your input on does this help us understand that the effect seen at 4 weeks is relevant because it has durability. It means that it affected people's lives other than just those 4 weeks.

This will not influence can we say repeat dosing because this is not studied. And if they are interested in showing there's a better effect after a second course, they will have to study that. So we're not

going to go there with these data because we can't make that leap.

In terms of how long it's labeled for use, the proposed labeling I believe said dosage and administration was for daily use. Now I'm hearing from the sponsor, daily use for 4 weeks. Is that correct?

MS. JOYCE: In terms of the indication for short bowel syndrome patients, it was always our intention that the treatment recommendation would be for 4 weeks because that is what we studied. We were not under any idea that the agency would even consider any kind of a labeling beyond the 4 weeks studied in the trial, so that was not our intention based on this particular clinical study.

DR. HOUN: Okay. So we are always faced at FDA that when you have a chronic syndrome, people don't study drugs for a lifetime. They study it for a few weeks. And is it relevant again that the study is applicable to a chronic condition? So that's all the input we're asking. So it's very complicated. You're right, Dr. Cara. But the implication is given what you've seen, all of what you've seen, give us your best integrated opinion on the endpoint that we saw at 4 weeks is relevant because it lasts a bit, and whatever "lasts a bit" it is we have now 12 weeks later, and that's relevant, or no, that's not long enough

to say it's relevant.

DR. GOLDSTEIN: Thank you, Dr. Houn. I wanted to get that clarification out on the table.

DR. KOCH: If I could just add a comment relative to what Dr. Houn said, the data that you have is you have a study where patients were in the center from week 2 to week 6. They returned to their home location between week 6 and week 18. Blinding was maintained. You have an assessment at week 18. And that assessment does show significant change between week 2 and week 18 comparing the combination group against the control group. That's the information you have. That's the concrete information you have. I can't tell you any better than anybody else what durability in the abstract means, but that is the concrete information that you have.

DR. WOLFE: Thank you.

Dr. Camilleri, do you have a comment?

DR. CAMILLERI: Just a point of information. I look now at this table, and at week 18 in the active treatment arm, there are 10 people who have no change in their IPN volume. There are 4 that increase and 2 that decrease. The people whose volume increases, their volume requirement ranges from 4 liters to 10.5 liters. And I think we need to keep that in mind when we think about overall durability of the response.

DR. WOLFE: I'd like to comment on that actually because to me I would interpret these data -- let's use a different parameter than we're used to, ulcer healing. To me this was durable in the majority of patients. One person absolutely failed miserably. No drug is perfect, and you had a couple of patients who continued to improve with time. So I don't think anybody here in this room -- even Dr. Wilmore would not claim that this is absolutely a perfect way of treating these patients. Some patients are going to fail for some unknown reason. That's a cause for further study to figure out which patients will fail and can they predict those patients in the future.

MS. JOYCE: May I just clarify one point that was made earlier with respect to the comment about it might be a certain thing on a given day? Because with respect to weight, that may be true. I know it is for me when I get on the scale on a given day, and there's nothing to attribute it to. But with respect to the endpoint and reduction of PN, that wasn't something that was significantly variable from day to day. This is what the patients were receiving at that time point. So I just wanted to make sure that it was understood.

DR. WOLFE: Any more questions or comments? Yes. We'll go around the table now and again at this point, unless you want to make some more comments, just

vote yes or no, and if it's yes, you're done. If it's no, you can state why if you'd like. That's fine. But also give a time you feel would be important so Tom can then write them down.

Dr. Goldstein.

DR. GOLDSTEIN: I believe I'm a non-voting member, Mr. Chairman.

DR. WOLFE: Oh, I'm sorry. I forgot that.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: A comment first, then vote. The treatment is for 4 weeks and then there's a 12-week observation after. When I compare it to other chronic conditions, medicines are approved for several other chronic conditions with 12-week treatment. Classically you'll need longer safety data and usually during that 12-week treatment phase, it's a continuous 12-week treatment. Not all conditions, but true for many.

For this, we have no information on retreatment. So I don't think we can comment whatsoever on that.

I think ultimately a study for a year follow-up after the 4-week treatment needs to be done.

For me at this point where the application is in time, I find this adequate to show a durability of an effect with an additional commitment to be done. So the

answer is yes.

DR. WOLFE: Dr. Cara, you're next.

DR. CARA: I really appreciate your clarification on this question, Dr. Houn, because that puts things in an appropriate mind set for me.

Given some of the caveats that I've mentioned previously regarding weight and hydration status, and given the fact that IPN volume is an important issue in individuals with short bowel syndrome, I think that the changes that you see between 6 and 18 weeks do demonstrate a durability of effect.

And just to put things in sort of perspective, if I were using growth hormone therapy for a child with short stature and 3 months later that child was still growing at an accelerated rate, even though we had stopped growth hormone 3 months before, I would say fantastic. That's wonderful. So I'm happy to see that most patients had a sustained effect.

Regarding the fact that we don't have any intermediate data, that would have been wonderful to get, but week 2 and week 6 are also only two points in time. So week 6 to week 18 I don't think is all that different. So it would have been nice to get additional data, but it doesn't necessarily sway my judgment.

Are there any longer-term studies that I would

suggest? It would be nice to continue collecting information to see if there is any waning effect, but I think that 3 months follow-up is appropriate. If it were feasible to do a phase IV study to evaluate continued effect, I would definitely encourage that.

DR. WOLFE: Thank you.

Ms. Cohen?

MS. COHEN: On the 18-week study, is that a one-shot day that they did of everybody, or was it a compilation? I'm a little concerned about how we arrived at these numbers, if it's the most favorable one of the 18 weeks or what exactly it is. I just feel it's not clinically enough. It needs more endpoints from my way of thinking.

DR. WOLFE: How much time would you recommend?

MS. COHEN: Well, I'd certainly recommend not jumping from 6 to 18 weeks, but I'd work towards 18 weeks. I think the nature of GH is such that they really need to do almost a year.

DR. WOLFE: Keep in mind again -- I'm going to clarify for the sponsor. This is not 6 to 18. This is 4 to 16 because the first 2-week period was a lead-in period of the study.

MS. COHEN: I understand that.

DR. WOLFE: 4 weeks of therapy.

MS. COHEN: I even got that.

DR. WOLFE: And 12 weeks of follow-up.

MS. COHEN: Yes, I even got that.

DR. WOLFE: So we're talking about basically a 3-month follow-up from the treatment of 4 weeks is what we're talking about.

MS. COHEN: I'm not satisfied. I don't think it's adequate. As I said, on the 18th week, I don't know what statistics or what. Was it 1 day? Was it a week? I just want to make sure.

DR. WOLFE: Do you want to clarify?

DR. GERTNER: Yes. Two clarifications, if I may.

One, the 18-week what we call time point is actually a 1 week's average from the week 17 through week 18 of PN requirements.

Secondly, as I mentioned in my main talk, we are conducting a 2-year survey of all patients discharged from this study and the data will be made available to the FDA.

DR. WOLFE: Thank you. So your vote is no. And how long do you want to go for?

MS. COHEN: If the company is willing to do 2 years, I am too.

DR. WOLFE: Okay, 2 years.

Dr. Shih.

DR. SHIH: As I indicated earlier, I don't think there is enough information to say this durability issue. My answer is no.

It's not only the time. It's also the frequency you measured this. You needed to measure this not at only one point. If you do a study, you should measure several points so that you know the variability. So I'm not very sure the data support this durability.

DR. WOLFE: I'm going to vote no. If you have two points, let's say, right here and right here, was the line between these two points like this or was it like this? You don't know because of the way the study was done. So for me durability at 12 weeks after stopping therapy is inadequate because atrophy can take place. I'd recommend, if you want to show durability, look a year later with intervals in between -- you can pick the intervals later on -- to measure all the parameters you possibly can, get as much information as you can. And we always recommend getting as much data as you can and looking at the data very carefully. So I'd recommend a year of follow-up before I would determine and I would conclude that it is a durable effect.

DR. LEVINE: I would vote 1 year and I vote no on the question.

DR. WOLFE: Dr. LaMont.

DR. LaMONT: Yes. I feel the measurements are probably adequate, although I'd like to point out that it doesn't seem like they were collected in the same way. The amount of IPN delivered between weeks 0 and 6 were collected by the investigators at the primary site in Massachusetts. And if I understand it correctly, these data at week 18 are either provided by the patient or by their provider. So they're not exactly the same. Is that correct? Yes.

MS. JOYCE: The data were provided by the referring and treating physician.

DR. LaMONT: Not by the patient.

MS. JOYCE: Not by the patient. And the only way to do that was to have done it that way, otherwise you would have had all the patients have to come back to the center to be reevaluated.

DR. LaMONT: Fine. Then I vote yes it is adequate. Thank you for clarifying that.

And I would say if you're looking for duration of effect, you have to keep going until it's no longer durable. It's like a kidney transplant. It could last 18 weeks or 18 years. So it could be that this would last months and months, but I'd say a minimum period, from what I understand so far, would be about a year.

DR. WOLFE: So you're saying the answer is no.

DR. LaMONT: No. Yes. Yes to the top one.

DR. WOLFE: Oh, I'm sorry.

DR. LaMONT: Yes, this measurement of IPN provided by physicians at week 18 is adequate to demonstrate durability of effect. That's yes. And I'd say 1 year follow-up. Is that clear, Mike? You're still frowning.

DR. WOLFE: I'm confused. Are you accepting the 18-week measurement as showing durability?

DR. LaMONT: Yes.

DR. WOLFE: Okay.

DR. SWENSEN: I vote yes.

DR. WOLFE: Dr. Camilleri?

DR. CAMILLERI: I vote no mainly because I don't think it's the only parameter that needs to be addressed in the assessment of the clinical efficacy of this treatment. With regard to timing of the follow-up, I want to remind us all that these are patients with short bowel syndrome. Their nutritional parameters are going to drop pretty rapidly if they're not on adequate nutrition supplementation orally. So I don't actually think that you need a year's follow-up data. I do believe like you do, Mike, that more frequent observations over a period of 6 months would probably be enough to give you the answer.

DR. WOLFE: So, Tom, what's the final?

MR. PEREZ: 5 noes, 4 Y's.

DR. WOLFE: So 4 to 5. And those who voted no, the effect ranges from 6 months to 2 years. Does that help?

It's now 3:18. Let's take a break until 3:35.

(Recess.)

DR. WOLFE: Question 4. I'll read it. Do you want to put it up? It's a short one but I'll read it. The data were primarily derived from a single nutritional support tertiary care center. Are these data generalizable to the population of short bowel syndrome patients?

If you will recall, I'll just briefly summarize. There were 41 patients in the study. 38 of the 41 were at a clinical facility affiliated with Brigham & Women's Hospital, and the other 3 patients were from a facility which was associated with the University of Nebraska.

So again, question, the data primarily, 94 percent or so of the patients or 93 percent, something like that, were from one center. Are these data generalizable to the population of short bowel syndrome patients?

Yes, we have discussion and we will start with Dr. Camilleri.

DR. CAMILLERI: I was impressed that patients

really came from several different parts of the country. This is a rare condition. I think the study has very carefully put patients through a very nice run-in period and study protocol. So in general, it would be nice always to have a second confirmatory study, but this is a very difficult patient population to evaluate and there are no more than a few or a handful number of patients in any center.

So I come down to feeling that in general these data probably are generalizable.

DR. WOLFE: Can I ask a question before we go any further? Does anybody need more clarification of this question? I think it's fairly straightforward. Do you just want to vote and make your comments? Does anyone object to that? Because it's pretty straightforward. So your answer is?

DR. CAMILLERI: Yes.

DR. WOLFE: Mr. Swensen.

DR. SWENSEN: Thanks. I think the aspect of this that I find disquieting, the point that is not generalizable is the quality of care that the patients who participated in this study received. I understand that they were not drawn from medical centers. Of course, that doesn't preclude that they began with and will return to extremely qualified clinical support teams. However, I do

know that it is very widely believed among the segment of the short bowel syndrome population that I'm acquainted with that standard of care and quality of care are serious issues for us.

And I have some misgivings about whether or not patients who receive a complex and demanding regimen like this one under the care of clinicians who have no special experience or training in nutrition support but may, indeed, be assigned to their patients by an insurance company -- I have very serious reservations that these results would be generalizable, and so I vote no.

DR. WOLFE: Thank you.

Dr. LaMont?

DR. LaMONT: Yes. I feel equally ambiguous. I think the data are generalizable to the syndrome but that the patients, as we've heard from the patient that came today, need to be monitored closely in a special center. It's kind of like the Lotronex story. As soon as that got out into the general population of doctors, it was often misused. So as the question is written, my answer is yes, but I put in the proviso that it needs to be in the setting of a specialized center.

DR. WOLFE: Dr. Levine?

DR. LEVINE: I think we'll discuss the validity of the science of having a single center, but I do agree

they were fortunate in having good geographic input from many other patients all over the country. I'm concerned, as the prior two speakers were, about the success and the reliability of throwing this out to the general practitioner or even the busy gastroenterologist and whether the capacity is there for adequate follow-up and treatment with this proposal.

So I'm a little ambiguous. I originally said no, but I feel as long as we're not voting here and we're not concerned that this is just a single center study per se, which I'm concerned about, but is this generalizable? I think it's probably generalizable. I give a weak yes.

DR. WOLFE: Okay. Put a small Y instead of a capital Y.

(Laughter.)

DR. WOLFE: Dr. Shih.

DR. SHIH: I'm very sympathetic to the difficulty of conducting a multicenter study in an orphan drug in a rare condition. However, considering the scientific question here, I have to say no. FDA usually asks for multicenter studies. So I will say no.

DR. WOLFE: Ms. Cohen?

MS. COHEN: Well, it's kind of a yes and no in a way because in the real world when doctors have 12 minutes to give each patient, it's going to be very, very

difficult. That's the problem. I think the information that they gathered was valid, but I think to translate it into the real world, it's going to be very, very difficult. So it's a yes/no no. Mr. Swensen said it better.

DR. WOLFE: The answer is no.

Dr. Cara.

DR. CARA: Yes, I think it is generalizable to those patients that are followed in a multi-specialty care setting. I do have concerns about its applicability to patients that are followed by physicians on their own or just get fragmented care.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: No. I'm uncomfortable with a single center study.

DR. WOLFE: I'm last and I'm going to say no, and the reason is that as a scientist I want my data reproduced by somebody else. It's not been reproduced. I'm not saying this study isn't valid. It is very valid. I'd like to see just a few more patients elsewhere, not even a complete study. I'd like to see just a few more patients in a few more centers with similar results. I'd be very happy.

DR. GOLDSTEIN: A comment.

DR. WOLFE: I'm sorry. Dr. Goldstein.

DR. GOLDSTEIN: I should point out that it is

highly likely, addressing Mr. Swensen's comment, that the company will engage in educational and related scientific efforts to make this important knowledge, if the drug is approved, known. So I think that ought to be kept in mind, teaching programs and the like.

The other thing is that 41 patients from all over the United States and two foreign countries in my mind is a surrogate for generalizability. Given the comparative rarity -- by definition an orphan drug -- of this particular indication, the opportunity -- for example, how many more patients are a few patients? You say a few patients more. It needs to be looked at with some discretion as to whether that's really necessary or practical.

DR. WOLFE: I want to comment just briefly, and this is purely scientific. What that proves is that it's not the water in Boston that does it. It's certainly not the air in Boston that does it. It's not Interstate 495. What it is it's generalizable to all patients all over the world and we can repeat it with other investigators. Right now it is primarily a single investigator generalizable to all patients everywhere if they come there.

DR. SHIH: I really concur with Dr. Wolfe's statement. As I said, I'm very sympathetic especially to the statisticians in the sponsor's group. They really did

a good job, and they analyzed and did consider the covariate analysis and so on and so forth. It's very hard to do analysis on so few patients. I will say this is a very good conducted study per se and a well analyzed study, but it's just a study that is a single center and it's not repeated. That's of concern to me. So that applies to this question of generalizability. For the study per se, I agree this is a positive study, but it's not repeatable in the current setting.

Earlier we heard a GCRC setting can do the job too and you can conduct another study in that kind of an out-patient. That will be very good.

DR. WOLFE: We can discuss what could be done in the future in question number 6, but right now the vote has been taken for this question and it is 4 yes, 5 no. Unless there's any specific comments germane to whether this is generalizable -- I think we all said that -- we'll move on to the next question. Any other questions or comments about this?

MS. JOYCE: Am I allowed to make one statement on this?

DR. WOLFE: A very brief statement.

MS. JOYCE: Yes. I do acknowledge and appreciate the comments with respect to the single and double study. I do also want to make mention of two

communications that we had with the agency that speak to this specifically, both in the context of a single center and having two centers, and it was understood that this would not necessarily be a roadblock to approvability but that we would have to have a strong p value and that there would not be a minimal number of patients required per site and that the statistical issues could be overcome by modeling and combining centers, et cetera. And I have two communications to that effect.

DR. HOUN: I think the word was "fileability."

MS. JOYCE: Actually we have an August communication where the division advised us that there was no statistical requirement concerning a minimum number of patients per center. If we were able to find another site that can enroll fewer patients, the issue of statistical analysis can be worked through by modeling, combining centers, et cetera. That was one communication.

There was an additional communication with respect to the fact that if we only had the one site, a p value of 0.05, based on data from two centers, would likely be considered a win by the agency, while the submission of a file based on these data would have some level of risk.

DR. WOLFE: I'm aware of this, and again, I've been the champion of no moving targets. But for me do you call a second center one of which provides less than 10

percent of the patients? So again, we can talk about this later on with regard to future studies. As I indicated in my response, I would like to see just a few more patients to corroborate this.

DR. KOCH: Yes. My understanding -- and the sponsor can confirm this -- is that although the second center only had 3 patients, it was 1 on each of the three arms and the two growth factor groups actually did better than the control patient among those 3 patients. Now, the sponsor can confirm this because I had asked this question earlier of them.

DR. WOLFE: One last, quick, 10 seconds.

DR. KENLEY: Just a couple comments. We did analyze it as a multicenter study. That wasn't the primary analysis because the primary analysis was in the protocol and we followed that. But because there was 1 patient on each treatment group, we included a center effect in the analysis and we got the same results.

DR. WOLFE: Thank you.

In light of these comments and this clarification, would anybody like to change their vote? Dr. Levine?

DR. LEVINE: I appreciate very much how difficult these studies are to carry out, and I don't know if a complete study would have to be carried out again.

But I have enough questions with the science, with the water in Boston, as you pointed out, et cetera, although there's a geographic, if we're saying in this question this is a single study and whether it was delegated as a single study, I'd say today I would change my vote to no because I feel we must have some more information. It may not be a major repeat of 41 patients, but it means somewhere else. Some of the details that we're concerned about and have been mentioned here should be addressed. And whether it's pre-approval or post-approval, I would like more than a single center. I do not consider Nebraska as being a multicenter study. So I would say no. My vote would change from a weak yes to a no.

DR. WOLFE: Dr. Cara.

DR. CARA: I would just like to clarify that I think that when it comes to efficacy of drug, I don't have a problem with a single study. What I have more difficulty with is reproducing the support systems that are actually in place at that one single location. If that is the issue, then obviously it needs to be able to be reproduced, and I don't think it can unless you're in a multi-disciplinary care setting.

DR. WOLFE: Just because I'm a little confused, the question was are these results generalizable. And you voted yes. Now your votes seem to almost say no. So this

time not around the room. Just raise your hand. How many say yes, this is generalizable information?

DR. CARA: Can we get clarification on what the agency is actually asking for here?

DR. HOUN: We are concerned that it's a small study, but we understand that this is an orphan indication. And we're asking your best advice in terms of what was studied, what was presented. Is it enough to say that no more studies are needed because we have enough results and confidence that it is in fact true and valid?

DR. CARA: So if I'm understanding you correctly, what you're asking in essence is, is this study in and of itself adequate to demonstrate safety and efficacy of the medication? That's what I want clarification on.

DR. WOLFE: You're asking for a point of clarification. Correct? I'll ask the agency to clarify it, not one of us.

DR. JUSTICE: So, no, this isn't the question about whether the drug should be approved or not. This is a question about whether or not the results can be extrapolated to the population as a whole.

DR. CARA: From a practical standpoint or theoretical standpoint?

DR. JUSTICE: Practical standpoint.

DR. WOLFE: Yes, Ms. Cohen.

MS. COHEN: I understood that the information derived, the generalization, you could then go out into the community, give it to physicians, and physicians should, therefore, treat patients. That's how I get it. Is that what you mean?

DR. JUSTICE: That's what we mean.

MS. COHEN: Thank you.

DR. WOLFE: Dr. Camilleri, I'm sorry. You had a comment before?

DR. CAMILLERI: No.

DR. WOLFE: Any other questions or points of clarification? Yes, Dr. Cara.

DR. CARA: I actually don't have a question but I do have to change my vote.

DR. WOLFE: We're going to vote again. So again, we're going to vote again by raising hands only, not around the room. How many vote yes, this is generalizable to all physicians, all patients, whether they're in Boston, San Francisco, Los Angeles, or anyplace else? How many say yes?

(A show of hands.)

DR. WOLFE: How many say no?

(A show of hands.)

DR. CARA: Can we clarify?

DR. WOLFE: You want to clarify further?

DR. CARA: Well, yes. Again, I think it's important to clarify that I don't think it's because of lack of efficacy of the medication. It's simply because the resources at this point cannot be duplicated by general physicians caring for --

DR. WOLFE: That's question number 6. We'll specifically discuss do we think it's effective and what other studies should be done.

DR. HOUN: Well, in addition, besides other studies, you might have recommendations on how to position the product so it could be used efficaciously by more than just that study center in Massachusetts.

DR. WOLFE: That's really important because when Lotronex was reconsidered, there were very specific guidelines in place for instruction, or else Serono providing an honorarium to Dr. Wilmore to go everywhere in the country, all over the world and help take care of these patients. He has plenty of time to do this.

Any other questions?

(No response.)

DR. WOLFE: Question number 5. Are there specific safety concerns considering the potential for long-term use of recombinant growth hormone in the treatment of short bowel syndrome patients?

We will now start at this end with Dr. Goldstein.

DR. GOLDSTEIN: We're talking about question number 4?

DR. WOLFE: Five.

DR. GOLDSTEIN: Five, okay. Are there specific safety concerns considering the potential for long-term use? Well, two committees now have asserted the safety of this material, and in the case of the previous committee, it was not potential in non-human growth hormone-dependent short stature, it was actual long-term use, five, six, seven injections weekly for a long time. So in that instance at least long-term safety was adjudged to be adequate. In fact, I think the other indication required larger doses than have been suggested here.

Those safety concerns that were adduced during the course of that trial were safety concerns that were in the main well known and well characterized, and I think the same thing is true since this is essentially the same drug or a very similar one.

So my answer to the question is that I have no realistic safety concerns.

DR. WOLFE: This question were going to discuss first, then vote by hand because this is conducive to going by hand.

Dr. Mangel.

DR. MANGEL: The studies evaluated 4-week treatment. The sponsor is asking for 4-week treatment. There is no data on whether or not there's efficacy with repeat challenge. If it was to be used as an alternative to 4-week treatment, my expectation is it would be episodic treatment in patients. I would not anticipate a continuous treatment.

DR. WOLFE: Dr. Cara.

DR. CARA: My comments are essentially the same. Since this is a 4-week course of therapy, I don't think that there are any other safety concerns per se. However, I am concerned about the indiscriminate use of the medication and perhaps the false sense of security that some individuals might have in using the medication at the expense of not having true multi-disciplinary involvement, but just see this as a sort of magic bullet sort of thing.

I think there are also concerns that are still unresolved in my mind in terms of what is true nutrition status versus hydration status, and I'd like to get more information in that sense.

DR. WOLFE: I'm sorry. Ms. Cohen.

MS. COHEN: Is it okay? I drank a lot of water in Massachusetts. So is it okay if I -- the brain is still functioning I think.

I just think there are long-term safety issues with growth hormones. I think we need to know more about that.

I think there's a lack of nutritional information in the clinical trial that they did.

I'm concerned about off-label use.

I'm also concerned about physicians, their lack of information on nutrition, how they're going to prescribe it, and I have great concerns about it going out into the community without good training.

DR. WOLFE: Dr. Shih.

DR. SHIH: The question is about a specific safety concern. I don't have a specific safety concern.

And this is about potential long-term use, and I think this is not an inexpensive treatment. So I think the potential for long-term use is undefined here. So I will say no.

DR. WOLFE: Dr. Levine?

DR. LEVINE: I don't think there's much evidence in the pediatric age group, but there certainly is post-marketing evidence of complications of continuous use, intermittent use. I wondered even in the AIDS wasting use that the sponsor had, if they speak of some post-marketing problems. Nevertheless, I think if you're talking and limiting it to 4 weeks, I think it's relatively safe. We

can all be concerned about the proliferative effects of growth hormone on malignancy, et cetera. But I think in the context of a 4-week period, it's reasonable and I think they've met the safety concerns.

DR. WOLFE: Dr. LaMont?

DR. LaMONT: Yes. I think there are specific safety concerns with this drug and virtually every drug that we give to patients. We've already talked about them.

We have a very high rate here of edema in patients who already are borderline and in relative imbalance regarding fluid intake. Then they have to be treated with diuretics or given more fluid or salt restricted. So that's definitely a safety concern for me.

I notice also -- and we didn't talk about this -- that it looks like some patients that received active drug in both categories with or without SOD and glutamine had an increase in platelet count. This again would be something I would be concerned about especially in patients with lines that can cause thrombophlebitis. So my answer is yes.

DR. WOLFE: Mr. Swensen.

DR. SWENSEN: I have no comment at this time.

DR. WOLFE: Thank you.

Dr. Camilleri.

DR. CAMILLERI: I have no additional comment to

the points made by Dr. LaMont.

DR. WOLFE: I do have a few comments. First of all, this question really doesn't have a tremendous amount of relevance because right now there is going to be a 4-week limitation for its use. There are no data that suggest long-term safety in adults. Adults are not children. There's a difference. The only indications are pediatric indications, except for slim disease, wasting from AIDS. Risk-benefit ratio. What can a drug possibly do that would overcome the benefit to these patients with HIV infection as they're wasting away?

Pediatric populations. How long has the drug been out? 15 years, 20 years? I'm not even sure how long it's been. 12 years.

VOICE: 40.

DR. WOLFE: 40 years.

(Off microphone speaker.)

DR. WOLFE: So for 15 years, it's been in its pure form. Pediatric populations generally don't have occult malignancies. So long-term safety will be an issue in adults in which you may have occult malignancies. This is a mitogenic factor as are many other peptides. So long-term use must be considered in the risk-benefit ratio. But they're not asking for that.

The other thing is that Dr. LaMont mentioned

edema is also an issue. It's more than edema. It's fluid retention. It can cause more serious difficulties than just cosmetic changes.

The other thing about whether you're to abuse it. I don't think third party payors would be interested in paying for it long-term.

I don't think there's been any long-term safety established in adults. I'd like to see if there is any, and I don't think there is. Not these doses certainly. So again, we have long-term data almost exclusively in the pediatric population.

Do you want to clarify?

DR. GERTNER: Well, yes, I would say that there are several thousand patients with AIDS wasting who have been treated with growth hormone at this dose for intermittent periods, usually of 3 months, and that the safety profile is there is no adverse safety issue that we are aware of apart from things that your attention have been drawn to today such as edema, hypoglycemia, which was actually extremely uncommon in this study, and everything is on the label.

DR. WOLFE: So the only really adults we had are people with advanced HIV.

DR. GERTNER: There is also, of course, a large and extensive treatment experience in adults with growth

hormone deficiency, but the dose is different in that population group.

DR. WOLFE: So now let's vote. The question again that we have here, are there specific safety concerns considering the potential for long-term use -- not short-term but long-term use -- of recombinant growth hormone in the treatment of short bowel syndrome patients? If you think there are, the answer is yes. Raise your hand.

(A show of hands.)

DR. WOLFE: There are 6 yeses.

How many say there are not?

(No response.)

DR. WOLFE: How many abstain?

(A show of hands.)

DR. WOLFE: We have 6 yeses, 3 abstentions.

We will move to the last question which has been divided into 6a and 6b. Right now we're going to talk specifically about the first part of the question. Do the data support the safety and effectiveness of recombinant growth hormone alone or in co-therapy with glutamine in patients with short bowel syndrome?

We will start with Dr. Camilleri this time.

DR. CARA: Could I get a clarification before we start the discussion? Is an answer of yes for that question yes without any additional studies concurrent? Or

is an answer yes, you recommend approval of the drug as a package now with no commitments? Or is an answer yes -- you know, to separate the two questions, for me I just need clarification.

DR. WOLFE: Dr. Houn, can I attempt a clarification and you tell me if I'm wrong? First of all, you can say yes and say there are additional studies you'd to do. They're not mutually exclusive.

Secondly, this question is not do you recommend approval of the drug. You're taking it for face value. Do you think the data presented today shows that they support the safety and effectiveness of growth hormone in co-therapy or alone with glutamine in patients with short bowel syndrome? So just take it for face value. Do you think the data that have been presented today support the fact that it is safe and effective in these patients? Is that correct?

DR. HOUN: They are looking to be found safe and effective, and if they are found safe and effective, they will be approved. So this is should it be approved because it's safe and effective. You can answer yes, but they've got to do these studies before, or the data don't quite support it. They need to do studies. Or the data do support it, but in addition post-marketing we recommend some of these other follow-ups.

DR. WOLFE: The question needs to be reworded then because otherwise that doesn't take into account question number 4 which was the most resounding no we had. So if we're looking for approvability, then we should change it to approvability.

DR. HOUN: Well, I would say this, that on number 4, the majority of members voted that the data were not generalizable, and there was a lot of concern because the studies were done in a specialized manner under special expertise, that that might preclude generalization. So your job is to tell us, those people who voted no, the data cannot be generalized, are there conditions under which you still could approve it but that would try to ensure that those issues of special education, special kinds of use or expertise needed could be labeled, product labeling, or a program of education with approval. Would that assure you'd get the results that could be generalized to other practices? So there are many ways to answer this. Give us your best advice on if you think it should be approved now, what are some suggestions for the best success for it.

DR. WOLFE: Can we change the question to the following? Would you mind? In our opinion is recombinant growth hormone approvable at the present time for the short-term treatment of short bowel syndrome, and if so, under what conditions?

DR. HOUN: I think you should just answer do you see right now there's data to support the safety and effectiveness of it. Okay?

"Approvable" has a regulatory context. That means companies get "approvable" and it means it's not for marketing approval. You have to do additional studies.

So just recommend whether existing data is presented to support safety and efficacy. Yes, but we're recommending also educational programs or labeling that says these kinds of precautions or this kind of advice on use. Or no, there's insufficient data now. They need to do X, Y, and Z studies. Then we believe there will be enough data.

DR. WOLFE: That actually helps me. Therefore, this question will be handled in the following way. We'll have a generalized discussion around the table, and then we'll go back again and give you a vote. You can then at that time say yes; yes with the following caveat; yes, the following caveat includes the following; or yes, it's great. Approved. You want to have it used by tomorrow, approved by tomorrow. So we'll go in general discussion.

DR. LEVINE: One point of clarification.

DR. WOLFE: Sure. By the way, I'd like to remain with using Roberts Rules of Order, and that includes points of clarification takes precedence over anything.

DR. LEVINE: You alluded, Dr. Houn, that we were going to vote on their study. Does that mandate that it includes glutamine as opposed to approving the growth hormone? Because the way this states it here, safety and effectiveness of the growth hormone and glutamine or in co-therapy. Are we allowed to comment on that and then decisively say with or without?

DR. HOUN: Yes, you're allowed to comment on that. Give us your best advice. Certainly the studies, as they were conducted, which included with and without glutamine, would go in labeling of the clinical trials. We would let physicians know what were the data and how the trials were conducted. If there are any other comments you have on this, give us your best advice.

DR. WOLFE: So again, I'd like to go around the room right now, unless you have a point of clarification, and just discuss the first part of the question. We'll then go back. You'll be able to give your vote with suggestions for future studies as part of your vote. That's how we're going to do it. Dr. Camilleri, we'll start with you.

DR. CAMILLERI: I looked at this in different bits and pieces. Efficacy I think I answered in response to question number 1 and 2, and in my opinion, despite all the negotiations and the prior agreements, the endpoint of

this study does not meet what I would regard as criteria to make this clinically efficacious therapy. Therefore, from an efficacy standpoint, especially in the context of growth hormone alone where the data were not as robust as the effects of growth hormone with glutamine in this particular study, I do not perceive that either of those two arms reached a clinically significant endpoint for efficacy.

To me effectiveness is not tested in a single clinical trial. Effectiveness is when you use the medication or the device out in the community and you appraise its applicability in the general population. It might be assessed in phase IV, but I would like us to think about that word should really be efficacy.

Third point. Generalizability. I have previously stated that in my opinion the breadth of the patient derivation for this study was sufficient to make me comfortable that the patients were typical of the type of condition that we need to treat with short bowel syndrome.

With the perspective of safety, I think that there's a lot of data already in the literature, very minor things that came up in the context of this study. And again in the surveillance program or phase IV, one could acquire more information on platelet count, edema, et cetera to make me quite comfortable that it would be safe. So I think there's some data gathering information which

could be acquired later.

DR. WOLFE: Mr. Swensen.

DR. SWENSEN: I know that there's a significant amount of interest among many people with short bowel syndrome in growth hormone therapy. It's been kicking around for a long time. It's been fairly controversial, but many short bowel syndrome patients continue to express an active interest in it. And they do that in the context where they are looking at potentially serious complications of short bowel syndrome such as TPN-associated liver disease or metabolic bone disease or venous access issues or whatever it might be. And although many of them certainly would not portray the quality of life on TPN in a highly negative way -- I mean, many of them would state unequivocally that they have a very high quality of life on TPN -- they certainly do want to dodge some of these bullets if they can, and it's in that context that they would judge this issue of safety.

I think that for the most part they would conclude that the safety issues associated with -- I say nothing about glutamine, but with growth hormone are far less threatening than associated with the complications that may prompt them to take this step.

On the subject of effectiveness, I just think that remains to be seen.

Did you make a distinction between approvable and approval that would bear on that?

DR. HOUN: In our regulations, "approvable" means that the application is not approved for marketing but can be if the company corrects these various deficiencies. "Approval" means the company can go ahead and market the product.

DR. SWENSEN: So such considerations as we're raising here might factor into your final statement to the company.

DR. HOUN: Right.

DR. SWENSEN: Thank you.

MS. JOYCE: Excuse me, Dr. Wolfe. I apologize for interrupting. I think it might be helpful to clarify whether the additional information that you would like to seek from the sponsor is required in a phase III context or in a post-approval phase IV. That's very important.

DR. WOLFE: I think that was implicit in the question and Dr. Houn's explanation.

Dr. LaMont.

DR. LaMONT: Yes. I think the data discussed here support safety and effectiveness in reducing the TPN requirement.

DR. WOLFE: Dr. Levine.

DR. LEVINE: I would have a caveat that I think

in the 4-week period they've shown probable safety. Effectiveness, probable, but I do not think it should be necessarily in conjunction with glutamine. In the analysis that was done and some of the statistics that were handed out, it was shown that if you looked at the effectiveness of glutamine, there was really no effect if you isolated the group with -- am I correct, Dr. Gallo-Torres, in one of your slides, that the one with glutamine and growth hormone versus growth hormone alone?

DR. GALLO-TORRES: It was actually the other way around.

DR. LEVINE: The other way around? Phrase it for me then.

DR. GALLO-TORRES: The co-therapy of the growth hormone with glutamine was more effective than the co-therapy of the growth hormone with SOD.

DR. LEVINE: Regarding that anyway, I'm not comfortable with the evidence. Even though the statistics did show in their analysis that glutamine had a marginal increase, I think it's something that I would like to have looked at again. So I feel comfortable with rhGH alone rather than in co-therapy with glutamine.

DR. KOCH: I just wanted to add a point of clarification. When you compare the combination of glutamine and growth factor to the control group, which was

the diet plus glutamine, what you're actually assessing is growth factor because the control is diet plus glutamine, and the combination is diet plus glutamine plus growth factor. So that comparison is actually addressing the effect of growth factor.

DR. WOLFE: With all due respect, I'd really like to limit the comments now to the panel.

Dr. Shih.

DR. SHIH: I think the data support. However, it doesn't support it adequately. In FDA's guideline, we read that the study has to be well-controlled, well-conducted, well-analyzed. I believe it was well-controlled and well-analyzed, but again, this is essentially a single-center study, so that's why I say it does not support adequately. Therefore, I think we need to have additional studies, which is the next question.

I actually see this as like a phase II study, not a phase III. Therefore, I don't think this is approvable conditioned on some post-marketing study. I think it's approvable conditioned on a phase III study. I view this as like a phase II.

DR. WOLFE: Ms. Cohen?

MS. COHEN: I listened to Ms. Boblitt, and I asked her questions specifically. And she is in the real world trying to get help, and there are going to be

zillions -- these 10,000 people. And I'd like to know where they are. Let's find them and let's see if we can get them in some clinical trials, not in the perfect setting, but in the real world setting. If you talk about 10,000 people, someone has to know where they are or they wouldn't have said there were 10,000 people.

But I am concerned what you went through. And you're intelligent woman, and you were smart enough to be able to seek something out. But the FTC talks about the typical and average consumer, and they have to deal in the world.

I am concerned about the edema. I really am.

And the other thing -- I don't know how to say it tactfully, so I'll do the best I can. There's been between FDA and this lovely company in Rockland, Massachusetts the idea of one clinical study or two. There's such a thing as intellectual curiosity and somehow you hope in science sometimes you seek out further information and you move out. So recognizing what I heard -- and I heard some distress back there -- as scientists and people with curiosity, sometimes you have to move on and say, well, you know, this is inadequate. I have to do something more. So I think the responsibility rests with a lot of us, and with due respect to them -- and I really appreciate what they've done -- I think it's the wrong way

to go and say, well, the FDA said we only had to do this. Let's move forward and say, well, we can do better and we can do more.

So speaking as a consumer advocate, I worry about the consumer, and if this is approved in the future or when it's approved, I hope we can get information out for physicians who will spend time enough and nutritionists who we can deal with. I think nutritionists should be involved in this program because this is all about nutrition, as well as medication.

So I hope I didn't offend anybody, but I had to say what was in my heart.

DR. WOLFE: Dr. Cara.

DR. CARA: Are we only addressing 6a now?

DR. WOLFE: We'll address 6b the next time.

DR. CARA: Given the agreed upon endpoints that we've discussed previously, I think that the data do support the safety and effectiveness of growth hormone alone or in combination with glutamine in patients with short bowel syndrome, given that it will be used in a specialized care setting with multi-disciplinary involvement and as an adjunct to dietary therapy.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: I have no safety concerns for the requested label indication of 4 weeks. Not a question that

I'm asking for an answer to. For the data presented, I believe there is efficacy of the compound over the placebo arm. I'm uncomfortable and I don't know what the regulatory precedent is for data only being derived from a single center. At the single center, the data were, I feel, fairly robust, but I'm concerned that it was only a single center.

DR. WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: I should point out once more that this is a rare indication comparatively. It is an orphan drug, and there are some very, very practical, real-world problems quite apart from high cost that would confront any sponsor doing this. Now, the sponsor can speak for themselves, but I would point out that in doing more, that ways have been alluded to here in which a -- I'll use the term controlled marketing or a way of providing this to patients like Brenda is it?

MS. BOBLITT: Yes.

DR. GOLDSTEIN: Yes. I remembered because that's my third daughter's name.

But there are ways of providing this in a scientific, reasonable fashion that would allow many patients to receive benefit from it because I fear that it is conceivable that if too high a hurdle is placed, it may not get done. Of course, the company can speak for itself,

but in evaluating all the real world practicalities, I think you have to look at it in this context.

DR. WOLFE: It's a difficult question to answer. Actually I was thinking the same thing about your long, lost daughter Brenda. But again, when you say "believe" -- a lot of people said "believe" around the room on the panel here -- belief is in religion and in science, you look at the facts. Again, yes, this is a rare entity. Yes, this is an orphan drug. That's why there are 41 patients and not 400 patients.

Again, I don't like moving targets. There was a target given. A multicenter study is not 92 percent of the patients or 93 percent of the patients at one site and the rest at another. So I don't think anyone here wants to see the study repeated.

On the other hand, my personal view is that -- has efficacy been shown?

Well, let's first do the easy one. 4 weeks of safety, not an issue. It's safe. It's been shown, and I don't see how there would be a problem, especially when one considers the risk versus benefit ratio. Even the edema in that short period of time is no concern to me.

The question of efficacy. Yes, in this center efficacy was shown. But I have to go back to question number 4 and I don't think it's generalizable at this

specific point. So because of that, I would have to say no. Effectiveness has not been shown in a generalizable fashion.

Now, we'll go around the room again and try to give, if you can, a yes/no. Then you can go a little further, if you want. While you're saying yes or no, please use one of those two words, not both. One or the other. And then you can explain it.

And then go on to the second part. What else would you like to see done? Again, you can say, for example -- it was brought up -- yes, this is approvable as is in a phase III study and you want more studies done and post-marketing surveillance to corroborate what has been found in phase III. If I'm wrong, please tell me. You can also say, no, it's not at this point. You'd like to see a few more patients done in different centers or whatever it is before phase III approval would be recommended.

So again, keep those in mind. I'd like to hear a yes or a no. 6a is yes or no. You can explain why you're saying it. That's no problem, but just please say yes or no for Tom's sake. And then if you want more studies, whether it's yes or no, say what studies you'd like to see. We'll start in the same order with Dr. Camilleri.

DR. CAMILLERI: No. I think a phase III study

with a different endpoint that is valid and clinically relevant needs to be done.

DR. SWENSEN: Yes. My concern with this is this sort of quixotic notion that the question of safety ultimately is going to fall into the hands of the physicians and clinicians who administer this intervention to the patients. I have serious misgivings that the standard of care is at a place where it can ensure safety for the large percentage of patients. So if I were going to recommend any additional studies, they would be that some attention be directed to who's going to be administering this therapy and whether or not they actually have the means to follow up on it in a credible and convincing way.

DR. WOLFE: You're answer is yes.

DR. SWENSEN: Yes, to 6a and then my comments concern 6b.

DR. WOLFE: Okay.

Dr. LaMont.

DR. LaMONT: My answer is yes to 6a. As I said before, it's a small study, a single center, but it has an adequate and clinically important endpoint. I think we need additional studies on dose and duration. I would like to see in future studies that we have intermediate time points such as at 2 weeks, 4 weeks, 6 weeks, and so forth.

I believe that either the package insert or the instructions from the FDA would restrict or attempt to restrict the use to centers that can adequately follow this kind of complex therapy.

DR. WOLFE: Dr. Levine.

DR. LEVINE: I would say yes to safety and right now no to efficacy. I would like to see a smaller study pre-marketing that involves perhaps two arms instead of three arms, if you have a glutamine one or if you have the all-three one. But in either event, I think you need to show some more efficacy for the reasons that Dr. Camilleri mentioned, and I think it would be nice to have perhaps on a smaller basis, almost like a pharmacokinetic study -- but I don't think you need a large number -- you could look dose and duration, certainly dosage variation, and I would recommend that too.

DR. WOLFE: I'm going to vote no, although I wish I could vote a provisional yes. But you can't. You have to say no as the data stands right now. Again, I'm trying to be consistent. I do not want to reinvent the wheel or all of a sudden say, no, we changed our mind, here's your new target. You were given permission for two centers. Now, if you want to get a third center, that's fine, but I'd like to see some more patients and that can be negotiated with FDA how many more patients there would

be at another center. I'm not saying repeat this thing, another 40 patients. I'm saying another 6 to 10 patients that shows the same trend continues in these other places that don't include such a stellar center in which everything is under ideal conditions. Once that's shown, it is truly a multicenter trial in a very small number of individuals which then allows for generalizability which then makes the drug approvable.

And the glutamine versus non-glutamine, that's between you and FDA as far as I'm concerned. My personal bias is I would include it.

I'm sorry. One last thing. I would want to see follow-up data so we can answer some other scientific questions. The ramifications are dramatic. If we can reverse the process, you could get a person off TPN entirely, that's very, very important. But for me 12 weeks isn't enough. I want to see multiple time points with multiple parameters at 12 weeks, 24 weeks, 48 weeks. It's almost a year, not quite. That's what I'd like to see.

DR. SHIH: I see this as a very successful phase II study. I would like to see a truly randomized, multicenter phase III study.

DR. WOLFE: Your answer is no.

DR. SHIH: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: I'd like to see come community clinics being used around the country, not very isolated kind of superior environment to do these studies. I think we have to include the real people in the real world.

I have some concerns that the studies are inadequate and I don't know that they can be extrapolated. The people on this panel think it can be. I'm not convinced.

DR. WOLFE: I take it you're a no.

Dr. Cara.

DR. CARA: This is a tough one. You talked about science and religion and somewhere they've got to come together. Right?

I'm going to vote yes on safety and efficacy. I think in terms of the parameters that were identified and discussed and according to the study that were agreed upon by the FDA and the sponsor, I think that the drug has been shown to be safe and effective.

I do have some other studies that I would recommend, however, or other issues that I would recommend that the FDA try to enforce, if at all possible, either before the drug is approved or after. And that is that I think establishing an educational support program for physicians and patients both is very critical, and the details of that can be decided upon by the FDA. But an

example could be a very effective web-based program.

There needs to be very specific guidelines for monitoring in patient selection. We haven't talked about patient selection a great deal, but I think that developing appropriate patient selection criteria, along the lines of what the sponsor identified as patient selection criteria for the study, needs to be done.

I also think that ability of physicians to at least prescribe the medication has to be monitored closely, and whether or not there needs to be an approval process in place as there was initially with growth hormone for children, I don't know. I'll leave that up to the FDA.

Obviously, setting up a post-marketing study I think would be critical to establish the long-term safety of the medication and its durability of efficacy, specifically in regard to nutritional status, but also as a way of looking at some of the surrogate markers that the sponsor alluded to, incidence of infections, quality of life, nutritional status, bone density, and so on and so forth. That should not be all that difficult to do.

Those are my suggestions.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: Also kind of on the fence. When I look at the data, I still see a substantial proportion of patients on treatment in comparison to the placebo group

which were effectively weaned off therapy. I also for the request of the label indication see no safety concerns. I do vote no, though. I'm uncomfortable with a single-center study.

My recommendation is that a 1-year study be done. The primary endpoint perhaps for that 1-year study could be at various time points the patients which were successfully weaned off TPN. I don't believe that the year study needs to be complete for the application to be approved for acute use, one-time use. However, I would like to see a 1-year study to address the durability effect when the drug is on the market.

I also believe there should be a registry to help ensure that proper use of the drug is being done, a measure to look at success of the drug.

DR. WOLFE: Any more comments?

(No response.)

DR. WOLFE: I just wanted to add one last thing I would recommend. By the way, I didn't think you could get away with a year. I want the short-term, just the additional few patients. 4 weeks. You could show it. That's it. The rest of the data is corroborating information which could help down the road.

I think it's very important in this day and age to start thinking of doing a study to look at the overall

cost. How does this 4 weeks of therapy when you consider all the savings in line sepsis? If it's a durable effect, what's the savings in TPN solutions? I think that's really helpful now as we're all worried about how much everything costs overall. I know the FDA doesn't care quite as much, but we do care quite a bit about that, and I think people in the community will care.

Are there any more comments or questions? Yes, Dr. LaMont.

DR. LaMONT: Yes. This is a naive question, but if this application were approved for Serostim, would it apply to all the other recombinant growth hormones or just to this one? Just this one.

DR. HOUN: Yes. The other companies would have to come in with their studies.

DR. WOLFE: Just as the prerogative of the chairman, I want to make one last comment. I really enjoyed this meeting because part of our job is to provide -- the FDA is free to take our advice or not. But I think we provided a lot of feedback, a lot of information in answer to the questions.

I hope the sponsor finds the comments helpful. I'm sure they wanted a more robust, affirmative response from us. I think everybody looked at the data very carefully and voted not what they believed, but what they

felt was evident by what was seen with regard to the presentations.

So I want to thank everybody for their hard work, and I'll see some of you tomorrow and I'll see some of you elsewhere.

(Whereupon, at 4:38 p.m., the committee was recessed, to reconvene at 8:30 a.m., Thursday, June 26, 2003.)