FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

THURSDAY, MAY 27, 2010

8:00 a.m. to 4:30 p.m.

The Inn and Conference Center

University of Maryland/University College

3501 University Boulevard East

Adelphi, Maryland

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I N D E X

I N D E X (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. BURMAN: Good morning. Welcome. I'd first like to remind everyone present to please silence your cell phones, Blackberrys, and other devices if you have not already done so.

I would also like to identify the FDA press contact, Ms. Erica Jefferson. If you are here, please make yourself known. Thank you very much.

My name is Dr. Kenneth Burman. I am chair of the Endocrinologic and Metabolic Drugs Advisory Committee. I will now call the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee to order.

We will go around the room, and please, introduce yourself. We will start with the FDA and Dr. Curtis Rosebraugh, to my left, and then go around the table.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II.

DR. PARKS: Mary Parks, Division Director, Metabolism and Endocrinology Products.

DR. ROMAN: Dragos Roman, Medical Team Leader, Division of Metabolism and Endocrinology Products.

DR. MOHAMADI: Ali Mohamadi, Clinical Reviewer.

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

DR. DOBS: Adrian Dobs, Johns Hopkins University.

DR. MORSE: Caryn Morse, NIAID.

DR. FELNER: Eric Felner, Associate Professor of Pediatrics, Emory University, Atlanta.

DR. GOLDFINE: Allison Goldfine, Associate Professor, Harvard, Joslin Diabetes Center.

DR. PROSCHAN: Michael Proschan. I'm a mathematical statistician at NIAID.

DR. BURMAN: Ken Burman. I'm Chair of Endocrinology at the Washington Hospital Center and Professor of Medicine at Georgetown University.

DR. TRAN: Paul Tran, the DFO for the Endocrinologic and Metabolic Drugs Advisory Committee.

DR. FLEGAL: Katherine Flegal,

Epidemiologist, Centers for Disease Control and Prevention.

DR. HENDERSON: Jessica Henderson. I'm the consumer representative.

DR. THOMAS: Abraham Thomas, Division Head, Endocrinology, Henry Ford Hospital.

DR. BISHOPRIC: George Bishopric, community representative.

DR. KUMAR: Princy Kumar, Chief of Infectious Diseases at Georgetown University.

DR. MOLITCH: Mark Molitch, an endocrinologist at Northwestern University in Chicago.

MS. SWAN: Tracy Swan, consumer representative, AIDS Treatment Action Coalition and Treatment Action Group.

DR. CARGILL: Vicky Cargill, Office of AIDS Research, Director of Minority Health and Clinical Studies.

DR. VELTRI: Rick Veltri, Merck Research Laboratories, industry representative.

DR. BURMAN: Thank you. For topics such as those being discussed at today's meeting, there are

often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion.

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

DR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the

Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of this committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have

potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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

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

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

Today's agenda involves a discussion of the

New Drug Application, NDA, 22-505, Egrifta, sterile lyophilized powder for injection, by Theratechnologies, Inc. The proposed indication for the drug is to induce and maintain a reduction of excess visceral abdominal fat in HIV-infected patients with lipodystrophy.

This is a particular matters meeting during which specific matters related to Egrifta will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made regarding the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Enrico Veltri is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Veltri's role at this meeting

is to represent industry in general and not any particular company. Dr. Veltri is employed by Merck.

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

FDA encourages all other participants to advise the committee of any financial relationship that they may have with the firm at issue. Thank you.

DR. BURMAN: Thank you. We will now proceed with the FDA opening remarks from Dr. Mary Parks.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

Dr. Parks?

DR. PARKS: Thank you, Dr. Burman. My remarks are actually very brief, not requiring any

slides. So I'll make it from the table here.

Today, the advisory committee panel will be hearing about Egrifta, or tesamorelin acetate. It's a novel therapeutic, hypothalamic-somatotropic axis to treat lipodystrophy in patients with HIV infection.

The specific indication sought is to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. You will hear from both the sponsor and the FDA, the rationale for targeting this aspect of HIV. You will also hear about the endpoint measures and what is the expected clinical relevance of reducing the primary efficacy endpoint, visceral adipose tissue.

These efficacy findings will need to be weighed against the safety findings, particularly in the setting of prolonged use of Egrifta. The agency looks forward to hearing the presentations of the sponsor. We also look forward to hearing the panel members' discussions and your overall recommendation on this drug application.

Thank you.

DR. BURMAN: Thank you. We will now proceed

with the sponsor presentations. I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interest and those based upon the outcome of the meeting.

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

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

I'd like to invite the sponsor, I believe, Dr. Ortega.

DR. ORTEGA: Good morning. My name is Martine Ortega. I am Vice President, Regulatory Affairs for Theratechnologies. On behalf of all of us at Theratechnologies, I am very pleased to welcome you this morning.

We appreciate the opportunity to be here with you today, and so we would like to express our thanks to the FDA for their support and cooperation, and we look forward to continuing to work with the agency to make tesamorelin an asset for the public health.

Tesamorelin is a human growth hormone-releasing factor analogue. It is a synthetic peptide comprised of 44 amino acids, with a hydrophobic chain at the N-terminus. This chemical modification decreases the degradation of the peptide, therefore,

increasing its half-life as compared to the natural human GRF.

Tesamorelin stimulates the natural secretion of growth hormone by the pituitary gland in a pulsatile and physiological manner. Unlike the exogenous administration of growth hormone, the biological secretion induced by tesamorelin administration will be modulated by the normal physiological pathway.

Additionally, tesamorelin's mechanism of action will be presented later by Dr. Grinspoon.

Tesamorelin is supplied in a vial containing a lyophilized powder to be reconstituted with sterile water for injection. The recommended daily dose is 2 milligrams to be administered by subcutaneous injection in the abdomen.

Theratechnologies is seeking approval for the following indication. Tesamorelin is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. I'll remind you that currently, there is no FDA-approved treatment for this indication.

We have a number of experts with us today to answer questions and take part in our discussions. The following speakers will contribute to this presentation.

Dr. Grinspoon will begin by presenting some background information on HIV-associated lipodystrophy, as well as the rationale behind the use of GHRH in this unique population.

Dr. Grinspoon is a professor of Medicine at Harvard Medical School and the director of the Mass. General Hospital program in nutritional metabolism. He also was the lead investigator for the tesamorelin trials in the U.S.

Following Dr. Grinspoon will be Dr. Christian Marsolais, Vice President, Clinical Research and Medical Affairs at Theratechnologies. Dr. Marsolais will present the tesamorelin clinical development program and the efficacy results. Dr. Marsolais will also act as the moderator for the Q&A session.

Afterwards, Dr. Graziella Soulban, Director-Clinical Research at Theratechnologies, will summarize

the safety results. And finally, Dr. Schambelan will conclude this presentation with an overview of the clinical need for treatment for lipohypertrophy in HIV-infected patients and his analysis of the benefits and risks associated with the use of tesamorelin in this indication.

Dr. Schambelan is Professor Emeritus of Medicine at the University of California at San Francisco and Associate Chair for Clinical and Translational Research.

With that, I would like to invite Dr. Grinspoon to continue this presentation. Thank you.

DR. GRINSPOON: It's really a pleasure to be able to speak to you today. I am the lead investigator for the Phase 3 clinical program. I am a consultant to Theratechnologies. I do not have any equity interests or any other financial interests in the company.

So as Dr. Ortega said, I will be discussing today with you background on HIV-associated lipodystrophy and some rationale for the use of GHRH in this population.

HIV lipodystrophy is a syndrome which refers to changes in body composition; particularly, as will be the focus today, lipohypertrophy, but also, importantly, lipoatrophy, and also, a mixed syndrome.

In terms of lipohypertrophy, patients experience increased abdominal girth. Interestingly, this is uniquely composed of excess visceral adipose tissue, but at the same time, significant loss of subcutaneous adipose tissue, making it unique from obesity, per se.

There is enlargement of the dorso-cervical fat pad, or termed buffalo hump. Women can experience increased breast size, and patients can experience single or multiple lipomas.

In terms of the lipoatrophy, there is loss of fat in the face. This can often be stigmatizing to patients. There's also loss of subcutaneous fat in the arms, legs, buttocks, and abdomen.

In terms of metabolic features, we can often see dyslipidemia. This is primarily manifested as increased triglycerides, but also, increased total cholesterol, increased LDL, and reduced HDL

cholesterol.

As will be discussed at length today, patients can have altered glucose homeostasis at baseline with this particular problem. They can experience abnormalities and perturbations in metabolic inflammatory markers and adipokines, including reductions in adiponectin and increased inflammatory markers.

It has become increasingly apparent that the changes in body composition are associated with the use of antiretroviral therapy. This is a slide taken from a CPCRA study of Shlay, et al. And note that it's published fairly recently, in the current era of HAART.

This study shows, on the left, subcutaneous adipose tissue and on the right, visceral adipose tissue. And the colors refer to the randomization to PI, NNRTI, or PI plus NNRTI. And you can see, focusing, first, on the subcutaneous tissue, an increase in subcutaneous tissue initially, but ultimately, in most groups, a reduction in subcutaneous tissue below the baseline level.

At the same time as the subcutaneous fat is ultimately lost over 48 months, visceral adipose tissue is accumulating, and therefore, you see a picture in which VAT accumulates and SAT is lost.

These data present an interesting conundrum to us today, because today HIV patients are living longer due to the success of antiretroviral therapy to improve immune function. But at the same time that HAART allows viral control, it induces long-term side effects that need to be managed, and that's why we're here today.

Today, a larger proportion of HIV-positive patients are, in fact, dying of cardiovascular disease. Therefore, modification of cardiovascular risk factors has become a significant focus of treatment intervention.

HIV-positive patients with excess abdominal fat express physical discomfort and psychological distress. Excessive abdominal fat may impact quality of life and treatment adherence or initiation.

Unfortunately, results from lifestyle and exercise studies have been very inconsistent, and if

you have questions on that, you can ask later. To date, no pharmacologic intervention has been approved by the FDA for the management abdominal lipohypertrophy in this population.

So to orient you to this syndrome, here are a number of pictures. On the top row are two patients, a male and a female, with obvious abdominal lipohypertrophy, one in profile and then the female both face on and in profile.

On the lower row, you can see, on the left, a patient with loss of subcutaneous fat in his face, hollow, sunken cheeks; in the middle-lower panel, a patient with a severe buffalo hump; and on the right-lower panel, a very important picture showing the complete loss of subcutaneous fat in a patient; and this patient might, also, at the same time, have increased visceral adipose tissue. You can see the veins very clearly; not because there's anything wrong with the veins, but because there's lack of subcutaneous adipose tissue.

This is a cross-sectional CT scan of a patient, on the left, with significant abdominal

lipohypertrophy. It's taken at L4. And you can see, in blue, that there's very little subcutaneous adipose tissue, but at the same time, in green, there's a significant excess of visceral adipose tissue. So this lipohypertrophy and increased waist circumference is uniquely composed of excess VAT, but lack of SAT.

To look at this in a more quantified fashion, we conducted a study in which we matched patients by weight and looked among patients in the normal weight and overweight category. On the left is VAT, on the right SAT. And you can see, in either the normal weight group or the overweight group, there is a significant excess of VAT in weight-matched patients, HIV in blue, control in white, whereas the converse is seen in terms of SAT. In both the normal and overweight group, there is a loss of SAT.

What is the prevalence of these abnormalities in HIV-infected patients? This is a slide that's difficult to read, but it comprises the studies that we are aware of looking at the prevalence of this condition.

To summarize, the data from the literature

indicate that the prevalence of excess abdominal fat accumulation, or lipohypertrophy, in HIV-positive patients is around 30 percent, and this continues to be seen in the current era of HAART.

I point out the study by Nguyen, et al, in 2008 from the Swiss HIV Cohort. This is a study of over 5,000 patients. It was published in 2008, fairly recently. And in that study, 22.3 percent of the patients showed abdominal fat accumulation.

Can we use waist circumference to identify HIV-positive patients with increased VAT? What is the feasibility and significance of this? A waist circumference of 95 centimeters reflects the point at which mortality begins to increase in non-HIV-positive patients, even after adjustment for BMI.

I draw your attention to the lower right-hand corner of the panel, and you can see the study by Pischon, et al, which shows waist circumference on the X-axis and relative risk of death on the Y. These are data adjusted for BMI. And you can see that at a waist circumference of 95, the relative risk of death increases.

A waist circumference of 95 for men and 94 for women were actually used in the Phase 3 studies, which you'll hear about today, to identify populations with increased VAT, and we were very successful at identifying population with excess VAT. You will hear about that.

But importantly, 25 percent of HIV-positive patients, indeed, demonstrate a waist circumference more than 95 centimeters. So you can use waist circumference as a surrogate to identify these patients fairly easily; and indeed, this is a relevant surrogate, because it's associated with risk of death in a large study.

Excess VAT is associated with problems in quality of life, belly image appearance distress and adherence to HAART. These are data taken from a particular tool that we will talk about more today, but we are plotting the distress related to the patient's belly on the X-axis and the visceral adipose tissue on the Y-axis. And you can see -- this is among a large cohort of patients, prior to any drug -- that there is an association between excess VAT and

worsening of distress the patient feels about their belly or abdomen.

Interestingly, today, you will hear data to suggest that we do reduce VAT, but the reduction in VAT comes in tight association with the improvement of belly appearance distress.

Can excess VAT affect adherence to HAART? Well, let's look at the data from the APROCO study. This is a study in which 277 patients were initially adherent four months after initiation of protease inhibitor-containing regimen. Twenty months after initiation of treatment, 30 percent of patients failed to maintain adherence. Sixty percent of non-adherent patient reported bigger belly or wider waist.

In a separate study by Plankey, et al, they looked at multivariate adjusted odds ratios associated with self-reported less than 95 percent adherence to antiretroviral therapy. In looking at this analysis, in yellow, you can see that any central fat gain versus no change was the one factor that most significantly predicted non-adherence in this study, even more so than loss of fat.

Excess VAT is also associated with metabolic abnormalities. This is a study that our group published a couple of years ago now and in this study, we compared patients with HIV lipodystrophy to age, BMI, gender, and race-matched subjects from the Framingham offspring cohort. We used dichotomized WHO cut-points in this analysis.

You'll see that there is, in blue, HIV, in white, non-HIV, a significant increase in the prevalence of hypercholesterolemia, high LDL, but it's dwarfed by the abnormalities in hypertriglyceridemia and low HDL.

To the right of the screen, you'll see markers of glucose abnormalities; and using a two-hour glucose test with a glucose more than 200, 7.0 percent demonstrated diabetes versus .5 percent of the age and BMI-matched control. More ominously, 35 percent of patients demonstrated glucose intolerance with a two-hour glucose more than 140. This is versus 5 percent of controls.

Looking at the FRAM data, you can see there is a significant and tight association between excess

VAT and hypertriglyceridemia, linking directly the metabolic abnormalities and the body composition abnormalities.

Circled in red, you can see, with increasing tertiles of VAT, increasing triglyceride levels. The converse is seen actually with SAT. It's the same general pattern you see among control men, but it's more exaggerated, because there's more visceral fat accumulation and higher triglyceride levels.

What about inflammatory adipokines? We published a study a couple of years ago and it's been confirmed by a number of groups now that adiponectin levels are lower in patients with HIV lipodystrophy. The blue bar represents HIV patients with lipodystrophy. The green and the white represent, respectively, HIV without lipodystrophy and control, all carefully age and BMI-matched. And you can see a significant reduction in adiponectin. And this is not a good situation, as low adiponectin levels increase cardiovascular risk.

In fact, when you look more carefully at the data, you can see a significant association between

trunk to total fat ratio and adiponectin levels. The higher the trunk fat to total fat ratio, the lower the adiponectin levels, and, conversely, with extremity to total fat, suggesting, again, a direct link between the body composition abnormalities and some of the inflammatory and metabolic perturbations.

The ultimate question is whether these patients have cardiovascular disease, and the emerging data really suggests this is, indeed, the case. This is a study published from the Research Patient Data Registry at the Mass. General and the Brigham. The blue line represents HIV patients, over 4,000 of them, and the white line represents non-HIV, and the patients are stratified by age.

You can see at any age, including young age, there's a higher rate of myocardial infarction in HIV patients compared to controls; and, in fact, this seems to increase with increased age of the patients.

Recently, some data came out from Guaraldi, et al, linking specifically excess VAT to cardiovascular risk in HIV patients, and this is important. In this particular study, a multivariable

generalized equation was performed, and you can see that VAT is associated with coronary calcium, a marker of subclinical atherosclerosis. This is true even in a model controlling for age, LDL, months of NRTI, and CD4 cell count.

Even more importantly, he presented, this year, data suggesting that VAT is not only associated with CAC, a cardiovascular risk marker, but CDV events, per se. And again, in a regression model, excess VAT was associated with events, and this is true when you controlled for exposure to ART and age.

So what then are the potential treatment strategies for this abnormality in HIV-positive patients? Well, first, it's important to note that numerous expert panels have looked at this and concluded over the years that there is no treatment right now, but there is a need for one. In 2010, there are still no approved interventions for the treatment of fat accumulation in this population.

The potential strategies that are available include the following. I don't have time to go into these at great length, but I'll summarize by saying

that lifestyle modification is always important, including diet and exercise; but unfortunately, the studies are very, very inconsistent in this regard and do not show the types of reduction in VAT you will see for tesamorelin today, and I'm happy to discuss that later.

Switching to antiretroviral therapies, another potential strategy, but, unfortunately, this, too, has not worked very well. Patients do not seem to lose the excess VAT even when they switch off antiretroviral therapeutic agents.

Insulin sensitizing agents are another very important strategy to consider. For example, metformin is an insulin sensitizing agent. It has been shown to produce modest reductions in VAT in numerous studies, but the problem is that it's also associated with generalized weight loss and loss of subcutaneous fat. So it's not selective like the agent you're going to hear about today.

I'll talk about GH and GHRH in the next few slides. So what are the potential ways in which we can manipulate the growth hormone-IGF axis to improve

metabolic abnormalities in HIV-positive patients? First, it's important to recognize that there is a very significant relationship between growth hormone and visceral fat.

In this study, we sampled growth hormone every 20 minutes overnight and showed a clear relationship, such that low growth hormone was associated with excess VAT. In fact, patients with lipodystrophy have a very significant reduction in growth hormone and a large percentage fail standard GH stimulized simulation testing.

So, of course, it's logical to consider giving growth hormone in this population, and I'm going to highlight two studies which represent the ends of a large spectrum of studies in this regard.

The study on the left is a study of high dose growth hormone. The study on the right is a study of low dose growth hormone. And I'm going to try and summarize the changes in VAT and other aspects of these studies for you.

The high dose study used a very large dose of 4 milligrams a day. It was a three-month study.

The IGF was very, very supraphysiologic. The SAT decreased. In other words, at high doses of GH, it's not discriminate to VAT. It oxidizes both VAT and SAT.

Triglycerides improved. Glucose dramatically worsened, any measure, fasting, two-hour, et cetera. And the safety was very poor. There were a lot of GH-related side effects. This was not approved by the FDA at this dose for this indication.

Low dose growth hormone, in contrast, had a different profile. It had a significant effect on VAT, but it was more on the order of around 9 or 10 percent. The study was done by my group. It was a very low dose study, .3 milligrams a day. We wanted to make it much more physiologic. It was a very long duration study, 18 months. IGF, as I said, was physiologic.

With low dose GH, there is a discrimination and SAT is not reduced. Triglycerides were improved. The overall safety was good. But I want to point out that even with lose dose GH, with IGFs largely in the physiologic range, the two-hour glucose level

increased by 20 points. And though you will see some small changes in glucose today with respect to tesamorelin, they are not of the same magnitude you see even with low dose GH, which brings me to GHRH.

Just as a simple primer, we all know that GH is produced in a pulsatile fashion from the pituitary in positive response to GHRH and negative responses to metastatin. The pituitary GH acts in the liver to make IGF-1, which feeds back on the pituitary and hypothalamus in a classic endocrine feedback loop.

Therefore, GH is pulsatile. Now, there actually have been some studies which were conducted by our group published in *American Journal of Physiology* to show that there's nothing wrong with the pulse generator in these patients. They have the same number of pulses. But the peak height and width of the pulses is off, which begs a therapy then perhaps to increase the pulsatile nature of this particular problem in these patients, and that's where GHRH comes in.

GHRH is known to augment pulse width and height without increasing the number of pulses, and in

fact, I'm happy to show you later data using tesamorelin in this regard, beautiful data, looking at effects on pulsatility.

So this rationale led us to conduct a pilot study in 2004. Now, this study was not with the product you're going to hear about today. It was with GHRH-1 to 29. This was subsequently withdrawn from the market, not for any safety reason, but for commercial reasons, by Serono.

But you can see that we saw a positive signal in this study, which led us to pursue the larger indication you'll hear about today. And you can see that there was a significant reduction in trunk fat, in blue with GHRH versus white with placebo. There was an improvement in the ratio of trunk fat to lower extremity fat. And lo and behold, not only was there not a decrease in extremity fat, there appeared to be a slight increase in extremity fat.

So there really was a redistribution from the center out the periphery of fat, no change in weight, and that's a theme today for GHRH. It really

doesn't change weight. By increasing lean and reducing VAT, it's kind of weight-neutral, but it redistributes fat.

In summary, what I've shown you today is that approximately 30 percent of HIV-positive patients demonstrate excess abdominal fat, comprised of excess VAT, but reduced SAT. This excess visceral adiposity contributes to metabolic abnormalities, excess cardiovascular risk in HIV-positive patients, increased body dysmorphia and distress, reduced quality of life, and may have a potential negative impact on adherence to antiretroviral therapy.

There are no currently approved treatment strategies for this. Improving excess visceral fat is a critical treatment goal for the HIV population. I think we can all agree upon that. There is a need for a drug that specifically addresses the unique problems of HIV lipodystrophy; those are increased VAT, reduced SAT, distress, reduced quality of life related to increased VAT, dyslipidemia, and reduced growth hormone.

Thank you very much for your attention.

DR. MARSOLAIS: Good morning. Thank you, Dr. Grinspoon. Lipodystrophy syndrome has a significant impact on people living with HIV. We refined our development strategy by adopting specific recommendations for the treatment of visceral adiposity from the Forum for Collaborative HIV Research.

The Forum for Collaborative HIV Research provides a neutral and independent platform that engages representatives from the government, the pharmaceutical industry, payers, community advocates, and members of academia. They made several recommendations for the development of new therapies to treat visceral adiposity.

First, the development of new therapies should be conducted with placebo control studies. Patient selection should be based mainly on waist circumference and waist-to-hip ratio, which correlates with accumulation of visceral adipose tissue.

The group also set some clear objectives to assess the efficacy of new therapies. Based on literature review in the obesity field and results of

the Phase 2 studies with GH and lipohypertrophy, a goal of 8 percent decrease in visceral adipose tissue was set as the primary objective for the development of new compounds for the treatment of HIV-associated visceral adiposity.

The group recommended strongly that the clinical benefit for the treatment of visceral adiposity be assessed with validated instruments that measure the impact on quality of life and body image. There should be no worsening in peripheral lipoatrophy. This is an important symptom of the lipodystrophy syndrome and it should not be exacerbated by therapeutic intervention for the treatment of lipohypertrophy.

The group also recommended monitoring of fleeing body mass, lipids, glucose, and IGF-1 levels. The clinical development plan for tesamorelin was based on those recommendations.

To evaluate the efficacy and the safety of tesamorelin, we conducted two large Phase 3 trials, including a total of 816 patients. This is the largest program completed so far to assess the new

treatment for this indication. The two studies were identical. The first one, conducted in North America, started in 2005 and the second study, including European sites, was initiated in February 2007.

The study design included two phases of 26 weeks duration each. For the main phase, the patients were randomized in a 2:1 ratio for the active treatment versus placebo. At the end of the main phase, a period of seven days was allowed for the re-randomization of patients into the extension phase.

Patients, who initially received six months of active treatment, were re-randomized to receive an additional six months effective treatment, the T-T group, or placebo, the T-P group. Therefore, one group of patients received active treatment for a total of 52 weeks.

During the entire presentation, the yellow color will represent the T-T group and the orange color will represent the T-P group. Patients who received placebo for the initial six months were switched to receive the active treatment during the extension period. This group, the P-T group, will be

presented in light blue.

Patients were enrolled in the study if they met the following eligibility criteria: HIV-positive male or female patients aged between 18 and 65 years; they had to be stable on ART at least eight weeks prior to study entry.

Abdominal fat accumulation during the context of treatment of HIV infection was measured by waist circumference and waist-to-hip ratio. We use a waist circumference of 95 centimeters or more and a waist-to-hip ratio of .94 or higher for males, and a waist circumference of 94 centimeters or more and a waist-to-hip ratio equal or over .88 for females.

Fasting blood glucose had to be below 150 milligrams per deciliter. We allowed these patients in the study based on the results obtained in a Phase 2 safety study conducted in diabetic patients in whom no impact on glucose homeostasis was observed.

Patients had to be on stable lipid-lowering agents and use of anti-diabetic insulin sensitizing agents, GH or GH agonists were excluded. The study endpoints were based on the recommendations from the

Forum for Collaborative HIV Research. The primary endpoint was a decrease of 8 percent in visceral adipose tissue from baseline, treated patients versus placebo.

Visceral adipose tissue was measured by CT scan at the L4/L5 level. Statistically, the criterion for a positive study was the lower confidence limit be below zero and the point estimate below the negative 8 percent decrease.

Secondary endpoints included lipid parameters, including triglycerides, and the total cholesterol to HDL cholesterol ratio. Serum IGF-1 level was monitored as a marker of efficacy and also, for safety assessment.

Patient-reported outcomes related to belly image were assessed with validated questionnaires. The primary objective for the extension phase was to assess the long-term safety of tesamorelin and, also, to look at the duration of effect over a 52-week period.

The presentation of the efficacy will start with the results of the first 26 weeks of the studies,

the main phase. After, we will present the results of the extension phase. For the baseline characteristics, no significant differences were observed between the treatment groups and the studies, even though the studies were conducted a year-and-a-half apart.

The mean waist circumference was about 104-105 centimeters at baseline. VAT area in centimeters squared was between 170 and 195, depending on the study. Among lipid parameters, mean triglyceride levels were above the upper limit of normal, with a value in the range of 223 to 252 milligrams per deciliter.

It is important to note that 46 percent of our population was on lipid-lowering treatment. We also monitored some baseline characteristics related to HIV status of the patient population. As you can see, patients enrolled in the study had fairly high CD4 counts. Viral load for most of the patients was undetectable, with only about 9 percent of patients with a viral load above 400.

The use of different classes of

antiretroviral therapy was similar between the different groups and studies, with the exception of the use of non-nucleoside reverse transcriptase inhibitors in the first study. However, when the statistical analysis was adjusted for the use of NNRTI, there was no impact on visceral adipose tissue.

These results are important. They show the symptoms of lipodystrophy of the patient population enrolled in the study. Patients with excess abdominal fat in the context of lipodystrophy were selected based on specific waist circumference and waist-to-hip ratio cutoffs.

The results showed that more than 86 percent of the patient population had at least one additional sign of lipodystrophy in addition to the abdominal lipohypertrophy. More than 70 percent of the patients had at least one sign of lipohypertrophy. Those patients suffer from body dysmorphia, not only abdominal obesity, thus increasing the stigma associated with HIV infection.

Treatment with tesamorelin was associated with a significant decrease in VAT. In our first

trial, we showed a decrease of 15 percent in VAT versus an increase of about 5 percent in the placebo arm. In the second study, we reached a decrease of 11 percent in the treatment arm versus a small decrease of about 1 percent in the placebo-treated group.

For both studies, we have surpassed the goal of 8 percent, as recommended by the Forum for Collaborative HIV Research. The effect on the reduction of VAT was similar for male and female.

In addition, it is important that a treatment of lipohypertrophy does not further decrease the amount of subcutaneous adipose tissue in this patient population. The results showed that tesamorelin preserves abdominal subcutaneous adipose tissue.

Patients enrolled in our studies were taking different ART regimens. The analysis of the combined Phase 3 trials shows that the efficacy of tesamorelin was similar regardless of the ART regimen used by the patients.

We have conducted an exploratory responder analysis to assess the percent of patients that would

reach the primary goal of an 8 percent of VAT. Based on the analysis with the intent to treat population and the last observation carried forward, 57 percent of tesamorelin-treated patients reached a primary objective of an 8 percent decrease in VAT.

It is also important to note that the LCF analysis, if a patient did not have adipose baseline CT scan, the baseline value was used for the analysis. For the per protocol population, with the observed case analysis, 69 percent of patients treated reached a goal of a decrease of 8 percent in VAT. In both cases, the tesamorelin response was double that of placebo.

The decrease in visceral adipose tissue observed in the studies was associated with a significant decrease in waist circumference at week 26. The decreases were 2.6 and 2.2 centimeters in the first and the second studies, respectively.

We have also observed an effect on trunk fat, with a total loss of approximately 1 kilogram, as well as the lack of clinical significant effect on limb fat. We observed a statistically significant

change in limb fat in the first study, but this small decrease was not considered clinically significant.

Finally, treatment with tesamorelin does not have a significant impact on overall body weight. The loss in total fat, mainly visceral fat, is compensated by a gain in lean body mass of a similar magnitude. Therefore, we can conclude that tesamorelin decreases excess abdominal fat with preserving subcutaneous adipose tissue.

We also assessed lipid parameters. In the first trial, the LIPO-010 study, the change from baseline in lipid parameters between the tesamorelin and placebo groups reached statistical significance. It is important to remember that triglycerides were the only lipid parameter above the normal range at baseline. The impact on triglycerides was significant and much larger than for the other parameters.

In the second trial, the change in triglycerides was in the right direction. The change was statistically significant versus baseline, but not versus placebo.

We also performed an exploratory analysis

with the data from the combined studies. The analysis on the combined studies shows an overall positive impact on lipid parameters. The lipid parameters are moving in the right direction, with the most significant effect seen with triglycerides. Once again, triglycerides were the lipid parameter with the most significant abnormality at baseline.

As Dr. Grinspoon stated earlier, HIV-associated lipodystrophy is associated with an inflammatory state. We found that treatment with tesamorelin was associated with significant decrease from baseline in plasminogen activator inhibitor and tissue plasminogen activator, as well as a significant increase from baseline in adiponectin, which is an anti-inflammatory marker.

One of the most important benefits of the decrease in visceral adiposity should be a positive impact on body image and quality of life. During our meeting with the FDA to discuss our plan for the Phase 3 clinical program, the agency recommended that we use questionnaires developed by Phase V Technologies. These assess the impact on body image and health-

related quality of life, with a focus on belly image.

The development of these questionnaires is consistent with the FDA guidance for industry. The conceptual model was developed based on the literature review, panel discussion with treating physicians, and assessment of the patients' perspective through patient focus groups and qualitative analysis of Web-based postings from patients with lipodystrophy.

This was followed by confirmation with in-depth patient interviews to establish content validity. The instruments assessing body image were then field tested in another sponsor's Phase 2 trial and subsequently confirmed in their Phase 3 trial.

The dossier and the development of the questionnaire was submitted to the FDA and approved for use in making labeling claims in 2004. It is also consistent with the recent 2009 FDA guidance for industry on the use of patient-reported outcomes to support labeling claims in medicinal product development.

For a subgroup of patients, the HIV, as well as the antiretroviral treatment, will be associated

with lipodystrophy, including increase in central adiposity and peripheral lipoatrophy. The changes in body appearance impact body events, including significant body dysmorphia and distress. Body image distress and distortion will then impact health-related quality of life.

Since the effect of the drug is the reduction of central adiposity, as measured by percent change in VAT, we focus primarily on belly image. The assessment of the patient-reported outcomes, therefore, includes two components; the first one, an assessment of body image with a focus on belly, and an assessment of health-related quality of life through questionnaires.

The key parameter of belly image includes belly size evaluation. It is important to note that this is not an estimation of belly size. It is an assessment of how patients rate their current appearance compared to their healthy look.

For belly appearance distress, patients refer to their current appearance and provide a rating of distress concerning the size of their belly, the

belly appearance distress being the most important parameter and agreed upon with the FDA prior to initiation of the program.

The third belly image parameter is the belly profile assessment. The patient is provided with a set of six belly silhouettes and chooses which match their current look and their treatment goal. This last assessment is also done separately by the physician.

The baseline characteristics of the population of patients enrolled in our studies indicate that a number of body parts are rated as smaller than the normal healthy look of the patient. The body part that is the largest from the healthy look is the belly.

The baseline values of the body image appearance distress rating also indicate that the body part which is the most distressful to the population enrolled in our study is the belly.

For the belly profile results at baseline, the red bars represent our patient population ratings of their current look at baseline. The green bars

indicate their treatment goal. Most patients want to look normal, so most patients pick the body shape on the far right-hand side of the graph.

For the minimal benefit, you can see that for this group of patients, they want to be very close to the ideal look, even if we ask if it's the minimal change they would like to see. This raises the bar significantly when comparing the patient's target look versus what can possibly be reached using a treatment or a therapeutic intervention.

The results of the belly image are presented in this forest plot. The results on belly image parameters are presented in responsiveness units. A responsiveness unit is a standard approach to present the effect size of patient-reported outcomes. A change of 0.15 is considered as clinically significant.

Treatment with tesamorelin does not have a significant impact on assessment of the belly size. However, it has a clinically significant impact on belly appearance distress and belly profile, as rated by the patients and corroborated by the treating

physician.

For the assessment of the overall body appearance distress, the results show an improvement in a number of body parts in tesamorelin-treated patients, including, at the far right, a statistically significant difference in the overall body appearance distress.

The results of our study also showed that there is a good correlation between the percent decrease in visceral adipose tissue and the change in belly image parameters scores, including belly appearance distress and belly profile, as assessed by the patient and the physician.

Finally, there is also a correlation with the different health-related quality of life scales, as shown here. The data from the main phase of our program demonstrate that treatment with tesamorelin led to a significant decrease from baseline in visceral adipose tissue, waist circumference, and trunk fat, while preserving abdominal subcutaneous tissue and limb fat.

Decreases in triglycerides were significant

versus placebo in the first Phase 3 study and trended favorably in the second study. We also have observed a greater improvement in belly appearance distress and belly profile in the group of patients treated with tesamorelin versus placebo.

The extension phase of the studies demonstrated that the effect of tesamorelin is maintained for 52 weeks. We reached a 17 percent decrease in visceral adipose tissue after 52 weeks of treatment. This is twice the 8 percent recommendation.

When patients are switched from the active treatment to the placebo, they regain most of the VAT lost during the main phase. The light blue bar shows that what we have observed in the main phase with the tesamorelin treatment. The mean percent change in visceral adipose tissue in the group of patients who switched from placebo to active treatment was around 13 to 14 percent.

The other report and finding from the extension study is that the abdominal subcutaneous tissue was preserved throughout the entire 52 weeks of

treatment.

Patients in the extension studies maintained their reduction in waist circumference, trunk fat, and triglycerides. Improvement was also observed for belly appearance distress and belly profile. Similar to the abdominal SAT, limb fat was preserved throughout the 52 weeks of tesamorelin treatment.

Thank you for your attention. I would like to ask Dr. Soulban, who will now present the safety results of our clinical program.

DR. SOULBAN: Thank you, and good morning. The safety of tesamorelin has been well characterized in our clinical development program. Today's presentation will focus primarily on our Phase 3 safety data.

Our safety program included standard safety assessments, as well as special safety topics unique to GH-related agents. The special safety topics included IGF-1 SDS, or standard deviation scores, various glucose parameters, immunology, including hypersensitivity reactions.

Before moving on to results of special

safety topics, I'd like to review the results of the Phase 3 clinical trials. I will present our safety using the same structure throughout. We will start with the main placebo-controlled phase of our studies, displayed on the left side, then move to the extension, which will be displayed on the right side. As a reminder, note that there's a 2:1 randomization of tesamorelin to placebo.

Looking into the main phase data, we see that similar percentages of patients remaining in study are fairly similar between tesamorelin and placebo. The main reasons for dropouts are comparable between the two groups. There is a 3 percent difference between tesamorelin and placebo, with 9.6 percent of patients in the tesamorelin group discontinuing due to adverse events compared to 6.8 of patients in the placebo group. However, this difference was not statistically significant.

Now, when we add the right side of the data for the extension phase, this allows us to observe events for patients continuing longer on tesamorelin, which is the T-T group, and patients ceasing exposure

to tesamorelin, the T-P group. The P-T group, which represents de novo treatment with tesamorelin, will not be presented, because all safety data in this group consistently mirrors what was observed in tesamorelin in the main phase.

In the T-T group, adverse events leading to discontinuation are reduced compared to the first 26 weeks of treatment. In the T-P group, the adverse event discontinuation rate is similar to placebo patients from the main phase of the studies.

Next, we look at the overall adverse events that occurred in more than 5 percent of patients, occurring more frequently on active treatment. Overall, the percentages of patients with adverse events in tesamorelin group are slightly higher, with 78.3 percent compared to placebo at 71.1 percent.

We also see that adverse events cluster around two groupings of events, injection site reactions that were characterized as erythema and pruritus and GH-related events that were reported as arthralgia, pain in extremity, peripheral edema, and myalgia.

Overall, the incidence of GH-related events observed in our studies with tesamorelin over 26 weeks were lower compared to GH administration in the same indication for 12 weeks.

When we add the extension phase and focus on the T-T group for long-term exposure, we see that the trends from the main phase diminish with regards to injection site reactions and GH-related events. What emerges is upper respiratory tract infections in the T-T group that exceeds 5 percent. However, this was not statistically different between treatment groups.

We also looked at events reported as serious adverse events. There was no difference in incidence nor in pattern of serious adverse events that occurred between treatment groups during the main and the extension phases. In the main and extension phases, no specific serious adverse event was reported by more than one patient in any treatment group, except for sepsis, which was reported by two patients in the tesamorelin group in the main phase. When you look at patients who have greater than one serious adverse event of intense severity, the numbers are also very

similar between treatment groups.

At the beginning of the presentation, we highlighted three special safety topics, which were IGF-1 SDS, glucose metabolism, and immunology. Even though tesamorelin is distinct from exogenous GH, per se, it will increase IGF-1 levels since they are surrogate markers for GH secretion, and, therefore, are measured as part of efficacy, as well as safety assessments.

In the safety presentation, IGF-1 values are presented as IGF-1 standard deviation scores, or SDS. IGF-1 SDS are IGF-1 values that are based on reference values derived from a healthy patient population that are age adjusted, as well as gender adjusted. In our main phase, 47 percent of tesamorelin patients went above an IGF-1 SDS score of 2 and 36 percent went above an IGF-1 SDS score of 3. As expected, there were only minimal changes in the placebo group.

During the extension phase, 34 percent of patients in the T-T group had an IGF-1 SDS score of greater than 2 and 23 percent greater than 3. As you will notice, the percentage of patients with an IGF-1

SDS score of greater than 2 or greater than 3 in the T-T group is reduced compared to what you observe in the main phase.

Three items that are important to note. The reduction in the percent of patients with in the IGF-1 SDS categories for the T-T group is not driven by dropouts, and this was confirmed with a completers analysis. The second is that the decrease in patients in IGF-1 SDS in the T-T group did not correlate with a reduction in efficacy as measured by VAT. Then third, this decrease was not due to lack of compliance, as an IGF-1 SDS decreases in patients that were also 100 percent compliant. As expected, the T-P group returned to baseline range values.

It's logical, also, to ask about another potential correlate -- if IGF-1 SDS correlates with adverse events. The increase in IGF-1 SDS categories does not affect the overall percentage of patients experiencing adverse events, highlighted for you in yellow, in the first row.

We further explored the data to see if increased IGF-1 SDS was associated to adverse events

known to be related to GH. What we found was that during the main phase, there was a general trend towards a small increase in incidence in GH-related adverse events. The exception was the meaningful progression across SDS categories for edema and arthralgia.

We looked at the extension phase in the T-T group, representing our long-term treatment. There is little or no difference in percentage of patients experiencing an adverse event per IGF-1 SDS category and the events of edema and arthralgia were no longer significant in the extension.

Our final IGF-1 assessment was to explore any possible connection between high IGF-1 SDS and cancer events in our trials, because of conflicting data in the literature about a theoretical potential link between high IGF-1 levels and cancer development. We could find no evidence of causal relationship between tesamorelin-treated patients, elevated IGF-1 SDS, and cancer events.

We analyzed the incidence of cancer in our Phase 3 program. A total of 15 patients experienced a

cancer adverse event. In the main phase, 1.14 percent of patients in our placebo group experienced a cancer event, while .92 percent in our tesamorelin experienced a cancer event.

In the extension phase, all groups combined, we had 0.95 percent of patients that had a cancer event. All these cancers were considered to be unrelated to study treatment by the treating physician, except for two events, both of which were Hodgkin's disease. One Hodgkin's disease case was on placebo and the other was on tesamorelin.

We looked at IGF-1 SDS for each of these patients with a cancer adverse event and in the main phase of our studies, only two patients out of five had an IGF-1 SDS above 2. In the extension phase, only three patients out of seven had an IGF-1 SDS of greater than 2.

The IGF-1 SDS distribution among patients experiencing a cancer event is similar to the IGF-1 SDS distribution among patients who did not experience a cancer event. However, we do recognize that exposure to tesamorelin is relatively short in these

studies and does not permit us to draw a definitive conclusion regarding long-term risk for cancer. This aspect will be addressed later when I discuss the risk management plan.

Next, we turn to another special safety topic -- glucose metabolism. GH products are expected to have some impact on glucose parameters. Even though tesamorelin is not a GH product, it will induce a secretion of endogenous GH. We looked at glucose assessments for the first 26 weeks, and the changes in these parameters were small. We did not observe changes across various glycemic parameters, with the exception of hemoglobin A1C, which demonstrated statistically significant change compared to placebo during tesamorelin treatment.

The mean change of 0.14 occurred at a baseline hemoglobin A1C of 5.26, which moved to 5.39, while still remaining in the normal range. When we follow these parameters into the extension phase, the elevations that were seen in hemoglobin A1C in the main phase are no longer observed.

While this data is encouraging for the

overall population, we also looked at the impact of subgroups of individuals through the use of categorical analyses.

At study entry, approximately 38 percent of our patients were IGT or IFG and 8 percent of our patients had diabetes that were controlled by diet alone. As displayed here, there are small increases in proportions of patients in IGT/IFG and diabetes categories in the first 26 weeks of treatment.

In the tesamorelin group, there was a 4.7 percent increase in the IFG/IGT group, while the diabetes subgroup experienced a 1.7 percent increase. This same trend was confirmed by a studies completers analysis, thus addressing the potential impact of dropouts.

We also did the same analysis using the 2010 ADA hemoglobin A1C definition, looking at percent of patients in the normal, pre-diabetes and diabetes category. For the first 26 weeks of treatment, we see a similar pattern to what was presented for the fasting blood glucose two-hour OGTT.

There were small categorical increases in

the zero to 26 weeks with regards to the proportion of the patients in the pre-diabetic category, increasing approximately 4 percent in tesamorelin versus 2 percent in placebo. Also, the proportion of patients in the diabetes category increased approximately 4 percent in tesamorelin versus 1.3 percent in placebo.

At 52 weeks, we use the same cutoffs for fasting blood glucose and two-hour OGTT in a subgroup of patients exposed for a year. The proportion of patients per category remained relatively the same, with slight decreases. This observation is supported by the statistical analyses I showed you a little bit earlier for the glucose parameters for 52 weeks. Once again, the same trend was confirmed by a studies completers analysis, as well.

Similar to the analyses done at 52 weeks for fasting blood glucose and two-hour OGTT, we performed the same analysis using the hemoglobin A1C cutoff. The proportion of patients in the pre-diabetic category increased slightly, with a marked decrease in the diabetes category.

Overall, as presented, we observed a slight

deterioration of glucose homeostasis in a small percentage of patients treated with tesamorelin, and it ranged from approximately 2 to 4 percent. Nevertheless, as highlighted in Dr. Grinspoon's presentation, tesamorelin's effect on glucose was substantially less than those observed with GH administration.

Just as we've seen with other peptides, there is a concern for antibody formation and hypersensitivity reactions. We defined and agreed with the FDA as to what we considered to be a hypersensitivity reaction to distinguish them from simple injection site reactions.

In our Phase 3 program, 27 tesamorelin patients experienced a hypersensitivity reaction, and one placebo patient. These reactions were mild to moderate in severity and resolved upon cessation of drug.

In the main phase of our study, 16 tesamorelin patients had a hypersensitivity reaction, while in the extension phase, 11 patients had a hypersensitivity reaction. None of these reactions

were characterized as anaphylactic in nature, defined as systemic life-threatening allergic reactions.

As mentioned previously, the safety program also assessed for the development of antibodies, because it is typically a response seen with peptide therapy. In our main study, approximately 50 percent of our patients developed tesamorelin IgG antibodies. This graph shows you that in the T-T group, our long-term data group, which are yellow bars, the percent of patients with tesamorelin IgG antibodies remained fairly stable throughout 52 weeks.

In the T-P group, the percent of patients with antibodies decreases across time, going down to 18 percent by week 52, showing seroreversion.

We also looked to see if IgG antibody status had an impact on IGF-1 levels or VAT. At week 26, the mean change from baseline in IGF-1 levels, which were a safety, as well as efficacy parameter, and the percent change of baseline VAT, which is an efficacy parameter, was similar and not statistically different between patients with or without IgG antibodies nor by different titer categories in the tesamorelin group.

While anti-tesamorelin antibodies had no impact on IGF-1 and VAT, we further examined the presence or absence of in vitro neutralizing antibodies, or NABs, to HGRF, human growth hormone release factor, and to tesamorelin.

To assess long-term safety at week 52, we analyzed in vitro NABs in patients that were IgG-positive and found that 5 percent had HGRF NABs and 10 percent had tesamorelin NABs. The presence of these NABs did not affect the IGF-1 levels or VAT.

After 26 weeks of exposure, the percent of HGRF NABs was similar was what was seen with 52 weeks of exposure. As seen in the T-P group, there was reversibility of in vitro HGRF NABs. Indeed, by week 52 or early termination, only 1.5 percent were HGRF NAB-positive, thus showing reversibility.

So taken together, tesamorelin has a well-characterized safety profile. We intend to utilize this characterization to guide the development of an assertive risk management plan.

The pillars of this risk management plan are fourfold; the first, to assure its safe use in the

HIV-positive population; second, to ensure use by the appropriate patient population; third, to have long-term safety follow-up; fourth, to have ongoing development of clinical guidelines.

In recognition of the theoretical risk of the elevated IGF-1 levels, we propose ongoing monitoring of IGF-1 levels and discontinuation of treatment in patients with an IGF-1 SDS of greater than 3 for more than 52 weeks.

Given tesamorelin's potential effects on glucose homeostasis, albeit small, we are proposing guidelines to address this effect. Patients with a past medical history of diabetes or presenting with diabetes based on fasting blood glucose or hemoglobin A1C should not start therapy with tesamorelin.

We recommend that fasting blood glucose and hemoglobin A1C be measured every 26 weeks of tesamorelin treatment and the decision to continue or to stop will be based on managing fasting blood glucose and hemoglobin A1C below the diabetes range.

In cases of suspected hypersensitivity reactions, patients will be advised to seek prompt

medical attention and treatment with tesamorelin should be discontinued immediately. To encourage the appropriate prescribing in the indicated patient population, tesamorelin will be exclusively dispensed through a targeted network of contracted pharmacies, with an ability to track each box of tesamorelin via a unique box serial number.

We also propose a long-term safety observational study that will follow both tesamorelin-treated patients and an untreated HIV group to gather additional safety data on potential increases of cancer risk in the clinical setting.

Additionally, ongoing development of clinical guidelines will occur through an independent panel of experts that will review the available data on clinical outcomes, cancer incidence, and IGF-1 on an ongoing basis.

Slide back, please. I'd like to invite Dr. Schambelan to discuss the clinical need and benefit-risk analysis.

DR. SCHAMBELAN: My name is Morrie Schambelan. I'm Professor of Medicine and a member of

the Division of Endocrinology at University of California-San Francisco. And unlike my colleague, Dr. Grinspoon, I've had little or nothing to do with the generation of the data that you've seen here today.

To answer Dr. Burman's question, I have been a consultant to the sponsor as they reviewed their benefit and risk analysis and in helping them prepare for this meeting. I have no stock in the company and I have no financial interest in the outcome of this meeting.

However, I do have an interest, a longstanding interest in seeing that safe and effective treatments are available for patients with HIV, particularly for the metabolic complications, which has been a major focus of my lab for the past 20 years.

My role today is to summarize the results of the trials in the context of what I consider to be an important and completely unmet clinical need, and, to that end, I'd like to begin by restating the problem and to illustrate just how devastating this can be for

affected individuals.

So as you've heard in the presentation that Dr. Grinspoon made, excess visceral fat accumulation in patients with HIV infection differs from the increase in VAT seen in patients with simple obesity. Particularly, affected patients often, and, I would say, nearly invariably, experience a concomitant loss of subcutaneous adipose tissue.

The increase in VAT in these patients is accompanied by metabolic abnormalities; most notably, insulin resistance and dyslipidemia. And importantly, the affected patients express physical discomfort and psychological distress due to the excess abdominal fat, which significantly impacts on their quality of life and can reduce the adherence to HAART, as you heard illustrated earlier.

So I thought I would start with -- I think the bone meeting people referred to this as a clinical vignette, which is a patient that was enrolled in a study that NIH funded a number of years ago in which we were looking at the effect of initiation of antiretroviral therapy or, I should say, in some

cases, converting people who were already on less effective antiretroviral therapy to HAART, and then follow their body composition and metabolic outcomes.

This is a patient who came into a study visit at nine months after starting HAART, and at that time, the CD4 count had increased nicely, the viral load was undetectable. But the patient said, "I feel really terrible because my belly is getting huge."

They asked him to take off the clothes and this is what he looked like, and this is so similar, I think, to the slides you've seen earlier that Dr. Grinspoon presented.

I think in addition to the very obvious visceral adiposity, the patient manifests loss of subcutaneous tissue in the arms. We didn't show the legs in this view. Now, I didn't have a "before" picture for this patient when he initiated antiretroviral therapy, but I did have a CT scan which we obtained on entry to the study.

So the left-hand panel shows the CT obtained prior to initiating HAART and the right-hand panel shows the CT at the time that that photograph was

taken. And I think you can readily appreciate the marked expansion in the visceral compartment, shown by the dark area, and the loss of subcutaneous adipose tissue, particularly in the dorsal fat pads and also, in the interior abdominal wall.

If you don't believe that picture, I can show you the data that were obtained when this was analyzed by the CT cut at L4/L5, as Steve mentioned earlier. This patient's weight changed very little during this nine-month period of time, but there was a remarkable increase in VAT, 31 percent, compared to his baseline value, while at the same time, the subcutaneous adipose tissue decreased about an equivalent percentage, 29 percent.

In addition, there was a change in overall body composition, as shown here by DEXA scan. In particular, the trunk fat increased by 1.5 kilograms and the limb fat decreased nearly 2 kilograms. And I have to point out that normal limb fat is approximately 7 kilograms by DEXA. So this patient has severe, severe lipoatrophy.

In addition, the patient experienced

metabolic complications. You've heard about these. It includes an increasing glucose, insulin, the HOMA calculation, and the lipid values. So the patient developed worsened dyslipidemia and worsened glucose intolerance in association with these body composition changes that occurred with initiation of HAART.

So what do we have to offer this patient? Well, first of all, there's nothing we can do for the lipoatrophy. I'm not aware of any therapy that can significantly increase the severe loss of peripheral fat that this patient has sustained. You can give subcutaneous injections and alter the facial appearance cosmetically, but you can't put fat back into the other parts of the body.

Although we would recommend that the patient pursue diet and exercise, I think it's highly unlikely we would have a major impact on this rather substantial amount of visceral fat that he had already accumulated. Metformin might reduce VAT, but wouldn't be a good choice here either, because the SAT was already so low, it is likely it would have become even lower and been more disfiguring for this patient.

Thiazolidinediones have a major theoretical advantage in treating this syndrome. They affect the adiponectin levels, among other things, but they just haven't borne out and there have been about seven trials now, randomized clinical trials, that have failed to show a decrease in visceral adipose tissue.

GH might have worked, but this patient was already ineligible for GH, because of the alterations in glucose metabolism that he had developed when he went on highly active antiretroviral therapy; and of course, this therapy wasn't approved by the agency for the management of this condition.

So I think, frankly, if I had tesamorelin available at this time, I would have seriously considered this for this patient, because tesamorelin, as you've heard today, significantly reduces visceral adipose tissue and waist circumference. It decreases trunk fat, when measured by DEXA. And it decreases triglycerides significantly in the first study, borderline significance in the second. But certainly, for the combined data, the lipid panels appear to be going in the right direction.

Importantly, for this patient, subcutaneous adipose tissue is likely to be preserved both on CT and DEXA scan, as you've heard presented here. Lean body mass might increase, and that probably accounts for the fact that weight doesn't change significantly in these studies.

Importantly, from this patient's perspective, the improvement in body image, using a validated reported outcomes tool, as noted in the study, showed a decrease in belly appearance distress, the belly profile, and the body appearance distress, and importantly, improvement in health-related quality of life. It correlates with the decrease in VAT.

When we looked at safety, and this you have to explain to the patient, as well, SAEs are rare and didn't appear to occur more frequently in tesamorelin-treated patients. There are GH-related AEs and injection site reactions that definitely could occur and the patients would have to be made aware of this, but most of these were mild to moderate.

There was a relatively low incidence of hypersensitivity reactions, 3 percent. These

typically resolve quickly and, fortunately, none of them were of an anaphylactic type. And the anti-tesamorelin antibodies and NABs that you heard described a few slides ago did not appear to impact on efficacy or safety.

IGF-1 levels, as has been detailed, did increase. It's an efficacy, as well as a safety measurement; 36 percent of the patients had an IGF SDS score greater than 3. This decreased at 52 weeks to 23 percent, and that did not seem to be as a result of dropouts.

However, and importantly, there appears to be no association between the overall AEs or cancer, although the numbers of patients, obviously, exposed here are relatively small.

In terms of glucose metabolism, fasting glucose and two-hour postprandial did not increase significantly. There was a small increase in hemoglobin A1C of .14 percent, but these, on average, were still well within the normal range.

Relative to placebo, when the categorical analyses were done, there was an increase in

prevalence of diabetes in the tesamorelin-treated patients, which ranged from 1.4 to 3.2 percent, depending upon what criterion you used for diagnosing diabetes, whether it was based on a glucose measurement or on hemoglobin A1C. And in patients who continued treatment for 52 weeks, the prevalence of diabetes appeared to decrease or at least it didn't increase significantly.

So in conclusion, I think that tesamorelin has a favorable benefit-to-risk profile when it's used to induce and to maintain a reduction of excess abdominal fat in HIV-positive patients with lipodystrophy. And thus, we have clinical data available that would allow an effective discussion about this potential therapy between physicians and appropriately selected patients.

Importantly, in terms of reassurance, there is a risk management plan that's been proposed, which is addressed at decreasing any potential risk through a REMS program, a controlled distribution system, and a long-term observational study, in particular, focused on cancer.

So I would conclude that in appropriately selected -- and I would emphasize that -- and closely monitored patients, tesamorelin treatment represents a unique option for the effective treatment of excess abdominal fat in HIV-positive patients with lipodystrophy.

Thank you.

DR. BURMAN: Thank you very much.

I believe that concludes the sponsor's presentation. It's 9:30, about, and we're going to go until 10:00 before we take a break. And so we have a half-an-hour for questions to the sponsor from the committee members. Please raise your hand and we'll take down a list.

We'll take Dr. Molitch first and then move on.

DR. MOLITCH: Thank you. I have a question for either Dr. Grinspoon or Dr. Schambelan. The benefit that is seen with visceral adiposity, it's projected that that's sort of a surrogate outcome for long-term cardiovascular benefit, if I understand correctly.

So I'd like to ask them what they think is the mediator between the VAT and the long-term cardiovascular benefit.

Is it the insulin resistance that is correlated with VAT? Is it the dyslipidemia that is correlated with that?

So if, in fact, those are the two major areas that sort of mediate that long-term cardiovascular adverse outcome, what do we say with this medication that's being proposed, where, in fact, there's no benefit in insulin resistance? And, in fact, there's a worsening of glucose tolerance. And the only benefit I saw with lipids was a reduction in triglycerides.

So can we project the long-term cardiovascular benefit as a result of looking at those two changes in triglycerides and increase in glucose intolerance?

DR. MARSOLAIS: I'd like Dr. Grinspoon to address the question, please.

DR. GRINSPOON: That's a good question. Thanks very much. Let me start, first, before we get

to this, with a slide relating hemoglobin A1C to VAT. Slide up, please. One thing that was not presented, but I thought would be interesting for you to see vis-a-vis your question, is that although there was a slight increase in hemoglobin A1C, we were very pleased to see that, in fact, the more that the VAT went down, the more the hemoglobin A1C went down.

So even though there was a slight increase in A1C, we postulate that the direct effects on VAT are net-net having an effect, particularly among the responders, and we were very pleased to see that.

Can I go back to the other slide, please? Slide up. So let me get back to your other question, which is why do we anticipate this to have a positive effect on cardiovascular disease?

One, I think, as I mentioned, with long-term treatment, I think that you'll have further significant reduction in VAT and not an aggravation of glucose intolerance. And in fact, with even long-term, more long-term therapy and taking out patients who are non-responders, you have the responders continue on treatment, you may even have improvement

in insulin. That remains to be seen.

But you also have significant improvements on a number of other cardiovascular risk factors. So let's talk about triglycerides. Triglycerides improve more in the tesamorelin-treated patients than placebo, particularly in the combined analysis.

The triglycerides improved in association with the VAT. So I didn't show you that slide, Dr. Molitch, but there is a clear association between the reduction in VAT and the improvement in triglycerides.

Number two, the more the triglyceride level was elevated at baseline, the more the triglyceride improved. So we're taking it from a very high level down to a more reasonable, but not perfect, level. The treatment of triglycerides is very, very inadequate in this population. You may not be used to it, but 50 percent were on lipid-lowering therapy, and we're very pleased to say that the reduction was even greater among the people on lipid-lowering therapy than not. And I can show you those data, if you're interested.

We think that the reduction in triglyceride

of 12.3 percent, or 43 milligrams per deciliter, among a group with stubborn elevated levels is quite significant, and that may contribute to improved cardiovascular risk.

Getting further to your question, the patients also experienced a reduction in waist circumference. This is a really important point. Over 52 weeks of treatment, the reduction in waist circumference was 3.2 centimeters.

If you remember the graph of Pischon, et al, and you can imagine it coming down in that graph by 3.2 centimeters, you would say, in the general population in a study that reduced waist circumference 3 centimeters, that's an improvement in cardiovascular risk.

We think that it may be potentially even a greater improvement in cardiovascular risk, because the reduction in waist circumference is primarily comprised of visceral fat, not lack of subcutaneous -- not reduction in subcutaneous fat. Again, those are all speculative, but we think those could contribute.

Finally, there were significant improvements

in adiponectin, as was shown. So inflammatory markers are improved.

So we think that the preponderance of evidence, though not direct, for sure, and I completely agree with you, would suggest that things are moving in the right direction. And I think that the reduction in triglyceride, the potential amelioration of insulin resistance over time, the reduction in waist circumference, the improvement in inflammatory markers may lead the way in this regard. Clearly, things are moving in the right direction.

Lastly, you might say, "Well, you have to balance this versus the increase in glucose," and we're very, very much aware of that, completely and utterly aware of that situation. And we proposed in the REMS that those who develop diabetes, that small percent, 2 to 4 percent, however you want to define it, be removed from treatment with this drug.

So we think that when you remove those patients and you have the net benefits in visceral fat, triglyceride, waist circumference, adiponectin, triglyceride -- for this specific patient population,

you're improving their cardiovascular risk.

Moreover, you're also making them feel better, which is a critical component of this. That would be my answer.

DR. BURMAN: Thank you. Dr. Cargill?

DR. CARGILL: Thank you. On slide 44, we're given information about the eligibility criteria and we're also told about people who were excluded. However, in the materials we were provided, we had additional information about exclusion.

I wonder if you have it on a slide. I had a specific question about one of the exclusion criteria.

DR. MARSOLAIS: Yes. We have a slide for the exclusion criteria.

Do you have specific questions for them?

DR. CARGILL: Yes. The question was I wanted to know about the estrogen that was noted. Was it simply estrogen or was it combination oral contraceptive, as well, to include progestin?

DR. MARSOLAIS: I don't have this information with me at the moment, but maybe we can get back to you right from the break and we'll have

the exact information for your response.

DR. CARGILL: Thank you.

DR. BURMAN: Before we go, I forgot to do one thing and that is ask Dr. Rosen to introduce himself for the record. Cliff?

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

DR. BURMAN: Thank you. And we do look forward to that further answer later. Dr. Dobs?

DR. DOBS: The patient population that you identified had the diagnosis of lipodystrophy apparently for 4.5 years. So my question is, how consistent is that diagnosis.

I assume that was by self-report, but in defining the population, how often do people go in and out of the diagnosis? And related to that is you used an 8 percent reduction in VAT as your outcome measure. I know that was agreed upon. But what is the biological rationale for that particular number?

DR. MARSOLAIS: I would like to ask Dr. Grinspoon to address the question, please.

DR. GRINSPOON: I'll start with the easier

of the two questions. The easier of the two questions -- may I have the slide from the MACS cohort? I think you're familiar with the MACS cohort.

So the question is how often do they go in and out of lipodystrophy or, I could maybe paraphrase it -- slide up, please -- do they continue to have lipodystrophy, the patients.

So let me say, before I get to this slide, remember, as Dr. Marsolais said, that patients had to have a high waist circumference, evidence of abdominal hypertrophy in the context of antiretroviral therapy. And the vast majority demonstrated some other abnormality, be it lipoatrophy or anything.

So we think these are truly lipodystrophic patients, not simply obese. The mean BMI was 29. It wasn't in the obese category. So we really think we identified a lipodystrophic population.

The data I'm showing you here are from Todd Brown and these data show that comparing HIV-negative patients, HIV-positive patients without lipodystrophy, and HIV-positive patients with lipodystrophy, on the right -- those who have lipodystrophy continue to have

an increase in waist circumference over time followed longitudinally, which we think suggests that the problem remains.

It certainly is not going the other way in the vast majority of patients. So that's the easier of the two questions.

How the FDA came up with 8 percent is, arguably, somewhat arbitrary, I must say. I think from studies of weight loss and BMI, there's 5 percent issues and then 10 percent is very good. I think that there are no hard data, we acknowledge that, directly linking reduction in VAT to CVD events. We acknowledge that.

So, therefore, when you're charting new territory, it's a little bit hard to come up with the exact right cutoff. So 8 percent, to the agency and to us, seemed a reasonably significant cutoff, between 5 and 10, which would seem to have clinical benefit.

Indeed, we are happy to see that the change in VAT was perceived to have a benefit by the patient. In other words, they felt better about themselves with that degree of reduction in VAT, and it was also

associated with improvement in triglyceride, et cetera.

So I think that we're a little bit in uncharted territory in terms of the exact percent you would want to have VAT reduced. We easily met the 8 percent the agency required of us.

Should the bar have been higher? I don't know. We probably could have met an even higher bar. As Dr. Marsolais said, we were approximately twice as high over 52 weeks.

DR. BURMAN: Thank you.

We have six questions we'd like to get to in 20 minutes. So please keep your questions succinct and your answers succinct, as well.

Dr. Thomas?

DR. THOMAS: What I'd like to know is when you look at the patients who have normal glucose tolerance, impaired glucose tolerance or diabetes, what's the conversion from normal to impaired or to diabetes, from impaired to either normal or diabetes, and then diabetes back to impaired or normal?

I especially would like to know what that is

in the 52-week study that stayed on treatment for the entire 52 weeks to kind of have an estimate on what the annualized rate of conversion is so you can compare that to other populations that have impaired glucose tolerance.

The second thing is, is there any mention of family history in relationship to that that may underscore those who are at highest risk? And third is people with normal or even impaired glucose tolerance have a risk for retinopathy and growth hormone is related to retinopathy.

So were there any measurements of endoscopy that were compared serially over the study?

DR. MARSOLAIS: I would like to ask Dr. Soulban to address the question, please.

DR. SOULBAN: So to address your first question, which is in different categories, those moving from normal into IGT and diabetes, and also, the reversal of some of those effects.

So this is for the zero to 26 weeks. And I'll walk you through this data, because this table is a little complicated. On the very left side, you will

see what the patients were at baseline. So you'll have the first row-normal, the second row-IFG/IGT, and the third row-diabetes.

So in the tesamorelin group, you'll see, for that specific subpopulation of 197 patients that were normal at baseline, 28 percent moved into the IFG/IGT of that subgroup, and 1.5 percent moved into the diabetes subgroup.

You'll note, continuing along the line, that it's 26 percent for placebo that move into the IFG/IGT category and 1.9 percent into the diabetes category. Going one row down, patients that started at IFG/IGT at baseline, again, for tesamorelin, it's 153 patients at the start. The yellow colors are showing deterioration. The pink or purple colors are showing improvements.

So you move from IFG at baseline. You have 13 percent that move into diabetes and tesamorelin in that subcategory. If you keep going along the line, for placebo, you see that 15.4 percent in the placebo subgroup that were IFG to begin with also move into the diabetes subcategory.

Looking at the purple that's highlighted on that line, those that started IGT in the tesamorelin group, approximately 22 percent returned to normal. And, in the placebo group, approximately 31 percent returned to normal.

Going down to the third line, we had approximately 20 patients that started off as diet-controlled diabetes, according to this definition, and out of the 20, 7 returned back to an IFG/IGT category and 3 returned back into a normal category with tesamorelin.

Similarly, when you look at the placebo patients, you have 7 that returned into an IFG/IGT category and 2 that come back into a normal category. So as you can see here, there's quite a bit of fluctuation in the groups.

You do have patients that move one way, but you have patients that move the other way in both groups, in the tesamorelin, as well as the placebo.

I think your question also asked about long-term for the 52 weeks.

Am I correct?

Slide up, please.

DR. BURMAN: If you would, please be succinct, because we could also ask for these slides to be sent out, which we will, so we could look at them.

DR. SOULBAN: Okay. So I can stop there. No? Continue? I'm sorry.

DR. BURMAN: Please, give an answer you think is appropriate, but succinctly.

DR. SOULBAN: Okay. So for the extension, note the smaller numbers in the extension, because patients are re-randomized into the T-T and to the T-P group. You see a similar fluctuation over time, with patients also improving in the IFG categories, in the T-T, the long-term group, and patients also improving in the diabetes categories, having 8 out of 10 patients improving in that category.

So there are fluctuations over time. But overall, for the 52-week period, we see, more or less, more stabilization compared to the zero to 26 weeks.

DR. BURMAN: Thank you.

I think those are important issues. Maybe I

could ask for those two slides to be -- made copies of and handed out to the panel, if that would be no problem for the sponsor.

Ms. Swan?

MS. SWAN: I have a couple questions about the VAT itself. How quickly does it return in people who discontinue tesamorelin? And have any of the increases exceeded the pretreatment levels in any patients who discontinued? Thank you.

DR. MARSOLAIS: We're looking at the moment for the CT scan. We have an assessment at week 13. This is the first assessment after the stop of treatment.

What we have on this slide, we can see that if we are looking at the orange bar, by week 26, this is where we have the maximum decrease in VAT. And by week 13, you can see that patient or the VAT of those patients that had decreased initially returned to almost their normal baseline value by week 13. They regain about 80-85 percent of their VAT.

Regarding the return to the -- see if they're exceeding. This is the average that we have.

I don't have the distribution by patients specifically for the return of VAT to see if some are exceeding. But on average, they are returning to their baseline value.

DR. BURMAN: Thank you.

Dr. Veltri?

DR. VELTRI: I'd like to have someone address, again, the correlation or perspectives in regard to cardiovascular risk. Three quick questions. Number one, do we really have a good sense of what's happening with the lipoproteins here? Obviously, there's some effect on triglycerides, but there's a little discordance between the two studies. There's no mention of LDL cholesterol or some of the other lipoprotein. Has that been studied more specifically?

Secondly, another major risk factor is blood pressure. I may have missed it, but is there any effect up or down in systolic and diastolic blood pressure in these patients?

Thirdly, probably the most validated biomarker, pro-inflammatory biomarker, is CRP and I notice that, on average, it's around 4.5 milligrams

per liter in the group, but there was no effect either up or down.

What do you think about that? Is that good, is that bad, or is that indifferent?

DR. MARSOLAIS: I will ask Dr. Grinspoon to address the question, please.

DR. GRINSPOON: I'm sorry. Let's start with the third one, CRP. Remind me of the question again. CRP did not change significantly. It trended favorably in the tesamorelin group versus the placebo. It went down in tesamorelin and up to the same degree in placebo.

But due to the very significant variability of this in this patient population, it does not reach significance. So it's, again, moving in the correct direction, but not statistically significant in contrast to others, like adiponectin, TPA, PAI-1R.

So when you look at the preponderance of the inflammatory markers, we think, in general, they're moving in the right direction. But you're right. CRP did not reach statistical significance. Unfortunately, CRP was only measured in the first

study.

I think that if we had the second study and could have combined the data, we would have shown a positive effect on CRP. That's a little point to remember.

Sorry. The first two questions? I'm sorry.

DR. VELTRI: Blood pressure.

DR. GRINSPOON: I do not believe there was a change in blood pressure. It didn't go up, didn't go down. It was just a vital sign measure for safety.

DR. VELTRI: On lipoproteins, LDL specifically, are other analyses more specific to lipoproteins?

DR. GRINSPOON: Yes.

Can I have the forest plot of the combined data, please?

These are the data that we have. So zero being the line, the vertical line, you can see, in the combined data analysis, there is a minor, but significant effect on total cholesterol and the important non-HDL cholesterol. We don't have data on LDL.

There's also a very close to significant increase in HDL, but these are relatively small. In contrast, there is, I think, a fairly significant almost 40 milligram per deciliter decrease in triglyceride.

Slide up, please. These are the data on LDL and you can see that there is not a significant effect by week 26 in the LIPO-010. There tends to be a trend toward an effect in the second study, but it did not reach significance.

So overall, we have an improvement in non-HDL, an improvement in total cholesterol, an improvement in triglyceride, and a borderline improvement in HDL, without an improvement in LDL.

You asked about lipids. This is another important way to look at it. So we broke the results down into patients overall, and this is triglyceride. You've seen this before. But the second line is no lipid-lowering therapy, and the third line is fibrates, the fourth line statins, and the fifth line is fibrates and statins.

We think it's pretty impressive that you

have these types of reductions on triglyceride on patients already on triglyceride-lowering therapy. We are not claiming in any way, shape or form this is a triglyceride lipid-lowering therapy, but it's interesting to see that you see this in the context of very heavily pretreated patients with very significant lipid abnormalities.

We don't have more specific lipoprotein particle size or anything like that. We could get that in subsequent studies. But, hopefully, that answered your question.

DR. BURMAN: Thank you. And you don't have APOB either, I assume.

DR. MARSOLAIS: We have this information only from the first study, in LIPO-010, and we didn't see any significant difference.

DR. BURMAN: Okay. Thank you. We have about 8 minutes, and we do have time in the afternoon for questions to the sponsor, as well. We have four people. I don't think we're going to get to them all. But in order, Dr. Proschan first.

DR. PROSCHAN: I wanted to ask about --

there's been a suggestion in slides 19 and 20 that this drug might improve adherence to ART. And I'm just wondering, on 19, for example, it says 30 percent of patients failed to maintain adherence and 60 percent of the non-adherent patients noted bigger belly.

Maybe 60 percent of the adherent patients also reported bigger bellies. So this doesn't help me to say whether this is really suggesting that there should be an adherence gain.

The other thing is that in slide 20, it looks like losing central fat is also almost significantly associated with increasing the risk of not being adherent. So I wonder if you want to comment on that.

DR. MARSOLAIS: Yes. Dr. Grinspoon will address the question for us here.

DR. GRINSPOON: You're right on both scores. In terms of the first question, I think we presented the APROCO data just as background. I think the more important question is did it affect adherence in our particular study.

In our particular study, the adherence was very high, at 98 percent. The reason this is true is because these are interested patients in a research study. So you could imagine that's higher than what you see perhaps in other natural history studies.

So we were at 98 percent and 99 percent of the extension phase, and we were at such a high adherence rate that we really weren't able to detect any improvement beyond 98 or 99 percent.

So although we raised the issue, we had such good adherence in our study anyway that we can't prove to you that we improved adherence in this particular study.

Now, regarding your second question, you noted that it was almost significant, that loss of fat in the abdomen. I think it's a bidirectional thing. I think there are some patients who have very significant lipoatrophy all over the place and there are some patients we see out there who are diminishing all over the place, and I think that they're uncomfortable with how they look.

I think some people can't distinguish

between loss of fat in certain areas in the abdomen. That's the best answer I can give you.

DR. BURMAN: Thank you. We have 5 minutes. Dr. Rosen?

DR. ROSEN: A very focused question on IGF-1. So about 25 percent of the subjects in the extension study still have more than three standard deviation increase in IGF-1. I want to know if you have a slide showing the absolute values, as well as the distribution, because the standard deviation for the mean level is 124.

So there's wide variation across serum IGF-1 in the treated group, and it would be helpful for you to define for me what the standard deviation is in that laboratory, because it's clearly different between the placebo subjects and the ones that were treated. And who are those individuals that are in the 3-SDS or even 2-SDS? Because I notice that Esoterix did the lab reference assays, but they used mean values age 17 to 40.

At 17, many of those individuals would be in the 250 to 300 range, and clearly, that's not the

normal range for individuals with a mean age of 48.

DR. MARSOLAIS: Dr. Cohen will address the question, please.

DR. COHEN: I'm Pinchas Cohen. I'm Professor and Chief of Pediatric Endocrinology at UCLA. And I'm a consultant to Theratechnologies on matters related to IGF-1, which is an area I've been studying for 20 years. I hold no stock in the company.

As you can see here, first of all, the absolute values of IGF-1 at baseline in both tesamorelin and placebo groups are similar to the general population, as assayed by Esoterix, with a mean SDS score of minus 0.4

More importantly, however, you can see that both at the baseline level of the placebo -- and in the placebo group, the standard deviation score -- the standard deviation of the SDS score is greater than 1.

In fact, if you look at the number of placebo patients who have an SDS score greater than plus 2, it's 5 at 26 weeks at the placebo group, and, in fact, it was 6 percent at baseline in both the

tesamorelin and placebo groups.

This indicates that the HIV population actually has a different distribution of IGF-1 levels and that while the means are similar to the population that was assayed by Esoterix, the variation is larger and SD scores are themselves larger.

I think that, in fact, the number of patients that were assayed in this study exceeds the number of subjects that were measured by Esoterix by a factor of at least 4, and this may represent a better normative range, certainly, for the HIV population.

I also want to point out that you would expect that only 2.3 percent of patients who are untreated would be above plus 2 SDS and only 0.1 percent would be above plus 3 SDS. In fact, you can see that in the placebo group, it's 5 percent for plus 2 and 2.5 percent for plus 3, which is why I believe that Esoterix's plus 3 SDS, in fact, represents the upper limit of normal of the HIV population.

I don't believe we have a slide of the distribution of the absolute values.

DR. ROSEN: Can I just ask you, very

quickly, what that SDS is? What is the standard deviation for us that you're using?

DR. COHEN: I'm sorry?

DR. ROSEN: When you talk about adjusting for standard deviation, what number is that? What is the standard deviation? Is it 48 nanograms per ml? Is it 60? Is it 120? What is the standard deviation?

DR. MARSOLAIS: We can ask Diane Potvin to address the question, please.

DR. BURMAN: In fact, if you could answer that important question very quickly, and then we'll take a break and we're going to come back this afternoon on more of these issues.

DR. POTVIN: I'm Diane Potvin. I'm the Director of Biometrics at Theratechnologies. So the SDS really was taken from Esoterix by age group and we had different age groups. It was up to 65 years old, so we had different years, group, and gender. And we subtract the mean and divided by the standard deviations from this healthy population.

We can check what were the exact mean values, because we do have them, but not on the

slides. So we can provide them to you.

DR. ROSEN: What I'm asking is, what do you use for your standard deviation for the measurement, because it's important for us to figure out exactly where these subjects lie at 6 months and at 12 months.

DR. POTVIN: Standard deviation was really different between the different categories. So we can provide it to you.

DR. BURMAN: Please do, and we're going to have time this afternoon to discuss that. I apologize to Drs. Kumar and Goldfine, but we will get to your questions this afternoon.

We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:15.

(Whereupon, a recess was taken.)

DR. BURMAN: Why don't we get started?

We will now proceed with our presentation from the FDA. I'd like to remind public observers at this meeting that while this meeting is open for

public observation, public attendees may not participate, except at the specific request of the panel.

I'd like to invite Dr. Roman.

DR. TRAN: Also, we're trying to resolve the heat or A/C in this room and we're going to leave the doors open to get some air circulation. Thank you.

DR. ROMAN: Chairman Burman, members of the committee, audience members, the purpose of my brief presentation is threefold. First of all, I will describe how Egrifta relates to the currently approved drugs that act on the hypothalamic-somatotropic axis.

Next, I will make a few comments regarding the endpoints that have been evaluated in the Egrifta Phase 3 trials. And finally, I will highlight some of the challenges that the agency is facing in establishing an accurate risk-benefit analysis for Egrifta when used for the treatment of VAT reduction in HIV-infected patients with excess abdominal fat.

Egrifta is coming in the wake of several drugs which have been approved with the mechanism whose pharmacodynamic effects are initiated along

different sites on the hypothalamic-somatotropic axis.

The Rhodes study with growth hormone more than half a century ago is pituitary growth hormone, human growth hormone extract. It continued with recombinant human IGF-1 and was followed by a close relative of Egrifta, a growth hormone-releasing hormone, and, more recently, by recombinant human IGF-1.

As such, the experience that has been accumulated with these products is expected to be significant in understanding the benefits and the potential adverse effects associated with Egrifta.

Many of these drugs share quite common pharmacodynamic effects. For instance, as expected, Egrifta and GHRH are very close. They share an identical amino acid sequence and they defer by the addition of a hexenoyl group at the N-terminal tyrosine in the case of Egrifta, which makes it more resistant to enzymatic degradation and expands its half-life.

However, in vitro, both products have a similar affinity to the growth hormone receptor, and

their basic mechanism of action is the same in terms of activator of the growth hormone receptor in the pituitary, followed by production and release of growth hormone.

There is considerable pharmacodynamic overlap between Egrifta and growth hormone. Both of them result in growth hormone receptor activation and, in one case, in the case of Egrifta, indirectly; in the case of growth hormone, directly. And they both initiate post-receptor events that are responsible for the lipolytic and anabolic functions of these hormones.

It should not be surprising, and we have seen already from the sponsor's presentation, that the adverse event profiles of Egrifta and growth hormone share significant similarity. As such, the considerable safety information that has been accumulated with growth hormone over half a century, in general, and over 25 years with recombinant human growth hormone is relevant to Egrifta.

Moreover, growth hormone has been studied, as indicated by Dr. Grinspoon, quite extensively in

patients with HIV and lipodystrophy over a range of doses from physiological to supraphysiological. And all that information certainly is useful.

Although drugs that act on the somatotropic axis have similar pharmacodynamic effects, they have been developed for different indications. For instance, growth hormone has been initially developed for the treatment of short stature in children and subsequently as a physiological replacement in adults with growth hormone deficiency.

It has also been approved for the treatment of wasting, as well as for the treatment of short bowel syndrome in pharmacological doses.

GHRH was initially approved as a diagnosis and for a test for growth hormone deficiency, and subsequently, as a therapeutic agent for the treatment of pediatric idiopathic growth hormone deficiency. Recombinant human IGF-1 was approved for the treatment of an orphan indication, primary IGF-1 deficiency, which is an umbrella term for Laron syndrome and Laron syndrome-like phenotypes.

Egrifta is seeking a new indication,

induction and maintenance of VAT reduction in HIV-infected patients with lipodystrophy. There are no drugs approved for this indication to date. The agency has reviewed the growth hormone application by Serostim, as has already been indicated, for this indication, but the indication was not granted to the manufacturers of Serostim.

The main reason has been the increase in insulin resistance that has been observed at the pharmacological doses that were evaluated, 4 milligrams daily and 4 milligrams every other day. And it is well known, as we all know, insulin resistance in itself is a cardiovascular risk factor.

Although the indication was not approved, the information regarding the Serostim clinical trials has been added to the Serostim label to inform practitioners about the safety issues that may be associated with this particular dose regimen.

I would like to move next to the second objective of my presentation and discuss a little bit the efficacy endpoints that were evaluated in the Egrifta Phase 3 pivotal trials. VAT was the primary

endpoint, and the trials were powered to demonstrate an 8-percent superiority to placebo.

The 8 percent number -- and it came up in discussion previously -- was a compromise of two different numbers. On one hand, the observed therapeutic effect on VAT reduction that growth hormone has shown at the time of the planning of the Egrifta Phase 3 trials. On the other hand, the 5 percent, which was, at the time, the threshold that a draft guidance for development of anti-obesity drugs recommended for drugs that seek approval for an anti-obesity indication.

The 5 percent benchmark is, as I said, the minimum and is also based on observations that have been made in obese patients, in non-HIV obese patients who follow lifestyle modifications. And in those cases, a 5 percent weight reduction, according to some data, was associated with benefits on insulin resistance, on dyslipidemia, and on blood pressure.

Therefore, this number should not be extrapolated to any other indication, even as a minimum, without a critical look at these variables.

The Egrifta Phase 3 trials included triglycerides and cholesterol as secondary endpoints, all metabolic biomarkers with cardiovascular implications, as well as patient-related outcomes related to patients' perception of abdominal size and distress associated with it. IGF-1 was also a secondary endpoint.

Body composition endpoints, such as lean body mass, total trunk fat, were relegated as additional endpoints. A special mention is deserved about waist circumference, because we heard a lot about it in the morning session, and it is particularly important, because it has correlated with VAT, in general, in patients with HIV and lipodystrophy and, as was indicated earlier, with risk of an increased mortality in obese patients with increased waist circumference.

Now, I would like to make a couple of comments about VAT and cardiovascular risk reduction. The agency has not approved any drug for any indication on the basis of VAT reduction as a primary efficacy endpoint, and the agency is not aware of any

pharmacological intervention trial that clearly establishes that VAT reduction lowers cardiovascular risk in HIV-infected patients with lipodystrophy or in any other population, for that matter.

In addition, the agency has to judge the cardiovascular benefits of VAT reduction in the presence of, A, a glucose metabolism deterioration that has occurred at least in a subset of patients, and, B, modest reductions in metabolic biomarkers or other endpoints who have cardiovascular relevance.

To be a little bit more specific, the triglyceride reduction effect was relatively modest and reached statistical significance only in one trial. Similarly, the changes in cholesterol tend to be relatively small and reached statistical significance in only one trial.

The waist circumference reduction showed a fairly small effect by 6 months, only 1.5 centimeters relative to placebo at 6 months, and no placebo comparison for the data at 12 months. Finally, there were no changes in mean blood pressure between Egrifta and the placebo, although blood pressure was not an

efficacy endpoint.

A few words about Egrifta and safety. As we had seen before, due to the pharmacological or pharmacodynamic overlap between Egrifta and growth hormone, it shouldn't come as a surprise that they share a lot of adverse events in common. However, there are two safety issues which, in our view, are emerging from the Phase 3 clinical program.

One is the worsening in glucose profile, with evidence of pre-diabetes progressing to diabetes on a subgroup of patients. And second is you already discussed excessive IGF-1 levels that are seen in association with the fixed dose regimen that was employed in the Phase 3 programs. That is a regimen that does not allow titration in patients who reach such high levels.

This is of additional significance, because HIV-infected patients tend to have a higher background risk of non-AIDS defining malignancies.

In a few instants, Dr. Ali Mohamadi will present the efficacy and safety analysis of the FDA. As you listen to his presentation, I ask you to be

aware of the following issues that are concerns for the agency, and these are issues that will be reflected in the agency's questions at the end of Dr. Mohamadi's presentation.

We are trying to find out from you, what is your opinion about the clinical relevance of VAT reduction with Egrifta in the HIV population with respect to cardiovascular risk reduction and patient-perceived benefits.

In addition, what is the significance of findings of glucose intolerance and the development of diabetes associated with Egrifta therapy and its impact on long-term cardiovascular risk?

Finally, what is the significance of the IGF-1 increase that has been associated with Egrifta therapy and how it will impact patients who will use Egrifta chronically, because what we have seen this morning, the discontinuation of the Egrifta treatment is associated with a reduction in both VAT effects and IGF-1 effects. And therefore, the treatment is expected to be chronic.

Thank you for your attention. And let me

introduce to you Dr. Ali Mohamadi, who is the primary medical reviewer for the Egrifta application.

DR. MOHAMADI: Thank you, Dr. Roman. Thank you to the sponsor. Thank you to the members of the public who have joined us.

Members of the committee, over the next hour, I plan to deliver a data-driven assessment of the items related to Egrifta that the agency has identified as being particularly meaningful for your consideration.

I plan to start very briefly with the trial overview and a description of the patient population, followed by an in-depth look at the efficacy findings. I'll move on and focus the majority of the talk on the safety findings and, in particular, three that the sponsor has already discussed, including IGF-1, glucose metabolism, and immunogenicity. And I hope that by the end of this talk, I'll have presented the information that is relevant and necessary for the committee to make an informed decision and discussion.

As has been mentioned a couple of times already, but I think warrants repetition, the sponsor

has proposed the following indication for Egrifta: the induction and maintenance of a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

Dr. Marsolais very nicely went over the clinical development program already. I don't mean to belabor the actual scheme of the main phase and extension phase trials, but a couple of points of importance.

First, this discussion, especially as pertains to efficacy, but in sum, is going to focus on the main phase studies, which I will refer to as Study 10 and Study 11. As you know, there was 2:1 randomization in this study for tesamorelin versus placebo.

The second point I'd like to make is when discussing efficacy, in particular, I plan on discussing the individual trials separately. As has already been discussed, the scheme for both of these plans and the protocols are identical. The patient populations are identical, and, therefore, we believe that the results should be reproducible.

In terms of the patient population, as already presented, HIV-positive males or females, aged between ages 18 and 65, who were on stable antiretroviral therapy for at least 8 weeks. The waist circumference criteria included males requiring a waist circumference at or greater than 95 centimeters, with a waist-to-hip ratio at or greater than .94, and females with a waist circumference of at or greater than 94 centimeters, with a waist-to-hip ratio of greater than or equal to .88.

For entry, patients must have a fasting glucose less than 150 milligrams per deciliter. This allowed a subset of patients who are considered diabetic to enter, but they may not have entered if they were either on anti-hyperglycemic medications or insulin. Therefore, they had to be diet-controlled diabetics. Patients on growth hormone were excluded. And patients, as you know, on stable lipid-lowering agents were permitted.

Moving on to efficacy. As has been previously mentioned, the primary endpoint for the main phase studies was the percent change in visceral

adipose tissue after 26 weeks of treatment.

There were a number of secondary endpoints. The ones that were protocol-defined included IGF-1, a number of patient-reported outcomes, triglycerides, and the total cholesterol-to-HGL cholesterol ratio. Other endpoints that were assessed included body composition and anthropometric measurements.

When discussing the primary endpoint, as has been mentioned previously, what is considered by the agency and the sponsor to be a clinically relevant VAT decrease for these main phase studies was a difference of 8 percent between tesamorelin and placebo. These were based on recommendations from the Forum for Collaborative HIV Research, which was convened in 2004.

I'm going to try and get the laser pointer to work, although I'm at a tough angle. Okay. I'm going to have to describe this, and I apologize.

This slide shows the percent change in VAT from baseline to the end of the main phase, or week 26, in both main phase studies. A couple of points to point out. For Study 10, which is represented in the

leftmost columns, the treatment difference between tesamorelin and placebo using least square means by week 26 was clinically significant, a 19.5 percent decrease for tesamorelin versus placebo.

The difference, also, for Study 11 was clinically significant of 11.7 percent VAT decrease by the end of the main phase. As you can see, the week 13 data is included just to show that this change took place rapidly and was sustained over the course of the main phase.

I'm going to present a number of figures that appear similar to this one. These are cumulative distribution function curves, in this case, showing the percent change in VAT at week 26 for tesamorelin versus placebo. Again, I apologize for the lack of a pointer. So I'll try and talk you through these.

As you can see, the curve on the left represents Study 10. The blue curve is patients who received drug. The red curve represents patients in the placebo groups.

On the X-axis, we have the actual percent change in visceral adipose tissue. And on the Y-axis,

you have the percentage of patients who had that corresponding VAT change.

So if you look on the X-axis in the leftmost figure, where VAT percent change is zero, and work your way up to where the zero line meets, for example, the blue curve, you can see that approximately 80 percent of patients had at least or greater a decrease in visceral adipose tissue than zero. In other words, at least 80 percent of the patients had a negative VAT change, which is a positive finding for this study.

Another thing to pay attention to in these following slides for cumulative distribution function is the separation between the curves. A greater separation between the curves indicates a greater treatment difference.

It's undeniable that both for Studies 10 and 11, there is a nice wide separation between the tesamorelin group and placebo groups in terms of the percent change in VAT at the end of the main phase. In the boxes, you can see the p-values indicate that both studies reached statistical significance.

As the sponsor has already mentioned, in the

extension phase, the decrease in VAT for patients who received tesamorelin for a total of 52 weeks, or the T-T group, was sustained, with a mean decrease of about 17.5 percent when you pool the two studies together.

In patients who were re-randomized to placebo, in other words, received tesamorelin for 26 weeks and then were switched to placebo, re-randomized, as you say, to placebo for 26 weeks, VAT re-accumulated quickly and consistently. And by the end of the 52 weeks, these patients had actually an increase in VAT of .28 percent from their original baseline.

These figures take a look at the time phase of the way in which VAT percent changed from week zero to 52 in the three different extension phase groups. So, again, apologizing for the lack of a pointer, if you look on the left, at Study 10, at the green curve, those are patients who were in the T-T group receiving tesamorelin for 52 weeks. These are completers only for both of these.

In the T-T group, as you can see, by week

13, there was a rapid decrease in percent VAT by week 13, which continued to decline by weeks 26 and 39, and plateaued and stayed steady by the end of the extension phase.

Patients in red represent the P-T group, patients who started on placebo and were re-randomized to tesamorelin at 26 weeks. In Study 10, these patients had a slight increase in percent VAT by the end of the main phase, but when re-randomized to tesamorelin, their percent VAT decreased at a rapid and sustained rate over the course of the extension phase.

The blue line represents patients in the T-P group, which are those who started on tesamorelin for the main phase and were re-randomized to placebo. As you can see, there was a significant treatment effect through 26 weeks and a rapid re-accumulation of VAT after discontinuation of drug.

In general, although the overall magnitude of change for patients on tesamorelin was somewhat less in Study 11, the results were similar.

Moving on to the secondary endpoints.

Following the primary endpoint, there are actually a total of 20 other endpoints that were evaluated by the sponsor; 16 of these were non-PRO-related and 4 were PRO-related.

Per protocol, the following endpoints were considered secondary endpoints; patient-reported outcomes, which included belly appearance distress, belly size evaluation, and belly profile; triglycerides; the total cholesterol-HDL cholesterol ratio; and, IGF-1.

In actuality, as I said, after the primary efficacy endpoint, the sponsor has evaluated a number of other endpoints as part of the main phase trial analysis. In order to establish a hierarchy for the most clinically important variables and to conserve Type I error, a gatekeeper approach was used, and it's shown on this slide.

Basically, using this approach, the treatment effect for the highest ranking secondary efficacy endpoint needed to be proven in order to move on to the next endpoint ranked below it. As a caveat, in order for the first secondary endpoint to be

considered, VAT, the primary efficacy endpoint needed to be proven to be statistically significant in terms of the difference between drug and placebo. Clearly, we've shown that that's not an issue.

This table depicts the rank order for Studies 10 and 11, which, as you can see, are slightly different. For Study 10, the PRO belly appearance distress is the first endpoint as far as the gatekeeper approach is considered, followed by triglycerides, and then total cholesterol-HCL cholesterol ratio.

For Study 11, the schema is slightly difference, with belly appearance distress and triglycerides being considered at the same time as the first endpoint, followed by total cholesterol-HDL cholesterol ratio.

At the request of the agency and as a purely supportive analysis, non-HDLC was used for Study 11 and triglycerides were not ranked. The point of putting together this gatekeeper approach was solely for labeling purposes.

To start with the topmost ranked in the

gatekeeper approach, patient-reported outcomes were done via questionnaires completed at randomization week minus 4 and then zero, 26, and then the extension phase, 52 or the end of trial, if that occurred prior to week 52.

The secondary efficacy PROs, as I mentioned, were belly appearance distress, belly size evaluation, and belly profile, which was reported by the patient. I mentioned in the gatekeeper slide that belly appearance distress was the only one of these that was considered in that ranking system. However, I'm going to discuss all of them, because I believe the results of all are important.

For belly appearance distress, in the assessment system, essentially, a more positive change at week 26 is associated with a better outcome. In other words, if you look at Study 10, on the left, at week 26, there was a net positive change of 11.6 for patients in the tesamorelin group versus 6.2 in the placebo group; and, for Study 11, a net positive 8.3 at week 26 for those in the treatment group versus 5.2 for those in placebo.

You may notice that there are two different p-values for Study 10. Per protocol, in Study 10, belly appearance distress was to be analyzed using a parametric ANCOVA, and Study 11 per protocol was to be analyzed using a non-parametric ANCOVA.

Following the end of Study 10's main phase, the sponsor approached the agency to ask whether non-parametric ANCOVA could be used for Study 10 instead. The agency did not agree. So what we're showing here on the left for Study 10 is the agency's or parametric ANCOVA analysis, and on the right is the non-parametric analysis.

For Study 10, the parametric analysis does not reach statistical significance, whereas the non-parametric analysis does. For Study 11, the non-parametric analysis does attain statistical significance.

This is a cumulative distribution function curve for Studies 10 and 11 for belly appearance distress. The reason that this is not as smooth a curve is that these are discreet variables.

But as you can see, and especially in

comparison with the separation in the curves for VAT, regardless of whether or not statistical significance was reached, there is a much smaller separation between the curves.

Belly size evaluation, again, was analyzed in a similar fashion as belly appearance distress. I've included the p-values for the parametric and non-parametric analysis for Study 10. And I apologize that in your handouts, the p-value by the parametric analysis or, as it says, per FDA analysis, was incorrectly put down as .075, when, in fact, it was .75.

Regardless, for Study 10, either way that these were evaluated, belly size evaluation did not reach statistical significance in terms of the difference between tesamorelin versus placebo, nor did it for the non-parametric analysis in Study 11. These are corroborated by the CDF curves, which, again, show a very minimal separation between curves for tesamorelin and placebo.

Finally, patient-reported belly profile was considered more beneficial with a more negative value.

Using the parametric analysis or the non-parametric analysis for Study 10, the difference between tesamorelin and placebo can be considered statistically significant. However, for Study 11, using a non-parametric ANCOVA, the results are not statistically significant.

These are the curves, again, demonstrating a relatively small separation between tesamorelin and placebo.

Moving on to the next ranked in the gatekeeper analysis, triglycerides, and this table shows the percent change from week zero to 26. We've done this, as I mentioned, in terms of percentages and, as you can see, in Study 10, the difference from placebo, for tesamorelin versus placebo, is 18.3 percent decline for those in the drug group. In Study 11, there is a negative 3.4 percent decline in those in the treatment group. This can be considered statistically significant for Study 10, but not for Study 11.

If you look at the CDF curves, irrespective, again, of what the p-values are and in comparison with

the VAT curves, you can see that the separation for Study 10, which is considered the statistically significant result, is still relatively small; and, in Study 11, there's barely any separation whatsoever. This was not a statistically significant result.

The next secondary efficacy variable in the gatekeeper approach was the total cholesterol-HDL cholesterol change from week zero to 26. Similar to triglycerides, the difference between tesamorelin and placebo achieved statistical significance for Study 10, but not for Study 11.

Non-HDLC, as I mentioned, was used by the agency as a supportive measure, as a secondary variable. Again, similar to triglycerides and similar to total cholesterol-HDL cholesterol ratio, the difference was found to be statistically significant for Study 10, but not for Study 11.

Finally, in terms of secondary efficacy endpoints, IGF-1 change from week zero to 26. There was a mean increase of 80 percent for patients in Study 10 receiving the drug versus a mean decrease of 5 percent for those in the placebo group.

Similarly, in Study 11, there was a mean increase of 88 percent for those who received drug and a small increase in placebo of 5 percent. Both of these treatment differences can be considered statistically significant. If you look at the CDF curves, you can see that these are more in line with the separation seen for VAT change.

Other endpoints that were considered and which I would like to discuss are endpoints considering body composition, which included total, trunk, arm, limb, and leg fat, subcutaneous abdominal tissue and lean body mass, as well as anthropometric measurements, which included waist circumference, which we've heard a bit about today, hip circumference, and waist-to-hip ratio.

This figure provided by our statistical reviewer shows the least square means treatment difference between drug and placebo for a number of efficacy endpoints considering body composition. Using VAT, at the top, which is the primary efficacy endpoint, as a comparator, you can see that patients have statistically significant decreases in both

studies for trunk fat, arm fat, and total fat. They also had a statistically significant increase in both studies for lean body mass.

As has been mentioned, it's important that subcutaneous adipose tissue not be significantly changed by the drug, and, as you can see, there was not a statistically significant change in either study between drug and placebo.

In terms of anthropometrics, as I mentioned previously, waist circumference, hip circumference, and waist-to-hip ratio have been assessed. In particular, I'd like to discuss waist circumference, which has been brought up on numerous occasions today.

As you can see, in both Studies 10 and 11, the treatment difference between tesamorelin and placebo was considered statistically significant. This is at week 26. I'd like to point out that in tesamorelin, there was a mean decrease of 2.6 centimeters at 26 weeks. And in placebo, there was also a decrease, albeit smaller, of .8 centimeters, making the treatment difference 1.8 centimeters over 26 weeks.

In Study 11, the treatment difference was smaller. In the tesamorelin group, patients had a mean decrease of 2.2 centimeters over 26 weeks versus a mean decrease of .8 centimeters for placebo, a treatment difference of 1.4 centimeters over 26 weeks.

Again, using the previous CDF curves as a basis for comparison, these two studies, Study 10, on the left, and Study 11, did demonstrate statistically significant results. However, the separation between the curves is rather modest.

In summary, for efficacy, two independent Phase 3 trials do confirm that the effect of the drug on decreasing VAT is greater than placebo at 6 months and that these changes are sustained through 52 weeks of treatment in patients in the T-T group.

Patients who were re-randomized to placebo showed a rapid and sustained re-accumulation of VAT and by the end of 52 weeks, after having been on placebo for 26 weeks, their levels of VAT are close to what they were at the baseline of the entire study. But as has been alluded to previously, the significance of this degree of VAT reduction on

cardiovascular risk is not entirely clear.

In terms of the secondary endpoints, the findings are less consistent. If you look at the individual studies, Study 10 has statistically significant results for belly profile, the PRO, triglycerides, total cholesterol, HDL cholesterol, non-HDL cholesterol, and IGF-1. Study 11, on the other hand, shows a statistically significant difference for belly appearance distress and IGF-1.

For other endpoints, there is agreement between the studies for the statistical significance in decreases in trunk, total and arm fat, increases in lean body mass, a decrease in waist circumference, and a decrease in waist-to-hip ratio. But as shown by the cumulative distribution function curves, the degree of separation, the degree of difference between patients receiving drug and receiving placebo is far less marked in most of these, with the exception of IGF-1, compared to VAT.

If I may move on to safety, as I mentioned previously, there are three topics that I would like to spend the majority of the time on. But first, I'd

like to talk about the topmost bullet, which includes deaths, significant adverse events, discontinuations, treatment-emergent adverse events, and cancer adverse events.

Briefly, there were 10 deaths reported through the entirety of the tesamorelin clinical program in all trials. Four cases were in the pivotal trials and 6 in the non-HIV non-pivotal trials. Among these patients, 8 were receiving drug and 2 received placebo.

Only one of these patients was considered to have a death that was related to treatment, which was a 49-year-old male who received tesamorelin in Study 11. This patient developed metastatic lung adenocarcinoma after being on treatment for 95 days. As a whole, it doesn't appear that there is a great difference between tesamorelin or placebo in terms of deaths.

Moving to nonfatal significant adverse events, in the main phase studies, the proportion of patients who had SAEs was similar in tesamorelin and placebo groups. The numbers were also similar in the

extension phase when looking at patients who were on tesamorelin for 52 weeks and those who were re-randomized to placebo after 26 weeks.

Really, there's no specific pattern that one can draw when looking at the significant adverse events that were reported by patients in either the tesamorelin group in the main phase or the T-T group in the extension phase.

For both the categories of adverse events that led to patient discontinuation and treatment-emergent adverse events, the specific adverse events, in general, can be categorized into three discreet categories -- those that are clearly related to the effect of growth hormone; those that are clearly elated to reactions at the injection site; and, albeit rarely, allergic or hypersensitivity reactions, including rash or urticaria.

The sponsor has already kind of gone over in good detail, I think, the discontinuations and the reasons for discontinuation. Approximately a quarter of patients in Study 10 who were treated tesamorelin discontinued versus 16 percent of those in the placebo

group. And in Study 11, again, approximately a quarter of patients who were on drug versus about 27 percent in placebo discontinued.

The percentages here don't show percentages of all patients in these groups who had, for example, adverse events as a reason for discontinuation. Rather, slightly over 40 percent of patients receiving tesamorelin both in Study 10 and slightly under 40 percent in Study 11 who discontinued had discontinuations due to adverse events.

As the sponsor has already discussed, approximately 10 percent of patients in the main phase tesamorelin group had an adverse event that led to discontinuation versus 6 in placebo. But when you look at the extension phase, only 2 percent of patients who were re-randomized to tesamorelin versus 4.4 percent of those who were re-randomized to placebo had AEs leading to discontinuation.

In terms of adverse events as a whole, in the main phase, there were similar proportions of patients in tesamorelin versus placebo who developed treatment emergent adverse events, and it's similar

when looking at the T-T group versus T-P group in the extension phase.

The sponsor has gone over cancer adverse events already. Briefly, as a whole, there was really no specific pattern of cancers that differentiate patients receiving drug versus those in the placebo group. But as the sponsor already mentioned, the limited duration of the study does limit the ability to make a full risk assessment at this point.

Moving on to the adverse events that we have determined that are of particular interest, we'll start with IGF-1 and changes in IGF-1. So during the main phase, as background, IGF-1 measurements were performed at baseline and then weeks 13 and 26.

As has already been mentioned, the mean IGF-1 standard deviation scores were within the low-normal range for both the tesamorelin and placebo groups at baseline. And in terms of the percentage of patients who had standard deviation scores greater than 2, they were similar, at about 6 percent for both groups.

Again, I'm sorry I don't have a pointer, but what I would like to point out here in specific and

which already has been mentioned is the rise in terms of the proportion of patients in the tesamorelin group who developed standard deviation scores greater than 2 and greater than 3 at week 26. Again, about 47 percent of patients who received tesamorelin ended up with a standard deviation score greater than 2. And over a third, 35.6 percent, had a standard deviation score greater than 3.

The week 13 numbers are shown to indicate that this rise occurs rapidly, with the numbers strikingly similar in terms of the standard deviation scores at weeks 13 and 26.

As has already been discussed, in the extension phase, IGF-1 measurements were performed at the beginning, week 27, and then week 39 and 52. At the beginning of the extension phase, the mean IGF-1 standard deviation score in the T-T group was 2.66, and for patients in the T-P group, it was 2.29. By week 27, about half the patients in both groups had standard deviation scores greater than 2.

This is a similar table to the one I showed a couple slides ago and it shows that in the T-T

group, as the sponsor has shown in their presentation, by week 52, patients who remained on tesamorelin, about 33 percent had SDS scores that were still above 2 and 23 percent with SDS scores above 3, whereas patients who were re-randomized to placebo had a rapid and sustained decrease in terms of their IGF-1 levels.

By week 52, patients in the T-P group, 5 percent had SDS scores greater than 2 and only 1 percent greater than 3. The trends in terms of the decline in SDS scores based on this data seems to show a steady decrease at week 39 to week 52.

This is data for completers only, showing mean IGF-1 standard deviation scores over time. Again, the green curves -- this has been broken down into individual studies. The green curves represent patients who were re-randomized at week 26 to tesamorelin, to the T-T group. These patients, as indicated in the previous table, had a rapid and sustained increase in IGF-1 standard deviation scores above 2 and close to 3 by week 26, and then a decrease close to or below 2 by week 52.

Patients in blue, the T-P group, had an

increase in IGF-1 standard deviation scores by week 26 and then a rapid decline when re-randomized to placebo. And conversely, patients who started on placebo and were re-randomized to tesamorelin at week 26 had a rapid increase in IGF-1 standard deviation scores at re-randomization.

The trends, in general, are similar for Studies 10 and 11, with patients ending up at week 52 with slightly higher IGF-1 standard deviation scores a little bit above 2 in the T-T and P-T groups.

When broken down by gender, the upper two figures show males and the lower two show figures for IGF-1 standard deviation scores over time. The take-home message from this slide, briefly, is that males compared to females did tend to have higher SDS scores, on average, over time, with their ranges ending up in Study 10 just below 2 SDS and just above 2 SDS in Study 11 versus females, who were closer to 1 at the end of Study 10 and about 1.5 at the end of Study 11.

Something that hasn't been mentioned at this point -- if it has, I apologize -- the percentage of

patients, the breakdown male to female was 85 percent male and 15 percent female across all studies. So in other words, when looking at the values in sum, you have to take this into account.

In summary, for IGF-1, tesamorelin increased mean serum IGF-1 above 2 standard deviation scores at 6 months and the effect was seen as early as 13 weeks of treatment. As many as a third of tesamorelin-treated patients had SDS scores after 52 weeks of treatment, which, again, the numbers that I showed did not take into account extension phase completers. It remains to be seen what the effect is of that, and discontinuation of tesamorelin undoubtedly resulted in a decrease IGF-1 to baseline levels. Those were the T-P patients.

The next adverse event of interest that I'd like to discuss is glucose metabolism. Per protocol, the applicant has supplied a number of different definitions with which to make assessments of glucose metabolism. These were based largely on the 2006 ADA recommendations.

Of their definitions, we would like to stick

with definition one, which is the closest to, actually, the most recent set of definitions put out earlier this year. This includes an impaired glucose tolerance being defined as fasting plasma glucose between 100 and 125 or a two-hour OGTT with a value between 140 and 199, and diabetes being defined as a fasting glucose of greater than or equal to 126 milligrams per deciliter or a two-hour OGTT greater than or equal to 200.

I addition, the 2010 ADA guidelines have included hemoglobin A1C as a new screening tool for the diagnosis of pre-diabetes and diabetes. We have chosen to include these -- sorry -- we've chosen to evaluate hemoglobin A1C levels of these patient populations to see if there's any additional data that can be gleaned.

The definitions from this year are as follows. Patients with A1Cs between 5.7 and 6.4 are considered pre-diabetic and patients with A1Cs greater than or equal to 6.5 percent are considered diabetic.

Fasting blood glucose and A1C were not the only two parameters that were studied by the sponsor.

To go through four in particular, as you can see from the topmost rows, the mean change in fasting blood glucose in patients on tesamorelin was an increase of 2.7 milligrams per deciliter over 26 weeks of treatment versus an increase in the placebo group of .7. This is not considered statistically significant.

For insulin and HOMA IR, the differences between treatment group and placebo are also not considered significantly different. For hemoglobin A1C, the results are considered statistically significant, but the mean changes are modest, with an increase of .1 percent for patients receiving tesamorelin versus a mean increase of .02 percent for those in the placebo groups.

However, in our review of individual patient data, what appeared, something that we would like to follow a little bit more closely, are the trends in blood glucose values and hemoglobin A1Cs, particularly among patients who began in either the impaired glucose tolerance or pre-diabetes range, depending on whether you looked at fasting blood glucose or A1C.

What we're going to provide in the next

several slides is a more descriptive analysis of the possibility that the drug may produce changes, significant changes in baseline in these two parameters. This is called shift analysis, where we have defined a shift as any measurement that was considered in a more severe category of glycemic control than the patient's baseline measurement.

In other words, if a patient began using hemoglobin A1C with normal glucose tolerance, basically, let's say, with an A1C of 5 percent, and at week 13, ended up with an A1C that was 5.9 percent, which could be considered pre-diabetic, that is considered a shift.

We are not considering in this analysis downward shifts. And also, we are not considering a shift of a large magnitude; for example, starting with 5, which is non-diabetic, and ending up with 6.7, which is diabetic, multiple shifts. Any movement from baseline to a higher value will be considered a shift for the following assessments.

So looking at fasting blood glucose, in the main phase, these were measured at baseline and then

weeks 6, 13, 19 and 26. We've categorized fasting blood glucose in terms of the category of glucose metabolism as per the sponsor's definition one, which is anything less than or equal to 99 considered normal; anything between 100 and 125 considered impaired fasting glucose; and anything at or greater than 126, diabetic.

As an example, if a patient started with a weak serum fasting blood glucose of 98, which is normal, and then had subsequent fasting blood glucoses of 95, which is normal, 204, which is diabetic, then back to normal for the next two, this is considered one shift.

This table takes a look at the percentages of patients in both the tesamorelin and placebo group who experienced shifts over the 26 weeks of treatment. We are only looking in this table and the following slides at patients who had data collected at every time point. In other words, if they missed a data collection or it wasn't collected for some reason, they are not included in this analysis.

As you can see, in the tesamorelin group, 49

percent of patient did not have any shifts whatsoever from baseline. A higher percentage of patients, 60.8, in the placebo group had no shifts. Looking downward, the difference, this approximately 10 percent difference is almost entirely made up by patients who had three or greater shifts.

Patients receiving drug, approximately 17 percent of them had three or greater shifts versus 7.5 percent of placebo-treated patients who had three or greater shifts. This indicates to us that there may be a trend toward more sustained elevation of blood glucose in patients on tesamorelin.

As another point of emphasis, in the questions to the sponsor, there was a question that was raised about the percentages of patients who start in one category and shift upward or downward. I'll show you different data or talk to you about different data for A1C, but it bears noting that although for patients who started in the impaired glucose tolerance and moved to diabetes, the proportions at week 26 were similar between tesamorelin-treated patients and placebo-treated patients.

When you look particularly at weeks 13 and 19, there is about a 10 percent difference, higher for patients in tesamorelin versus placebo. For example, in week 19, about 11 percent of patients who started with impaired glucose tolerance and received tesamorelin moved to diabetes versus 3 percent of patients who were on the placebo group.

It's difficult to explain why, at the end of 26 weeks, at that single time point, the numbers were similar, at about 13 to 15 percent; but for each preceding point, the tendency to shift was higher among patients who received drug.

This slide takes a look at individual patients who had shifts in fasting blood glucose at any point during -- sorry -- at three or greater points during the trial. What we're looking at here in the two leftmost panels are trends of patients over time. Each patient's individual value at each time point is connected by a blue line. And remember that this is a 2:1 randomization of drug to placebo.

As you can see, regardless of the randomization, for fasting blood glucose, there does

appear to be a trend upward in patients receiving drug to levels above 126 compared to placebo. We've also, in the rightmost panel, added trend lines using regression analysis, which shows that the slope for patients who are receiving drug product, in blue, is somewhat greater than that of those in the placebo group. Again, these are only patients who had three or greater shifts from baseline.

We did a similar analysis for hemoglobin A1C, which was collected at weeks zero, 13 and 26 in the main phase. Again, anyone with an A1C at or less than 5.6 percent was considered to have normal A1C. Patients between 5.7 and 6.4 were considered to be pre-diabetic, and those with A1Cs at or greater than 6.5 percent-diabetic.

Again, not to belabor the point, but to provide an example, a patient who, at week zero, had an A1C that was normal at 5 percent and then subsequent A1Cs of 5.9, which is considered pre-diabetic, and 5.1, which, once again, is back to the baseline normal level, was considered to have a single shift.

This is a similar table to fasting blood glucose, showing the percentages tesamorelin versus placebo, the tendency of patients to shift and the number of times that they would shift.

As you can see, in the tesamorelin group, 73.5 percent of patients did not experience any shifts whatsoever, versus 83 percent in placebo. This difference of approximately 10 percent seems to be evenly distributed among patients who had one shift and two shifts.

In a similar analysis to what I talked about before and what was brought up by the sponsor, if you look at patients who started in the pre-diabetes category and, by the end of the main phase, shifted to diabetes, approximately 25 percent of patients who were defined as pre-diabetic by A1C shifted to diabetes. This is in comparison to 11 percent of patients who started with pre-diabetes in the placebo group and shifted to diabetes.

This is a similar table to the one before, showing individual patients and their A1C trends over time. Again, we are only looking at patients in this

case who had data measured at all time points and, also, in patients who had two shifts.

So looking at the far left, you're looking at patients in the tesamorelin group. In the middle, you're looking at patients in the placebo group. And, to the right, you're looking at linear regression curves, which, again, indicate a larger slope of the curve in patients who were receiving tesamorelin versus those who received placebo.

Based on this information, our statistics team did an analysis specifically looking at patients who had A1Cs in the diabetic range at any point of the study. Basically, they wanted to compare the number of patients who developed A1Cs at or greater than 6.5 percent during the main phase in drug versus placebo group.

The upshot of their analysis, which I'll show you in the next couple slides, is that tesamorelin was found to be statistically significantly different than placebo in terms of the percentage of patients who developed diabetes after 26 weeks of treatment.

The initial analysis looked at all patients, regardless of their initial baseline A1Cs. So in other words, it included patients who started with A1Cs in the diabetic range. When you removed the patients who started with A1Cs in the diabetic range, the results were similar and statistically significant.

This table looks at the initial analysis, which is all patients who had an A1C of 6.5 or greater at any time point during the trial.

As you can see, when comparing tesamorelin versus placebo for Study 10, the risk difference was 5 percent for patients receiving drug, with an odds ratio of 7.9; for Study 11, individually, again, a risk difference of 5 percent, with a slightly smaller odds ratio of 2.6. And when you do an integrated analysis, the odds ratio for all patients who developed A1Cs 6.5 or greater was 3.6 for the drug group, which was considered statistically significant.

When you removed the patients who started with A1Cs at or greater than 6.5, again, the risk difference was 4 percent for Study 10 and 3 percent

for Study 11; and, when looking at both studies, the odds ratio was 3.4, with a statistically significant p-value.

Finally, this figure takes a look at individual patients' trends in terms of their hemoglobin A1C changes from baseline to week 26. So to walk you through this, patients in blue are those in the tesamorelin group and patients in red are in the placebo group.

The red triangles indicate their baseline A1Cs, with the blue circles indicating their A1Cs at 26 weeks. Looking at Study 10, on the left, again, taking into account that there's a 2:1 randomization schema, there are a significantly greater number of patients in the tesamorelin group who had A1Cs that started at less than 6.5 and moved greater than 6.5.

In this analysis, the only patient in the placebo group who had an A1C of greater than 6.5 actually started at about 6.8, and by the end of trial, was at 6.5.

If you look at Study 11, on the right, the results are similar, with a greater proportion of

patients starting pre-diabetic or even not diabetic at all and moving to the diabetic category in the tesamorelin group versus placebo.

Another thing to bear in mind is if you look at the actual horizontal lines, it indicates the magnitude of change over 26 weeks, which, in general, was greater for patients on tesamorelin versus placebo.

For the extension phase, the results were less striking. Patients who remained on tesamorelin for a total of 52 weeks had a mean increase of about 2 milligrams per deciliter from the initiation of the study at week zero to week 52, whereas patients who were re-randomized to placebo had a decrease from week zero to week 52 of 2.02 milligrams per deciliter.

In terms of A1C, patients in the T-T group had a mean increase of .07 percent from week zero to week 52 and patients in the T-P group had a similar value. In terms of shifts, although patients in the T-T group did tend to shift more frequently than those in the T-P group, there was really no discernable difference, especially when compared to the main

phase.

So in summary, for glucose, there are no clinically meaningful changes in terms of mean actual values of fasting blood glucose or A1C during the main phase, but a more detailed analysis of trends and shifts seems to indicate that there is a move toward worsening glucose status in patients receiving drug in the main phase for both fasting blood glucose and hemoglobin A1C.

Furthermore, the analysis provided by our statistics team shows that there is a statistically significant difference in terms of the proportion of patients who developed diabetes in the tesamorelin group versus placebo. And data for the patients who received tesamorelin for 52 weeks was less conclusive.

I briefly want to go through immunogenicity, which has been looked at closely by the sponsor already. In specific, what I want to talk about is the actual scheme of testing.

So all subjects in the Phase 3 program were tested for antidrug antibodies at baseline and then also at weeks 13, 26, 39 and 52, or end of trial, if

that occurred at a different time. Furthermore, subjects who were found to have antidrug antibodies were then assessed for in vitro neutralizing antibodies to both drug and GHRH.

As the sponsor has presented, patients in the tesamorelin group were likely -- approximately half of them ended up developing anti-tesamorelin antibodies at week 26. If you look at baseline, approximately 2 percent had anti-tesamorelin antibodies, and at week 26, 48 percent. The majority of these patients developed low level titers, only 19 percent with titers at or greater than 400.

Looking at the difference between the 50 percent of patients who developed anti-tesamorelin antibodies versus the 50 percent who did not, there was not a significant change between groups for either percent change in VAT or IGF-1.

When looking forward at the extension phase, the proportions of patients who received tesamorelin for 52 weeks and had antibodies at the end of the trial was similar to that at week 26. In other words, about 45 percent in the T-T group had anti-tesamorelin

antibodies at the start of the extension phase and about 47 percent had them at the end.

Patients who were re-randomized to placebo had a marked decline in terms of the percentage who had antibodies at the end of week 52, with 55 percent at the start of extension phase showing anti-tesamorelin antibodies versus only 18 percent at week 52.

When you look at the entirety of the 52 weeks, whether a patient was antibody-positive or negative at week 52 didn't play a major role in terms of differences in the decrease in percent VAT or increases in IGF-1.

As I mentioned, patients who were anti-tesamorelin antibody-positive were then tested for neutralizing antibodies to growth hormone-releasing hormone and to the drug itself. First, to talk about patients in the T-T group, this subset of patient was tested for neutralizing antibodies at the end of their entire treatment period; in other words, at week 52.

There were 122 anti-tesamorelin antibody-positive patients who developed anti-tesamorelin

neutralizing antibodies at week 52, or about 20 percent. In comparison, of the 122 patients who were anti-tesamorelin antibody-positive, 12 of them developed anti-GHRH neutralizing antibodies, or about 10 percent.

Not to belabor the point, but the presence or absence of neutralizing antibodies to tesamorelin did not play a great role in terms of the difference in percent VAT or IGF-1 change. Similarly, patients with anti-GHRH neutralizing antibodies were tested for IGF-1 change alone, and, again, there really was not a significant difference in terms of patients who were neutralizing antibody-positive or negative for IGF-1 change.

Patients who received drug for only 26 weeks, so those in the T-P or P-T groups, had neutralizing antibodies tested at the end of their treatment cycle. So in other words, if you were in the T-P group, you had neutralizing antibodies tested at week 26; and, if you were in the P-T group, you had neutralizing antibodies tested at week 52.

Of the 171 patients who had positive anti-

tesamorelin antibodies, 54 percent of patients who were treated for 26 weeks had anti-tesamorelin neutralizing antibodies versus 7 percent who had anti-GHRH neutralizing antibodies. But this slide, once again, shows that the presence or absence of anti-tesamorelin neutralizing antibodies was not clinically significant in terms of the percent VAT change or IGF-1 change in patients who were treated for 26 weeks nor was there a significant difference in terms of the IGF-1 change for patients with anti-GHRH neutralizing antibodies.

Finally, and for the sake of completeness, there was one other schema for testing neutralizing antibodies. Patients in the T-P group, so who were on tesamorelin for 26 weeks and who were on placebo -- re-randomized to placebo for the following 26 weeks, all had neutralizing antibodies to GHRH tested at week 52.

Of these patients, the ones who were found to be neutralizing antibody-positive also had their sample from week 26 tested, and a comparison was made in terms of the chronology of the development of

neutralizing antibodies in this patient subset at week 26 and week 52.

As shown here, of these patients, 4 of them at week 26 were found to be GHRH neutralizing antibody-positive, which is about 3 percent, and this declined at week 52 to 1.5 percent. Again, the numbers are small, but for completeness, I wanted to show that this was the only group of patients in which neutralizing antibody development was tested over time.

So in summary, for immunogenicity, about half of patients developed anti-tesamorelin antibodies after either 26 or 52 weeks of treatment. In vitro neutralizing antibodies to the drug itself developed in about 20 percent of patients who received drug for 52 weeks and about 31 percent of patients who received it for 26 weeks, and there doesn't seem to be an impact in this group on IGF-1 or VAT.

In vitro GHRH neutralizing antibodies developed in about 10 percent of patients treated for 52 weeks and 7 percent of patients treated for 26 weeks, and, again, there doesn't seem to be an impact

on IGF-1.

Finally, there is little information as a whole on the temporal development of any of the neutralizing antibodies, with the last group I mentioned, the last slide, being the only group in whom that has been tested.

As far as wrapping up safety, there don't appear to be significant imbalances and significant adverse events among patients in the tesamorelin versus placebo groups. Most adverse events, in general, in patients who were treated with drug were either already known to be related to growth hormone itself or reactions at the injection site.

In terms of IGF-1, about half of patients treated have standard deviation scores greater than 2 and about 33 percent or so have standard deviation scores above 3 after the main phase. And when you look at patients at the end of the extension phase, about a third still have SDS scores greater than 2, and about 20 percent, in fairness, have standard deviation scores greater than 3 after the extension phase.

In terms of glucose metabolism, patients who receive the drug do show a small mean increase in fasting blood glucose and hemoglobin A1C compared with placebo after 26 weeks. And in order to kind of flesh this out, analysis of shifts in fasting blood glucose and A1C do seem to show a trend towards worsening states of glucose tolerance, and, in specific, among patients who start with impaired glucose tolerance or pre-diabetes at baseline.

Looking at immunogenicity, finally, changes in VAT and IGF-1 do not appear to be affected by antidrug antibodies or neutralizing antibodies to the drug or GHRH, but there is a lack of longitudinal data on progression of immunogenic markers, except in a small subset of patients.

I'd like to close by just offering acknowledgments to the large team that was of immense assistance. Thank you all, and I'm sure there are more that I left out.

DR. BURMAN: Thank you to both of you.

We will now have clarifying questions from the committee for the FDA from 11:30 to noon, and then

take our break at noon. Please raise your hand and we'll prepare a list.

Dr. Thomas?

DR. THOMAS: When you did your CDF curves looking at visceral adipose tissue, you mentioned about 80 percent of the subjects reached that zero line. Since you're using minus 8 percent as the criteria, I was just curious what the minus 8 percent number is on your distribution curve.

DR. MOHAMADI: I have to walk back up to the podium.

DR. TRAN: Actually, if you want to sit there and just tell me what slides you need, I can bring it up.

DR. MOHAMADI: Yes, thank you. It would be slide 10.

So this is rough, but just looking at the curve itself and looking at the numbers we have, at least 70 percent, I would say, reached the 8 percent threshold.

DR. BURMAN: Ms. Henderson?

MS. HENDERSON: I had two questions. Number

one, were there any other quality of life measurements taken besides the belly profile, belly distress? And the second one is, out of the 10 deaths, that there was one that was related to the drug. What specifically about that one death was related to the drug and not the others?

DR. MOHAMADI: Just for the second question first, I would have to actually go through that. I will take a look at that and find it for you. Off the top of my head, I'm not 100 percent certain.

Could you repeat your first question for me? I'm sorry.

MS. HENDERSON: Were there any other quality of life measurements?

DR. MOHAMADI: There were health-related quality of life questionnaires, which we didn't evaluate, because they were not considered as part of the secondary efficacy variables.

So the main ones, again, were the -- and, actually, what I should -- so this is the belly appearance distress, belly size evaluation, and belly profile. And I should mention, we reported the

findings of the patient-reported belly profile findings, but, also, there was a physician-reported belly profile questionnaire which we did not evaluate.

DR. ROMAN: If I can make a comment with respect to the second case. In our judgment, it is nonrelated as judged by the investigator. So we really do not know or do not have any immediate information about what made the investigator think that the adverse event of death was related or not. Maybe the applicant has.

I just wanted to make one more comment with respect to the first question. The 8 percent is a modus operandi and it's not a measure that the division has accepted as fully as an indication of efficacy in the broader context.

DR. BURMAN: Thank you.

Dr. Dobs?

DR. DOBS: Two short ones. One is you said you did not analyze downshifting. Is that because it didn't exist, the numbers were too few?

Then the second one is a little bit more general. From my understanding, growth hormone, as a

carcinogenic molecule, has only been tentatively sort of the point of view for colon cancer and prostate cancer. And I wondered if there was some other data that I wasn't aware of.

DR. MOHAMADI: Thank you. In terms of the first question, we didn't analyze downshifting, because if you look at the percentages, the largest percentage of patients who downshifted were those who started with diabetes, but the numbers were remarkably low.

For example, for fasting blood glucose, looking at the number of patients who started with diabetes and downshifted, there were 9 to 15 in total.

I may defer the second question regarding other --

DR. ROMAN: The way I understand it, the second question was referring to prostate cancer and other cancer adverse events that may have been related to the growth hormone. To my knowledge, we haven't done any analysis specific for any adverse events, because -- specific cancers. Because they are so rare events in the trial, we didn't have too much data to

analyze.

DR. MOHAMADI: From what I've read in the literature, the two -- you're correct -- the two largest -- in acromegalics, anyway, the two most common cancers look to be breast cancer in pre-menopausal women and prostate cancer, although there are patients who develop thyroid cancer, as well.

DR. BURMAN: And colon cancer, right?

DR. MOHAMADI: And colon cancer. I apologize.

DR. BURMAN: Dr. Proschan?

DR. PROSCHAN: So regarding the diabetes endpoint, it seems to me that the big difference between the analyses the FDA did and the analyses that the company did is you were looking at multiple time points and looking at number of shifts, whereas they were looking at 26 weeks primarily.

So I gather that your thinking is that there's error associated with this, with whether you're above or below a cut-point. And so by looking at multiple time points, you can be sort of more confident if you see several of them.

I'm wondering, another possible way to try and become more confident is maybe to just look at the average of all the measurements and see how many peoples' average shifted them up, and I'm wondering if you did that, as well.

DR. MOHAMADI: We didn't, and actually, the reason that we did it as we did was to minimize the impact of potential dropouts. The curves that we've shown are for patients who had values collected at each time point. So it's theoretically possible that patients who dropped out may have brought down the average value at each individual time point.

As I mentioned while I was up there, something that we look at and really couldn't make a lot of good sense at is, as the sponsor has mentioned, at week 26, the frequency of patients who started especially in the pre-diabetes category and shifted upward to diabetes was similar between tesamorelin and placebo. But at each preceding time point, there were more patients in the tesamorelin group.

These are the sorts of things that we decided we wanted to look at patients who had each

time point accounted for, because we worry that the effect of dropouts may be altering the data.

DR. PROSCHAN: Okay. Related to that point, if you put up slide 64, it's amazing to me how many people in Study, I guess, 11 -- well, the one on the right side -- how many of them are right at 6.5.

So for the purposes of trying to make a determination are they above or below, there are a lot that are right on the border, which makes it kind of difficult to make too much sense of looking at a single time point. There are some that really were very close to going either way.

DR. MOHAMADI: Agreed. But as a cutoff point, we figured that the ADA's most recent recommendations were probably the most appropriate to use.

DR. BURMAN: Thank you.

Dr. Kumar?

DR. KUMAR: I have a very specific question regarding protease inhibitors and whether -- when you looked at these shifts, did it make a difference whether they were on a protease inhibitor or on an

NNRTI?

DR. MOHAMADI: I have to apologize that we did not do that analysis.

DR. KUMAR: So if I could ask the question another way, because we have always known that protease inhibitors, especially the older protease inhibitors, had significant effect on glucose metabolism.

How do we know that being on a protease inhibitor, that many of our patients are on, on this drug would not make the glucose metabolism even worse?

DR. MOHAMADI: I suppose it is theoretically possible, but I am not sure.

DR. KUMAR: Thank you.

DR. MOHAMADI: I apologize.

DR. BURMAN: That's an important question. I just wondered, although we want to focus on the FDA, if the sponsor had a quick response to that question.

DR. MARSOLAIS: Yes. We have something to help address the question. Dr. Soulban will address the question.

DR. SOULBAN: What we actually looked at is

-- we didn't look at the specific analysis of what percent of patients were on protease inhibitors and follow them through time with regards to glucose.

We did look at glucose-related adverse events by ART regimen in tesamorelin-treated patients in the Phase 3 study, and we did not have many glucose-related events in our studies. We had approximately 9 patients that reported a glucose-related adverse event.

As you can see here, the numbers are very small, with 7 patients in the NRTI plus PI group and 4 patients in the NRTI and NNRTI group. So the numbers are very small.

DR. KUMAR: This doesn't get to the question I'm asking, but this is a glucose-related adverse event. It's very different from the question that I asked.

DR. SOULBAN: Correct. Correct. Yes. We did not do those analyses specifically.

DR. BURMAN: Thank you. Thank you for coming up. Dr. Molitch?

DR. MOLITCH: Did you do an analysis looking

at IGF-1 levels versus the worsening of glucose tolerance; and, similarly, did you do one of IGF-1 levels and correlate them with VAT changes?

DR. MOHAMADI: To the second question, it appears that IGF-1 and VAT do not go along.

DR. ROMAN: With respect to the VAT correlation, to my knowledge, we have done such an analysis and there was no correlation between IGF-1 and VAT.

DR. MOLITCH: And how about the glucose tolerance status?

DR. ROMAN: We did not do that analysis.

DR. MOLITCH: Maybe the sponsor later can answer that, too.

DR. BURMAN: Sure. If the sponsor doesn't mind, we could do that later or if you have a quick answer now, that would be fine, too.

DR. MARSOLAIS: Yes. We did the analysis with IGF-1 and VAT. And this is the correlation that we have shown, which is statistically significant with a Spearman value of .2, or minus .2, for the correlation between the decrease in the VAT and the

IGF-1, change in IGF-1.

The second question was the link between IGF-1 and glucose, and, for that part of your question, we haven't done the analysis.

DR. BURMAN: Thank you.

Dr. Bishopric?

DR. BISHOPRIC: I hope I'm not repeating. But in terms of downshifts, on withdrawal of therapy, when the patients went on to the placebo arm, did you compare -- did people mostly downshift back to their normal range, so the withdrawal of therapy would basically correct an issue?

Secondly, it was stated that the FDA had never approved a drug based on a VAT parameter. Has it ever been asked to approve a drug on a VAT parameter before?

DR. MOHAMADI: If Dr. Roman can answer the first question, I can pull up the data for the first question.

DR. ROMAN: The only situation we're aware of is the Serostim application I mentioned in my previous discussion. That's the only case that comes

to my mind. I think VAT made it into one of the labels as a secondary endpoint or additional endpoint, but was not the basis for an approval.

I think it was a label for an adult. It was HOMA deficiency indication, where, generally, the approval is based on demonstrating statistical significance in body composition endpoints, such as in body mass or sometimes trunk fat reduction and additional other endpoints, along with quality of life.

DR. BURMAN: Dr. Goldfine?

I'm sorry. Please.

DR. MOHAMADI: Just to briefly answer your second question. If you look at the differences between patients who were on tesamorelin for 52 weeks, the T-T group, versus those who were re-randomized to placebo, the proportion -- if you compare the two of those groups together in the extension phase, the proportion of shifts is almost identical in terms of starting in one category and moving downward to another.

There's no real major difference over time,

and it appears that, as a whole, patients who started in one category most often stayed in the same category by the end of 52 weeks in the T-P group.

DR. BURMAN: Thank you.

Dr. Goldfine?

DR. GOLDFINE: You may not know the answer to this, but was the glucose data masked as safety data? And what was the ability of other care providers to add in diabetes therapies, because that could potentially mask both the A1C, the glucose data, and the potential impact of this? And if not, maybe the sponsor can answer that.

DR. BURMAN: Does the FDA want to answer that?

DR. ROMAN: Yes. I think my understanding was that per protocol, you could not start the second treatment, but I would like to hear the specifics from the applicant.

DR. BURMAN: Sure.

DR. MARSOLAIS: Yes. We have the information for that question. I would like to ask Dr. Soulban to speak to the data and Dr. Grinspoon

will complete the answer, also.

DR. SOULBAN: So if I understood the question correctly, you wanted to know if patients actually started on anti-diabetic agents during the study?

DR. GOLDFINE: Correct. And also if it was masked, because there could also have been an effective education for the higher blood sugars as they crossed these established thresholds.

DR. SOULBAN: Across our main and pivotal, our main placebo-controlled study, as well as the extension study, we had a total of 5 patients that, during the course of therapy, added an anti-diabetic drug.

One patient in the main phase added glyburide and they were on glyburide for only a week. And in the extension phase, we have 4 patients that added metformin.

Overall, these changes -- this occurred in very few patients. We had a handful of patients, literally, that added on anti-diabetic drugs and, as you can see from the efficacy results, nothing really

changed in that regard.

DR. GOLDFINE: And was the glucose data masked for safety data to the providers?

DR. SOULBAN: I would have to come back to you. You're asking if the sites were blinded to the glucose data, correct?

DR. GOLDFINE: Yes.

DR. SOULBAN: I believe that wasn't the case. I believe they were aware of their glucose values.

DR. GOLDFINE: Can I ask one more related -- or, I guess, you were going to finish the answer to that.

DR. ROMAN: Dr. Grinspoon can complete the response, and if we may, also, regarding the question of the increase of glucose at week 26 and the fact that we see in the extension some decrease in some of the glucose parameters, Dr. Grinspoon can also address that question, if you want.

DR. GRINSPOON: Getting to the point of who went on anti-diabetic therapy, as you can see from Dr. Soulban, a very, very small percentage of patients

went on anti-diabetic therapy; I think 5 patients or something like that, so less than 1 percent, which we took as a good sign.

Second of all, it was mentioned that the FDA was curious why the glucose went up relative to placebo in the earlier 13 week, and it's not at all uncommon in growth hormone studies to see an earlier deterioration in glucose with a tend toward a greater normalization later.

I think we followed the pattern of many growth hormone-related studies, which leads me to think that there is an insulin antagonistic effect initially that tends to be overcome by the reduction in visceral adipose tissue at the end that kind of wins out a little bit. And I interpret that based on our slide relating VAT to glucose. So we're not out of line with other therapeutic strategies.

One last point. The patients who were on drug, who went off drug, had a normalization, in general, of their glucose. So they can be identified and it's not a persistent abnormality that tends to stay on post-discontinuation. It just reverts back to

normal.

The last point is that there is a relative increased risk ratio of over 3, we agree, for diabetes, but you're talking about numbers of 4 percent versus 1 percent.

The very last point is that we agree with everything that is said. I would not personally want to increase glucose in any diabetic patient. Therefore, we are completely agreeing that such patients, over 6.5 -- and as this gentleman over here -- I'm sorry, I don't remember your name -- but pointed out that most of the ones who you're counting as increased are right in line.

We agree to take all those people out. They should not get this drug. We are agreeing with that. And we're also pointing out that we actually took patients with diabetes into this study, and possibly, that was a mistake. And we're proposing in the REMS to limit it to people without diabetes.

So I think all those things together will greatly mitigate against this detectable, but arguably, small signal in glucose.

DR. BURMAN: Thank you.

Dr. Goldfine, did you have a follow-up?

DR. GOLDFINE: My other question, though, may also be more specific to the sponsor. So we're going to get to ask them later. I'll hold it.

DR. BURMAN: Dr. Schade?

DR. SCHADE: I have one question. It may be just that I don't quite understand how this is efficacy data. And that is, as I understand it, the comparison of the efficacy data was the percent improvement or decline in VAT with the drug that we're talking about today, and the number that we're kind of using is 8 percent.

But what I'm really asking is -- I understand that the drug did cause a decrease in VAT. My question really is, how effective was the drug in returning the patient to the pre-morbid state.

In other words, some of the data I saw was, well, the VAT or the abdominal girth decreased by 1.3 centimeters. But if the patient had increased his abdominal girth by 50 centimeters, then we're talking very small efficacy.

On the other hand, if he just increased it by 3 centimeters, then we're talking about a 50 percent efficacy. So rather than comparing it to placebo -- and that's the data I saw -- what I really want to know, did any of the patients return to their pre-morbid state over a year's time with the use of this drug?

How good is this drug at improving the VAT relative to the pre-morbid state?

DR. BURMAN: Does the FDA want to address that?

DR. ROMAN: The way I understand it in the dataset is that patients who were treated for six months with tesamorelin and were re-randomized at six months and continued to one year would be the only group that we can analyze for up to one year. And in that group, the percent VAT reduction was 17.5.

DR. SCHADE: You mean percent relative to the pre-morbid state?

DR. ROMAN: The reduction from baseline.

DR. SCHADE: In other words, the drug improved those patients 17 percent. So they still had

83 percent to go to reach the pre-morbid state. Have I got that concept?

DR. ROMAN: We don't have the data for the pre-morbid state, other than we have the data at baseline for this subgroup of patients. And based on that data at baseline, the mean value, the reduction at week 52 was --

DR. SCHADE: But at baseline, they all had increased VAT, didn't they? Because that's why they were entered into the study.

DR. ROMAN: That's correct, yes.

DR. SCHADE: So I want to know how close to normal did they get with this drug. That's my question. In other words -- isn't that a reasonable question? Am I missing the point here?

DR. ROMAN: I think it is, and maybe the company has an answer to that, too.

DR. SCHADE: We don't know whether this drug gets them down 1 percent or 99 percent relative to the pre-morbid state. It seems to me that's the clinical question that all physicians who are treating these patients need to ask.

DR. BURMAN: And by pre-morbid state, you mean months or years before they entered the trial.

DR. SCHADE: Yes. And you could use norms. You could use large population norms. In this group, we ought to know what the average pre-morbid abdominal girth is.

DR. GRINSPOON: Can I address this question?

DR. BURMAN: Please.

DR. MARSOLAIS: Dr. Grinspoon will address the question.

DR. GRINSPOON: I'm sorry. It's so hard to sit and listen to such good questions and not be able to answer them.

DR. SCHADE: I don't know if this is a good question or not.

DR. GRINSPOON: It's a very good question.

DR. SCHADE: I'm just trying to understand if this drug works.

DR. GRINSPOON: It's a very good question. The average VAT at baseline in this group was around 170 to 180. The normative data show it should be 130. Thus, they're 50 centimeters above normal. It brings

them down about 20 to 25 centimeters. Okay? That's the bottom line.

It reduces about in half the excess that they have. Okay?

DR. SCHADE: That's the question I wanted to ask. About a 50 percent improvement.

DR. BURMAN: Thank you.

Dr. Veltri?

DR. VELTRI: Yes. A question to the FDA. In an attempt to better understand the glucose homeostasis, you looked at some post-hoc analyses. My question is, I'm having some difficulties understanding the qualitative subjective body image changes that were recorded to the correlation to the more objective quantitative changes to VAT.

So the question is, have you looked at, in a post-hoc manner, either categorical changes, quartile, quintile, or greater than 8 percent VAT reduction to actual scores that were patient-reported outcomes?

In other words, I'm trying to get a sense as to whether these body image changes really correlate to some more objective measure to see whether or not

they're real or not.

So, for instance, the waist circumference changed less than an inch, essentially. So it would be hard for me to understand, on the average, a patient would really see that as anything on a body image score. So I'm just trying to correlate qualitative to quantitative.

DR. ROMAN: We haven't done any correlation between different subgroups of patients based on the PRO results and VAT reductions. Part of it would be because the mean changes were relatively small to start with. And maybe more importantly, I think probably we have already alluded to that, it's kind of hard to expect -- at least in my judgment, when I look at the dataset, it's kind of hard to expect very significant changes in PROs that measure the abdominal volume or some kind of individual impression, subjective impression of the abdominal size, when actually your abdominal circumference doesn't change too much.

So the way at least I look at the PROs, important as they are, they measure something that's

related to size and the size has changed relatively small. So they have to be integrated with the abdominal circumference and, obviously, with the VAT in the sense that the abdominal circumference correlates with the VAT. But we have not done any of those subgroup analyses.

DR. BURMAN: Thank you.

We have 10 minutes. Two questions that I know of, and I have one, as well.

Dr. Thomas?

DR. THOMAS: Two quick questions. One is you had mentioned that you thought that the fasting blood glucose was a better measure. The only question -- I may have misunderstood that, because to me, it would sound that the A1C is a better measure when you're not repeating these fasting blood glucose measurements over time. The glucose tolerance test, I think, is a reliable measure and reproducible.

DR. GRINSPOON: If I said that the fasting blood glucose was a better measure, I misspoke.

DR. THOMAS: I may have misheard it.

DR. GRINSPOON: I'm not ascribing a -- I

apologize if I said that. I misspoke.

DR. THOMAS: I may have misheard.

The other question is, in most of the studies that have looked at it, statins seem to cause an increase in diabetes or impaired glucose tolerances. And since many of these patients were on statin therapy, was there any look at those who were on statins, those who hadn't had it (unclear) during the course of the study, or discontinued, and their impact on the glucoses?

DR. GRINSPOON: We didn't specifically look at the impact of statins on glucose parameters, although, as the sponsor mentioned, about almost a half of the patient were on statins.

DR. BURMAN: Thank you.

Dr. Rosen?

DR. ROSEN: I want to go back to something that Steve Grinspoon alluded to. And if you could pull up slide 64 and then slide 65, and ask the FDA, how do you reconcile the absence of statistical difference in the extension study zero to 52 weeks versus the risk increase from zero to 26 weeks.

How do you explain that difference? Is it a difference in the number of subjects that went on to the extension, or is there an effect, a modulating effect of increasing growth hormone, as was suggested, that may ameliorate some of the glucose intolerance? Because, again, the risk is there, but you have a one-year study where the risk is not there.

DR. ROMAN: I don't think the data are that easy to -- or that robust with respect to the 52 weeks, because they don't have really a control. Basically, the 52 week group is a subgroup of the initially randomized patient, which has been very re-randomized.

So in a way, it's an enriched group, which has other baseline characteristics and so on and so forth. So it could be, as it was -- maybe Dr. Grinspoon already mentioned that there is some adaptation and then the initial changes later on are no longer significant. But they can't account for the potential effect of dropouts.

We don't have the same patients who are followed for 52 weeks.

DR. ROSEN: Do you know what the relative proportion that did not -- that entered the extension study? I mean, was it 50 percent of the people who continued on and re-randomized or 80 percent?

DR. GRINSPOON: It was a significant percent. Perhaps the sponsor could specify. But it was a good percentage.

DR. MARSOLAIS: Yes. The rate of dropout in the main phase was about 26 percent, 25 percent, which was the same for the placebo and the active treatment, and most of those patients were re-randomized.

Do you have the distribution with the patients, the graph? It's only a small number of patients that were not re-randomized to the extension phase.

This is with the distribution of patients with the complete -- a combination of both. Then we have 413 patients that completed the main phase and of this, you have 247 that were randomized to the P-T group and 138 to the T-P group; therefore, a total of 385 or something like this, very close to the total that completed the main phase.

DR. BURMAN: Thank you.

We only have a couple of minutes, and I have a question, I guess, more to the sponsor rather than the FDA. The questions relate -- and if you could have quick answers, if possible.

How reliable is a CT at L4/L5, and how reproducible is it to assess visceral adiposity, number one? Number two is I didn't hear anything about growth hormone levels. And number 3, what about other pituitary hormones, such as thyroid hormone, because growth hormone administration can affect thyroid function?

DR. MARSOLAIS: I can address the first question. Then I will ask Dr. Grinspoon to address the two follow-up questions.

CT scan, there have been a number of publications using the CT scan to assess the VAT and it seems to be a very reliable measure, and we have used a central laboratory or central center to do the analysis.

All of the sites were blinded to the results and the analyses were done completely blinded and

randomly. Then we used a very high standard to look at the evaluation of the VAT value.

DR. GRINSPOON: I think the published reproducibility is on the order of 2 to 3 percent, at the most. It's way within the change. So you would not expect the change to be confounded by that.

It's a good question about pituitary hormones, because other GH memetics do increase other pituitary hormones, like cortisol in thyroid. This did not. There was no affect on other pituitary hormones.

What was the middle question?

DR. BURMAN: Growth hormone levels.

DR. GRINSPOON: Yes. Growth hormone levels are pulsatile, as you know, and to get a random level is not meaningful. So we use the IGF. We also measure an IGFBP-3, similar results.

DR. BURMAN: Understand. Good.

Then I think what we will do now is break for lunch. We will reconvene again in this room in one hour at 1:00 p.m. Please take any personal belongings with you that you may want. The ballroom

will be secured by FDA staff during the break.

Panel members, please remember there should be no discussion of the meeting during lunch amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 11:57 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

DR. BURMAN: Why don't we get started for the afternoon session?

Good afternoon. We're starting the afternoon session and our plans are, first, to have the OPH session. We plan on going through until 5:00, if we need to, this afternoon.

With regard to the OPH session, both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information

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

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

The first public session speaker is Deborah Sergi-Laws. Welcome.

MS. SERGI-LAWS: Hello. My name is Debbie Sergi-Laws. I would like to begin my presentation by stating I have no financial ties or holdings with Theratechnologies and EMD Serono. I have received minimal compensation for travel and expenses.

I am a 50-year-old registered nurse, residing in Sarasota, Florida. I have been living with HIV for 25 years, and, needless to say, this has changed my life considerably.

Instead of being a wife, a mother, and furthering my nursing career, I am a woman with AIDS, on disability, a widow, and childless. Serving as an AIDS educator, a peer navigator, and a speaker on the Person with AIDS Speakers Bureau has enriched my life. I have educated and shared my experience for over 19 years with groups such as children and schools, middle school and high school, high risk youth, health professionals, community groups, and incarcerated adults.

As a peer mentor, my main goal is to work

with patients with achieving adherence for their treatment and also, providing support for other persons living with HIV and AIDS.

I have taken many combinations of therapies to treat HIV and have been involved in numerous clinical trials. Since 1999, one of my consistent complications that I have experienced is from lipodystrophy. Lipodystrophy has resulted in excess abdominal fat, the development of a buffalo hump, elevations in my cholesterol, triglycerides, and blood sugar.

These side effects have caused abdominal fullness and bloating. I have even been described as looking like I had barrel around my midsection. Just as an example of that, I like to dress to camouflage it, even though my main concerns are my physical health.

My body, when I look at it, is not a body that I know that is me. It is somebody else's body when I actually see it, because this is not what I'm used to and this is not what I would like to have my body to be like. But I have no control over that with

all the remedies that I have tried so far.

This hard belly fat made it hard for me to bend over without having discomfort or shortness of breath. The buffalo hump caused neck and shoulder pain. This required narcotic pain management, therapeutic massage, acupuncture, chiropractics, and eventual surgical removal of a 1.5-pound fatty tumor on my cervical neck area. The elevations in my lipids and glucose have been a continual concern for additional cardiac complications.

My physical health has always been my first priority, taking precedence over any cosmetic effects this lipodystrophy has caused. I have tried dietary changes and exercise, without improvement.

In 1999, I started Serostim for two 12-week cycles. I saw and felt improvement from this treatment. Side effects, though, resulted in stopping this, despite the improvements. When hearing of the tesamorelin clinical trial, I was hopeful to get relief from my worsening symptoms. My experiences during the tesamorelin clinical trial from April '06 to April '07 were both encouraging and positive.

I noticed a decrease in my abdominal girth, improvement in my cholesterol, triglycerides, and blood sugar. I felt really good on this trial. My energy level increased. The bloating and fullness decreased, and I could comfortably button my pants, which I hadn't been able to do for a very long time.

My HIV remains stable on treatment. One of the many positive aspects of the tesamorelin for me was how well I tolerated the drug. I have always had considerable side effects to many medications and have numerous severe allergic reactions. On tesamorelin, I had no side effects and no allergic reactions.

After this positive experience, I had optimism that tesamorelin would be approved by the FDA and become available to me and others. Having this medication available would help in managing this life-altering side effects of lipodystrophy. This would also allow me to continue on my current successful HIV medication regimen without compromise.

For over a quarter of a century, I have been living with HIV and its many complications and side effects. When I found out that I was going to have

the privilege to speak on the behalf of myself and others, I shared this with other people with HIV and AIDS. They were thrilled, as I am, that our voices were finally going to be heard.

I would like to thank you -- excuse me. I would like to really thank you. Kind of actually saying that just kind of choked me up a bit, because it feels like so often those of us living with HIV and AIDS speak to each other about how we wish changes would occur and how other people --

(Microphone times out.)

DR. BURMAN: It's okay. Please finish.

MS. SERGI-LAWS: As persons living with AIDS, we often discuss are people listening, do people care, is there compassion out there. And just being involved in this process has showed me that there are people that care and there is compassion and there are people that are working for the help that we need to go on and live a healthy and prosperous life.

So I would really like to thank you for including me as a patient in this decision-making process, which could profoundly affect my quality of

life.

Thank you once again.

DR. BURMAN: Thank you very much for coming from Florida for your testimony. Thank you.

The next speaker will be Ms. Lisa Hamilton.

MS. HAMILTON: Good afternoon. My name is Lisa Hamilton, and I'm very happy to address this panel. Before I begin, I want to let you know that I do not own any stock in Theratechnologies or EMD Serono. Additionally, I've only been minimally compensated for my travel expenses.

In August of 1999, I was diagnosed with HIV. I started antiretroviral medication in June of 2000. During this time, I was dealing with fear, anger, betrayal, and consequently, embarrassment. I was dealing with the side effects of my HIV medications and I began noticing that I was gaining quite a bit of belly fat.

By 2002, I had accumulated visceral fat in my abdomen and my quality of life began to decrease. When people would mention my weight gain, my thoughts and concerns were focused not around the size of my

clothes, but around the health risks associated with this additional abdominal fat.

Due to the fact that I'm less than 5 feet tall and as the excess fat began to accumulate in my abdomen, it became very uncomfortable and even painful at times when trying to bend over, tie shoes, or pick things up from the floor.

As my condition continued with excess abdominal visceral fat, it became more and more uncomfortable and painful to perform normal activities of daily life.

Worrying that the abnormal fat distributions on my abdomen would increase the risk of heart attack, high blood pressure, and a variety of other conditions, I spoke with my doctor about clinical trials expected to come about in the next couple of years. I asked my doctor to please keep my name at the top of the list for whatever trials were specifically for decreasing visceral abdominal fat.

My concerns grew regarding health conditions that could come about because of the accumulation of fat in my abdominal area. I did all I could do to

maintain a healthy lifestyle. I ate chicken and fish instead of red meat and pork. I ate more vegetables than starches. I ate fruits instead of processed desserts.

My frustration centered around the fact that I was doing everything I knew to do to maintain a healthy lifestyle; yet, the abdominal visceral fat remained. I tried many things, as well as other treatment options.

I discussed these depressing and frustrating feelings with my doctor, as I was physically and psychologically burdened. My doctor informed me of a clinical trial for a drug called Serostim. I joined this clinical trial and I had very limited benefits. I continued through the end of the trial with very minimal change or improvement. Ultimately, the clinical trial was ineffective.

In early 2005, my doctor's office presented me with the option of joining the tesamorelin clinical trial. I joined, hopeful as ever that this trial would yield a better outcome for me. I remained in this trial for a year and achieved tremendous results.

I never had any injection site reactions, and the ease of reconstituting the medication for delivery was a big plus. The lipohypertrophy decreased dramatically, thereby increasing my range of motion and ease at performing activities of daily living.

With the decrease of abnormal fat accumulation of the abdomen, I felt the quality of my life returning. My coworkers would comment on the weight loss and they would congratulate me. My thoughts, again, centered around the health benefits of the clinical trial and the reduced risk of heart attack, diabetes and stroke. I would thank them and I would mention that I was mainly happy with the health benefits I received and not the weight loss itself.

Adhering to this medication regimen was easy and, if given the opportunity, I would stay on tesamorelin for life. This improved my quality of life so much and the physical and psychological burdens were lifted.

Since I've been off the tesamorelin and the abnormal fat accumulations of the abdomen returned, my

fears regarding heart attack, hypertension and stroke have returned. It has once again become uncomfortable and painful when bending over, tying shoes, and picking up a dropped item from the floor.

I was, just this past week, diagnosed with moderate obstructive sleep apnea. As an educated person, I felt the need to research this condition. Over and over again, I read that weight gain and obesity are key players in obstructive sleep apnea. I cannot help but wonder, if I was still on the tesamorelin, if I would be diagnosed with this condition.

As someone who has benefitted physically by being able to perform activities of daily living and psychologically, my hopes are that this panel will decide favorably regarding the quality of life benefits tesamorelin has to offer all the people suffering from abnormal fat accumulation of the abdomen.

I'd like to show you when I was on the trial. These are some photos of the benefits I received. Thank you very much.

DR. BURMAN: Thank you very much.

Mr. Jeff Berry?

MR. BERRY: Good afternoon. My name is Jeff Berry, and I'm here today testifying on behalf of the AIDS Treatment Activist Coalition's Drug Development Committee in support of the letter submitted May 17th. And I'm testifying free of any conflicts of interest. Neither Theratechnologies nor EMD Serono have contributed financially to me or to ATAC or funded my travels to the University of Maryland to offer this testimony.

Lipodystrophy, notably, abdominal fat accumulation, has been a serious problem for people living with HIV since the mid 1990s, with reports surfacing soon after combination antiretroviral drug treatment became standard of care.

For nearly 15 years, it has gone without a tried and true treatment modality. Switching antivirals does not work. Diet and exercise modification are of extremely limited benefit, and no pharmacologic agent has been proven to be both safe and effective to date.

ATAC has always taken this very seriously. In fact, it is one of the only non-antiretroviral drug development issues that the drug development committee has closely followed over the past 10 years. We are very much aware of the data concluding that visceral fat accumulation is associated with an increased risk of cardiovascular disease.

Though Phase 2 and Phase 3 studies of Egrifta were not designed to show a reduction in cardiovascular risk, we believe that the potential benefit is there and that studies should be conducted that reductions in visceral fat using drugs like Egrifta are associated with a decreased risk of cardiovascular disease.

What the reported data do show are clear benefits with respect to body image and body distress. This cannot be overstated given the profound emotional effect lipodystrophy has on people living with HIV.

It is conspicuous and stigmatizing, an overt sign of HIV infection and illness, and according to the collected data and countless anecdotal reports, significantly affects psychological wellbeing, quality

of life, willingness to commence antiretroviral therapy in light of lipodystrophy fears, and adherence levels among those on antiretroviral therapy.

We are also encouraged by Egrifta's safety profile. While we've shared many of the FDA's concerns regarding Egrifta's predecessor, Serostim, we believe that the data reviewed by the advisory committee today clearly indicate that Egrifta's moderate efficacy outweighs its risks.

The risk of diabetes is minimal; the IGF-1 fluctuations have not been associated with an increased risk of clinical events; and, the documented neutralizing antibodies have not been tied to any untoward effects.

While we urge this panel to recommend the approval of Egrifta, we do so with conditions. Phase 4 evaluations of Egrifta-associated VAT reductions on the risk of cardiovascular disease should be conducted. Though a study evaluating the drug's effects on hard endpoints, such as myocardial infarctions, may be difficult, studies looking for associations between VAT decreases and vascular

functioning are feasible.

Phase 4 studies exploring Egrifta-associated VAT reductions on other clinical endpoints, such as fatigue, gall bladder disease, liver disease, osteoarthritis, pulmonary function, and sleep apnea.

Phase 4 studies exploring Egrifta in combination with exercise and/or diet modification to determine if VAT can be synergistically decreased. A Phase 4 gender-balanced clinical trial evaluating the safety and efficacy of Egrifta in HIV-positive women with lipohypertrophy compared with men.

Importantly, the approved labeling should spell out the indication for Egrifta treatment, along with indicators of effectiveness while receiving therapy, to ensure that the risk-benefit ratio is maintained for each patient. Those slides (unclear), CT scans, such as those used in the studies, will be difficult in the clinical setting.

Waist circumference, waist-to-hip ratio, and basic psychological body image assessments are much more feasible and should be employed by clinicians when considering patients for Egrifta and while

monitoring their progress, or lack thereof, at regular time points for as long as treatment is continued.

Finally, we urge this committee to recommend approval of Egrifta as a medical reconstructive modality. We strongly urge against reviewing, approving or labeling Egrifta as a cosmetic treatment. Though Egrifta-associated VAT reductions have not yet been established as a marker of reduced cardiovascular disease risk, its effects on patients' body image perceptions, sense of wellbeing, and quality of life is substantial. This is no different than breast reconstruction following a mastectomy, an unquestioned medical approach to minimize the negative psychological effects stemming from vital, but disfiguring treatment.

People living with HIV have been waiting for nearly 15 years for an effective and safe treatment option for lipodystrophy. Compounded by the fact that no other pharmacologic agents have entered Phase 2 or 3 studies for the treatment of lipodystrophy, we firmly believe that the agent currently before this panel and the FDA should be approved.

Thank you.

DR. BURMAN: Thank you.

On behalf of the panel and the FDA, I'd like to personally thank all three of the participants. And we recognize this is really a critical part of the meeting and appreciate your efforts. I'd also like to thank Mr. Berry for the letter that his coalition sent, as well.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as public comments.

Now, the agenda -- it's almost 1:30, about 1:25. We're going to have follow-up on questions this morning, clarifying questions from the committee to the FDA and to the sponsor, and we'll do that until 2:00 and then we'll have the panel discussion.

I'd first like to ask the sponsor to come up. There were, I guess, four issues that came up this morning that we asked them to clarify that they will

briefly discuss. Thank you.

DR. MARSOLAIS: Yes. Good afternoon. We would like to discuss -- well, first of all, we had a question this morning regarding the use of estrogen. We have the answer, and the use of estrogen was not allowed in the study. Only progestin was allowed in the study.

There are three other points that we'd like to address. There will be a discussion regarding the IGF-1 ranges and the SDS. There will be, also, the glucose sustainability; and finally, the correlation between the PRO and the VAT, as requested this morning.

We'd like to start with Dr. Cohen, who will address the question regarding IGF-1 and SDS score.

DR. COHEN: I'd like to respond to panel member, Dr. Rosen, who wanted more detail about the SD scores provided by Esoterix. As you can see here, Esoterix provides normative ranges, means, and SD scores for various age groups.

The majority of the patients in this study fall into the 40 to 60 age group ranges, where the SDS

are just over 40 nanograms per mil, which is quite small. Also notable is that Esoterix's normative ranges were based on a relatively small number of patients, far smaller than the number of participants in these studies.

Also important is that the SD calculators provided by Esoterix do not utilize log transformed mechanisms of calculating and may be inaccurate at higher IGF-1 values. This is also important in the context of the wider variation in IGF-1 that we have noted to the panel earlier.

You can see here that among the nearly 800 patients enrolled in the Theratech studies, the variation in IGF-1 levels was substantially larger, even though the means were similar. In fact, as compared to the slide that I've just shown you, the SD score is about 50 percent larger for the same age groups, being in the 60s rather than the 40s.

This indicates that the upper limit of normal for the 97.5 percentile for this HIV population prior to treatment is approximately at the level of the plus 3 SDS value that is provided by Esoterix.

That is why we recommended to Theratechnologies to use this value as the cutoff for a decision to discontinue therapy as part of the REMS approach, where patients with elevated levels above that will not continue on drug after 52 weeks, which I think is a reasonable approach to ensure safety.

That will include about 20 percent of the patients on this study. And by the way, that was not different among completers and non-completers.

I think that would answer Dr. Rosen's questions. Thank you.

DR. MARSOLAIS: The other point --

DR. BURMAN: Mark, let him finish and then we're going to have a panel discussion.

DR. MARSOLAIS: The other point we'd like to address is the glucose sustainability, and Dr. Schambelan will address the question.

DR. SCHAMBELAN: Actually, before that, I want to clarify the question about retinopathy. So there were no adverse effects reported for retinopathy, but there was no formal funduscopic examination performed.

Could I have this slide up first? There was a point made in the FDA presentation about the potential effect of dropouts on the fact that the data seen at week 26 differed from the analyses that were done with the inclusion of multiple intervening points.

As you can see here, for people that were study completers, the differences between the tesamorelin-treated and placebo groups were pretty much the same as they were in the initial population that were presented in the core.

You can see there is an increase in the occurrence of diabetes of 3.4 percent versus 1.5, which is actually a lower risk ratio than that that was seen in the full study. And then if you look at the extension phase -- next slide up, please -- there is the same, I think, somewhat comforting observation that over this longer period of time of exposure to drug in people who were study completers, not any dropouts here, the increase in IGT or diabetes is quite small.

Then I just want to make one final point to

sort of emphasize something that Steve Grinspoon alluded to, which is to try to understand, in the biology of treatment with growth hormone and, I would argue, perhaps with tesamorelin, the observation has been made in a number of studies, including studies we published, that when you initiate, let's say, low dose growth hormone treatment, after a month, there is an impaired insulin sensitivity.

We did hyperinsulinemic euglycemic clamps to determine that. And then when following the same patients out through a six-month total exposure to the drug, these values returned to normal and/or to baseline. And I should say, in people with increased visceral adiposity who are not HIV-positive, there was a study published in the late '90s in the JCEM in Scandinavia, where they actually demonstrated that with longer exposure to low doses of growth hormone, there was a tendency, if anything, for insulin sensitivity to get better than it was at baseline.

So I think some of the reasons that we're seeing differences between what we observed at week 26 and what is seen by adding in the earlier points might

possibly be explained by that.

DR. BURMAN: I think they sponsor -- if you could be really succinct on this last point, but please give us your information.

DR. MARSOLAIS: The last point is regarding the correlation between the PRO and the VAT. And we had in the core presentation this slide, and we have shown that there's a good correlation between the response and the PRO and the VAT.

We also have performed tests for the correlation between the VAT and the waist circumference, and, again, we have shown a very good correlation between the response and the PRO, as well as waist circumference.

Maybe if it's possible for one last point. They asked us if we had a correlation between IGF-1 and the change in fasting blood glucose, and we had the time to do that calculation over lunch and we can show the results.

Slide up, please.

We can see here that there is no correlation between the change in IGF-1 and fasting blood glucose.

There is no correlation. It's not statistically significantly different.

DR. BURMAN: Thank you very much for bringing us up-to-date on those points. We now are going to open the floor up for questions from the panel to either the sponsor or the FDA, just in the order in which we have them.

Dr. Molitch, you wanted to follow-up on one issue earlier.

DR. MOLITCH: I was interested in the presentation of the IGF-1 data that Dr. Cohen had presented. It looked like there was no decrease with age, in general, in the HIV patients, is that correct, as opposed to essentially every study in normal individuals?

DR. MARSOLAIS: I will ask Dr. Cohen to answer the question.

DR. COHEN: If I could have that slide again up, please? Thank you.

You can see that there is a small age-related decline from 176 in people in their 30s and 40s all the way to 148 in 50s to 70s. Whether this

decline is statistically significantly different from the non-HIV population needs to be calculated separately. But I think this followed the general trends that you would expect as effect of age.

Also notable that this is males only and we didn't have an opportunity to do the same analysis for female as of yet due to limited sample size.

Did that answer the question, Dr. Molitch?

DR. BURMAN: Thank you.

Let me give everyone a heads-up. The questions that we already have, and we'll take them order, are Drs. Kumar, Goldfine, Ms. Swan, Proschan, and Dobs. And so, Dr. Kumar, I think you had a question from this morning.

DR. KUMAR: Thank you, Dr. Burman. I want to request and see if I could ask my first set of questions, because they relate to inclusion-exclusion criteria, if I could just ask that. And then if you'd permit me, a different one after everybody else goes.

My questions are mainly to the sponsor. My first question is I understand that patients had to be on a stable antiretroviral drug for eight weeks to

enter. What percentage of patients, if any, changed their antiretroviral therapy while on the study?

DR. MARSOLAIS: We have that information, but regarding the minimal time prior to study entry, the inclusion criteria, it was a minimum of eight weeks. But in reality, they had been on stable ART for much a longer period of time.

DR. KUMAR: No. My question is how long --

DR. MARSOLAIS: I will also address the question regarding the change in antiretroviral. I don't have the exact time as you're requesting with how many months they were unstable, but we have looked at patients that had no change or only a change within the same class of drug and we looked at the impact on the VAT decrease, and there is no impact on the VAT decrease.

We also looked at the percentage of patients, which is only 63 patients, that had a switch of ART regimen during the study. And once again, when we look at the decrease in VAT, it is statistically significant and it's similar for both groups.

DR. KUMAR: Thank you. My next question is,

could you tell me a little bit more about how you incorporated exercise into this? Was it a formal -- explaining to patient, exercise was left up to the patient? And how did you capture this data?

DR. MARSOLAIS: What we told the patients and what was in the protocol is that patients should not change their either exercise or diet during the study. Whatever they were doing before coming into the study, they have to continue the same lifestyle, if you want, during the study. That's the only information that we gave to our patients.

DR. KUMAR: And did you capture anything in a systematic way of what percentage of patients exercised on a regular basis?

DR. MARSOLAIS: No. This was not captured in the study. However, since we have a placebo group, if there are any patients that were changing their habit, this should have been captured by the fact that we had a placebo arm. The effect would have been the same in both arms.

DR. KUMAR: My third question is, Dr. Grinspoon had shown a picture in his introduction

about the effect of lipohypertrophy on women and two very articulate women spoke about that. But I couldn't help but see that only 15 percent of your patients that were enrolled were women.

What did you, as a sponsor, do to more actively encourage participation of women?

DR. MARSOLAIS: First, maybe if we look at the percentage of females in our study, when we compare to other clinical trials in HIV, this is usually a fairly similar percentage of females that we have in HIV.

We also recruited sites across the U.S. and Europe trying to, if you want, at least have a good proportion of women in the study. But it is a number which is very similar to other types of clinical trials in the same field. And Dr. Grinspoon would probably like to add to this question.

DR. GRINSPOON: We tried our best to recruit women. As you know, recruiting women is very, very difficult into clinical trials, particular detailed, metabolic trials.

At our own site, we advertise in community

advertisements. We target women specifically. We make advertisements for women. I think many sites around the country do that.

We certainly are no lower a percentage of women in our study than at other comparable studies. And luckily, the studies were large enough to make an independent assessment among women to show that VAT was significantly reduced in tesamorelin versus placebo distinctly in women.

You can see right here, which Dr. Marsolais alluded to, but we just didn't have time, and you can see the least square mean for the male and female are really almost identical, which is very interesting and reassuring that we were able to show a benefit in women, even though we didn't have the largest number of women in the study.

If there are further studies with this, we'll continue to target women as creatively as we possibly can.

DR. BURMAN: Thank you.

Dr. Goldfine?

DR. GOLDFINE: Thank you. Dr. Kumar asked

my first question, which had to do with exercise. My second question has to do with trying to understand the differences in the lipid profiles between the two trials that we're considering.

Over the period of time between them, there were major differences from the PROVE-IT and the JUPITER about the use of statins in these populations. Was there a difference in add-in to the first trial over that period of time of statin use that could have led to some of the apparent improvements in lipids?

DR. MARSOLAIS: We looked in many criteria regarding the difference between the two trials and we couldn't identify any significant difference that would lead to the difference in the results. And the use of statin was also similar in both trials overall.

DR. GOLDFINE: Including add-in, not only just baseline therapy.

DR. MARSOLAIS: Yes.

DR. GOLDFINE: Okay. I have one other question then on the -- I'm trying to understand why, with the percent loss of visceral adipose tissue that you saw, that the questionnaires were not more

promising than they were.

When you look at the belly profile assessment, it's look as if the patients always rated it against where they thought ideal would be rather than where they thought ideal would be at the beginning of the study. And in obesity, which is clearly a completely different scenario, patients often, as they lose weight, continue to think that they ought to look even better than they do.

Did you have a moving target for the reference that would have diminished the ability of this to see that they were feeling like they were improving?

DR. MARSOLAIS: I would like to ask Dr. Turner to address the question.

DR. TURNER: Good afternoon. My name is Ralph Turner. I'm the Vice President of Phase V Technologies. I'm a psychologist by training. It's our group that developed the body image impact scale, although I have no financial interest in Theratechnologies.

If I understand your question, is your

question with respect to the belly profile whether they were using the profile as a reference to their idea look?

DR. GOLDFINE: If you look at question 3 on the BPA, it looks as if they're asking them if they thought that their profile was not normative at the beginning, to rate what they thought the minimal improvement would be. And it looks like, from the calculations that were presented, that they always did it as a ratio to what they thought ideal would be.

DR. TURNER: No. Thank you for your observation. We asked those three questions at every visit. The analysis is of current look only across the trial.

DR. GOLDFINE: Thank you.

DR. TURNER: You're welcome.

DR. BURMAN: Thank you.

Ms. Swan?

MS. SWAN: I wanted to ask a question about indication in a little more detail. How would efficacy be measured? Do you plan to have something on the label, waist-to-hip ratio, waist circumference,

CT, patient self-report, doctor-patient measurement? What specifically would a clinician be looking for if they were prescribing this to somebody?

DR. MARSOLAIS: Yes. It's something that we've discussed and I would like Dr. Grinspoon to address the question.

DR. GRINSPOON: May I have this slide up, please?

It is an important consideration how to monitor patients with this particular drug. And we all understand that getting a CT scan is not realistic, other than in a research setting. So the good news is that there is another surrogate marker that tended to go down. It went down significantly and correlated very significantly with VAT, and that was waist circumference.

Now, I know you might be saying, well, it only went down 1, 2 centimeters, or something, but the fact is patients did perceive it. It correlated with their PRO. And I pointed out earlier that this 2 centimeter reduction in waist circumference is virtually all VAT and no SAT. So it may be a

different kind of waist circumference reduction than you might be used to thinking about in regular obesity.

Among those obtaining a pre-specified 8 percent reduction, i.e., those being official responders in the eyes of the FDA -- and that was 60 to 70 percent -- their reduction in waist circumference was 3.5 centimeters; so very easy to detect.

Obviously, if you're a clinician, you're going to listen to the patient and monitor feedback as to self-perception of body image and general wellbeing. Certainly, we would ask ourselves, are the patients feeling better about their body, and we know that it was a very significant correlation seen between waist circumference and VAT.

So the bottom line is we would use waist circumference to look for progress. I think if you were a clinician, you put someone on this, 13 weeks went by, 26 weeks went by, no reduction in waist circumference, patient not feeling better, they shouldn't stay on the therapy.

Conversely, if someone goes on it, they are a responder, they're doing well, their waist circumference is going down and they feel better, they would probably stay on it, and you don't need a CT to determine that.

The last point is whenever you decide whether something is good or bad for someone, you have to do a risk-benefit analysis, obviously. So along with that thinking comes the obvious concern about safety. And, in that regard, clinicians should be taught to look for hypersensitivity and to discontinue people with hypersensitivity, that 2 to 3 percent, discontinue patients for significantly high glucose, as discussed in the REMS, and to discontinue patients for IGF SDS more than 3.

So there's easily measurable things which we hope will allow patients who are responders to continue with long-term treatment.

DR. BURMAN: Thank you.

We have 15 minutes for two questions, that I know of.

Dr. Proschan?

DR. PROSCHAN: Yes. The FDA, in the packet that we got, the briefing packet, had some, I thought, enlightening graphs that were in the statistical review toward the end of their briefing packet.

I'm wondering if you have the slides that are there. Do you have those as slides? In particular, the one I wanted to see was one that's on page 7 of the statistical review.

DR. MOHAMADI: No. I'm sorry. We don't have slides for that.

DR. PROSCHAN: Okay. Because that -- it's sort of hard to describe. But it does seem to indicate that there are some people who had very dramatic reductions in triglycerides on the drug. And those, obviously, would have to be the ones that started very high, because they have a reduction of 800, some of them.

You do see that quite a few more of those in the treatment group than the placebo. So it does look like for people who most need to reduce their triglycerides, the drug is doing that.

DR. MARSOLAIS: Maybe we can address the

question with the -- we have a correlation of triglycerides at baseline versus triglyceride change. And this is where we have the correlation to address your question, with a very good correlation, statistically significant.

DR. BURMAN: Thank you.

Did the FDA have a comment on that?

DR. ROMAN: No comment.

DR. BURMAN: Thank you.

Dr. Dobs?

DR. DOBS: I have a couple of small questions. I know that testosterone was allowed during the study. Did men go on and off of this and did it affect your outcome?

DR. MARSOLAIS: Yes. Well, in the first study, we did a stratification for use of testosterone. We didn't see any impact. And what we have observed in the study is that the use or no use of testosterone gives the exact same decrease in VAT. Therefore, that stratification was not implemented in the second trial.

DR. DOBS: Next, the women, the mean of the

group was 48. Were the women different? Were they menstruating? Were they post-menopausal? I know estrogen wasn't allowed, you said.

DR. MARSOLAIS: Dr. Grinspoon will address the question.

DR. GRINSPOON: For that one, I don't have a lot of detail. I don't know. The age was similar and you can look at the baseline characteristics, if you want, which doesn't exactly address your comment.

But you can see that there were differences in VAT, as anticipated, waist circumference, although I might add that waist circumference was very, very significantly enlarged in the women, I mean, massively enlarged. The SAT was higher.

So women seemed to have relatively more SAT in lipodystrophy compared to men. So there were some biological differences, but I don't have a lot of data with respect to menopausal status or anything like that.

DR. DOBS: And I have one other small question. It's interesting, you're saying for the monitoring, you're going to do it at 52 weeks if the

IGF-1 level is too high. Why are you recommending to wait so long? Should it be monitored throughout the course of treatment?

DR. MARSOLAIS: This is something that we discussed, also. I'd like to ask Dr. Cohen to address the question, please.

DR. COHEN: Like this panel and the FDA, I take the issue of elevated IGF-1 very seriously, and I know Theratechnologies does, too. With that in mind, exactly how to address this question is a very difficult one.

What is the cutoff that should represent a cause for discontinuation? What is the time point that should be used? It's not a trivial question. I feel quite comfortable that a year of therapy, even with elevated IGF-1 levels, does not represent a significant long-term risk.

I think that because the dynamics of IGF-1 over the course of one year of therapy is not linear and does drop, it makes sense, although one could debate it, that one should follow this over a full year, when we know that, at that point, 80 percent of

the patients will be within 97.5 percent of the baseline population.

Nevertheless, I think that the general approach is going to be that this type of data will be reviewed on an ongoing basis. There is going to be a proposal for an observational study and a steering committee for such a study will develop further clinical development guidelines to address exactly this question. Should 52 weeks be the time that would be the decision point for discontinuation? That seems to be the best proposal at this time.

DR. DOBS: So the recommendation is not to even test it until 52 weeks.

DR. COHEN: My personal approach would be that one could measure it at 26 weeks, but this is not, I think, something they --

DR. MARSOLAIS: This is mainly like the initiation discussion that we had, but this is certainly something that we will discuss with the FDA in the next week and see what will be the best approach to assure safe use of the drug.

DR. BURMAN: Thank you.

If I could follow-up on that for a second, just to make myself understand. You don't have any data on IGF-1 levels for more than a year in an agent that you're considering the drug for a longer period of time.

DR. MARSOLAIS: At this stage, no. The patients were treated only for 52 weeks. But this is the information that will be collected in the long-term safety observational study.

DR. BURMAN: Thank you.

Dr. Thomas?

DR. THOMAS: Just a series of quick questions. The first one is, this is a fixed dose for a medication that's injectable. Is the formulation possible to be made in a way that the dose can be adjusted?

DR. MARSOLAIS: This is also something that was discussed. At the moment, as you see, it's only the fixed dose, that's quite true. But the drug is available in two vials of 1 milligram and this is something that we discussed in terms of a Phase 4 program, that it would probably be important to look

at titration studies to see if it would be possible to adjust the dose according to the IGF-1 levels.

DR. THOMAS: I think Dr. Veltri asked about blood pressure changes, which I don't remember the answer, if that was answered. And then if there are any measurements of kidney function, such as changes in GFR or measurements in nitrogen balance during the course of the study.

DR. MARSOLAIS: Regarding the blood pressure, it was not a pre-specified endpoint for the study, and patients that were enrolled in the study had normal blood pressure. Patients with abnormal blood pressure were excluded from the trial, and it was measured only during the vital signs then and we didn't see any significant difference.

Regarding the kidney function, we didn't do those type of analyses in the study. Sorry.

DR. THOMAS: Anything on nitrogen balance?

DR. MARSOLAIS: That wasn't done either in the study.

DR. BURMAN: Thank you. And nothing on cardiac echoes.

DR. MARSOLAIS: No, not directly.

DR. BURMAN: Okay. Thank you.

Two more questions. We have about 7 minutes.

Dr. Kumar, and then Dr. Veltri.

DR. KUMAR: Thank you. My first question is, do you have any patients that had a hypersensitivity reaction that then just re-challenged themselves? And, if so, do we know what happened to them?

DR. MARSOLAIS: Yes. I would like to ask Dr. Saxon to address the question, please.

DR. SAXON: I thought I came all this way for nothing. Thank you.

I'm Dr. Andy Saxon. I'm a Professor of Medicine at UCLA School of Medicine. And the question was, do patients who had hypersensitivity re-challenge themselves. The answer was yes.

It wasn't by design, but by default. The first group of patients, actually, was six patients, if I'm correct, in the retrospective study, that were found retrospectively, and, in fact, five of those

continued giving them. One had continued reactions.

In the prospective study, it turns out, of those 9 of the 12 of them that continued to give them, 9 of them continued to have reactions. And so it's reassuring. That's not what is recommended, obviously.

But even with those, these patients, some of them with -- these are daily injections -- never got a serious reaction. The most serious reaction, they took Benadryl, they were gone in 30 minutes. So whatever those reactions are, one can see the first one and stop.

So there were patients who gave them for a long time, in spite of reacting, which was not recommended and it's going to be part of the package, do stop. It's a very small number. It was only 2.9 percent. But we certainly don't want to push on a patient who has really got a problem.

DR. KUMAR: When is the earliest time that patients see it? If they are going to have a hypersensitivity reaction, when do they get the hypersensitivity reaction?

DR. MARSOLAIS: I will ask Dr. Soulban. She has all of the information regarding the time of the occurring of those events.

DR. SOULBAN: So it varied across patients. We had approximately 27 patients that had a hypersensitivity reaction. And for four of those patients, they had it within the first day, so the first time they dosed. And typically, it occurred within a few minutes of dosing.

Then we had one patient within the seven-day period and two within 2 to 4 weeks, and then you'll see a spreading across time, two and three patients across time. But typically, the onset of the reaction would happen just a couple of minutes after injecting themselves.

DR. KUMAR: Thank you.

Regarding the sepsis patients, what were the bacteria? Were any of them MRSA?

DR. SOULBAN: I'm trying to see if we have data on the sepsis patients. We did have two sepsis patients, both occurring in the tesamorelin group. Those were the two only similar AEs occurring in

tesamorelin.

I'm sorry. We don't have detailed information on those two sepsis patients. Maybe we can come back with some more information.

DR. BURMAN: Thank you. The last question of this session, Dr. Veltri.

DR. VELTRI: I guess this begs the question on cardiovascular safety. You have planned, based on your risk management strategy, a long-term observational study for cancer. And, obviously, from a cardiovascular perspective, that would also beg the question of looking for effects on stroke, MI, et cetera.

Now, obviously, you're going to be excluding patients with diabetes as a CHD equivalent. So has the sponsor thought of adding or somehow enriching a population looking at clinical events on a cardiovascular safety perspective?

DR. MARSOLAIS: The first goal of the long-term observational study was really to look at the potential impact of IGF-1, but it is certainly something, based on the comments and discussion we

have today, something that we can probably consider, also, including in the observational study. And that will also happen with further discussion, most likely, with the FDA.

DR. BURMAN: Thank you all very much. Thank you to the FDA and thank you, for the sponsor. We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate, except at the specific request of the panel.

Let me give you an outline of the session. It's now about 2:00. We're going, at most, until 5:00. Obviously, we want to have a balance between good discussion, but also meeting the time limits and having enough time to talk about the questions.

We're going to combine some of the questions. So the questions on VATs will be combined. And what we're going to do is open the floor up for discussion for about 15 to 20 minutes for the whole panel and then go through individually each of the questions, which I will now consider four questions, combining three of the other ones, on VAT, spending

the most time on the last question, which is the only voting question.

That will leave about 35 or 40 minutes for each question, and we'll go around the table and ask everyone -- specifically, the voting members -- to give their opinion regarding each of the questions, because the FDA definitely wants full discussion by everyone, as well, and get everyone's opinion.

So it's 2:00 now, and I'd like to open the floor up for a discussion for 15 minutes of any issues anyone on the panel wants to talk among themselves, bring up an issue, or raise any specific comments.

Ms. Swan?

MS. SWAN: One concern I have about Egrifta is given the prevalence of HIV among African-Americans, Latinos and Latinas, and diabetes risk factors, et cetera, there was real underrepresentation in this trial, and I hope that that would be a prime consideration of the agency and the sponsor to make sure that post-marketing studies include people who are hardest hit by the epidemic.

DR. BURMAN: That's a very good point. I'm

sorry. Yes, please.

DR. CARGILL: I know the question came up this morning and somehow we didn't quite get back to that, but I would like to not only echo that, but, also, particularly given I don't know if we ever saw or heard data in response to the original question about family history and people with glucose, as well.

Again, because HIV disproportionately impacts those groups that Ms. Swan has mentioned, but, also, they often have very deep family histories of this, it will be, for many reasons, important to obtain this data.

DR. BURMAN: And you're speaking specifically of family history of hyperglycemia.

DR. CARGILL: Yes.

DR. BURMAN: And if I would, I'd just ask the sponsor, do you have any information on family histories, quickly?

DR. MARSOLAIS: No. Unfortunately, we don't have any information on family history.

DR. BURMAN: Thank you. Dr. Schade?

DR. SCHADE: Yes. I have one question.

It's not clear to me the relationship between treatment and diabetes. What is not clear to me is if a patient develops a hemoglobin A1C of 6.5 or 6.6 and then I treat the patient and get the hemoglobin A1C down to 6.4 or 3, does the company recommend continuing treatment with their pharmaceutical agent, or are they then, once they have this diagnosis of diabetes, irrespective of treatment, banned from treatment?

DR. BURMAN: Would the sponsor like to answer that question?

DR. MARSOLAIS: Yes. At the moment, what we're recommending is that, mainly, it will be two consecutive visits, like, starting at week 26, where it will be the first measure of HB A1C. If it's above 6.5, there will be a second measure at week 13; and, if it's above, then the patient should stop treatment. If the value is below 6.5, then they can continue treatment; still monitor it for another 13 weeks and readjust based on the value of the HB A1C. If there's a continued increase, the patient should be stopped.

DR. SCHADE: Well, my question is, is that

irrespective of diabetes treatment. In other words, if I then treat the patient with one of my many diabetes drugs and improve them, is it okay for me to continue therapy?

DR. MARSOLAIS: I will ask Dr. Grinspoon to address this question.

DR. GRINSPOON: I would think yes. I would think that there's an early warning period in which we look for the people that have a propensity to this, give them some time for the doctor to understand, to talk to the patient, to understand this.

In that window period before they get kicked out, you can do what you want, which is have them go on a diet, da-da-da-da, go on an insulin sensitizing agent, all the power to you. We don't know any interactions between those. We're not aware of any.

If you can get the glucose stabilized and get the benefit on VAT, I think that would be wonderful. In fact, there should be further studies of that, actually.

DR. BURMAN: Thank you. I'd like to raise a question for the panel, which, to me, is the seminal

question, which is we're talking about an agent that is useful in lowering visceral adiposity. But visceral adiposity is a poor surrogate for insulin resistance or lipids.

It's a surrogate, but it's a surrogate for a surrogate, if you will. And then the endpoint of cardiovascular outcome is not -- there are no issues here at all. There's no data. There are no data.

So I wanted to raise for the committee, what do the experts in lipidology and diabetes and insulin resistance and growth hormone on this panel think about that indication and the long-term potential effects?

Secondly, what does the panel think about prolonged growth hormone elevations or IGF-1 elevations for years? In some people, there's, as you saw, minimal elevations and some more moderate for a long period of time, which is really mimicking mild acromegaly.

I'd just like to raise those, because I think those are the two seminal issues, at least in my mind. Dr. Dobs?

DR. DOBS: Well, it's a very difficult question, because we don't really know what the story is in non-HIV people, meaning in people that are non-HIV-infected and you're able to reduce their visceral fat, what does that really do, because it may be just a biomarker for hyperinsulinism, but it may also have pathophysiological effects, as well, meaning a more metabolically active or increased free fatty acid.

So it may be true physiological or maybe just a biomarker, and we really don't even know what it does in non-HIV people. But these are questions that I don't think we're going to have the answer for, who knows, in decades from now to really be able to answer that.

I think the thought is that we know that the risk is bad and the thought is that perhaps intervening on that might produce some short-term benefit with hyperinsulinism and long-term benefit with cardiovascular disease.

But what we've all said many times around this table already is that those studies will really -- - certainly, the long-term studies will probably take

decades.

DR. BURMAN: Even the post-marketing studies, when they're analyzed, even if they show a detrimental effect, you're stopping the drug, if you will, post-hoc.

DR. DOBS: You mean if one assumes that the glucose -- if there's glucose intolerance, one stops the drug, or what Dr. Grinspoon suggested is that probably in clinical practice, people will add on a diabetic agent.

So I think in post-marketing, there might be the opportunity to see what happens in the long run with glucose intolerance, or more intensive physiological studies can be done to look at the physiology of insulin and glucose in the presence of this new medication.

DR. BURMAN: Thank you. And of course, there are other detrimental potential effects, as well, on polyps and cancer perhaps. Can I ask, Dr. Molitch, as a growth hormone expert, what are your thoughts?

DR. MOLITCH: I'm certainly not happy about

people being 2 and 3 standard deviations above the mean in their IGF-1 levels for years and years and years, certainly. That's the kind of range that we do see in patients with acromegaly and is associated with increase in morbidity and mortality.

We try very hard to get those levels down into the normal range. So here, we're doing the converse. Similarly, in patients who are treating with true growth hormone deficiency, we give them growth hormone. We aim to keep their IGF-1 levels in the middle of the normal range and not to supranormal ranges for fear of those same adverse cardiovascular effects and potential cancer effects, which I think are certainly far from being proven. So it is a concern to me.

Coming back to your first question, if I may, it was my original question that I asked, the link between increased visceral fat and cardiovascular disease. What is that link? And the fact that we would expect to see, with a decrease in visceral fat, an improvement in insulin sensitivity and a lowering of glucose levels, and that might be part of the

beneficial effect we might see with lowering visceral fat. But in fact, we don't see that here.

The growth hormone or the increase in growth hormone and increased IGF-1 seems to obliterate that potential beneficial effect. So there will maybe a total disruption of visceral fat changes with cardiovascular outcomes, and that's what concerns me here.

DR. BURMAN: Thank you. Does anybody else have any comments on those specific issues? Dr. Goldfine?

DR. GOLDFINE: I actually have a couple of questions. One is on the impact of the dysglycemia. And I think that there is more pre-analytic and analytic variability in the glucose values in that the day-to-day variation in the glucose tolerance test is much greater than that for the hemoglobin A1C. And so I actually put a lot of stock on the hemoglobin A1C measure, per se.

There are numerous studies. Most of them look at either fasting glucose or a post-load glucose and demonstrate that even within the normative range,

increases do carry very significant hard outcome, cardiovascular or mortality, risk from the increases.

Probably the most pressing study is one that came out of New Zealand about a year ago or two years ago by Brewer and company, where they looked at the effect of hemoglobin A1C on approximately 49,000 people. It was actually a health survey and on mortality. And there are increases in mortality even across the normative range.

So while the individual risk here is, obviously, extremely low given the magnitude of change, it's probably not linear in that the risk even in crossing these normative ranges is probably present. And on a population level, it could potentially disrupt the potential benefits.

If you look at the aggregate data for the acromegalic adverse events, which I believe was on slide 80, in case anybody wants to bring it up, while each individual potential adverse effect was actually low, if you look at the aggregate, it looks like there was almost 10 percent more aggregate risk of acromegalic adverse events developing.

Again, as Dr. Molitch pointed out, we do try to drive people to the normative range in our therapeutic clinical practice. And over time, it suggests that we actually are potentially inducing a very low grade chronic issue that would be of concern and make me feel that a cardiovascular outcome -- since we're being asked to accept that the visceral adipose reduction, on top of making patients feel better and being able to bend over, which is actually very important, they are quality of life issues, it's also important to their long-term mortality and safety.

There are other studies, albeit extraordinarily small, that look at omental resections and do not demonstrate. So there was one published approximately two months ago from the group in St. Louis, where they took two cohorts of patients -- this is very flawed by being extremely small data. But they had a group with Roux-en-Y bariatric surgery with omentectomy and without omentectomy, and they also had a group who underwent solely omentectomy. That group was not randomized or masked in treatment.

After a year, with very careful clamp measures, and other insulin secretion in action, they did not demonstrate metabolic benefits, other than a very small borderline statistically significant drop in triglyceride level, which has not been as clearly demonstrated to have cardiovascular outcome benefit.

In that study, they were removing approximately 800 -- so it was about .8 kilograms of visceral adipose tissue. And when I do the calculations based on the average individual starting at about 180 and approximately the 18 percent loss, you're probably decreasing by about 25-27 grams of adipose tissue, which is much less than that from the full removal that did not see benefit.

So our leap of faith is that the reduction in visceral adipose tissue is going to be beneficial to cardiovascular outcomes, which, when offset against the low grade increases in IGF-1 and the increases potentially in hemoglobin A1C and dysglycemia, may not end up yielding what we would be very hopeful from the decrease in visceral adipose surrogate endpoint to find ultimately.

DR. BURMAN: Thank you. Those are good points. We haven't discussed at all hepatic fat, and there is, obviously, a lot of literature on hepatic fat being more related to insulin resistance than visceral fat, but we don't have any information on that.

Dr. Thomas?

DR. THOMAS: I have found the diabetes impact glucose tolerance data to be somewhat confusing from both the FDA and the sponsor. It's bidirectional and you might expect that in a short-term study, some patients may get improvement from the changes in lean mass and in visceral fat, and some people may not.

That's why I think family history and other risk factors for diabetes are important to assess and should be done. The one thing I wanted to mention specifically about this point is I don't think this should be done as an observational study. This really has to be done as a trial, if the medication is approved, because in observational studies, the diagnosis of diabetes is fraught with being misdiagnosed.

Patients may think they have diabetes and they don't. They may be put on a medication for diabetes and actually are being treated for something else unrelated to diabetes.

So if you're going to approve this, and this is an important issue about the development of diabetes, then you really need to have a placebo-controlled trial afterwards to look at what is the true incidence of diabetes over time. And you need to look at risk factors, though, risk factors of family history, ethnicity.

Because the ethnicities were so low in terms of minorities, who are much higher risk for diabetes than probably the Caucasian group that was the majority of the patients in the study, that's going to be an important factor, as well.

The second thing is related to this. Because of the issue of retinopathy and what we now know, which we didn't know a while ago, that retinopathy exists early in people with normal glucose tolerance. It's up to 8 or 10 percent. It exists in people with impaired glucose tolerance.

In growth hormone, before laser therapy was available for retinopathy, destruction of the pituitary in the 1960s and early '70s was a treatment for advanced retinopathy. And in trials with growth hormone and diabetes later on, there was an increase in retinopathy.

So if we're going to give a treatment that has potentially many years to lifelong chances of being used, we really need a proper assessment of retinopathy, starting at baseline and changes over time, with fundus measurements, endoscopy reviewed by ophthalmologists to see what is this risk, because you also need to make a recommendation to patients in this study, if they're going to be on this medication for a long time, should they get annual eye exams beyond what eye exams they may get for other causes of HIV retinopathy, the infections they get, the chorioretinitis. They may need routine surveillance for retinopathy, which we can address.

Other risk factors, like blood pressure, we know that long-term with growth hormone, abscess and acromegaly, blood pressure goes up. There are changes

in EGFR and nitrogen balance. All of those things we presume, like blood pressure, contribute to the excess mortality and acromegaly.

So we need to know these things. And the cardiovascular trial, as a result, also should be a trial, not observational, because I think the worst thing that will happen is -- it's happening in July -- is five-six years from now, we get some meta-analysis, a review of data from claims bases, from insurance companies or an HMO, saying there's a suggestion of a cardiovascular signal. And then we're going to meet here again -- probably not me, because it will be five years from now. I won't be on term.

But we're going to be talking about should we be doing trials that are randomized to see if there's a cardiovascular risk. So I think just like the diabetes drugs are having this done now early on after approval, I think this should be something that's planned as part of the approval process, if the medication is approved.

DR. BURMAN: Thank you.

Any other comments from the panel or issues

that the panel think are important to raise? Dr. Molitch?

DR. MOLITCH: In all due respect, coming back to the retinopathy issue, I think it's actually not an issue. I think the old issues on pituitary ablation were totally uncontrolled and for very far advanced retinopathy, and I think they can just be discarded.

There have been studies looking at giving some metastatin to diabetic patients, reducing growth hormone to see if it would have any effect, and it did not. So I think that at least that part we probably don't need to worry too much about. All of the other issues certainly are germane, however.

DR. BURMAN: Thank you.

Dr. Proschan?

DR. DOBS: Maybe it's addressed to Dr. Molitch, is the issue of doing echoes for cardiomyopathy in the long-term because of the acromegalic heart. And, actually, I think that's what the old term data showed people died of.

DR. BURMAN: Agree.

Dr. Proschan?

DR. PROSCHAN: Concerning the diabetes issue, I think it is a little confusing, but I think there is an increase in diabetes. It makes sense that there's a statistically significant change in HB A1C. So if you're close to the limit, it's going to probably push you over the limit. And I think that's what the data show when you look at -- when you look at a single time point, I think there's a lot of error caused by the fact that people are right on the border. And that's why I think you want to look at consistency.

So I like the number of times you go to a worse category, and I think that analysis does show that there's an increase. I think it's small, but I think it is real.

DR. BURMAN: Thank you. Anybody have any other -- Dr. Schade? I'm sorry.

DR. SCHADE: I have a comment and a question for Mark. We're talking about diabetes like it's a fixed number, and the fact is, I'm a strong proponent of treating impaired glucose tolerance or what you

call pre-diabetes, because the comment we heard over there that you start seeing complications before you reach the "diagnosis" of a fasting to 126 is real.

To think that there's a difference between going from 6.3 to 6.4 versus 6.4 to 6.5 and suddenly having diabetes I think is a myth. I think you can get complications of the spectrum and a continuum.

I would agree with you that the population data shows that the higher your A1C, the more likely you are to get complications. So it's not good to go from 6.3 to 6.4. It's not good to go to 6.5, et cetera. But to think you're okay if you're below 6.5, a hemoglobin A1C of 6.5 is a myth.

So I think we know that this drug will cause insulin resistance. Therefore, it will raise A1C to some extent, is real. I'm not particularly worried about it, as a diabetologist. I treat impaired glucose tolerance and I can treat this impaired glucose tolerance these days with the many drugs we have. So the diabetes, quote, doesn't concern me as much, but I understand the concern of the panel.

The question I have for Mark Molitch is

totally different. And the question I have is, are you worried, Mark that there's something -- anything bad going to happen to the pituitary with continual stimulation at these high levels for three, four, five, six, and seven years?

DR. MOLITCH: No. There are clearly tumors that make growth hormone-releasing hormone and they can cause growth hormone cell hyperplasia. And then if you get rid of the growth hormone-releasing hormone-producing tumor, that all tends to resolve.

So you could get hyperplasia. You could have true acromegaly that occurs in that setting, but it goes away when you get rid of the excess source of the GHRH.

DR. SCHADE: So you don't get adenomas with continual stimulation.

DR. MOLITCH: Correct, not in humans.

DR. SCHADE: Okay.

DR. BURMAN: Thank you. All good points. Dr. Morse?

DR. MORSE: I just wanted to add that there is some literature in HIV that hemoglobin A1C

underestimates glycemic control, and I haven't heard anyone mention that. So it may be that using hemoglobin A1C cutoff that works for the general population may not be appropriate in this setting.

DR. BURMAN: Is that even without the context of hemoglobinopathies?

DR. MORSE: Yes. It correlates with specific antiretrovirals and some others.

DR. BURMAN: Thank you. Dr. Veltri?

DR. VELTRI: Just a comment about the IGF-1. I'm in pediatric endocrinology and, for the most part, we have a tremendous number of kids on growth hormone for various reasons. And I know we don't generally follow-up IGF-1 levels in our treated growth hormone patients, at least as a group.

We watch their growth, we watch their bone age, and we make assessments based on our starting dose. But the number of times that we've gotten IGF-1s or that I've seen them for whatever reason, they're actually pretty high and higher than you would expect for the child's age or even the bone age.

Thinking about it, for some of the kids that

we have and especially some kids that we treat for idiopathic short stature, those kids have normal IGF-1s and normal growth hormone levels upon stimulation.

So some of these kids are getting the medicine for 10, 15, almost 20 years while they're in our practice or at least have that potential, and I know we're not seeing anything. Granted, the ISS indication has only been around since 2003, but growth hormone, at least in its form that we're using it now, has been around for 25 years.

So I don't see any real worry on IGF-1, its effect today, but then, again, I'm looking at kids, most of them under 20 years of age compared to the population that you're talking about here. But the potential for the number of years you're going to use the medication is very similar to our population.

You're talking at least 10, 15, 20 years, hopefully, I would think, in the big picture, for preventing cardiovascular disease in HIV patients. Well, it's the same thing, at least from a time standpoint, in our population.

I think kind of what Dr. Schade had said

there, this A1C change of .1 percent, I'm not worried about this wonderful p-value, but we don't see .1 percent as a real issue for diabetes. And if you're worried about the 6.4 going to 6.5 and you treat these patients for glucose intolerance, you're going to get -- well before you get there anyway. So you're going to be treating a lot of these patients beforehand.

So I'm just not terribly impressed with the diabetes standpoint. I'm actually much more focused on the visceral fat, which I know will come up in a couple months at a different meeting, but I think that's the bigger role here as far as diabetes is concerned and cardiovascular disease.

DR. BURMAN: As a pediatric endocrinologist, can I ask you, are you aware of studies following children who have gotten growth hormone administration for decades, 10 or 20 years, and whether they get an increased risk of cardiovascular disease or cancers?

DR. VELTRI: I am aware of no studies of kids getting the medicine that long and getting cardiovascular disease. I know when we have a patient that has growth hormone deficiency and has a cardiac

abnormality, it's just a tremendous concern between us and the cardiologist. Do you want to put this kid on growth hormone or continue it if they have some cardiovascular problem? And most of it's congenital heart disease. But I'm not aware of any that have received it that long.

The biggest risk population related to growth hormone, I think, in our patient population, are the brain tumor kids. And the big worry was if they have a brain tumor and you put them on growth hormone, are you going to re-stimulate that tumor, even if you think you've eliminated disease, whether it be from surgery or from radiation.

We have one of the best centers in the country related to brain tumor and endocrine clinic, and Dr. Lillian Meacham has put these studies out, giving them growth hormone. Even in those that you would think would be at higher risk for developing or redeveloping tumors, it doesn't occur compared to the general population.

DR. BURMAN: Thank you.

It's 2:25. Are there any further issues

among the panel before we go through each of the questions that anyone wants to raise for the panel? No?

Then what we'll do now is go through the questions. And in the packet, there are six questions, but three of them are very similar. So we're going to combine those, and there will be four questions.

What we'd like, the FDA would like, is for us to go around to each voting member -- each member -- and see what their specific opinions are, because we want input from everyone so we can make the best decision.

So the first question, which is on the board -- I'm sorry. One other thing. We're not going to take a break. I don't think there's time, rather end early. So if anybody wants to get some refreshments or whatever, please get up and feel free to do so.

With regard to the first question, "Please comment on the findings of glucose intolerance in development of diabetes associated with Egrifta therapy and its impact on long-term cardiovascular

risk." We'll just start on one side and then go to the other.

Maybe, Dr. Schade, do you want to start?

DR. SCHADE: Are we going to comment on just this one or is this the four questions?

DR. BURMAN: Sorry. This is number one and there will be four specific questions. This is the first one.

DR. SCHADE: We're working on getting number one here.

DR. BURMAN: Thank you. Three, four, five are combined. So do you want me to read all the questions?

DR. SCHADE: No. I'm just trying to see number one, which has been taken off. Okay. It is not a great concern to me. I have lots of treatments for diabetes and impaired glucose tolerance. I'm a strong believer that you don't wait until you reach diabetes before you treat.

Therefore, if I have one of these patients and they are developing impaired glucose tolerance, I'm going to treat it. And I have a lot of choices

these days, and I just don't think this is a major concern. It's certainly a minor concern. I'm not trying to negate it. But it's not a major concern.

DR. BURMAN: Dr. Dobs?

DR. DOBS: I, too, have really not that many concerns about it. There is a relative increase of diabetes, it looks like, but the absolute risk is still low. And this is a population where there's a high background of getting older, generally getting more obese, and having other risk factors, such as medications, to increase the risk of diabetes.

DR. MORSE: I agree the risk is real and it appears to be rare. Luckily, it's reversible and I think with close monitoring, we could manage it well. So I'm not very concerned about long-term impact on cardiovascular risk.

DR. FELNER: I have very little concern. In fact, I would have said exactly what Dr. Schade had said.

DR. GOLDFINE: I would mimic closer to Dr. Morse, I think, that it's very small. It is probably real. I think it is reversible and manageable. And

on the population level, I'm uncertain in how that will play out for long-term cardiovascular risk.

DR. PROSCHAN: I think it is real. I don't think it's an artifact. It does seem to be a small difference in HB A1C, and I don't know what the tradeoff is. If you reduce fat, maybe that more than offsets possibly a small increase in risk.

I don't really know that, but it does seem small, but real.

DR. BURMAN: My comments are that there are no clinically significant changes in the mean values for fasting glucose, fasting insulin, or HOMA, and a statistically significant, but clinically irrelevant, potentially irrelevant, mean change in A1C was observed with a change of, as was mentioned, .15 percent versus .04 percent, which is statistically, but not clinically significant.

The percentage of patients with glucose intolerance increased in the treatment group from a baseline of about 38 percent to as high as 53 percent during subsequent measurements. In contrast, the percentage of patients with glucose intolerance in the

placebo group remained about the same, 39 percent versus 48 percent.

Therefore, I come to the conclusion, as well, that there's a statistically significant rise in hemoglobin A1C, but probably that's clinically insignificant. But I definitely agree with Dr. Schade that it's a continuum and it's certainly something that should be monitored.

DR. FLEGAL: I also concur that there does appear to be true increased risk and it is statistically significant, although small. I guess the other thing, I don't really know how to balance this, is the population of patients for whom this drug will be used versus the general population.

The ethnic composition is somewhat different and whether some groups at high risk of diabetes are sort of underrepresented a little bit in the patient populations. So I think that's something that definitely there should be an eye on, because this will increase cardiovascular risk, although to a minor degree and perhaps there are offsetting issues. But it's certainly something that needs to be looked at

carefully.

DR. ROSEN: I would tend to agree with the other speakers that the absolute risk is low. It's potentially manageable, and I think it's very hard to go from that slight increase in hemoglobin A1C to long-term cardiovascular risk.

So I think it's manageable and I don't think that it's a major issue for me.

DR. HENDERSON: I agree that it's not a major concern. It appears there's a subpopulation that might have an effect on glucose, but it could be managed or they could be taken off the drug.

DR. THOMAS: Because patients with diabetes were excluded, the magnitude of change isn't very large. So it's not really something that can't be treated medically. But I do think, as many have mentioned, the risk for cardiovascular disease starts early, well before the diagnosis of diabetes.

So risk factor management and proper follow-up is what I think is the emphasis of these changes, should be reflected in terms of practice. So I think that's the concern. And because these are small

changes in such a small duration of time, you won't be able to see any signal. So that's why follow-up studies are important to look at this.

DR. BISHOPRIC: I would reflect all the other comments and just say that because it seems the problem is treatable and the drug is removable, that it would be a manageable complication.

DR. KUMAR: Not only do I think the risk is real, I think it's much more significant, because the patient population that was studied in this and shown in this trial is very, very different from what we see in clinical practice.

The patients that we are seeing in clinical practice were not represented in this patient population. We are seeing more and more people of color. We're seeing more patients with obesity, general overall obesity, and with other risk factors.

So I think, to us, with all the other antiretroviral combinations, just adding one more drug to treat diabetes is going to be significant. So to me, as a clinician, seeing these patients, managing these patients, even the small risk of diabetes would

be something that I would take -- which would be of great concern to me, especially knowing that patients with HIV infection, even in this era of HAART, have increased risk for cardiovascular disease.

DR. MOLITCH: It's hard for me to separate out the diabetes and the cardiovascular risks. The diabetes itself is relatively modest and itself is easily treatable. On the other hand, with the decrease in visceral adiposity, I would expect a substantial improvement in glucose levels, improvement in insulin sensitivity. And, in fact, we see things going slightly in the opposite direction.

The biological effect is actually pretty substantial. We're not just having a slight increase in glucose levels. We're reversing what should have been expected with the decrease in visceral adiposity.

I think there's a lot of biology going on here that's sort of being hidden and masked, and so I'm very concerned about that. And I think it totally abrogates the linkage that's being made between the reduction in visceral adiposity and cardiovascular risk, that it's just broken, it's not there anymore.

The diabetes itself is relatively easily manageable. Cardiovascular risk is another thing entirely.

MS. SWAN: I am concerned about the diabetes to a certain extent, but for me, it underscores the need for long-term follow-up, additional studies, and clear guidelines for what is appropriate monitoring.

Both for clinicians -- since all of you are experts here and there are going to be people that might possibly be administering this drug that don't have the background of knowledge that people here do about endocrine and metabolic issue, and that the risk-benefit ratio is clearly spelled out to patients who want to use this.

DR. CARGILL: I am a bit concerned about the glucose intolerance. However, I'd like to echo what was said earlier, that I think that what we have here is glucose intolerance lumped into a question with long-term cardiovascular risk.

I think what we have here is some significant confounding, particularly, that may happen in the future. In a population that was 76.6 percent

Caucasian, to see the signal that we saw here does not necessarily reflect what we're going to see in clinical practice.

I echo Princy's comments that in my practice, it's 97 percent African-Americans with very deep family histories of diabetes. That will be an issue. However, that's further confounded by these individuals already bringing their own cardiovascular risk superimposed upon cardiovascular risk that's associated with just having HIV infection.

So I think what we see here is we do see some reason for concern, but on the other hand, I think we have to be realistic about this and understand that this is heavily confounded and what we're going to be looking to is additional studies that we set some very solid parameters around so that we can start to unlink this, because right now, it is heavily confounded.

DR. VELTRI: Well, my only comment is I see some schizophrenia here in the sense that we have drugs that lower glucose intolerance. We're asked to do cardiovascular outcome trials. And here, when we

have an increase on some of these parameters, we're kind of dismissing a little bit the potential for adverse long-term cardiovascular risk.

So I guess from an industry perspective, there's a little bit of a disconnect here for me. My own personal feeling is I think that the data, I think, does show biologic plausibility of what we're observing, although modest increase in glucose intolerance, hemoglobin A1C, et cetera.

I think the development of diabetes can be managed, obviously, and even before frank diabetes is manifest. Indeed, the trial did have fasting blood sugars up to 150, I believe, here. So there clearly were some maybe diet-treated diabetics.

The impact on long-term cardiovascular risk is uncertain, as there's competing risks here with the VAT, but yet the glucose issues. So what appears to e a biologic plausibility may end up being a real cardiovascular risk.

So I don't think we have enough data today to make that assessment.

DR. BURMAN: Thank you all. I have the task

of summarizing this for the record, which, of course, is difficult. But let me summarize and see if there are any strong objections.

We agree that cardiovascular disease is a risk factor; that HIV is a risk factor for cardiovascular disease; and, that increased visceral adiposity is a problem, as we've heard from the OPH session, both with image and potentially with insulin resistance, although the link between visceral adiposity, insulin resistance, as well as growth hormone, and with cardiac hard endpoints is not exactly clear.

The results on diabetes show that there's a statistically significant change in A1C that probably is not clinically significant, and the disease could be treated if it shows up.

We do want post-marketing studies that are detailed, and we're going to be talking more about those. And we make the point that diabetes and hemoglobin A1C is a continuum and that an arbitrary cut-point of 6.5, for example, is just that, just arbitrary.

As was pointed out by Dr. Kumar, the population studied is not representative and it's not known or not clear at all that the other populations would have the same responses.

We do want long-term studies with regard to carcinogenesis and that a year-long study is not adequate for that. We don't understand the mechanism by which diabetes develops. As Dr. Molitch says, when the visceral adiposity decreased, you'd expect maybe a benefit on metabolic effect, and that visceral adiposity is a distant surrogate for cardiac endpoints.

Does anyone want to add or modify that summary? Okay. Thank you all very much. I thought that was an excellent discussion.

Let's move to question 2, as listed here. "Please comment on the increase in IGF-1 levels associated with Egrifta therapy and concerns associated with chronic use of Egrifta with respect to long-term cancer and cardiovascular risks."

We've touched on this a little bit. Dr. Veltri, let's start on your side.

DR. VELTRI: I really have no comments. There's no data right now that I can really talk to. It's just an open-ended question. I just don't have any comments.

DR. CARGILL: I think we've heard some suggestion that this is not unusual in other settings. Again, I think it is something that we would want to monitor, but I don't see this right as something, at least for me, that I have as much concern as I do, for example, in number one.

MS. SWAN: I think monitoring over the long term will be important, because I'm not sure how much of the information we've heard is applicable in the context of immune disregulation; not deficiency, but disregulation and risk for cancer.

DR. MOLITCH: I think the risk for cancer is actually quite low, although it's probably finite, but very low, from looking at long-term studies of growth hormone-treated individuals and people with acromegaly. It certainly deserves long-term surveillance, but I'm not sure it's high enough to limit looking at this medication.

The cardiovascular risk, I think, is a concern. The elevated IGF-1 levels really are reflective of elevated growth hormone levels, also. And certainly in patients with acromegaly, they get closely correlated with increased cardiovascular risk.

Whether the increase in growth hormone was then related to the increase in glucose intolerance, again, may be partly contributing to that cardiovascular risk. So I think it's a concern and would clearly need to be studied more carefully in the long term.

DR. ROSEBRAUGH: Can I just ask a question and use an FDA prerogative here?

DR. BURMAN: Dr. Rosebraugh, of course.

DR. ROSEBRAUGH: I am a little curious, if you wouldn't mind commenting. You've mentioned several times we should monitor and do further testing for cardiovascular type outcome things.

So it would help me if I could hear the panel members discuss whether they are talking about a randomized trial. And if you are, if it was post-approval, how practical do you think it would be to do

that study?

The reason why I'm asking is we heard some very compelling testimony about how people suffer with this disorder. And so I'm wondering if you can really do a randomized trial, if this is approved, and do it post-approval. Would people really go into a trial where they have a 50/50 chance of not getting a drug that might make them feel better?

If you think that trial is not practical, how would you suggest that we try to evaluate for cardiac outcomes?

DR. BURMAN: Maybe we can back up and go around. Dr. Veltri, do you want to comment specifically on that? Then we'll move around.

DR. VELTRI: Well, that's what I was kind of asking you, how would you structure a cardiovascular trial, outcomes trial, when you would exclude diabetics, for instance, CHD equivalent patients. It would be feasibly difficult to do, but somehow you'd need to think of a way to enrich the populations.

In this particular case, though, I think we don't really know what the VAT means. Certainly,

there are some things that are going favorable, but some things which are not; favorable, some of the lipid parameters, but not the glucose parameters.

So I think it's scientifically and ethically still an important question to ask and I think it's not like it's impossible to do, especially if you're going to use an enriched population where you're going to have events.

I still think a double-blind, randomized control trial would be the way to go here, but the details would need to be worked out. I think it's feasible, but it would be more difficult.

DR. CARGILL: I actually don't understand your difficulty. As I'm sitting here listening to you and think about having heard this compelling and very important public hearing testimony and also, what I see in my own practice, I was not, I must confess, thinking in terms of a randomized control trial as much as looking through what has been presented to us as a way to have network pharmacies and ways to control who gets it.

Actually, as part of that, could we ask for

the recording of specific data and as people are provided with this drug, that there be guidance given as to specific laboratory tests that can be included as part of that, so that we have a track over time.

I know that's difficult and it may not be feasible, but I just think when you -- to me, if I think of trying to do this as a randomized control trial, I don't really understand how one can do that, with all due respect, just because you would have some of the same difficulties you just alluded to.

MS. SWAN: I would hope that it would be possible to do long-term observational follow-up and a randomized control trial. My fear, and I know this panel is not -- your purview is not pricing, but this is going to be very expensive.

Given the state of AIDS drug assistance programs currently and the uncertain future with health care reform, participating in a trial may be the only way some people are able to gain access. So if they are randomized into a control arm, they haven't forfeited their opportunity to try a drug.

I really hate to say that, but it's a grim

reality.

DR. MOLITCH: I would be in favor of a prospective randomized trial for five years or more. Monetarily, that would be a difficult thing to do, I'm sure. But I'm impressed with some of the slides that were shown by FDA that -- for example, 17, 19, 21 were ones that looked at belly appearance distress and the differences between the two groups and the spread of values was actually very minimal.

So that there clearly are people who are getting placebo who lose a lot of belly size, also. Then, in fact, it may not be all that obvious what you're getting from a clinical basis. So I don't see a reason that a prospective randomized trial could not be done on a long-term basis, with the major theme being a true cardiovascular outcome.

DR. KUMAR: I'll pass on that question.

DR. BISHOPRIC: I would wonder if a randomized trial might not be necessary, because of these risks and the cardiovascular risk in general. To capture the data of what happens with the visceral adipose tissue might require a long-term trial, about

the only way to get it.

DR. BURMAN: Because we hadn't reached you before, maybe you could also comment, if you wanted, on the rest of the question.

DR. BISHOPRIC: Yes. As to the cardiovascular risk and how I would evaluate it, it sounds like, again, it needs to be followed, and I balance this with my consideration of the testimony of how people suffer with this condition in their day-to-day life and their perception and their social isolation, which I think also carry considerable morbidity.

DR. THOMAS: We can't assess what the cardiovascular risk is from the data we have. It's too small a study, too short a time. And the group at risk isn't as enriched as some of the other groups that usually are these types of studies, like people with diabetes.

However, I do think you have to have a randomized trial to look at this. And if you look at beyond this population, you're going to approve this for a surrogate marker, visceral adipose tissue, which

has not been shown to -- if alterations in that have any effect on outcome.

It's different if you're looking at LDL cholesterol, where there's enough studies and experience to show that that change in the surrogate marker is good enough to look at cardiovascular events.

If you're going to look at other populations, this is the HIV population, you may get other applications for visceral adipose tissue in other diseases.

If you don't do the study here, how are you going to know that's an appropriate surrogate marker? We've been fooled before. Dr. Rosen, of course, knows more about this than I do, but bone density used to be the marker for osteoporosis. And we've been fooled by that in the past and now we use fractures.

There are many diseases where we use surrogate markers and they're not effective for hard outcomes, death, cardiovascular events, fractures, et cetera. So this is the first drug that you may approve for a surrogate marker that's not been defined

in terms of changes in outcomes. I think you're obligated to do a randomized trial prospectively.

DR. BURMAN: But, Dr. Thomas, if I can ask the hard question, should it be done pre-marketing or post-marketing, given the difficulties that were raised in getting people to be in a placebo trial?

DR. THOMAS: I think this is just going to be my personal opinion. I would prefer, if the medication was approved, that it would be done post-marketing. And the reason I say this is there is no other treatment for this disease.

I know I don't see many HIV patients as I use to, as more of the people who take care of them are comfortable with the lipid issues and diabetes issues. But when I used to, I was always struck by the profound issues with body image, the changes in fat distribution, and the fact that when patients are out in the community, it's a marker that identifies who is on treatment.

They go to a gym and everyone knows who's their peers that they have HIV. That psychological distress is profound. We used to see a lot of orphan

drugs and we approved them, because that's the only agent that's available that's effective.

I think if we had other agents out there or on the horizon, I might feel different about doing it before approval. But because this has been going on for such a long time and it's such a severe impact on psychological wellbeing, I would feel hard-pressed to require that you wait the five years or longer that it might require, because of the cases that you'll need to hit the incidence to judge between a placebo and a medication trial.

DR. BURMAN: Thank you.

DR. HENDERSON: As a cancer survivor, I was most interested in this question. But it comes down to you can't really make comments on the long-term risk without having long-term data.

But I was concerned with this one lung cancer death that they related to the drug and still didn't get a clear answer. To me, that was alarming that a person would have lung cancer within a 52-week period and die and it would be related to the drug.

But the comments that Dr. Felner made me

feel a lot better in general. And I do agree with the other comments that the benefits of the short-term will probably outweigh any long-term risk.

I would like to suggest a long-term follow-up studies, maybe a registry. I think that would be good.

DR. ROSEN: So I will take the stance that I think I'm very worried about the IGF-1. So one thing that's really important, and Mark alluded to it briefly, is we're stimulating both growth hormone and IGF-1.

But unlike growth hormone treatment both in children and in the studies we and others have done in adults, you can't adjust the dose. You don't titrate down this dose. So you've got IGF-1 levels in the 300 to 400 range chronically for as long as these people are being treated.

The truth of the matter is we don't have the data, but we're very concerned about long-term high levels of IGF-1. So I am concerned about that.

In terms of cancer, it's unclear. The data are not great. There's as many conflicting studies as

there are negative studies. But they're certainly using IGF receptor antagonisms in Phase 3 trials all the time and that's a concern, because they work in some of these patients.

So I would be very concerned about that. I think there's so many things going on metabolically in these individuals once they're getting treated, they're getting growth hormone increases, they're getting IGF-1 increases.

Sure, you get a lipolytic effect and you reduce visceral adipose tissue, but there are other things. And I agree that we probably should have seen something of a more positive signal and it's probably being balanced by the growth hormone, not the IGF-1. I think the growth hormone is probably what's having a negative effect.

So I'm concerned about that and I think when you can't titrate to levels that are reasonable, it raises some concern that this is a lifelong therapy and you have a choice of either taking it or not.

Very impressed with the public comments, and I think all of us feel that this is a very important

problem, besides some of the numbers and the levels of IGF, but these social issues that are involved.

I'm a huge fan of randomized control trials, but we're talking about large numbers for a long period of time to look at hard cardiovascular outcomes; so 3,000 or 4,000 subjects maybe for three or four years.

I don't think it could possibly be done post-marketing. I don't think anybody who has availability to the drug and suffers from this is going to want to be randomized to placebo.

So I just don't think it can happen for cost, for ethical issues. I'm not even sure it could get through an IRB. If this was an approved therapy, then you could randomize somebody to placebo to look for harm, which is what you're looking for.

You're looking for harm, which is cardiovascular risk. So I think that that would be a very difficult sell on a number of levels.

So in sum, I think this area, the IGF, is much more disconcerting to me than the glucose intolerance, which I think -- as we talked about, it

was there at 26 weeks, a signal, but at 52 weeks, among the long-term extenders, it wasn't there.

So I think the IGF issue still remains to be resolved and that's my biggest concern.

DR. FLEGAL: Well, I think we really don't have the data, so I don't see how you can answer the question, in a sense, without doing some sort of further investigation.

I guess I'm sorry to hear things a little schizophrenic, where, on the one hand, it's not clear whether this reduces your VAT enough that you can tell whether you're on the drug or not. On the other hand, that this is going to make a difference when you go to the gym, everyone is going to know you're on the therapy.

So it's not very clear to me just how much this is really going to make an individual difference that people are going to know what treatment they're on and whether that makes a trial completely impossible. And we seem to be sort of hearing both sides of that question, which I think is a problem.

Here, we have something that -- the public

testimony is very compelling. I'm not sure it fully matches all the data that we're seeing and there's a lot of potential for risk here that we don't really know about.

Also, the data on visceral adipose tissue and cardiovascular risk is very indirect. Waist circumference is very highly correlated with just overall body fatness. So I'm not convinced by these studies that show that waist circumference adds to BMI, that this is actually showing you anything about visceral adipose tissue or whether it's showing you just about fatness as opposed to lean mass, to some extent.

I'm also not sure that reducing VAT with this method would really give you the complete answer as to whether that could be extrapolated to other situations and other ways and modalities of reducing VAT.

I guess the bottom line is that I'm kind of on the fence about the whole thing, but I do feel we really need to know more about the risks of this drug before we just go ahead and say, yes, it's so

compelling that everybody should be taking it.

DR. BURMAN: I agree, obviously, with the comments made and will make the further comment that at 26 weeks, the combined group had a mean significant increase in IGF-1 level of 107 nanogram per mil, whereas it actually went down by 7 nanogram per mil in the placebo group.

At the start of the extension study, after 26 weeks, with treatment, mean IGF-1 levels had increased by 93 percent in the T-T group and 100 percent in the T-P group. So those are significant increases that frequently make the level outside of the normal range, and is a concern.

On the other hand, only 3 of 17 patients who had cancer had an IGF-1 level greater than 3 standard deviations above the starting mean, which is somewhat encouraging, although I would like more data. And I emphasize the importance of more data on all of these risks, not only for cancers, but including colon cancer, breast cancer, and prostate cancer, as well.

I wonder, as well, if there shouldn't be a time limitation on the medication, as there is for

other medications in endocrine that we deal with, because we don't really know the long-term effect over a year, really. But if we extend that reasonably to maybe three to five years, that might be a reasonable approach.

Mike?

DR. PROSCHAN: Who knows? We don't have the data really to answer this question. I think one thing is clear, though, and that is that you can't go off this medication and expect it to continue to help. That was shown in the extension phase. So you are going to have to take it long term.

I always worry a lot about approving something on the basis of a surrogate precisely because that usually means a small short-term trial, where you don't see all the possible harm, you don't see the cardiovascular harm, if there is any, or cancer harm or whatnot.

So I'm always pro trial. The problem is, as has already been pointed out, that if you do it post-marketing, no one is going to sign up for the trial, unless perhaps -- I mean, maybe it's possible to do

different dose levels, a lower and a higher dose, and then see if there's a bigger risk of these cardiovascular events in the higher dose. I don't know. That's the only possibility that I think people will actually sign up for possibly.

DR. GOLDFINE: I think our FDA presenter said it very well. The study duration limits the risk assessment. I can't tell whether it's the growth hormone or the IGF, per se, that's giving the risk. I am moved not only by the standard deviation spread of the IGF and the absolute levels that are above normal, but also by the excess of acromegalic adverse events, of which I actually put the glucose into the same bin.

So when I look at the long-term effects of growth hormone excess, again, the malignancies most common are breast, prostate and colon. They're also among the most prevalent of the tumors.

That said, we can say that acute treatment doesn't seem to unmask malignancies that may be indolent. That does not mean that we have any knowledge of what it will do to the growth or promotion of additional malignancies over time,

especially given that the treatment is going to have to be sustained.

I also don't know specifically whether brain malignancies, where these are commonly used, are ones that tend to have IGF-1 receptor signaling being particularly active within them in relative comparison to others.

So with that in mind, I think that I am a little hesitant about approving based solely on a surrogate outcome if our assumption is that we're actually down to potential cardiovascular benefit, because patients with HIV have cardiovascular risk and abdominal obesity is associated with that risk; therefore, if we're reducing the obesity, we're reducing the cardiovascular risk.

If that's going to be the assumption that we're taking, then I think that a trial that will look at what we actually really think that we're treating becomes important.

I am moved by the fact that while the patients actually gave very heartwarming testimonies, when you actually look at the curves of separation, as

Dr. Molitch pointed out, they are much less compelling as to whether or not they really had tremendous benefit.

I don't think it would be impossible to enroll patients in a study nor do I think it's unethical if the benefit that they actually manifest right now is a decreased abdominal girth of unclear medical significance, albeit of quality of life significance. I don't think that that's an unethical trial to continue to do nor do I think it would be impossible to enroll into.

DR. FELNER: I actually have more concern with the IGF-1 than I do the diabetes, even though maybe my last comments about the IGF-1 made it seem like I didn't care or didn't have concern. But I do have more concern about that than I do the diabetes issue.

But I think one of the things about these levels, if you just focus on elevated levels, these are folks that, for the most part, we were told to have a blunted growth hormone pulsatility response, but I don't know what their IGF-1 level is.

I'd love to assume and I think I can assume that they're probably normal, in the relatively normal range before they go into the study. But their elevated levels just tell us they're getting the drug.

So is there any problem with them getting the drug? Well, in one year, granted, it's not a long time, but there hasn't been a real blip, other than a high level. And you can make the argument, I think, that most are starting to think about, which is, well, let's see five years of no blip and then we won't have a problem.

But I think with the need to have something here for these patients and if you're going to make the argument, as we are making the argument, that folks with HIV are living a lot longer, but now they're starting to develop the problems you would expect with longer life, with just cardiovascular problems from what we think may be this increased weight or at least this increased visceral adipose tissue.

But I just don't see a reason to put this on hold because of the IGF-1 level. I thought the

registry idea -- we deal with that in growth hormone for kids. That's what we've been doing for years with registries.

I think doing the long-term post-marketing study, for the reasons that have already been discussed, will be very difficult to do, although I did like Dr. Proschan's idea of the different doses. I think that would be at least a neat way where you could get patients to still buy into it and say, "Well, you're going to get the drug, you're just going to get a different dose."

But I can't see anything different than a registry or different dosing to check on that. But you're still going to look a long time for cardiovascular effects. You're not going to find this out in a year or two.

It's the same issues that we're talking about with the diabetes drugs. So I don't see it as being a problem today, but I would be more than happy to be told I'm incorrect somewhere down the line. But I think you need to at least put them on it long enough to -- or allow it to go through.

DR. MORSE: I like the idea of a registry, as well, and I agree with Dr. Goldfine. I think we would have to do a clinical trial. I actually think we could recruit one. I think if we enriched it, especially for lipodystrophic patients with the real full lipodystrophy syndrome, so visceral adipose tissue and dyslipidemia and possibly insulin resistance would be some issues with that.

I think we could recruit and I think it's the only way to address this cardiovascular disease issue. And there's enough patients, as much as they're concerned about body changes, they're also concerned about cardiovascular disease risk.

So I actually think most patients would understand the need for a placebo-controlled trial.

DR. DOBS: I think that a placebo-controlled trial is pretty unrealistic for a safety outcome, because of the numbers of patients that would be required over a long period of time. So although it's ideal, I think it's really impractical, either pre-marketing or even post-marketing.

I think I'm not that concerned about the

long-term cancer risk and I think what I've seen of some animal data, it looked pretty good. But some of these questions might be able to be answered backing up to a bit of a pre-clinical model, as well. And certainly, what Dr. Henderson said about a registry might be another way of monitoring this.

The cardiovascular risk is certainly a complete unknown. I have more of an uncomfortableness with the IGF-1 levels of not being sort of natural and the unknown of it more than any reality of it and would feel more comfortable if there were some stopping rules at the low end, maybe not waiting until 52 weeks.

I think the monitoring that the company recommended would be one good approach. But I would feel strongly that if there was a little bit more monitoring and development of stop rules, it might be helpful.

DR. SCHADE: I will comment on the cardiovascular risk. It's my belief anyway that a clinical trial is absolutely impossible either pre-marketing or post-marketing if you want a randomized

type of trial.

We've heard some of the problems, such as being able to recruit enough folks. The real problem with doing it is you have a cardiovascular risk that's relatively small compared to many other risk factors, such as hypertension, hyperlipidemia, et cetera, that all require treatment.

So for example, if you try to do a randomized trial and I then, as a physician, decide to treat the glucose intolerance, then all of a sudden I'm suppressing your endpoint. In other words, no longer do you have diabetes.

So the concept of a randomized trial is that both groups don't change their treatment. And if anybody looks at the treatment of any of these big risk factors for the last five years, the recommendations for treating, for example, LDL has continually dropped. Now, we're down to 70 milligrams per deciliter, where it used to be up at 130.

These things keep changing. In fact, even the diagnosis of diabetes has changed in the last year. So what you treat and what you don't treat has

changed. So there is no way, because medicine is moving so quickly, to hold the two groups the same for five years. It's an impossibility.

So what I would recommend is a post-marketing observational study where you follow people for five years and then divide them into quintiles or quartiles, whatever you like, and then look at your highest and lowest quartile and you do the appropriate statistics to see if there's a difference between high IGF-1s or diabetes or whatever you want.

But it's going to be absolutely impossible to do a randomized control trial for the fact that the treatments for all the risk factors, which you have to treat. You can't let hypertension be hypertension. You can't let hyperlipidemia be hyperlipidemia. And you can't let diabetes be diabetes without treating.

So you're suppressing all these risk factors, and then you're trying to see the effect of a very small A1C of 6.5, which is miniscule compared to an A1C of 9, on the outcome. It's just not possible.

DR. BURMAN: Thank you.

Before I summarize, Dr. Parks, further

comments?

Then let me summarize this question, again, a difficult task.

But it seems like the consensus of the committee, and I'd like your approval for this, is that the risk of cancer is low, but real, and the patients need to be monitored and have IGF-1 levels.

I will remind you that the company proposes that patients who have an IGF-1 level greater than 3 standard deviations after one year will be removed from the study. I think that's important.

There was also discussion raised by Dr. Rosebraugh about whether there can be a prospective study, and there's a difference of opinion in the group, with some members thinking that it's possible, others thinking it's less likely.

But in any case, if not possible for a prospective five-year study with hard outcomes, then it would be reasonable, as Dr. Schade just mentioned, for a retrospective study, observational study, dividing the group into different quartiles or quintiles and seeing what the risk of cardiovascular

disease is and of cancer.

The growth hormone should be measured, as well as IGF-1. I think there was a suggestion that there should be a time limit for this agent, even if the IGF-1 levels remain within the proper level, and that there has to be a registry for monitoring these patients in a very meticulous fashion.

Anyone have any modifications? Dr. Thomas?

DR. THOMAS: Not a modification, but I would like to have some comment from our FDA colleagues about this, this issue about a randomized trial, is it feasible or not.

I echo Dr. Veltri. It's really schizophrenic to hear we can't have a trial, because it's too many patients. It's too expensive. There's too many factors to modify. And yet that's the demand now for all diabetes medications, pre- or post-marketing, for approval, to have a randomized trial to look at that for cardiovascular risk.

So if we're looking at VAT as a cardiovascular risk surrogate, it seems inconsistent to say that we could not do a trial for factors like

population number, too difficult to do, pre- or post-. There's an inconsistency and I think it would help, at least for me, in clarifying how I'd vote at the end, to hear what your thoughts are.

DR. ROSEBRAUGH: Yes. I wanted to introduce in to you all's thinking, because I had several comments about trials and it sounded to me like people were mentioning post-marketing trials and randomized trials.

So I wanted to be part of the conversation what the practicalities of that are or aren't, particularly when you're approving the only drug that would be used for a quite devastating problem. And I wanted people to specifically think about that in the context of it's okay to tell us we ought to do that, but can we do it or not.

So I wanted to kind of hold you all's feet to the fire and say do you think you can do it or not, is it ethical or not.

Now, Dr. Parks and I were kind of having sidebar conversations as we were hearing this, because we were going, you know, this is going to be kind of a

tough trial, particularly if you're not allowing diabetics in it and that sort of thing, because you have to have events and it's going to last for a while and will people really be randomized.

But we did hear quite a few very useful comments, I thought, about if we were to pursue that, how we could do it. Am I going to tell you whether we can do it or not? No. You're supposed to be helping me with that. That's why you guys are here.

The one thing I did want to mention, there did seem to be a little bit of confusion on this being a trial to evaluate for harm. In reality, if you are trying to see if VAT is a surrogate or not, then this really isn't a trial for harm. This would be a trial for benefit.

Dr. Parks, anything to add?

DR. PARKS: Yes. I actually wanted to touch on that, because up until this point, when I heard several members of the panel suggesting a cardiovascular outcomes trial, my assumption was that your hope was that this was going to be a cardiovascular risk reduction trial, demonstrating

superiority or benefit.

It wasn't until Dr. Rosen mentioned that it's not to show harm, was to demonstrate no harm, and, perhaps not right now to answer, but perhaps when you get to the voting questions, because it's going to have to revisit the issue of the design of a cardiovascular outcomes trial, if members can discuss what their intent is here, because clearly, if the thought is to show no harm, the design of the trial is very different from a superiority trial.

The issues that Dr. Schade brought up may also play into what type of -- what the objectives of the trial are.

I didn't comment to Dr. Thomas in terms of what is it that the agency is asking here. I agree with Dr. Rosebraugh here that we're seeking advice from a panel of experts. The example of the diabetes drug development program was that for years, we were hearing that why isn't this being done, why don't we have these answers, and so we took it to an advisory committee to hear, is this something that's feasible, a two-day advisory committee.

So consider it that this is the same situation. We're hearing from several members today a cardiovascular outcomes trial should be done, but we need a follow-up on that. It's not just a matter of saying a cardiovascular outcomes trial should be done.

We want to hear, where you've made that suggestion, is that feasible.

DR. BURMAN: Thank you. It's 3:15.

DR. SCHADE: Can I just, before -- I hate to interrupt you, but am I permitted to disagree with the chairman?

DR. BURMAN: I hear it all the time. I'm always disagreed with.

DR. SCHADE: I would just like to raise the issue about a time limit on this drug. I'm against putting a time limit on, because I can foresee treating a patient with this drug, them having a wonderful response, and then after three years, I have to tell them that they no longer can get the drug, because we know, within a few weeks, they'll go back to their original state, and the patient asking me, "Where is the data that suggests something bad is

going to happen to me if I discontinue the drug," and I have to say, "I don't know of any data, but the FDA told me to do it."

As a physician, I don't want to be in that position. I think there are some drugs, and we use them in endocrine, that do have time limits, because they've been shown, this drug, to cause cancer in animals after a couple of years. That's different.

Here, I haven't seen any data that we are going to get into a bad situation and I'd rather follow, do this prospective follow-up, post-marketing study, and if something comes up, say, okay, a time limit.

But I think it would be a mistake to put a time limit on this drug for that reason.

DR. BURMAN: Thank you. Of course, we want open discussion of all types, and that's very helpful.

The issue now is it's 3:15, and the last question, the voting question, of course, is the most important and we want to spend an hour on that question.

So we have 45 minutes and we're going to

combine Questions 3, 4 and 5, because they're very similar. We're going to read them and then start with Dr. Veltri and go around quickly. And we need to do this in 45 minutes, to comment on the clinical relevance of visceral adipose tissue reduction with Egrifta in the HIV population.

Then question number 3 is with respect to cardiovascular risk reduction. Question number 4 is with respect to patient-perceived benefits. And question number 5 is with respect to adherence to antiviral therapies. And we're going to combine those in a manner hopefully that will be more efficient. And then we'll have an hour for the voting question.

So, Dr. Veltri, would you mind starting?

DR. VELTRI: No problem. Well, I think the sponsor and the FDA have both concurred that the data on VAT reduction into two trials was positive and you combined them. And, clearly, it's beyond 8 percent. So that's there. That's clear, I think.

In regards to the respect to cardiovascular risk reduction, as we've said, that is a surrogate. And I think, Mr. Chairman, you said surrogate of a

surrogate, and that's probably correct. And there's no data there. And therefore, I can't really comment on whether that's good or bad or indifferent.

In regards to the patient-perceived benefits, I think that although there are maybe inconsistent statistical measures there and there may be a modest effect, I think there is an effect there and there certainly is a correlation with VAT and those patient responses, although modest, at best, I think.

Finally, in regards to adherence to antiretroviral therapies, I don't think I've seen enough data to really conclude that the VAT itself reduction is correlated to adherence. I just haven't seen that data.

There were quite a lot of slides there, but I don't think I saw any data that specifically addressed that.

DR. CARGILL: I can do this succinctly. First of all, in terms of with respect to the reduction of visceral adipose tissue reduction, as has been said, and we've seen the data, that the 8 percent

was previously agreed upon and the sponsor clearly exceeded that.

Secondly, in terms of respect to patient-perceived benefits, again, while I think that the data are a little -- are not as striking as perhaps the 8 percent, I think there is the trend that we've seen. There has been some, what I would say, "modest benefit" and then, in addition, what we've also heard in open testimony.

Then, third, in terms of adherence, I think that the data that we saw were potentially difficult to interpret, since we had some suggestion that people, perhaps even after they had a response, may have become less adherent.

Certainly, I think the literature on this would tend to support that adherence to antiretroviral therapy with the problems of visceral adipose tissue are suggested, but are, shall we say, confounded by other factors, since adherence in them itself is a complex issue.

MS. SWAN: It's hard for me to comment on number 3, because I don't think we really know what

the link is and that we need to explore what the clinical relevance of VAT reduction is going to be, and that that's very important.

As far as number 4, the clinical relevance, in the HIV population, I think there could be few things more difficult for someone to deal with in feeling like they have lost control of their body and that despite their efforts to do things to maintain their health or improve it, it's not paying off; and, that anything that makes you feel like you're using something that can be synergistic with your self-care efforts and show you a benefit can't help but help.

That's extremely important, and in a way, that's deeply linked to adherence. And I can't show you research results. But I can tell you, I've talked to a lot of people who say, "I don't want to start on those drugs, because everyone will be able to look at me and know that I have HIV."

So the issue is not just staying on them once you've started. It's even seeking treatment when you need it. And particularly now that the treatment guidelines for HIV are starting therapy at a higher

threshold, it may be more likely that people will develop this sort of complication. And there's a huge benefit to letting people feel like they can make choices to have control over their health.

DR. MOLITCH: I think I've stated before, the relationship that I think of VAT to cardiovascular outcomes was sort of the major reason to do the study to begin with, is my understanding, the link to cardiovascular disease and I just think that that link has been broken here because of the changes in glucose that occur with the growth hormone increase.

So I think we just don't have any link here at all at this point and I think that would need hard outcomes. So I don't think that it's there for that one.

I think, clearly, the patient response as far as their physical benefit as far as reduction in waist circumference and the fat deposition probably is quite real, and my guess is that there's a wide spectrum of responses.

So that instead of looking at the overall average, you probably have some patients that are

losing 10 centimeters and others that are not, and you may have some people that are very, very responsive. So I think that that could well be a very good reason to have this drug available for such patients. And clearly, look at responders and if somebody is not responding within three to six months, then that may be a time to stop rather than going on for a year blinded to IGF-1s and all these other type of things.

So I think there clearly is a link to the physical changes and I don't think there was sufficient data presented for number 5 to look at the adherence to antiviral therapies. I don't think this study provides that data, at least that I have seen.

DR. KUMAR: Clearly, the data showed that it decreases visceral adipose tissue, but I want to make a couple of comments on that. Even though Studies 10 and 11 had the same kind of patient population, I was a little surprised that the difference in the visceral adipose tissue decrease was quite different in the two. It was minus 19.5 percent in Study 10 and minus 11 percent in Study 11.

So I really don't know, in a bigger clinical

practice, what really is going to be the decrease in visceral adipose tissue. There's no data that was presented that in any way created the link between the reduction in visceral adipose tissue and cardiovascular risk, and many other panel members spoke to that, and so I'm not going to say anything further regarding that.

But I would like to comment on some of the patient-perceived benefits. I didn't see any data presented regarding -- other than that was very articulated by -- very articulate presentation, I saw nothing presented regarding buffalo hump or other parts anywhere else other than in the abdomen. I didn't see any of the data.

I also want to make the point that when patients complain of how disfiguring treatments or overall the synergy between HIV and treatments can be, again, as a clinician, I want to remind myself that there's no data on this regarding where lipoatrophy is concerned. And in many ways, that is as disfiguring as lipohypertrophy is, and there is nothing in this data that it changes lipoatrophy.

Yes, it's very important to recognize that the drug that we are looking at doesn't worsen subcutaneous atrophy, and I think that is excellent that it doesn't decrease it, but there's nothing that says that it in any way improves lipoatrophy, which is equally, equally bothersome to patients.

So there's nothing in anything that I am seeing here, that as a clinician, that I can say that this is going to improve antiretroviral therapy or want patients to start antiretroviral therapy or keep on therapy, because it does nothing to the other component that is equally disfiguring.

People said when they go to the gym, they want to make sure nobody knows that they're HIV-positive. It is very true, but it does nothing to the other equally component that is lipoatrophy, and I want to be able to say that.

DR. BISHOPRIC: Well it's been said many times about the lack of correlation between really hard data about the removal of visceral adipose tissue and cardiac benefit, but maybe one day the cardiologists will thank us for having looked at this

question. So it may be irrelevant, but in the future, it might be more relevant to another group.

I think that the level of suffering for people who have this disease was really well delineated by our two community speakers and I thank them for that; the degree of suffering, isolation and misery produced by this is really -- I don't think we've touched on it enough. And so I think that it has an enormous impact.

I don't know how many people are noncompliant, because I think most people on therapy know that, at this point, drug switching is not going to get rid of it and going off will not get rid of it. But I do think there is an enormous reticence of people to start therapy because of being identified, because of not looking good, and just the sense of oncoming misery because of these drugs.

So I think that that has an enormous eventual impact on people actually starting therapy and then staying on it. Thank you.

DR. THOMAS: So for question 3, since visceral adipose tissue -- this issue about whether it

should be a trial for harm or benefit, since it's a surrogate marker, the ideal trial would be one to look at benefit, if you were just looking at visceral adipose tissue as the outcome.

At some point, that will have to be done, if not for this agent, for any other agent that comes forward that looks at reduction of visceral adipose tissue.

You could run this as a trial for harm, because there is a secondary benefit that's very important to the patients, which is the change in body appearance and body perception. So if that's important enough for patients to take the medication and you showed no harm, that would be okay, too.

I know the trials would be different. The numbers would be different in order to achieve whichever outcome you're doing.

But ideally, for the question, does visceral adipose tissue reduction improve cardiovascular outcomes, you'd have to do a benefit trial. But you could, because of the population having secondary benefit, could do a no harm trial.

In terms of question 4, they're statistically different. I was kind of surprised that the actual effect in appearance wasn't as great as I would have thought it might be.

But anecdotally, from the patients who testified earlier this afternoon, it clearly is an important issue. And I know from my own clinical practice and experience, it's an important issue. So I think that's actually a very meaningful factor to help patients going forward.

For 5, I don't see any data that was presented that's looked at this. We all have anecdotal stories or suggestions that there's a relationship. So that might be something worth looking at in a post-marketing study or at some point to see is this really helping with adherence or initiation of therapy.

DR. HENDERSON: As the consumer representative, I was very pleased to see that at least we had some data on patient perspective, because a lot of the applications have absolutely zero data on patient perspective.

That said, I'm grateful for that. However, the belly profile was not enough, and I think it was obvious from Deborah and Lisa's testimony that the belly profile is incomplete in what we were calling patient-perceived benefits.

This data didn't address the activities of daily living or the energy or the psychological wellbeing or the social wellbeing that Deborah and Lisa talked about.

So I'd really, really like to have more quality of life data in not just the next study that comes out of this, but in other drug applications, as well.

DR. ROSEN: So I want to just spend a little time on item 3, because I think we have a bit of confusion. I was just looking at the FDA definitions of surrogate markers and biomarkers.

I think what we have is that VAT is a surrogate marker of response to treatment, and that, I think, is defined by the FDA. So they looked at how visceral adipose tissue responded to this growth hormone-releasing analogue, and there was a positive

response. So that's a positive effect on a surrogate marker for treatment.

But I think VAT is really only a biomarker. It's not truly defined yet as a direct effect on cardiovascular events. We have yet to prove that it is also a surrogate marker for cardiovascular disease.

I think that's the rub. It's that, yes, they accomplished what they set out to do, which is often the case, with a compromise of an 8 percent, that they got to 15 percent. So they clearly were able to show that this is a surrogate marker for treatment efficacy.

The question that we're struggling with is what about VAT as a biomarker for cardiovascular disease, and we don't have the answer to that. And I think that's the missing link that Mark has been mentioning in the past.

We just are not able to make that link between being able to show that you did reduce visceral adipose tissue and you had a positive effect on cardiovascular risk. I think that's the major dilemma.

I haven't seen any data yet from this that says that this treatment has a positive effect on cardiovascular disease. So if we're going to approve a drug, we are really approving it for a surrogate indicator for treatment and as a possible -- as a biomarker for possible cardiovascular risk.

I think then you're treading on some thinner ice in terms of treating only a surrogate of a surrogate, if you want to call it that.

I think that the compelling data from the public testimony suggests that for item number 4, there is some clinical relevance to what has been demonstrated.

I think the problem is that the markers of patient perception are probably not very sensitive and I think that that's one of the issues that -- we looked at a number of different questionnaires and materials to try to measure how the abdominal girth is changing, and I think part of the issue may be in the measures, not in the fact that this is probably ineffective therapy.

So I think we have to be careful about

extrapolating and saying, gee, the curves are very close. Remember, you're using questionnaires that may not be as sensitive as we'd like them to be.

So I do think that there's probably some clinical benefit. And I don't know, because I really haven't been able to parse out, whether this improves compliance or not. So I think those are my brief answers to the three questions.

DR. FLEGAL: I think other people have already made some of these comments. But to me, there's this question of whether the increased cardiovascular risk in people with HIV is even due to visceral adipose tissue to begin with. We don't even know if that's exactly why this is happening.

Then we have a very indirect link here that somehow if this was -- I think, clearly, this drug reduces visceral adipose tissue, that seems pretty clear. Does it reduce cardiovascular risk?

Well, there's an awful lot of assumptions you would have to make. Why was the risk increased to begin with? What is the role of visceral adipose tissue? Is the link broken, so that biologically, the

improvement in risk you might expect from reducing visceral adipose tissue is not something we're necessarily going to see, just like the problem with diabetes.

I think there is some feeling that it's almost like a quality of life issue. The public testimony is very compelling and I respect, definitely, the people who testified, but we don't know how their experience would compare with other people's. And quality of life was not even a secondary outcome that's looked at, and quality of life assessment is a more complex topic to study in different ways; like, what about ADLs and so on.

In terms of quality of life, also, of course, there's the lipoatrophy, which may still reduce your quality of life, although perhaps in a different way.

So I kind of feel like we're a little bit flying blind in that sense. The most compelling thing is something that wasn't really even studied, and the links are very indirect between the action of this drug and any potential in cardiovascular risk and some

of the indications that it might actually possibly increase cardiovascular risk, not even decrease it.

So I feel like there's a big gulf between the things that are most compelling and the things that we have any data on.

DR. BURMAN: Thank you.

I'm going to pass, in the interest of time. It's 3:34 and we have an important question of the vote and we want to get there around 3:50 or 3:55, so we'll have a whole hour. So I'll include my comments in the summary and pass to Dr. Proschan.

DR. PROSCHAN: I'm not sure I have much to add to what's already been said. I think with regard to 3, we really don't know. Probably, but we really don't know.

With four, patient-perceived benefits, I think the case has been made for that. And number 5, adherence, I don't think the case has been made for that. It makes sense that it would be increased, but I don't think there's really that much evidence of that. So maybe.

DR. GOLDFINE: So, Dr. Rosen, I think that

the indication that they're going for is actually to reduce visceral adipose tissue. Therefore, I would say that they've clearly demonstrated this. That's not actually a surrogate endpoint then.

I think that they clearly demonstrated this by CT scan imaging, which is extraordinarily precise and reproducible, and they've been more difficult to quantitate that from the patient's assessment, because I think that's actually got a lot more variability in it.

If you think about the mean difference, and, clearly, there's a range, there are individuals who respond much greater than the mean and the mean. A kilogram of fat is about the size of your fist and 20 cubic centimeters is about 20 grams of fat. The 1.5 centimeter reduction would be about a belt tightening.

For individuals who have more profound disease, I think this makes it all very hard to quantitate and measure in the assessments that were actually able to be used. And that's why the magnitude of change, on average, may have missed that.

So I think from the lowering of visceral

adipose tissue that was set out to be done, I think that they clearly made it. The link we're being asked to make then is with respect to cardiovascular reduction.

I agree with Dr. Rosen that that visceral adipose tissue is now a real surrogate endpoint. And so the question is if we're doing this for their reduction in body fat or because we believe there will be additional benefit of the drug, and, for that, I think there can be a trial and I think it is looking at benefit.

I'm happy if a benefit-driven trial comes out with equipoise. I believe we can actually treat the other emergent issues as they come out. But I think that the question we are being asked is about whether or not there's potential cardiovascular benefit, and I think we have equipoise from the potential reduction in visceral adipose tissue and the potential concerns that are being raised by not seeing the metabolic benefits that we might have anticipated.

For the other two, I agree with everybody that we really didn't have enough data about the

adherence, and I covered the patient-perceived.

DR. FELNER: Like our chairman, in the interest of time, I'll save these comments for my final question.

DR. MORSE: I don't have a lot to add to what everyone else has already said. I would just say that I do think treatment readiness will improve with the availability of a medication for a toxicity like this. And whether it will impact adherence, I think, is unclear.

As Dr. Kumar said, with patients having lipoatrophy, that seems to be a major issue with adherence. We haven't seen a lot of evidence that that would change on this medication. Thanks.

DR. DOBS: So it seems clear that the drug will reduce VAT. Whether or not it's any better than good old exercise, as we've been told several times, has not been proven, although part of me feels it probably would be equal to major, intensive lifestyle modification.

The basic question about whether or not reducing VAT really makes a difference for

cardiovascular disease could be answered in this study or could be answered in a non-HIV population, as well.

It is too bad that it seems to not have had an effect on some of the other stigmata, because I'm concerned that the abdominal waist circumference could be just mistaken for obesity. So I think there has be some clear delineation there.

DR. SCHADE: I don't think we have enough data to comment on three or five. I do think, from what we heard, that there is good evidence that some of these patients really benefit psychologically, because it does decrease VAT.

This will not be the only drug for this indication. Twenty years ago, I only had a sulfonylurea, and now I have lots of drugs. None of the drugs I have are very good, but I can combine them and do things with them.

That's what we need to do. I think we need to start giving physicians drugs to treat these conditions that are very worrisome to patients, and I strongly would support a yes for number 3 that, in fact, at least data to the contrary that we haven't

heard, that patients' perception and a decrease in VAT is a real benefit for these patients with HIV.

DR. BURMAN: Thank you. Thank you all. Let me summarize, to the best of my ability, and open this for discussion, if you agree or disagree.

With regard to question 3, clinical relevance of VAT reduction in the HIV population with treatment with respect to cardiovascular reduction, as was pointed out, decreasing VAT was the goal -- the primary objective of the study, and this was accomplished. I think everyone agrees.

The unknown link is how this relates to cardiovascular outcomes, and that needs to be studied further.

There was discussion whether there should be a trial and whether that trial should be a benefit trial or a no harm trial. As was brought up, there seemed to be some discussion regarding that, that the cardiac outcomes in relation to that are speculative at the present time and that everyone agrees, for this question, as well as question 5, more data is required.

With respect to question number 4, which is the clinical relevance of VAT reduction by treatment in HIV patients with respect to patient-perceived benefits, there seemed to be consensus and appreciation of the patient testimony this afternoon, that was quite impressive. That perceived benefit seems to be important.

It is mainly, as Dr. Kumar pointed out, on lipohypertrophy, not on lipoatrophy, which needs to be studied, as well. The tools that study body perception were used and showed that there was a benefit and this has a benefit on the potential daily living and psychiatric outlook of these patients.

There was a discordance between the small quantitative changes in waist circumference and the perceived benefit that was obtained in the questionnaire, and that we need further information regarding other psychological aspects, such as body image, such as quality of daily life and psychological profile.

With regard to question number 5, commenting on the clinical relevance of VAT reduction with

Egrifta, with respect to adherence to antiretroviral therapies, compliance is an important issue.

Compliance does not seem to have played a major part in the VAT impression and in the VAT changes. There was a suggestion that the potential effect of noncompliance on the IGF-1 data -- for example, in Study 10, the noncompliance was found in 26 percent of patients, while, in Study 11, it was 39 percent.

This suggests that in compliant patients, IGF levels may be even higher, although that is not known. But there seemed to be consensus that compliance did not play a major role in the findings that were seen.

Any comments or modifications of that? Then thank you all.

So now let's move to the most important issue, of course, which is the final question and the voting question. And let me get my notes here.

The question is, "Does the overall risk-benefit assessment of a fixed dose regimen of Egrifta, tesamorelin, 2 milligrams per day support its approval

for the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy?"

We're going to vote yes, no, or abstain. If voting yes, please indicate and discuss the basis for this recommendation. Discuss whether any recommendation should be made in regard to duration of use, targeted population, and safety monitoring. Please discuss whether any additional studies, including cardiovascular outcomes trials, should be conducted post-approval.

If voting no, please discuss basis for this recommendation. Please discuss what additional studies, including cardiovascular outcome trials, would be necessary to address deficiency or deficiencies.

So the question in front of us now is, "Does the overall risk-benefit assessment of a fixed dose regimen of Egrifta, tesamorelin, 2 milligrams per day support its approval for the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy?" Voting yes, no, or abstain.

I'm going to read how we're voting and then

open the floor for any final questions of clarification before we vote. We will be using the electronic voting system for this meeting. Each voting member has their voting buttons on your microphone, yes, no and abstain.

Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. I will read the vote from the screen into the record. Then we will go around the room and each individual who voted will state their name and vote into the record -- and record their vote into the record, as well as the reason why they voted as they did, and, hopefully, we'll discuss the issues that were just mentioned.

So let me open the floor up for any pressing questions regarding the voting system itself or any critical questions regarding any of the issues that you want to bring up before we vote. Okay. Surprising.

So I think we're ready to vote. It's flashing, so just lock in your vote.

DR. TRAN: Please press firmly on your choice. If you're not sure, you can press it again.

(Voting.)

DR. BURMAN: Reading the vote into the record, there are 16 yes votes, zero-no, and zero-abstain. What we'd like to do now is go around the room. If I'm not correct, it's Dr. Veltri -- I'm sorry -- Dr. Cargill, yes.

If you would read your name into the record, give your vote, and then discuss the issues that were brought up.

DR. CARGILL: Victoria Cargill. My vote was yes, for the following reasons. The indication sought for Egrifta, reading directly from the record, is indicated to induce and maintain a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. The sponsor clearly met that.

Additional reasons are because there is no question that this condition does cause, as we have heard, a fair amount of psychological distress, as

well as difficulty in functioning. And while we do not have absolute compelling data, we have data that suggests that Egrifta is helpful in this regard.

Moreover, these have been associated with depression and depression has been incontrovertibly associated with poor adherence and poor outcomes and disease progression.

Secondly, the recommendation with respect to duration of use, I think that we will need to use markers, because there are going to be individuals for whom this therapy will, as we have already seen in the data, be problematic, such as glucose intolerance.

With respect to questions that were raised by FDA around the types of monitoring, I think that we can look at this in several ways. What I was struggling to articulate earlier, and I apologize, was the whole idea of a registry. I'm glad that it was raised and someone could actually be coherent. That is one way.

The second is an observational cohort, but I would say that would be somewhere to take a look at not only a factor such as glucose and hemoglobin A1C,

particularly given that the population that was studied does not completely reflect the population that's heavily impacted by the epidemic; but, thirdly, because we have questions around quality of life and activities of daily living.

Thirdly, then a study to also allow us, if it's observational -- or it could be dose-ranging -- to study cardiovascular risk factors and benefit. And that was the reason for my vote.

MS. SWAN: Tracy Swan. I voted yes for all the reasons that Dr. Cargill just stated, and, additionally, because there's no other treatment for this condition.

I think I've been intermittently giving a long list of studies. I'd like to see the one I haven't mentioned, an induction maintenance, maybe starting at the 2 milligram dose and going down to 1 milligram dose to see if you can preserve all the benefits and perhaps lower some of the risks.

I would like to see a minimum of five years of follow-up and a very diverse cohort enrolled in what will either be a randomized control trial, an

observational study, or, hopefully, one of each.

Thank you.

DR. MOLITCH: Mark Molitch. My surprising yes vote. Clearly, it did reduce abdominal fat. I'm impressed with the patient disability and perception and benefit that they received along this, and my guess is that there are some people who are major responders and there are some people who are non-responders to the medication, giving an average value that's not terribly great.

I have a lot of "buts" here that I think should be incorporated in the future. One is I think that, in fact, people know within three months, it looks like, whether they are responders or not as far as a decrease in abdominal fat. And so I think that there should be an initial assessment at three months to decide whether people should go on to future therapy or not.

I think that IGF-1 should be monitored over the course of treatment and that there should be an ability to reduce the dose to maintain IGF-1 levels within that 3 standard-deviation mark and perhaps even

2 standard-deviation mark. Very concerned about the whole idea of one assay business and why the IGF-1 patients should be different from so-called normal individuals. That bothers me a lot and needs to be addressed separately as a side issue.

I think the issue with regard to cardiovascular outcomes is certainly not shown at all. And whether there's an adverse cardiovascular outcome or a benefit in cardiovascular outcomes, I think we don't have any clue at this point in time, but deserves study and should be studied over the course of time, whether this is through some registry or through some prospective placebo-controlled trial, which I kind of prefer, but may be difficult to do.

But that clearly does need to be done for this study, because it does have potential risks and, again, a cancer registry for these patients, as well, should be done in the future.

DR. KUMAR: I am Princy Kumar, and I voted yes, for the reason that the sponsor, in two very dense studies, did show that their primary endpoint in decreasing adipose tissue in patients with

lipohypertrophy.

However, I would like to add a couple of caveats to that, and the first is under no circumstances should this yes vote be taken to imply that in any way I believe or agree that there's any cardiovascular benefits associated with that.

It's not proven, it's not shown, we do not know, and there has to be some way in which we will be able to understand the cardiovascular risk, especially in our patient population that, in this era of HAART, has increased cardiovascular mortality.

The second thing that I would like, as a clinician, is more specified criteria on which patient -- at what point and what measurement can we do, in practical terms, to say, "You are not going to respond. They have given it to you for so many months."

Is it three months? At that point, you're not going to respond any further. It's a waist circumference decrease of how much?

So I really would like, as a practicing clinician, very, very concrete criteria on when to

stop. So those are things.

How can we look at long-term cardiovascular? I really don't know. I think it will be very -- I would like, clearly, a prospective study. I don't know how practical that's going to be.

At a minimum, having a very kept registry would be, at the barest minimum, what we need to do.

DR. BISHOPRIC: I'm George Bishopric. I voted yes, because I felt the company clearly met the target of 8 percent and I felt that the degree of suffering that these patients experience and the fact that there is no other agent warranting approval.

I also feel that the 19 percent and 11 percent decreases in visceral fat probably underestimate the visual improvement that patients see. And those hard numbers were a lot more easily to evaluate than these soft numbers from surveys that looked closer together.

So I felt that the measurements we gave probably don't give a sufficient impression of how good the result can be in many patients.

As for follow-up, I think everyone has

covered kind of the cardiovascular, that we all want some kind of follow-up for that and probably for the IGF, and these will have to be done in some post-marketing studies.

I'm very happy that it passed.

DR. THOMAS: Abraham Thomas. I voted yes. And what I'd like to just say, as other people brought up, this, in a way, was an easy decision in terms of what we were asked from the actual data.

The sponsor was asked to show a reduction in visceral adipose tissue. They did that. They showed a change in the perception or improvement in patients' opinions on treatment in terms of their body morphology and psychological -- well, maybe not psychological stress, but just in terms of their appearance.

So that's what they were asked to do. They did that very well in a series of clinical trials that were very supportive of that.

To paraphrase Nelson Watts, who was a former chair of this committee, he says it many times. "When there is not evidence-based medicine, there is

eminence-based medicine." And everything else pretty much we were asked to do, there is no data, not just in HIV, but in any area.

So, of course, we really can't comment and all you've heard is really just our opinions and conjecture. So to find those answers, you're going to have to do trials or registries to see what's important.

Now, maybe it doesn't have to be in the HIV population. The lipodystrophy and atrophy is so devastating to these patients that if you couldn't recruit the proper number of patients for a randomized trial, my personal opinion is that's okay, because the appearance that they get with the medications, that's sufficient enough. The benefit from improving that is sufficient enough to probably outweigh, in the opinions of the patients, any potential harm that they do.

I don't think there should be a restriction on duration of time, because at least as far as we know, when you stop the medication, the benefits go away.

Finally, I harped a lot about diabetes and the risk factors before diabetes, but I'm going to say something that seems a little strange. I don't think we should be restricting those people who have diabetes.

If someone has diabetes and they're well controlled, I think they should have an opportunity, because they're suffering the same psychological issues with body image and identification in their community of being on HIV treatment.

There is a benefit on lipids, which really wasn't talked about too much, just briefly, and we don't know all the risk factors for cardiovascular events. There's glycemia, there's blood pressure, there's lipids, and if you get a benefit of reduction lipids that are favorable cardiovascular-wise and their A1C is 7, who's to say that's worse than never starting the medication at all when they get positive body imaging effects.

So even though the sponsor is saying that they're not going to give it to diabetics, I actually think it's probably okay to give it to patients with

diabetes who are under good control.

DR. HENDERSON: My name is Jessica Henderson, and I voted yes. Clearly, the VAT reduction was shown. And my main reason is for quality of life. Even though we didn't have hard data on comprehensive quality of life of the patients, I think we can assume that that was true for many of the patients, that their quality of life was improved.

We have precedence with that with hormone replacement therapy, which also has increased risk for heart disease and increased risk for cancer, but yet we will allow women to make that choice of quality of life. I think that's important.

My favorite suggestion for labeling was that non-responders be taken off the drug after 28 weeks.

DR. ROSEN: I'm Cliff Rosen, and I, surprisingly, voted yes. And I hate surrogate markers, but, actually, the target that they were asked to achieve is 8 percent reduction in visceral adipose tissue, which is a surrogate for abdominal fat, and they did it.

Surprisingly, in the short-term data, there

are few safety issues. So I didn't feel uncomfortable. Somebody mentioned earlier that this is not a hard choice when you look at what you were asking us to do.

The harder questions really are what should we do, if this drug is approved, in terms of follow-up. I'm very concerned about IGF. I think that I would agree that if the short-term responders are non-responders, then they probably should come off the drug.

There's going to have to be some way or some labeling that's going to have to be put on about frequent following of IGF-1, because I think that's going to be a long-term issue that will not be resolved. It's currently hypothetical, but it certainly raises enough concerns that both the patient should be aware of it and the prescribing physician should also be aware of it.

So either a registry or something that's going to allow for a longer-term follow-up if a person is committed to this kind of therapy. So I am actually comfortable with my decision.

DR. FLEGAL: We're glad you're comfortable with that. This is Katherine Flegal, and I also voted yes, again, for the same reasons. They hit the target. I think this should be approved for something for which there's no other treatment, which can impact quality of life.

But I also would concur with the previous statement that this does not mean that -- that this should not be taken as an endorsement of saying that reducing VAT will reduce cardiovascular risk, because that really hasn't been shown.

I think at least some clearly defined follow-up to the risk management plan made sense, and a registry, at least, to see what the experience is is very important.

DR. BURMAN: Ken Burman. I voted yes. I actually found this a difficult decision. We recognize the importance of insulin resistance and cardiovascular disease in this population, but on the other hand, there is little evidence that the surrogate we're using has a direct or indirect link to cardiac endpoints.

In the cardiac outcome trials, it would be important that I recommend that it would be important to measure apoB as well as LDL particle number and size, as well as non-HDL. It would e relevant to compare the effects of the agent on lipids and insulin resistance against more standard therapies, some of which they had been on.

The beneficial effects of tesamorelin in decreasing triglycerides was small and variable. It was 52 milligram per deciliter in Study 10, which was significant, and 19 nanogram per deciliter in Study 11, which was not significant.

Statistically significantly more patients in the tesamorelin group developed diabetes and had an increase in their A1C, but I think, as mentioned, that can be treated.

The long-term effects in these patients of raising IGF-1 on aggravating the growth of colon polyps and cancer, as well as other tumors, as well as on cardiac structure and function, as well as on Kaposi's sarcoma, a largely unknown; the effect of inducing glucose tolerance in diabetes needs to be

1 further analyzed, and the long-term effects of GHRH
2 antibodies are unknown.
3 There is also a controversy regarding the
4 relative importance of visceral fat as compared to
5 hepatic fat, which hasn't been measured in this study.
6 And it's disconcerting that discontinuation of
7 tesamorelin resulted in a return of visceral adiposity
8 and insulin resistance.
9 On the other hand, the benefits of the body
10 image and the testimony of the OPH shouldn't be
11 minimized, specifically, discussing further, I think,
12 that consideration should be given to a time limited
13 use, or at least the post-marketing study results, if
14 they come out, should modify that use.
15 With regard to specific trials, I think the
16 testimony from ATAC was quite impressive and their
17 document was impressive. They recommended, and I
18 agree, that there should be Phase 4 studies assessing
19 the relationship between decreasing VAT with
20 cardiovascular and cerebrovascular endpoints.
21 Studies should also address other
22 parameters, such as quality of life, pulmonary

function, sleep apnea, as well as liver and cardiac abnormalities. The benefits of additional synergistic measures, such as exercise and diet alteration, should be studied.

Gender specificity and other populations should be studied. And as already noted, CT for VAT assessment is not going to be clinically available. So we have to use a surrogate, which is waist and hip circumference.

Lastly, there should be a study assessing the benefits of tesamorelin as compared to standard therapy, including the synergistic use of dietary modification and lipid treatment.

But overall, I think the advantages of the medication of meeting the goal of decreasing visceral adiposity was accomplished, but I certainly have many comments and potential restrictions in the application.

DR. PROSCHAN: I'm Michael Proschan. I voted yes. I think, like other people said, the company did what they were asked to do. They showed clear benefit on the primary endpoint, and I think

everyone knew, including the FDA, going in, that there was really no way they would be able to show benefit on the cardiovascular outcomes.

I also think that they, overall, showed benefit on some secondary outcomes that may also have a benefit. Of course, there were a couple of concerns, but the diabetes concern, I think, is there, but I do think it's a small impact and I think that that can be managed.

To me, the fact that they showed benefit, basically, psychologically, that's important, I think. I think some of the worst pain that we experience is psychological. So if you can improve someone's outlook on life, I think that's very important.

DR. GOLDFINE: Allison Goldfine. I also voted yes. I think that they laid out a development plan and they demonstrated quite clearly that they met what was in the development plan, and that was very important to me.

I think that there is no other treatment available, and there is equipoise for risk. So I don't take lightly that things were revealed that have

potential signal, but there was also potential benefit, and I think the equipoise was very important.

I would like to say that I also agree that people show that they are responders or not responders by a reasonable timeframe and that that would be a reasonable point to potentially suggest additional studies. If you have a non-responder post-marketing, one might want to look at those individuals separately, because the rate of gain may actually be different.

So while you're not necessarily seeing decrease in visceral adiposity in those individuals, they may have less gain. And so that would be an area that they could potentially explore further.

I don't think there was adequate minority coverage, which was a little surprising given the prevalence of HIV in minority populations. And I feel very strongly that we are having an assumption that the reduction in visceral adiposity will actually be above and beyond the psychological benefit, which is what I think is very important.

I think that we should consider some

labeling that the effect of the decrease in visceral adipose tissue on cardiovascular outcomes has not been established. I think it would be reasonable to add some of the caveats about what long-term exposure to excess growth hormone may be from patients, for example, who have acromegaly. And you may want to limit the fact that while we cannot completely extrapolate that to this population, these are reasonable things to be monitoring for considering.

I think a registry is absolutely essential, as a minimum, because once one goes beyond the clinical trials and the Phase 3 development to marketing, patients won't have the same inclusion-exclusion criteria nor are their visits scheduled monitored as closely.

So the registry becomes very important for that reason, but I actually think that there is an enormous leap, that we are actually doing something for cardiovascular benefit. And, therefore, I would really like to see a benefit trial and I think that that is actually feasible, although there's been some dispute about that from the group.

I think that the reason, also, that there are these potential risks that have many of us concerned makes this a very important thing to be doing.

DR. FELNER: Eric Felner. I voted yes. Most of what I based my decision on was what many of you spoke about. I think it was interesting that questions one through five were about 1,000 times harder than question 6.

We deal with this, a lot of times, wanting to change the question that we're supposed to be voting on, but this was very simple at least just to answer the question that was asked.

I think that if you actually based your last answer in the voting question on the first five choices, I think most of us would have put no, because most of these questions were not -- the answers were no, if you looked at it very objectively.

I think that I'm actually happy that this was approved, because I look at this from the diabetes standpoint. I actually look at this outside of the HIV population, because I see almost no patients with

HIV. But I see a lot of kids that are obese. I see a lot of kids that already have Type II diabetes that are already making their way to having a very difficult life with diabetes and obesity.

Here we have something that has been proven to reduce, at least in a year, reduce this visceral adipose tissue, which I believe, even though it hasn't been proved or disproved, its relationship to cardiovascular disease in any form, but I think that is the real key for all of our obese patients and all of our diabetics, that if you can lower that -- there's no drugs that do it, other than this one.

Exercise does it, but we know how well that goes along with our patients. But I think that's a tremendous benefit that we'll learn from other fields, not just the HIV population, but what you can do from the visceral fat.

I guess the other thing, I do like the idea of the non-responders. I looked at that, but I think it took somebody a lot smarter than me to actually make the comment, so I would jump on board. But I think that's a great answer for these patients in the

first few months that don't respond. Get them off the drug.

But looking at this from a registry I think is the easiest way to do it, probably the best way to do it. And, again, I have familiarity with our growth hormone registries and they seem to work pretty well for identifying long-term side effects.

DR. MORSE: I'm Caryn Morse. I voted yes, for the same reasons as the rest of the group. I think the sponsor demonstrated reduction in visceral adipose tissue, patient benefit, and there's a niche, a clear need for this.

I don't think there should be any limits on duration and agree that we need guidance for clinicians on when it's appropriate to stop or how to manage patients that aren't responding.

I'd also like clear guidance for clinicians on how to distinguish which HIV patients would really benefit from this. It is sometimes difficult to distinguish the just obese, overweight patients from the truly -- true patients with lipodystrophy syndrome. So helping us with that, and then how to

sort of monitor patients.

What's going to be the appropriate interval for monitoring for the sugar things? Does everyone need oral glucose tolerance tests? And then stopping criteria, as well. And I would like to see a prospective randomized controlled trial looking at cardiovascular disease benefit.

DR. DOBS: My name is Adrian Dobs, and I voted yes. I did so because I think that overall, the risk-benefit ratio was clearly in favor of the benefit.

I do think that there needs to be a fair amount of education to go on here for physicians to ensure that they're using it for HIV lipodystrophy, with increased waist circumference, and not for generalized obesity.

I also think that they should not exclude a well controlled diabetic, since it may be helpful in that realm, as well. I think there is an opportunity here to really understand some basic physiology about the effect of VAT, whether it be a biomarker or as a physiological direct effect.

That could be studied with either the large clinical trials that we've been discussing or the more intensive patient-oriented studies, and that could be in an HIV or a non-HIV.

Is there a role of this medication for just patients with elevated VAT who are at risk for cardiovascular disease? I think that, obviously, that's an exciting question that can't be answered at this present time.

The monitoring, I think I would feel more comfortable with IGF-1 levels being measured sooner than one year. I think I'd also be more comfortable to set a goal. There may not be data to say this yet, but if one could reanalyze it and think in terms of that maximum effect -- I know it didn't correlate that well, but maximum effect for VAT was attained t maybe high normal or within 2 standard deviations of IGF-1 levels, I think I'd feel more comfortable.

I think there clearly needs to be a sense of stopping the medication if it doesn't work and trying to delineate and educate physicians on what would be that criteria.

DR. SCHADE: I'm Dave Schade. And I voted yes, because I think that the risk-benefit ratio is greatly in favor of benefit. And I pretty much agree with what the panel says.

I think the company did a very nice job of presenting their data. I think they did a terrible job of giving any type of firm recommendations to physicians on how to use this medication.

That may be because they felt they'd be overstepping their bounds or whatever, but I would strongly recommend that Dr. Molitch, with his great influence, contact the Endocrine Society -- I'm serious -- and the Endocrine Society should come out with recommendations on how to use this drug.

There are at least three issues they need to address, and one of them is what do you do with a patient who continually has IGF levels that are greater than 3 standard deviations above the norm, because we're all worried about that group.

I think the Endocrine Society needs to clarify what they do about patients with diabetes. Now, what I would favor, of course, is if this drug

does not cause deterioration of the glucose control, the it ought to be used in patients with diabetes.

I think we should not exclude patients with diabetes. The reason I think we didn't see any of that data presented is because diabetic patients were excluded from their scientific studies. But I think patients with HIV and diabetes should not be excluded from using this drug.

So I would recommend that the FDA not include any language about excluding diabetes. They can certainly say that there is no data supporting the use of this in diabetes, but I would hate to see all my diabetic patients potentially being excluded from this medication.

The third, even bigger issue is when and how do you deal with patients who don't respond, because I'm concerned that physicians will continue prescribing this medication for years, even if there is no response, because there's no direction on how they should monitor it and at what intervals they should use it.

So I think there's a lot of physician

knowledge that needs to be put out by some group. I mentioned the Endocrine Society. It could be any other group that feels competent to do that.

But just to put this drug on the market without guidelines that specifically tell or suggest to the physician how to use it I think would be a great mistake.

DR. BURMAN: Thank you all.

Mark?

DR. MOLITCH: I had enough difficulty saying yes with this study for recommending possible approval. And now, when I hear the comments around the table, Dr. Felner is already proposing off-label use for something that hasn't even gotten a label, and that is to treat obese adolescents who may or may not have diabetes.

Had I known that was already going to happen, I would never have voted for approval. I think that's a very, very dangerous path to take and I think that this should be a very, very limited approval for exactly what's been specified, and I would be very, very hesitant to use it outside of that

until we get lots and lots of experience.

DR. BURMAN: I think we all agree with that. I think we all agree with that. Do you have any --

DR. FELNER: Of course. I mean, I'm trying to think about it from my standpoint. But if it has only to be used in HIV patients, obviously, it won't come up anywhere else. Correct? Right? If it's approved for patients with HIV.

DR. BURMAN: Good. Thank you for that comment.

I would like to ask, Dr. Parks and Dr. Rosebraugh, do you have any other comments, anything else you want the panel to discuss since we're all together, any issues left unresolved, in your mind?

DR. PARKS: Just our closing remark, but if you have other issues you want to address.

DR. BURMAN: No. I think that would be great, please.

DR. PARKS: On behalf of the FDA, I'd like to thank Dr. Burman, members of this advisory committee for the discussion and deliberations today. I particularly would like to thank the panel members

for not changing the advisory committee questions.

I think this is the first meeting I've been to where the panel members did not ask for the question to be changed. So we must have done a pretty good job writing the questions.

We did hear today some very, very important pieces of information, pieces that perhaps the agency clearly needs to go back and also analyze issues with respect to different types of protease inhibitors used. There were also certain issues raised with respect to statin use. We have a list of that. So we'll clearly go ahead and do that.

While the advisory committee panel members' votes were far from equivocal, the discussion certainly informs of that there is still quite a lot of work to do, which we will be doing so in the next couple of weeks to months with the company.

So on that note, I also would like to thank the company for your work with us, particularly in the last three months in preparation for this advisory committee.

I also would like to thank the speakers

during the open public hearing for your very, very powerful testimony. And then last, but not least, I'd like to thank the FDA review team for their excellent job. Clearly, in the last three months, it's also been very difficult for them, as well.

So with that, no further ado. Thank you.

DR. BURMAN: Thank you.

Dr. Rosebraugh, any comments? No? Thank you. I would also, on behalf of the committee, like to thank the FDA, specifically Dr. Parks and Dr. Rosebraugh, Drs. Roman and Mohamadi for their nice presentations, and, of course, Mr. Tran, Paul, who we work with virtually on a daily basis. And really, this couldn't occur without his great work.

It's a privilege to serve on the committee and a pleasure to work with the members of the FDA. They've been professional and cooperative in all of my interactions.

I also would like to thank the sponsor for the very nice presentation; the OPH speakers, again, which were very powerful and very important in this process; and also, like to thank the panel members for

their very active participation and their travel to get here.

That all having been said, I'd like now to adjourn the meeting. Thank you.

(Whereupon, at 4:20 p.m., the meeting was adjourned.)