FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY COMMITTEE (BRUDAC)

Tuesday, December 6, 2016

8:00 a.m. to 4:10 p.m.

Thomas Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning, everyone. My name is Vivian Lewis, and I'd like to welcome you to this meeting of the Bone, Reproductive, Urologic Drugs Advisory Committee meeting. I'd like first to remind everyone to please silence their cell phones and other devices if you haven't already done so. I'd also like to identify Andrea Fischer, the FDA press contact. There she is. She's right there.

In calling the meeting to order, I'd like to start by going around the table to my left and having everyone identify themselves.

CMDR BONNER: Good morning. LaToya Bonner, acting DFO for BRUDAC.

DR. CHAI: I'm Toby Chai, professor of urology from Yale University.

DR. DMOCHOWSKI: Roger Dmochowski, urology, Vanderbilt University.

DR. BAUER: Good morning. Doug Bauer, University of California, San Francisco, Department of Medicine, epidemiology and biostatistics.

DR. DRAKE: Mathew Drake from the Mayo Clinic in Rochester, Minnesota. I'm an endocrinologist.

DR. BISKOBING: Diane Biskobing, Virginia Commonwealth University, internal medicine, endocrinology.

DR. BRAUNSTEIN: Glen Braunstein. I'm an endocrinologist, Cedars-Sinai Medical Center at UCLA School of Medicine.

DR. McCAMMON: Kurt McCammon. I'm a urologist from Eastern Virginia Medical School in Norfolk.

DR. HANNO: Phil Hanno. I'm a urologist at Stanford University.

DR. DANIELS: Selena Daniels, FDA, Clinical Outcome Assessment Staff.

DR. EASLEY: Olivia Easley, medical officer, Division of Bone, Reproductive, and Urologic Products, FDA.

DR. KAUL: Suresh Kaul, medical team leader, Division of Reproductive and Urologic Products, FDA.

DR. GASSMAN: Audrey Gassman, deputy director, Division of Bone, Reproductive, and Urologic Products, FDA.

DR. JOFFE: Hylton Joffe, director of the same division.

DR. NAHUM: Gerard Nahum. I'm the vice president of Global Clinical Development at Bayer HealthCare Pharmaceuticals.

DR. BURMAN: Ken Burman, head of endocrine at Medstar Washington Hospital Center and a professor at Georgetown University.

DR. ADLER: Robert Adler, endocrinologist at the VA Hospital in Richmond, Virginia and Virginia Commonwealth University.

DR. SANDLOW: Jay Sandlow. I'm a urologist at the Medical College of Wisconsin in Milwaukee.

DR. BRANNIGAN: Bob Brannigan, professor of urology at Northwestern University in Chicago.

DR. SCHLEGEL: Peter Schlegel, urology,

Cornell.

DR WEINFURT: Good morning. Kevin Weinfurt. I'm a professor of psychiatry at Duke University.

DR. GILLEN: Daniel Gillen, professor and chair of statistics, University of California at Irvine.

DR. THOMAS: Abraham Thomas, endocrinologist and chief of medicine at New York University, Lutheran.

DR. BISHOPRIC: George Bishopric, pathologist, University of Miami.

DR. CURTIS: Kate Curtis. I'm an epidemiologist in the Division of Reproductive Health at CDC in Atlanta.

DR. HOWARDS: Stuart Howards, urologist at the University of Virginia and Wake Forest Medical School.

DR. LEWIS: Thank you.

For such topics 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 only 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 this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during the break or at lunch time. Thank you.

Now, I'd like to pass things over to Commander LaToya Bonner, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

CMDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Bone, Reproductive, and Urologic Drug 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 the 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 this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, 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 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 special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, 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 the discussion of

appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis. This is a particular matters meeting during which general issues 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 have made concerning the topic at issue.

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

this meeting is to represent industry in general and not any particular company. Dr. Nahum is employed by Bayer Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an 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 relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. LEWIS: Thank you. We'll now proceed with the FDA's introductory remarks from Dr. Hylton Joffe.

FDA Opening Remarks

DR. JOFFE: Good morning, everybody. I'm Hylton Joffe, the director of FDA's Division of Bone, Reproductive, and Urologic Products. I'd like to welcome you all here today. What I'd like

to do in the next 15 minutes is give an overview of the objectives and scope of today's meeting, provide some background, go over the agenda, and then show the questions that we'll be asking the committee to discuss and vote upon.

The objectives today is to identify appropriate clinical trial design features for drugs that are proposed to treat secondary hypogonadism while preserving or improving testicular function. A major goal is actually to identify what would be acceptable efficacy endpoints to show that drugs for this condition confer clinical benefit to the patient. To ensure appropriate expertise, we supplemented our usual committee with additional urologists, endocrinologists, experts in fertility, obesity, and patient-reported outcomes.

Products that are being investigated in this drug space include estrogen agonists and antagonists such as clomiphene, and enclomiphene, aromatase inhibitors and gonadotropin receptor agonists such as human chorionic gonadotropin.

Now, it's important to note we're not talking about testosterones today because, if anything, testosterones can suppress spermatogenesis, whereas the drugs that are being investigated in this space are intended to either preserve or improve testicular function.

These drugs have very important side effects. These side effects include but are not limited to concerns of venous thromboembolism with estrogen agonists and antagonists, bone loss, and fetal harm with aromatase inhibitors. But today, we're not focusing on the safety profile of any specific drug.

This advisory committee is a little different to a typical one. Usually we bring a specific drug to a panel, ask them what they think of the benefits and the risks, and whether those benefits outweigh the risks and support approval. Here, we're earlier in the process. We're talking about clinical trial design features, and we're specifically focused on what's needed to establish clinical benefit of these drugs.

There have been some very important recent developments with testosterone therapies that directly bear on today's discussion, so I want to take a few minutes to provide an update here for everyone.

Testosterone therapies are approved as replacement therapy by showing in registration clinical trials that they can increase testosterone levels from below the normal range into the normal range for young, healthy, eugonadal men.

This paradigm supports an approval in men who have what we call classic hypogonadism. These are men who have an intrinsic pathology of their hypothalamic pituitary testicular axis due to specific well recognized medical conditions, such as Klinefelter syndrome, Kallmann syndrome. In these men, the goal is to restore testosterone to normal levels.

However, in recent years, testosterone has been widely used in a different population, in men who have what we call age-related hypogonadism. And these are men who have no apparent reason for

the low testosterone other than advancing age. In this population, it hasn't definitively been demonstrated that raising testosterone in these men confers clinical benefit and is safe.

So because of this widespread use in this different population, FDA convened an advisory committee meeting in 2014 -- I see some familiar faces from that meeting -- to discuss the appropriate indicated population for testosterone. And the committee overwhelmingly concluded that the efficacy and safety of testosterone have not been established for age-related hypogonadism, and they said that the available evidence supports an indication for testosterone only in men who have classic hypogonadism.

So the committee stated that if you're a testosterone and you are an indication for age-related hypogonadism, just raising serum testosterone isn't enough. You need to show changes on other endpoints, clinical endpoints, meaning endpoints that assess how a patient feels, functions, or survives.

This is very important because FDA believes that the advice we got from the advisory committee in 2014 applies anytime you're seeking an indication in men who do not have classic hypogonadism. Age-related hypogonadism is one such example. But another example FDA believes is hypogonadism attributed to obesity.

Just as with age-related hypogonadism, we don't know that raising testosterone definitively leads to clinical benefit and is safe, so too with hypogonadism associated with obesity. And I want to take this one step further. We believe that this applies not only if your testosterone is being tested in hypogonadism associated obesity, but even if you are non-testosterone, we believe that you need to show something beyond raising testosterone. And that's because on the prior slide, the committee clearly said that the available evidence supports indication only in men with classic hypogonadism.

Let me take a moment here and talk about treating secondary hypogonadism while improving

testicular function. FDA has approved several drugs that induce spermatogenesis in men who have azoospermia, meaning no sperm on semen analysis at baseline, that's attributed to secondary hypogonadism. And the approval paradigm has been to show that the drug can take these men with secondary hypogonadism and azoospermia and raise sperm concentrations above a specific threshold, for example, 1 million sperm per mL.

This approach raises some interesting questions. For example, in today's existing understanding of science, is such an approach still reasonable because we have existing assisted reproductive technologies such as ICSI, or intracytoplasmic sperm injection, where you need very few sperm to fertilize an egg and lead to pregnancy?

Also, what about other semen parameters? If you show something raises sperm concentrations but you have some other problems with your sperm, then whatever your sperm concentration is, it's kind of irrelevant because if you've got other problems

that are preventing fertility, having more sperm with those problems still isn't going to solve your fertility problem. This raises the question of when should we be asking for an endpoint of pregnancy in the partner?

We'll discuss a lot of these issues today. One question will be whatever paradigm folks think is reasonable for azoospermic men with secondary hypogonadism, should the same approach be used for men who have oligospermia, which is sperm counts below normal but not zero? And also, should the approach be the same or different for men who have classic hypogonadism compared to those who do not have classic hypogonadism and have azoospermia or oligospermia?

On this slide, I just want to share FDA's perspective on drugs that are intended to treat secondary hypogonadism while improving testicular function. If a company is seeking an indication that's narrowly focused on fertility, what they would need to do is use an acceptable endpoint for fertility, and we'll discuss that today. But FDA

doesn't think that such a company would need to show improvement in other hypogonadal signs or symptoms, again, because they're seeking a very narrow indication related to fertility associated with hypogonadism. However, such drugs would presumably be approved for shorter term use with discontinuation when fertility's no longer desired.

If a company wanted, in addition to this fertility indication, a broader hypogonadism indication, then in that setting, additional clinical endpoints would be needed.

I want to now turn to treating secondary hypogonadism while preserving testicular function. And I'm going to focus here on men who do not have classic hypogonadism and specifically on men who have hypogonadism associated with obesity because this is an area of interest for drug development.

What's been put forth is that raising testosterone while preserving sperm concentrations could establish evidence of clinical benefit. But FDA's view is that that approach cannot really establish clinical benefit, and here's why.

First, as I explained earlier, raising testosterone by itself, FDA views cannot establish clinical benefit in men who do not have classic hypogonadism, such as men who have hypogonadism associated with obesity. So we think a product would need to show improvement on hypogonadal signs or symptoms, otherwise, the need for therapy hasn't been clearly established.

Now, what about this other endpoint, preserving testicular function? Well, our view is that just preserving testicular function isn't evidence of clinical benefit either. If you take a man who's got normal sperm counts, and you treat him for three months or four months, and show their sperm concentrations are still normal, presumably you could achieve that just by withholding the drug.

If raising serum testosterone concentrations by itself cannot establish clinical benefit for these drugs and preserving testicular function by itself can't do so, when you put the two together, FDA believes you still can't establish clinical

benefit using these endpoints, and you need endpoints that assess how patients feel, function, or survive.

This slide shows the agenda today. We'll have three series of presentations. Our first presentation is by Dr. Sergio Oehninger. He's our guest speaker and expert in fertility, and he'll be talking about issues related to fertility and hypogonadism. He's the director of Reproductive Endocrinology and Fertility at The Jones Institute for Reproductive Medicine. He's also professor and vice chair of the Department of Obstetrics and Gynecology at the Eastern Virginia Medical School.

We'll then hear a presentation by three drug companies that have collaborated to present their views on what clinical trial design features should look like for drugs in this space. You'll then hear from FDA. And throughout the presentations, there will be opportunities for the committee to ask clarifying questions of the presenters. After lunch, we'll have an open public hearing, and then we'll have committee discussion and voting.

So I'd now like to walk you through the discussion and voting questions so that committee members can start to frame the issues as they hear the presentations. There are two discussion questions and three voting questions. The first discussion question reads as follows:

For drugs intended to treat secondary hypogonadism while preserving existing testicular function such as maintenance of sperm parameters or demonstrating continued fertility, we'd want the committee to discuss the patient population that should be enrolled in the clinical trials; how should preservation of testicular function be defined and assessed; what are acceptable endpoints for demonstrating clinical benefit for men who have classic hypogonadism, as well as those who do not have classic hypogonadism when the intent is also to preserve testicular function; and then any other trial design features that should be considered.

The second question is similar to the first question, but here we're talking now about improving testicular function. The first question

was talking about preserving testicular function. So this question reads, for drugs intended to treat secondary hypogonadism while improving testicular function, for example, improved semen sperm parameters or amelioration of infertility, we want the committee to discuss similar issues, again, the patient population that should be enrolled in clinical trials; how improvement in testicular function should be defined and assessed; what are acceptable endpoints for demonstrating clinical benefit in classic hypogonadism, in men who do not have classic hypogonadism, and any other trial design features that should be considered.

Now we have three voting questions after those discussions. The first one reads as follows. For products intended to treat men with hypogonadism attributed to obesity, is raising serum testosterone concentrations into the normal range for young, healthy, eugonadal men and preservation of spermatogenesis as assessed by maintenance of sperm concentrations sufficient for establishing evidence of clinical benefit?

If you vote no, we'd like to hear what endpoints you think would be needed to provide sufficient evidence of clinical benefit for these products. And if you voted yes, we'd like you to comment on how preservation of spermatogenesis should be defined based on sperm concentrations and provide an explanation for your definition.

The last two questions are multiple choice questions. The next question reads as follows. For products intended to treat men with classic secondary hypogonadism who have azoospermia or oligospermia, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit?

Your choices are A, yes, but only for azoospermia; B, yes, but only for oligospermia; C is yes for azoo- and oligospermia; and then D is no. And we'd like your rationale for your answer. And if you voted D, meaning no, in other words you don't think raising sperm concentration above a specific threshold is sufficient in these men, we'd like you to describe what endpoints you think would

be needed to provide sufficient evidence of clinical benefit.

If you voted yes, meaning either A, B, or C, we'd like you to specify the threshold for sperm concentration that should be exceeded to establish evidence of clinical benefit and explain why you selected that threshold.

Now, the last voting question is very similar to the one I just mentioned. The main difference here is that the previous question focused on men who have classic hypogonadism. This last question is focused on men who do not have classic hypogonadism. So think of age-related hypogonadism or hypogonadism associated with obesity.

Here we're saying, for products that are intended to treat men with secondary hypogonadism and azoospermia or oligospermia, but who do not have classic hypogonadism, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit? And it's the same multiple choice options and the same discussion

points will be asking you to comment on.

With that, I want to thank you for your attention, thank everybody for coming, and I look forward to an interesting discussion.

DR. LEWIS: Let's now proceed with a presentation from Dr. Sergio Oehninger. Apologies if I mispronounced your name.

Presentation - Sergio Oehninger

DR. OEHNINGER: Thank you very much for the invitation to participate and to speak to this group. The outline of my presentation is depicted here. I will briefly review some aspects of the physiology of the hypothalamic pituitary testicular axis; define the hypogonadal states; mention about impact of age and other comorbidities; treatment of men with hypogonadism; fertility concerns; speaking about basic semen analysis; and touching up on sperm function and quality assays; and something about the future and potential studies. There are no conflicts of interest for me to declare.

It is well known by most in this group, testicular function is governed by the hypothalamus

and pituitary following the classic pathways of GnRH, stimulating FSH and LH release of the [indiscernible] pituitary, LH acting upon the Leydig cell to stimulate testosterone secretion, FSH governing the seminiferous tubule where spermatogenesis happens; feedback occurring back to the pituitary and hypothalamus via inhibins, testosterone, the Leydig cell product, and also estrogen, oestradiol, all negative feedbacks.

This is more of a simplistic way of the way the axis functions because we know there is a tremendous amount of product [indiscernible] and regulation within the testicles between interstitial cells and seminiferous tubules. There are too many to describe here. The process of spermatogenesis starts with spermatogonium undergoing mitoses, leading to spermatocytes that did undergo meiosis. And this leads to the different stages of spermatids, and finally spermatozoa are being produced, millions per day.

It is clearly established that FSH plays a role in initiating and maintaining spermatogenesis,

and for completely normal spermatogenesis, both FSH and testosterone are important, but also the intratesticular testosterone levels are important. This is highlighted by studies that give better outcomes using FSH and hCG versus FSH plus testosterone in some of these patients with testicular defects.

But not only is the axes functional, as I mentioned, but they're also peripheral, regulatory mechanisms. For example, at the level of the adipose tissue, we have the leptin and the others that can have a direct effect on the spermatogenesis via testosterone. The adipose tissue is a place of aromatization of androgens to oestradiol, and both leptin and estrogens can have a significant influence in neurons at the hypothalamic level that regulates also GnRH.

So GnRH is not only regulated by the feedback of steroids, but also by hypothalamic neurons that really can affect and generate positivity. Example is the kisspeptin system, which can be modified in cases of obesity because

of leptin resistance or insensitivity.

The classic hypogonadism is defined as low levels of testosterone, under 300 nanograms per deciliter and can be primary or secondary. Primary is the hypogonadotropic hypogonadism, which is the result of testicular failure to produce adequate levels of testosterone and can be identified by low testosterone and elevated FSH/LH levels, which is the traditional working system feedback, negative feedback.

In this case, it was impaired Leydig cell and seminiferous tubule functions, which results in reduced testosterone synthesis, but also hypospermatogenesis. Classic examples are Klinefelter, toxicities, orchitis, and others.

As opposed to primary, secondary is a hypogonadotropic hypogonadism, which is the presence of low testosterone, but is the result of GnRH or gonadotropin deficiency, hypothalamic or pituitary, and it's also called central and therefore has low testosterone and reduced gonadotropins. This can be congenital,

genes such as the KAL-1 syndrome gene, GnRH receptor, gonadotropins, many other genes, and also genes, for example, associated with obesity like leptin, leptin receptor, and prohormone convertase. It can be acquired, secondary to pathological processes, tumors, granulomatosis, infections, and others.

Recently, the term "adult onset hypogonadism" has been coined, and it is estimated that the adult onset hypogonadism is a measurable clinical biological syndrome characterized by low testosterone with its associated symptoms, but low or normal gonadotropin levels. So as such, it is clinically distinct from classical primary and secondary hypogonadism because the testicular deficiency is associated with a failure to mount an adequate compensatory response to the low testosterone levels. Unclear prevalence of the syndrome, but it's estimated to be present in probably more than 5 million men in the USA, according to some recent reports.

This is clearly associated with common

comorbidities that we see in our patients. Aging, it has been described that Leydig cells become less responsive to gonadotropins and the number of Leydig cells declines with age. GnRH production declines with age. In addition, the androgen negative feedback suppression may be increased. All of this can disrupt the axis.

Obesity can affect fertility via hypogonadism and its impact on sperm production, but also atherogenic effects causing erectile dysfunction, diabetes mellitus type 2, several medication effects, sleep disruption and stress, all present in these populations.

For example, how does obesity affect fertility in men? The postulated mechanisms, if you look at the right side of the slide, the control of the kisspeptin neuron, which regulates the GnRH neuron, which of course regulates the secretion of LH and FSH, this kisspeptin neuron is regulated by estrogen, which may be increased in obesity because of aromatization in the periphery insulin resistance and leptin itself with

resistance, which may disrupt therefore the firing of kisspeptin neurons, thereby affecting GnRH secretion and creating hypogonadism.

The impact of obesity can be further defined in this slide. There is peripheral increased aromatization of testosterone, peripheral vascular disease causing erectile dysfunction, and reduced sex hormone-binding globulin. All this leads to reduced sperm count and the question about whether obesity and/or aging, or a combination, can affect quality of sperm; for example, as measured by DNA damage or DNA fragmentation.

Another important question that will have to be answered in the future is the impact on fertility and metabolism in the next generation by sperm released under these conditions.

This is a study from Europe published recently on hypothalamic pituitary testicular axis disruption in older men. As you can see, in the upper part, you see testosterone levels and free testosterone levels measured in blood according to age of the males, 40 to every 5-year intervals.

And you see how testosterone levels and free testosterone levels clearly go down with age with an apparent inflection point around 70 years for LH, which is here going up as a result of the feedback, and the SHBG also going up. This is what happens in this population of, quote, "aging males."

If you add confounding variables such as BMI, here you have the same curve of testosterone/free testosterone, LH, and sex hormone-binding globulin. But now, according to percentiles of BMI, in red is the highest BMI. You can see that all these abnormalities are increased as the BMI gets higher, therefore it becomes an important confounding variable to take into consideration.

In the European male aging study, this nice curve has been used to define the populations of men studied and ranges from 40 to 80 years of age. Here you can see this is the level of LH, the cut-off used for defining hypogonadism or testosterone around 300 -- picograms -- nanograms

per deciliter and LH 9.4 units per liter.

Here you have the group of non testosterone and high LH, that's primary hypogonadism. Low testosterone and low LH, that's secondary hypogonadism. This is the group of eugonadism. This is a particularly interesting group of men that has what's called compensated hypogonadism. They have a higher LH, and they're compensating there by the testicular function. And it's important that for men with abnormal out of eugonadism, most of them have secondary hypogonadism, which is therefore a frequent observation in this population.

How do we treat this disease? Testosterone replacement therapy has been the primary option, obviously, unless fertility is a concern or if there are contraindications to the use of testosterone. That has to be done with adequate monitoring taking into consideration risks and safety. More studies are needed to define exactly how testosterone should be used. Patients on testosterone need to be monitored. It's debatable

whether this affects many who are not cardiovascular. This is prostate cancer, cancer, prostatic hypertrophy, cytosis and infertility.

Obviously, I'm speaking more now on the reproductive side. Infertility is a side effect of testosterone treatment. Testosterone treatment is basically a form of male birth control because it will suppress endogenous LH and FSH production, which leads to testicular atrophy, both a seminiferous tubule effect and a Leydig cell effect, and results in severe oligospermia or absolute azoospermia, typically within 3 or 4 months of use.

The recovery of spermatogenesis, if you're using testosterone as a birth control and you discontinue testosterone treatment, is dependent on the duration and intensity of treatment along with a baseline fertility status. This is an important fact to remember, the baseline fertility status.

In a study of 200 men, the medium time to regain sperm counts of more than 20 million was 3 and a half months, and only 46 percent of men

returned to a baseline at an average of 6 months. So there is recovery, but it's variable. Therefore, it is critical to understand that men with impaired fertility before initiating testosterone treatment may remain permanently azoospermic, and all men of childbearing age should be asked before the initiation of this therapy, whether they are considering children or not.

It's described in this study that we're starting to find out that some urologists and other practitioners report using testosterone to treat fertility when in reality it is a birth control.

This is a nice study coming from China where you see the changes in sperm concentration. This is a logarithmic scale of sperm concentrations. So this would be 100 million sperm per milliliter, this is 10, and this is 1. This is the number of months, and this is the participants that were treated with testosterone, endocrine rate, and this is in Chinese men.

You see the initiation of therapy with good sperm counts, then there is a suppression phase,

efficacy, and then recovery. And you can see the very dramatic responses in terms of lowering sperm production from averages of 80 million sperm, down quickly to under 1 million sperm, and even lower in azoospermia in some cases, and then recovery happening in a variable period of time.

What are non-testosterone therapies? Well, if there is hypogonadism and its secondary or primary, what treatments do we have available? Gonadotropins are the only FDA-approved medications to treat hypogonadism. We talk about clomiphene citrate. We talk about aromatase inhibitors. We mentioned some other selective estrogen receptor modulators such as clomiphene itself, and maybe some products that may be on the horizons such as selective androgen receptor modulators.

What is important in the treatment of men with hypogonadism that want to preserve testicular function is the possibility of keeping their fertility status. That's where I'm going to stop a little bit on the analysis of the semen.

As a reproductive endocrinologist, I'd like

to show this slide that is very basic and obvious to most of us, but it takes two to tango. When you evaluate the infertile couple, you have to assess the female and the male at the same time. Fertility is a complex and multifactorial process.

Questions are about how do you define fertility and which endpoints to evaluate. You evaluate pregnancy and live birth -- these are very multifactorial processes -- using surrogate endpoints such as analysis of spermatogenesis and the semen, which are somehow what we typically do in reproductive medicine. When we assess our patients, we talk about the so-called basic semen analysis. We will manage and base very briefly sperm function and quality assays to assess sperm function.

The semen analysis has been defined by the World Health Organization laboratory manual for many years, and it's the gold standard we all follow. It is quoted that "semen analysis is used in both clinical and research settings for investigating the fertility status of men, as well

as monitoring spermatogenesis during and following male fertility regulation or other interventions." So it's a good tool as a surrogate endpoint for fertility.

You see here in red the new reference values published by WHO in the last edition in 2010. For us that have been working many years in the field, this is previous data that had resulted in the previous reference values. What is important here are the new values of normality for the basic semen parameters, which are viability, concentration, total motile sperm, per mL or per ejaculate, progressive motility, and morphology.

These are the results of well-designed studies looking at men who achieved fertility within a year. These numbers reflect 95 percent confidence intervals so that, for example, now the normal sperm count, or a number that we keep in mind now, is 15 million sperm per milliliter when we in the past talked about normal counts being between 20 and 100 or 200 million per milliliter.

What these new numbers mean is that there

were men able to achieve pregnancies with as low as 15 million sperm, and this obviously will not apply to all the population. But these are the numbers that we follow nowadays, and I think it's important to assess concentration, motility, total motile sperm pre-ejaculate, progression of motion, and the assessment of morphology by the so-called strict criteria.

The strict criteria we think are important criteria to identify what are the normal forms versus abnormalities. And looking at the semen this way, it seemed interesting that even very fertile individuals have not more than 10-14 percent normal forms in their ejaculates. Therefore, there is a proportion of sperm that are being ejaculated that are dysmorphic. I would also probably call them dysfunctional, and it is interesting to look at the data from this point of view also.

In vivo, the sperm must go through the cervical mucous and travel into the fallopian tube to meet the egg. There are similar processes that

appear at this stage that obviously cannot be identified by the semen analysis, which is just a short, one view of sperm after ejaculation.

There are processes of hyperactivation and changes in the sperm motility parameters that allow the sperm to get to the egg, bind, and fertilize probably under the effects of progesterone and follicular fluid, released into the fallopian tube, and then the interaction of the hyperactivated sperm with the egg to hopefully result in fertilization.

For us that have been investigating sperm functions after sperm separation, not only in vivo but also in vitro, we were therefore interested in knowing more about this critical sperm function at the level of fertilization. And if this is an egg surrounded by the zona pellucida -- and that's a parameter in space -- once the sperm hyperactivates and gets to the egg, they will bind to the zona pellucida in a very specific manner.

They will undergo the so-called zona pellucida induced acrosome reaction that allows

them to penetrate the zona to then get into the perivitelline space, and now fuse the rim of the oocyte to then penetrate the egg. That's done by a single sperm in the normal situation. And that leads to many processes resulting in egg activation through calcium movements inside the egg, pronuclear formation, and embryogenesis starts. All of these processes can be investigated somehow in the assessment of extended semen analysis in vitro, but these are very difficult endpoints for any clinical trial.

The analysis of ejaculated sperm relies today on basic semen analysis. There are some sperm function tests, but even though they do exist, they are very cumbersome and difficult to perform clinically. There are other assays to assess sperm quality, and one of the interesting topics today is the examination of chromatin structure and DNA integrity and fragmentation.

The so-called sperm function tests are nothing but bioassays of gamete interactions. WHO has now defined them as research procedures, so

they're not clinically daily procedures done in any lab. They are sperm-zona pellucida binding assays, acrosome reaction assays, and others, but these are not clinical in the clinical setting approved for it.

We also investigated age and semen quality. As men age, is it like wine? Is it wine and cognac? Do we get better with time, or is there a point where we're over the hill and nothing is going to follow in terms of fertility, or sperm production, or sperm quality?

Some studies have been done showing -- this is a particular study in 2003. Showing here, we have volume. We have multiple sperm parameters according to age, 20, 40, 60 years of age. You see a decline in volume, sperm motility, concentration, progressive motility, this is total count, and total morphology -- total progressively motile sperm.

So the trend is obvious for all the sperm parameters, and applying statistics, volume and progressive motility are clearly statistically

declining factors with age. That's another factor to take into consideration.

This is I think a very good study showing the relationship between middle age and some of the selected genomic difference in sperm. This is age at 20, 40, 60 years. This reflects DNA fragmentation. This is done through the sperm chromatin structure assay. It's a flow cytometry assay taking care of the structure of the chromatin.

This is PCR for achondroplasia genes, so these are potential mutations that would increase with age. This is analyzing sperm with fluorescent in situ hybridization for chromosomes X, Y, and 21, showing the following.

There's a clear increase in DNA fragmentation as assessed by this assay with age. There's a clear increase and statistically significant increase in the presence of some mutations. And there is another association with aneuploidy, which is a very interesting factor and is clearly different from what happens in the

female counterpart. These elements are also to be taken into consideration as we move on to try to help men of more advanced age achieve pregnancy.

Now, do sperm DNA integrity tests predict pregnancy with IVF? I feel honored to have Dr. Schlegel here in this audience who was an author in this article. But if you compare sperm chromatin assay flow cytometry and TUNEL assay -- we worked more on the TUNEL assay, and there are many studies published in the literature to see how they would predict, in these cases, IVF. There are no studies for natural fertility.

The answers were, and the American Society for Reproductive Medicine Committee Opinion confirmed, that the existing data do not support a consistent relationship between abnormal DNA integrity tests and reproductive outcomes. At present, the results of sperm DNA testing alone do not predict pregnancy rates achieved through natural conception or intrauterine insemination, in vitro fertilization, or ICSI, intracytoplasmic sperm injection. They are wonderful research

tools, and we keep doing research, but there are no thresholds or even methods that are universally approved to indicate which are the best tests.

So if we go back to the treatment of hypogonadal states, for non-testosterone therapies, keeping in mind central cases can be treated by exogenous gonadotropins, so they are FDA approved. And I will go and touch upon these ones, and Clomid, and aromatase inhibitors in the next slides.

These are all the studies but still very elegant and show their point very well. These are men that have hypogonadotropic hypogonadism, and these men are particularly men with -- or secondary men that have idiopathic hypothalamic hypogonadism and Kallmann syndrome, and are treated with GnRH pump or a combination of hCG and hMG. hCG is LH. hMG is a combination of FSH and LH.

You can see that when you start treating these men that have hypogonadism, hypogonadotropic hypogonadism, the volume of the semen of the testes increases rapidly considering the initial volume

before therapy. This is manifested well after, quickly, in appearance of sperm.

These are men with azoospermia, and you see here the appearance of first sperm in the ejaculate. This is duration of treatment in months. These are different types of these cases of hypogonadism. But to make a long story short, you see appearance of sperm in 4 months, 6 months, and duration of treatment until pregnancy around 6 months to 10 months.

So these are wonderful cases to treat because you go from azoospermia to certain levels of sperm resulting in pregnancy in a few months. This is because the testicular function is intact in these men. And this slide shows that very well because if you see the duration of treatment and the sperm concentration needed to achieve a pregnancy, you can see that with lower counts under 15 million sperm, many of these men were able to achieve pregnancy.

This is important to remember, but also to remember that in these cases, these men probably

have normal testicular function and can quickly achieve pregnancies relatively quickly with lower than expected sperm counts, which may not be the case at all for other populations that have dysfunctional spermatogenesis, aging, diabetes, and obesity.

Other therapeutical alternatives will be discussed later. An alternative approach is to use selective estrogen receptor modulators such as Clomid, which is used off label. This is not an FDA-approved medication. Clomid is a mixture of enclomiphene citrate, which is the trans-isomer and cis-isomer. They are different because in Clomid, the trans-isomer has antagonistic properties in the receptors, and the cis is an agonist and has a very long half-life, and that has been more implicated in women with potential effects, secondary effects. Industry has looked at, for example, enclomiphene citrate as a way to go because of these properties.

Clomiphene acts at the hypothalamic pituitary level as an anti-estrogen, therefore increases the release of gonadotropins. Aromatase

inhibitors on the other hand, such as letrozole, or commercially known as Femara, these are type 2 inhibitors, non-steroidal competitor inhibitors such as anastrozole or letrozole, and act in a very different way because they are inhibitors of peripheral aromatases, but they also lead to selective estrogen suppression.

This slide review is how these medications work: the hypothalamus, pituitary, sertoli cell, Leydig cell, GnRH, FSH, LH, and distortion of the negative feedback and estrogen feedback. Clomiphene citrate acts through the hypothalamus pituitary as an anti-estrogen, selective estrogen receptive modulator, whereas aromatase inhibitor will act in the gonad to suppress the aromatase enzyme that converts testosterone to estradiol, therefore decreasing this negative feedback.

Important facts to remember in the global process of spermatogenesis, high levels of intratesticular testosterone are necessary for normal spermatogenesis. In men, it appears that estrogen derives mainly from aromatization of

testosterone in adipocytes. But remember, aromatase is present in bone, brain, and the hypothalamus.

There are animal studies to suggest that high intratesticular estrogen levels may impair steroidogenesis and spermatogenesis, so this could be an important element to take into consideration when treating some patients. Despite success in some studies, but not all, there are no long-term data evaluating the efficacy of aromatase inhibitors, and therefore their use cannot be routinely recommended at this time.

If you look at the selective estrogen receptor modulators and you look at aromatase inhibitors, anastrozole and letrozole, these act through aromatase inhibitors and estrogen receptors. All of them will increase testosterone, and all of them will increase LH. But the anti-estrogens will increase estrogen, but the aromatase inhibitors will decrease estrogen, and that could be of importance in certain men, as it reflects it may be a better outcome related to

spermatogenesis, may be.

A multicenter prospective study using enclomiphene citrate versus AndroGel, so versus testosterone -- this is clomiphene citrate and Clomid, the trans-isomer versus testosterone. You can see how treating these hypogonadal men versus placebo, both medications increased testosterone, clomiphene more than testosterone itself. Obviously, if you look at gonadotropins, testosterone will decrease LH, but Clomid will increase LH through the receptor antagonism. And if you look at sperm count -- that's a very interesting part of this study.

These are two studies, but let's just concentrate on this left-sided study, looking at mean sperm concentration of men treated, in green is baseline and light green is 16 weeks of treatment and varies with percentage change. You can see that clomiphene will maintain sperm production in these cases. Testosterone will decrease negatively, absolutely, so that clearly clomiphene citrate will increase testosterone and

LH and probably maintain spermatogenesis.

In this case, these are comparisons of clomiphene citrate and an aromatase inhibitor. It's a randomized prospective, double-blind trial assessing testosterone in hypogonadal infertile men. And you can see that both compounds, Clomid and aromatase inhibitor, will increase testosterone as expected. This is anastrozole, and they both will increase testosterone to estradiol ratio, which may or not be a parameter to follow up in these patients, more Clomid than the aromatase inhibitor.

If you look at the semen analysis in these individuals, these are individuals that start with a concentration baseline, a sperm number around 30 million. These are not oligospermic men, but both compounds will maintain the production of sperm while increasing testosterone and LH.

Swerldoff and others have come up with a list of emerging medications for treating male hypogonadism. This is probably not a complete list, but we see here the interest of

pharmaceutical companies in developing other androgens, other selective estrogen receptor modulators.

It was interesting to see also SARMs, selective androgen receptor modulators, so that one could hypothesize on the presence of a compound that has testosterone effects that are good for spermatogenesis on the skin but are negative effects; for example, regarding the prostate and other potential side effects of this compound such as similar to what we see in women where raloxifene is a SERM that has inhibitory effects on breasts and endometrium but protects bone. So the manipulation of these compounds would be easily targeted -- well, could be targeted to compounds that affect different points in this whole system.

If the objective of a drug in men with secondary hypogonadism is to maintain fertility, then the questions become, first, it's important to have knowledge on the prior fertility status of the gentleman, presence of comorbidities, are we going to look at changes in semen parameters,

establishment of pregnancy and time to pregnancy.

The goal of treatment should be -- by any given drug, whether it's central, hypothalamic pituitary, or peripheral -- testicular effect on looking at sperm numbers, or function, maybe DNA or others, and try to stimulate fertility and what are the sperm thresholds to be considered.

Pregnancy, we'll define it as a multifactorial issue, therefore much more difficult to analyze, and if we're going to study natural conceptions, or like was mentioned before by Dr. Joffe, what about the fact that today, reproductive endocrinologists can, in the treatment of male and female infertility, offer different therapeutic options from urological interventions, medical, inseminations, or IVF?

Today was a wonderful tour of intracytoplasmic sperm injection, and we can do the treatment with very low sperm counts. But again, this is a big overview of this interesting question that this panel is analyzing, and I want to thank you again for the invitation. Thank you.

Clarifying Questions to the Guest Speaker

DR. LEWIS: Thank you, Dr. Oehninger. Could you take a few questions? Yes.

Are there any clarifying questions for Dr. Oehninger? And if you do have any questions, please state your name first for the record before speaking. Dr. Burman?

DR. BURMAN: Ken Burman. Just a clarifying question on page 13, slide 26. In the new WHO guidelines 2010, the morphology, 4 percent with the variation given, is that 4 percent normal?

DR. OEHNINGER: Yes. That's the new threshold of normal sperm forms. The WHO has agreed. This is analyzing the sperm with the so-called strict criteria, which most fertility clinics probably have adopted by now.

DR. BURMAN: Thank you.

DR. LEWIS: Dr. Hanno?

DR. HANNO: Thank you. Phil Hanno. What is your take on giving such importance to the etiology of low testosterone in terms of how to treat it or whether to treat it? I'm just interested in that.

How do you see that?

In other words, primary -- classic versus not classic?

DR. OEHNINGER: I think the significance is to determine the etiologies because if you are able to treat a primary cause such as pituitary tumor, then you have another way of treating the patient. So in that regard, always it would be better to know for sure.

DR. HANNO: Right. But if someone comes in with a low testosterone and they don't have a primary cause, do you lean more toward not treating that person or -- like how do you see that as being the crux of the issue as we've heard earlier?

DR. OEHNINGER: Well, I see more -- the couples that I see more are more for fertility-oriented couples. So in the non-fertile population, I think it all depends on the severity of the signs of deficiency of testosterone. So once you reach certain thresholds, you probably want to treat them given the right medication to treat them.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: Glen Braunstein. We know from the studies from the European male aging study, that if you take obese individuals and have them lose weight, their testosterone goes up.

Do you know the effect of weight loss in obese individuals on semen parameters?

DR. OEHNINGER: Good question. I think we need more studies to address that question. I don't know of any real data that addresses that. When we deal with these men, definitely weight loss is a way of trying to approach the problem just like treating the female with PCO and obesity to lose weight. But I think we need more studies to know how much weight loss influences any sperm recovery, depending on testosterone.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: So you had on slide 40 and 41 a study involving gonadotropin releasing hormone in azoospermic men. Have there been any other studies involving men with low sperm count, oligospermia, where any agent has increased fertility or shown

signs of doing that?

DR. OEHNINGER: Well, yes. These are particular men that have hypothalamic pituitary hypogonadism, and those are the ones that will respond very well to exogenous -- typically will respond very well to exogenous testosterone. But in the majority of patients we see in the fertility clinic, these are not -- many of them do not have any pituitary deficiency. They have normal FSH/LH.

In those men with oligospermia, or severe oligospermia, that have normal FSH/LH, we and many others have tried exogenous gonadotropins. Those usually do not result in any improvement in sperm count in those cases, normal gonadotropin men.

MS. SORSCHER: And you didn't find anything in the literature addressing that population with the --

DR. OEHNINGER: Say that again.

MS. SORSCHER: You're describing clinical practice, but I was asking if there were any published studies?

DR. OEHNINGER: Yes, there are published

studies. Yes.

MS. SORSCHER: And there's no effect on sperm count for men --

DR. OEHNINGER: Right. Yes.

DR. LEWIS: Thank you. Dr. Sandlow?

DR. SANDLOW: Hi. Jay Sandlow. I would like to clarify the reference ranges for the new WHO guidelines. That 15 million per milliliters, actually the 5th percentile of fertile men, so that would not be something we would consider normal sperm count. So I think we have to take that in consideration when we're talking about endpoints.

DR. OEHNINGER: Yes.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: Just to clarify, certainly there are a number of published studies that have looked at azoospermic men with attempts to treat them either with gonadotropins, or SERMs, or aromatase inhibitors. And unfortunately, most of those studies were uncontrolled, so there's a small proportion of men who are azoospermic with medical therapy who will have sperm detected in the

ejaculate. There's also some control patients who probably would have it detected as well. So the efficacy is not well demonstrated, but it's been published in a number of different studies.

DR. LEWIS: I'll go, and then you can go. I think this was a really good overview. Thank you. I do have one sort of general question/comment. You talk a lot about a repletion of testosterone, and I assume you're talking about total testosterone. Could you comment on the importance of free versus total, especially for an obese population?

DR. OEHNINGER: Well, I think that those are points also that are somewhat controversial, whether you measure the morning testosterone or you measure 24-hour testosterone, and how significant it is to assess the testosterone to estrogen ratio.

I think that we deal more with the definition of testosterone with the morning testosterone measure under 300 nanograms per deciliter. It's an interesting question, but I cannot give you a straightforward answer there.

DR. LEWIS: Thank you. Dr. Chai?

DR. CHAI: Toby Chai. I was wondering, are there any ways to determine the resilience of a hypothalamus pituitary testicular axis, any testing to look at the reserve or response, and look at that phenotype and look at who might be treated?

DR. OEHNINGER: Are you talking about central causes where there is hypothalamic pituitary deficiency?

DR. CHAI: Well, that could be part of it. I was just thinking about the whole unit as a unit to test and probe who might be more responsive, because the concept is this isn't I think a uniform state of one or the other, and there's probably a range within the different types, whether it's primary or -- well, obviously primary is testicular failure, but in terms of secondary --

DR. OEHNINGER: Right. But even within the central, there are variations. But the definition, if we agree, is not of adult onset hypogonadism where the pituitary levels may be normal or not. So there are degrees of this abnormality. So I'm

not sure how you can re-identify or create an algorithm to define those differences.

DR. LEWIS: Anyone else?

(No response.)

DR. LEWIS: Okay. Thank you.

At this point, we'll move on to the industry presentations.

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 advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, interest in a sponsor, including equity interest and those based upon the outcome of 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 presentation, it will not preclude you from speaking.

We will now proceed with industry presentations.

Presentation - Michael Wyllie

DR. WYLLIE: Good morning, and thank you very much. My name is Dr. Mike Wyllie. I'm a simple scientist. I have no clinical perspective. And my role here is actually to moderate what I hope is going to be an action-packed hour or so. By way of disclosure -- and I will make a disclosure on behalf of everyone at the end of the presentation, but I am actually on the Repros Board.

First of all, I would like to thank Dr. Joffe and his colleagues for setting up this forum with a very, very clear agreement. I think we all know why we're here and what's expected of

us. I just want to reiterate for the record that although we have this in several occasions, the objective is we're here to discuss the appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis.

So what about the presentations you're going to hear over the next few minutes? Our presentations are designed to give the panel enough information to help the discussions and answer the questions. This is a wee bit unusual, the Scots would say as well, not because this is not really a product-oriented outcome, but it's a non-product oriented outcome that covers three different drug classes, different indications, and potentially different proposals.

The sponsors are itemized here. There's MHB Labs, and they have a novel formulation of hCG. Veru, they're going to make a presentation as well of talking about SERM for infertility. And then

bringing up the rear is Repros. They're going to talk about estrogen antagonist for obesity-associated secondary hypogonadism.

So this could take forever, but we're in a fortunate position that all three companies obviously agree on the need for non-testosterone therapies, so that's the starting point. So what we're then going to do is to try and condense as much of the generalities into an overview at the start, and then we're going to look at each sponsor and give them a few minutes to talk about their own particular potential clinical trial design; otherwise, it would be a little bit like trying to describe the whole of incontinence in one talk, when we know there's stress incontinence, overactive bladder, and lots of associated with BPH. We think that's the easiest way to do this, and I hope that everyone feels that is appropriate.

Here's the agenda. An apology for those that looked at the published agenda. There's a slight change in the order but not in the handout given to the agency, so it's as you're looking at

just now. And in terms of disclosure, as I promised, there are the presenters here, all the experts, and there are a few experts apart from the ones in the panel sitting behind you as well. All are either company employees or have received expenses to come to this meeting and also in recognition if there's any lost time in their clinical practice.

So at this point, hopefully I've given you the introduction and our objectives, and we'll start with the formal agenda, so over to Dr. Khera.

Presentation - Mohit Khera

DR. KHERA: Good morning. I'm Mohit Khera. I'm a practicing academic urologist at Baylor College of Medicine in Houston, Texas. Today, I'd like to discuss treatment considerations for secondary hypogonadism.

First, I would like to define secondary hypogonadism. Secondary hypogonadism, also known as hypogonadotropic hypogonadism, is defined by low serum testosterone concentrations in association with low or normal serum concentrations of

luteinizing hormone. Testosterone may be inappropriate for the treatment of many cases of secondary hypogonadism. There is a clinical need for non-testosterone to treat secondary hypogonadism.

There are several disadvantages with testosterone supplementation. These include suppression of testicular androgen production; suppression of spermatogenesis that may cause infertility; increased risks of androgen abuse and dependence; and finally increased risk of transference to children and women.

There are three non-testosterone approaches for treating secondary hypogonadism, which I'd like to present to you today. The first is direct stimulation of testicular Leydig cells, the second, estrogen receptor antagonists, and finally selective estrogen receptor modulators, also known as SERMs.

There are several advantages of non-testicular formulations over conventional testosterone formulations. These include

preservation of testicular volume; maintenance or improvement in spermatogenesis; decreased potential for misuse and abuse; and finally, a decreased potential for accidental transference.

In order to understand the mechanism of these non-testosterone formulations, one must understand the hypothalamic pituitary gonadal axis. GnRH is secreted from the hypothalamus in a pulsatile fashion. This in turn increases LH and FSH secretion from the anterior pituitary. FSH stimulates sertoli cells, which then produces testosterone -- excuse me, sperm from the testicles, and LH stimulates Leydig cells, which then produces testosterone. Both testosterone and estrogen negatively feed back on the hypothalamus and anterior pituitary, resulting in a decrease in FSH and LH, and thus a decrease in testosterone and sperm production.

The mechanisms of these three non-testosterone formulations are depicted in this illustration. The first formulation involves using products that would directly stimulate LH

production and bypass the hypothalamus and the anterior pituitary.

The second formulation is a estrogen receptor antagonist, which blocks estrogen receptors in the hypogonadism and anterior pituitary. This in turn inhibits the negative feedback from estrogen and results in an increase in LH and FSH. And finally, SERMs, which also bind to estrogen receptors in the hypothalamus and anterior pituitary. SERMs serve as antagonists within the brain and have very similar mechanisms of action as estrogen receptor antagonists.

The first non-testosterone approach is direct stimulation of testicular Leydig cells. The goal is to stimulate LH receptors on testicular Leydig cells to produce testosterone. Human chorionic gonadotropin, or hCG, directly binds LH receptors in the testis and stimulates Leydig cell production of testosterone. hCG has also been shown to be an effective treatment for restoring serum testosterone levels in the normal range. hCG has long been used for the treatment of male

infertility.

The second approach is the use of estrogen receptor antagonists. Estrogen receptor antagonists block estrogen receptors in the hypothalamus and pituitary. These antagonists block the normal negative feedback of circulating estradiol. The net result is an increase in LH secretion, which leads to an increased testosterone production.

The third approach is the use of SERMs. SERMs competitively bind to estrogen receptors in the hypothalamus and pituitary gland. SERMs differ from pure estrogen receptor agonists and antagonists in that their action is different in various tissues. It's important to realize that in the brain, SERMs act as antagonists. The net result is an increase in LH secretion, which leads to increased testosterone production. Some studies have found improvement in sperm production with the use of SERMs.

Next, I would like to discuss the advantages of treating secondary hypogonadism with non-

testosterone formulations. The first advantage is the maintenance or improvement in spermatogenesis. Realize that exogenous testosterone serves as a natural contraceptive. Exogenous testosterone significantly decreases LH and FSH production from the anterior pituitary, which subsequently results in decreased production of sperm and testosterone from the testis. The end result can be azoospermia and testicular atrophy.

In an earlier study by the WHO, they assessed the use of testosterone therapy for male contraception. They gave 271 men 200 milligrams of testosterone enanthate every week. Sixty-five percent of these men became azoospermic at 6 months. The mean time to azoospermia was 120 days. In terms of sperm recovery, 84 percent were able to achieve a sperm density of greater than 20 million at a median of 3.7 months. However, only 46 percent of men were able to return to a baseline sperm density at an average of 6.7 months.

The second advantage is preservation of

testicular volume. In this earlier study by Palacios et al., they assessed the effects of exogenous testosterone on testicular volume. Thirty-nine hypogonadal men were treated with 200 milligrams of testosterone enanthate weekly or bi-monthly for 4 months. Fifty-four percent of the men had testicular atrophy at 4 months.

In those men who were treated with weekly or bi-monthly testosterone enanthate, they experienced a 19 percent and 16 percent loss in testicular volume, respectively. Of the 46 percent of men that did not experience testicular atrophy, up to 12 additional weeks of testosterone therapy resulted in a 23 percent loss in testicular volume in 76 percent of these men. A decrease in testicular volume was directly related to a decrease in sperm count.

The third advantage is decreased potential for misuse and abuse of testosterone therapy. This year, the FDA added a new warning regarding the risk associated with abuse and dependence of testosterone in other anabolic androgenic steroids.

Unlike conventional testosterone formulations, non-testosterone formulations rely solely on the testicles' ability to produce testosterone. Thus, non-testosterone formulations are unlikely to achieve supraphysiologic levels of serum testosterone as seen with exogenous testosterone formulations.

The last advantage is the decreased risk of transference. As many of you are aware, topical testosterone products carry a black box warning for the risk of secondary exposure and transference. Non-testosterone formulations would not carry this same risk.

I would like to summarize with these last two slides. There are several distinctions between conventional testosterone formulations, such as testosterone gels and injections, and non-testosterone formulations, which I've discussed previously. All of these formulations restore serum testosterone levels. However, while conventional testosterone products have been show to suppress spermatogenesis, non-testosterone

formulations could potentially maintain or restore spermatogenesis.

Similarly, while conventional testosterone products have been shown to suppress intratesticular testosterone production, non-testosterone formulations could potentially maintain or restore intratesticular testosterone production.

As discussed earlier, treatment with conventional testosterone formulations can result in testicular atrophy, while non-testosterone formulations could potentially maintain and restore testicular volume. And finally, testosterone gels currently carry the risk of transference and potentially would not be seen with non-testosterone formulations.

Thank you for your attention. Next, I'd like to introduce Dr. Edward Kim, professor of urology at the University of Tennessee, to discuss sperm concentration endpoints for fertility.

Presentation - Edward Kim

DR. KIM: Good morning. I am Edward Kim,

and I am a practicing urologist in Knoxville, Tennessee. I will be discussing why sperm concentration as a measure of impaired spermatogenesis is an appropriate treatment endpoint for infertile men with hypogonadotropic hypogonadism. I will then provide a specific example of how sperm concentration can be used in a clinical trial.

I'd like to start out first with the Endocrine's Society Guidelines definition of hypogonadism. This guideline states that hypogonadism in men is a clinical syndrome that results from the failure of the testis to produce physiologic levels of testosterone. This is the androgen deficiency component and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic pituitary testicular axis.

The important point from this definition is that an abnormal sperm concentration is an important criterion for determining the presence of hypogonadism in infertile men. Although sperm

concentration is not necessary or used clinically for evaluating the broad population of hypogonadal men, its use is critical for assessing the severity and guiding treatment decisions in male factor infertility.

The next definition that should be highlighted is infertility. According to the American Society of Reproductive Medicine, infertility is the inability to achieve a pregnancy through natural means after one year of trying. Natural means does not refer to intrauterine insemination or in vitro fertilization, also known as IVF.

In some form, the male factor is contributory to 50 percent of infertile couples. When looking at men with infertility, oligozoospermia, and hypogonadotropic hypogonadism, we recognize that this subgroup of men is relatively small. By our estimation, 16,000 to 56,000 U.S. men may have this condition annually. For clinicians, this presentation is well recognized because we commonly evaluate this

population with a testosterone level.

The semen analysis has become the key clinical laboratory test for male factor infertility. For example, the American Society of Reproductive Medicine states that semen analysis is the cornerstone of the laboratory evaluation of the infertile male and helps to define the severity of the male factor.

According to the World Health Organization's fifth edition laboratory manual, also known as the WHO manual, semen quality is accepted as a validated measure of male fertility in reproductive toxicology, epidemiology, and pregnancy risk assessments.

Sperm concentration is a direct measure of spermatogenesis. Clinicians use sperm concentration as an important endpoint for decision-making, referrals, and use of assisted reproductive procedures. As an example, we use sperm concentration, not motility, morphology, or total motile count, as the primary basis for genetic testing or for further consideration of

endocrine evaluation.

The WHO manual for the evaluation of human semen is the recognized reference for a normal semen analysis. A sperm concentration of greater than or equal to 15 million sperm per milliliter is considered to be normal. The term "oligozoospermia" is impaired sperm production below the lower reference limit of normal. The clinical relevance is that oligozoospermia correlates with reduced spontaneous fertility in the male. Oligozoospermia is a primary basis for interventional treatments such as assisted reproductive techniques, namely intrauterine insemination, also known as IUI, and IVF.

I would note that the WHO manual does not reference total motile count as a clinically useful assessment of fertility as there is no consensus as to what constitutes a normal total motile sperm count. Of all the parameters that likely relate to natural pregnancy outcomes, sperm count and morphology are the only parameters that have been associated with time to natural pregnancy.

Motility is less predictive. For men who have oligozoospermia and hypogonadotropic hypogonadism as a cause for male factor infertility, improvement in sperm concentration is an acceptable clinical benefit. To understand the clinical relevance of sperm concentration in male infertility, let's take a look at how the WHO defined reference ranges of normal.

The WHO studied fertile men from 14 countries who were able to initiate a spontaneous pregnancy within 12 months. The study of fertile men was a significant and meaningful advance from the 4th edition manual. The key finding that is used clinically is 15 million sperm per milliliter.

Fifteen million sperm per milliliter is the 5th centile for sperm concentration in men who fathered a child within 12 months of unprotected sexual intercourse. This methodology was determined to be an acceptable analysis for determination of a normal reference range with an outcome of spontaneous pregnancy. In contrast, total motile count does not correlate with

spontaneous pregnancy, but with a more invasive treatment known as IUI.

Treatment for oligozoospermic men with hypogonadism should not be measured by a couple's outcome, but by rather the improvement in sperm concentration. Analysis of pregnancy rates results in the introduction of female factors that confounds interpretation of effects of a drug on spermatogenesis. Hypogonadism is defined as an abnormal number of spermatozoa and diminished production of testosterone, not by the inability to initiate a pregnancy.

Sperm concentration correlates with time to spontaneous pregnancy. An increasing sperm concentration was directly linked with an increasing probability of conception up to 55 million sperm per milliliter. In other words, the higher the sperm count, the quicker the time to pregnancy. These results confirm what we see in clinical practice. This is why our goal is to improve sperm counts.

There has been debate about the use of total

motile sperm count as an outcome measure for male fertility. With this table, I'd like to highlight several important differences. First, there's no accepted normal for total motile sperm count. In contrast, a normal sperm concentration has been defined as greater than or equal to 15 million sperm per milliliter by the WHO.

Second, sperm concentration was defined by the WHO as a measure of spontaneous pregnancy. Total motile sperm count has been used as a guide for intrauterine insemination, an assisted reproductive technique that does not correlate with spontaneous pregnancy. These paths to pregnancy are quite different. Finally, sperm concentration is utilized by society guidelines for clinical decision-making. While total motile sperm count incorporates motility, it is not used by society guidelines.

MSS-722 represents a specific fixed combination of trans- and cis-clomiphene isomers as an oral tablet. It is being developed to treat infertile men with oligozoospermia caused by

secondary hypogonadism. As a selective estrogen receptor modulator, clomiphene stimulates endogenous testosterone production. It is currently being used off label to treat men with oligozoospermia. The current approved indication is for the treatment of ovulatory dysfunction. Currently, there are no FDA-approved oral therapies for male infertility.

In a meta-analysis from 2013, Chua reported a statistically significant increase in sperm concentration and pregnancy rates. Results have been inconsistent for a number of reasons. Potentially important factors are the inconsistent blend of cis- and trans-isomers in generic formulations, lack of an established dose or schedule, and inconsistently defined patient populations.

To assess clinical benefit, the clinical trial will be a randomized, double-blind, placebo-controlled study. Patients eligible must have male factor infertility with a sperm concentration of less than 15 million sperm per

milliliter and a low testosterone level due to hypogonadotropic hypogonadism. Patients are treated for 2 cycles where each cycle is 2 and a half months. Two and a half months represents the approximate time required for one cycle of spermatogenesis.

At the end of 2 cycles, a semen analysis is collected and sperm concentration is measured. The primary efficacy endpoint will be sperm concentration after 2 cycles representing 5 months total time. The primary analysis will be the percentage of men who have normal sperm concentration, meaning greater than 15 million sperm per milliliter in the drug versus the placebo group as a responder's analysis. Sperm concentration will also be determined after a 3-month recovery phase off drug to assess the durability of treatment.

Men who have a normal sperm concentration are considered a responder. Men who still have an abnormal sperm concentration are considered non-responders. Clinical benefit is a higher

number of responders in the treatment group versus placebo.

The expectation is that this product will be used for the acute treatment, meaning less than or equal to 5 months, of oligozoospermia in men with hypogonadotropic hypogonadism as a cause of male factor infertility. Men who will remain oligozoospermic will be referred for more aggressive treatments. Testosterone levels are not intended to be a primary endpoint of study.

Let us recall that the definition of hypogonadism includes a failure of the testes to produce a normal number of spermatozoa. Based on this definition, the measurement of sperm concentration should be a valid clinical endpoint for the assessment of a treatment for hypogonadism in male infertility. Sperm concentration is the cornerstone of the laboratory evaluation of the infertile male and helps to define the severity of the male factor. This testing helps define what additional testing, treatments, or procedures may be required.

Because the WHO 5th edition defines 15 million sperm per milliliter at the lower reference range of normal, it's cut-off represents an established clinical endpoint. Remember that 15 million sperm per milliliter was determined to be clinically relevant because of its correlation with the initiation of spontaneous pregnancy.

MSS-722 will be used to treat infertile men with oligozoospermia and hypogonadotropic hypogonadism. Using a responder analysis in a small but well-defined group of infertile men, sperm concentration can represent a valid endpoint for the treatment of hypogonadotropic hypogonadism. Non-responders may need more aggressive treatments such as IUI or IVF.

With that, I would like to turn the presentation over to Dr. Khera, who will be discussing human chorionic gonadotropin. Thank you.

Presentation - Mohit Khera

DR. KHERA: I would next like to discuss human chorionic gonadotropin, or hCG, as a

non-testosterone formulation for the treatment of secondary hypogonadism. hCG is a natural occurring hormone. It is currently the only approved drug for the treatment of secondary hypogonadism. There are over 40 years of clinical experience and regulatory approval with hCG. As mentioned earlier, hCG directly acts on Leydig cells of the testis to increase endogenous production of testosterone. There are currently new formulations in development.

hCG is best known as a serum marker for pregnancy. It is produced by syncytiotrophoblast cells found in the placenta and in the gonads. It mimics the action of LH to bind endogenous testosterone production. Realize that hCG bypasses the pituitary and the hypothalamus, and acts directly on the testicles themselves, and thus is very effective for classical secondary hypogonadism.

There are currently several new clinical uses of hCG. hCG is best known as a fertility treatment to induce spermatogenesis in azoospermic

men with secondary hypogonadism. It is also used frequently to stimulate testosterone production in men with secondary hypogonadism. hCG has been used for preservation of fertility in men undergoing testosterone therapy. It has been used in the pediatric population to treat cryptorchidism. And finally, it's been used for ovulation induction in women.

hCG administration has been shown to increase serum testosterone values as seen in the following two studies. The first study by Liu et al, was a double-blinded, randomized, placebo-controlled trial of 40 men with androgen deficiency treated with hCG injections twice weekly or placebo. They found a stable increase in serum testosterone levels within normal range just after 3 months of treatment.

In the second study by Roth et al., they evaluated 37 healthy men who were first treated with GnRH antagonists and then treated with low doses of hCG daily or testosterone gel for 10 days. As seen in the graph on the right, they were found

to have a linear dose-response relationship between low-dose hCG and serum testosterone levels.

hCG alone or in conjunction with human menopausal gonadotropin or recombinant human FSH has been shown to restore spermatogenesis in some men with azoospermia and secondary hypogonadism. hCG therapy alone has also been shown to maintain sperm production for up to 2 years in previously azoospermia men.

hCG has been shown to preserve fertility and intratesticular testosterone production in men on testosterone therapy. In the first study on the left by Hsieh et al., 26 men were treated daily with testosterone gel or weekly testosterone injections. These men were also given hCG, 500 units, every other day for an average of 6.2 months. After 6 months, there was only a slight decline in sperm density and motility, which was not statistically significant.

In the second study on the right by Coviello et al., 39 healthy men were randomized to receive testosterone enanthate, 200 milligrams every week,

plus hCG at doses of zero, 125, 250, or 500 units twice weekly. Despite supraphysiologic doses of testosterone, high levels of intratesticular testosterone were maintained with administration of low-dose hCG.

Already approved indications for hCG are the following: patients with secondary hypogonadism as stated in the label; selected cases of hypogonadotropic hypogonadism in males; cryptorchidism not due to obstruction; and finally, induction of ovulation for female fertility.

There is currently a need for new hCG formulations. Current formulations are inconvenient as they require reconstitution of lyophilized powder, refrigeration after reconstitution, and self-injections 2 to 3 times per week. These inconveniences can be a challenge for patients to initiate therapy and also to remain compliant and persistent with therapy. Finally, there's a need for more convenient formulations such as longer-acting duration of action or greater stability.

The following are trial endpoints for new hCG formulations. An extended release hCG formulation in development is expected to follow current hCG indications. The FDA briefing document recognizes hCG as an effective therapy for men with classical secondary hypogonadism. The FDA approval paradigm for TRT is acceptable for patients with classic hypogonadism because replacing testosterone in these patients is clearly necessary for the development and/or maintenance of secondary sexual characteristics. It seems reasonable that new hCG formulations would follow the FDA approval paradigm for TRT.

In terms of clinical trial design features, hCG products would have the same inclusion/exclusion criteria as for testosterone products, plus an LH cut-off of less than 9 units. The trial design would demonstrate that new hCG formulations achieve key pharmacokinetic endpoints used for testosterone products as illustrated in the table on the right.

Products approved on the basis of this trial

would include a statement on the label that the effect of this drug on spermatogenesis has not been evaluated. Additional indications beyond classical secondary hypogonadism as preservation or improvement of spermatogenesis would require additional clinical endpoints.

Finally, this slide shows populations and trial endpoints for potential new hCG formulations. As mentioned before, it is anticipated that extended-release hCG formulations would pursue the approved classical secondary hypogonadism indication. For this indication, serum testosterone levels alone would be sufficient. If sponsors pursue additional indications or claims for male infertility, it would seem reasonable that they would be required to assess sperm concentrations as additional trial endpoints.

Thank you for your attention. I would next like to introduce Dr. Frederick Wu, professor of medicine and endocrinology, University of Manchester, to discuss diagnostic characteristics of hypogonadism in secondary hypogonadal

populations.

Presentation - Frederick Wu

DR. WU: Good morning. My name is Frederick Wu. I'm a professor of medicine and practicing endocrinologist based at the University of Manchester UK. In this session, I would like to discuss the importance of making a correct diagnosis of hypogonadism in men presenting with low testosterone and consider the implications for optimal clinical management.

Much of the information I'll present comes from published data generated by the European Male Aging Study or EMAS. To set the scene, this circuit diagram describes normal testicular function, which includes both androgen-driven secondary sexual characteristics and fertility, which is regulated by pituitary gonadotropins LH and FSH and the hypothalamic gonadotropin releasing hormone, GnRH.

In the normal man, the pituitary secretes LH, which stimulates synthesis of testosterone in the testes. Some of testosterone is converted to

estradiol via enzyme aromatase. Both testosterone and estradiol therefore provide negative feedback to the hypothalamus and pituitary, completing the control loop.

Now, this roadmap provides the core principle underpinning our routine clinical practice in which we diagnose hypogonadism in patients according to the presence of either testicular or hypothalamic pathologies, categorizing them into primary or secondary hypogonadism.

A vital important reason for making this differentiation is that while primary hypogonadism represent an end-organ failure of the testes, which is unresponsive even to high levels of gonadotropins, in secondary hypogonadism, the testes are only understimulated but still able to make testosterone and sperm if enough gonadotropins are present.

This same approach to differentiate between primary and secondary hypogonadism in clinical practice can easily be applied to segregate a

cohort of over 3,000 men, age 40 to 80, from the general population. By simply measuring testosterone and LH and using accepted thresholds for the abnormal -- so total testosterone of less than 300 nanograms per deciliter and LH of 9.4 units per liter -- we can split the men into 4 quadrants: eugonadal with normal T and LH, compensated hypogonadism with normal T and high LH, primary hypogonadism with low T and high LH, and finally secondary hypogonadism with low T and normal or low LH.

Accordingly, 12 percent of this population can be classified as biochemically hypogonadal with a testosterone less than 300 nanograms per deciliter. And you see that the majority of these men have secondary rather than primary hypogonadism.

Let's look at the causes of hypogonadism. In this slide, the key underlying causes of primary hypogonadism are shown, and you'll note that an important cause of secondary hypogonadism is obesity.

Now, you've seen this slide before, but allow me to show you the difference between BMI and age in terms of their respective hormone relationships. The top two panels show total and free testosterone levels stratified by BMI for normal, overweight, and obese represented by different colored symbols at each of the 5-year age bands. You can clearly see that increasing BMI from normal through overweight to obese is associated with decreasing total testosterone, which is independent of age.

Free testosterone also shows progressively lower levels of increasing BMI, which is also independent of age even though free testosterone declines more with age than total testosterone. The bottom two panels show the hormone relationships with increasing age. Stratifying the LH and SHBG data in the same way, you can see a very different pattern.

Increasing age is associated with progressively higher LH, which is independent of BMI, while SHBG on the right shows the effects of

increasing age as well as BMI. Putting these together with obesity, LH does not respond to progressive fall in testosterone, indicating functional hypothalamic pituitary suppression.

The EMAS cross-sectional data also evaluated various risk factors that could predict secondary hypogonadism. BMI emerged as the most important predictor. In fact, the risk was proportional and rose with higher BMI. But does BMI lead to low T or does low T lead to high BMI?

We looked at this in a group of men who were essentially eugonadal at baseline. A subset of 140 eugonadal men with normal testosterone levels at baseline subsequently developed secondary hypogonadism after 4.3 years of follow-up. Analysis of this prospective data shows that development of incident secondary hypogonadism in these previously eugonadal men was predicted only by obesity at baseline, but not any other potential candidate risk factors. This provides support for the contention that obesity predisposes men to secondary hypogonadism.

These men with obesity-associated secondary hypogonadism are an important group that is currently underserved, and this diagram is a simple visual aid to understanding this patient population. Of men 18 to 64 years in the U.S., approximately 35 percent will have a BMI above 30, and of those, 23 percent will have low testosterone and LH, evidence of biochemical hypogonadism. Of these men, 17 percent would be symptomatic and may potentially seek treatment.

So what are the symptoms that these men might report? Well, there are a plethora of symptoms, many of which are difficult to measure and present differently in individual patients. Some of the more specific symptoms and signs are shown on the left, but many men present with less specific complaints as shown on the right.

Because these men are symptomatic and deserve treatment, professional societies have developed treatment guidelines. These guidelines were published following changes in class A labeling for testosterone products, which

recommended that they be used only for classical hypogonadism. But you can see clearly that professional treatment guidelines continue to support the need for therapy in men with diagnosed hypogonadism, whether classical or non-classical in origin.

But how appropriate is testosterone therapy in patients with secondary hypogonadism who wish to have children? So let's look at the hPG axis diagram again. In the absence of other approved alternatives, the guidelines suggest exogenous testosterone. Exogenous testosterone treatment will inhibit the normal gonadotropic regulation of testicular functions, and treating secondary hypogonadism with testosterone will therefore further suppress gonadotropins, decrease sperm production, and prevent recovery of pituitary testicular function.

Men with secondary hypogonadism not only want to have the androgen deficiency symptoms improved, but many will also wish to have their fertility preserved. Their clinical needs are

therefore not met by testosterone replacement, and alternatives that can stimulate rather than suppress gonadotropins should be considered. Because of this, many patients are being treated currently with off-label Clomid to achieve that goal.

In conclusion, secondary hypogonadism associated with obesity is a reversible suppression of the hypothalamic pituitary function, which is well characterized and easily diagnosable. Current treatment guidelines recommend testosterone replacement therapy, but this is not optimal for these men. Other strategies to reverse the gonadotropin suppression in order to encourage recovery of endogenous testosterone safely while preserving spermatogenesis are preferable to exogenous testosterone in the treatment of men with secondary hypogonadism.

I'll now hand over to Andrew McCullough.

Presentation - Andrew McCullough

DR. McCULLOUGH: Thank you.

I'm a clinical urologist from Boston,

Massachusetts. My name is Andy McCullough, and I'd like to present the case for intervention at the level of the estrogen receptor in the treatment of secondary hypogonadism.

As we heard from Dr. Wu, obesity is the leading cause of secondary hypogonadism. Hence, if secondary hypogonadism is acquired via weight gain, it should be improved with weight loss. The Camacho paper notes that well. With weight loss, as seen on the left, we can see significant improvement in endogenous testosterone production. Conversely, as seen on the right, with weight gain, there's a significant decrease in testosterone.

So what's the connection with estrogen? Obesity results in increased aromatase expression. This increased expression causes a relative increase in estrogen compared to testosterone. As Vermeulen showed, the relative estrogen increase results in decreased pituitary LH release. Conversely, increasing LH results in an increase in testosterone.

We have 40 decades of experience with SERMs

demonstrating the increased LH in testosterone. Isn't an anti-estrogen a rational approach for the treatment of secondary hypogonadism in obese men? Let's look at the difference between the effects on LH release resulting from the use of anti-estrogen versus exogenous testosterone gel.

Here we see a comparison of enclomiphene and a topical testosterone sampled over a 24-hour period. As you may recall, Vermeulen showed that obesity dampens the LH release. The graph on the left shows that treating with an anti-estrogen enhances the LH release after 6 weeks, as shown in the green. In contrast, the graph on the right shows the dramatic suppression of LH secretion with exogenous testosterone treatment. In case you missed it, it's the green line on the X axis.

So although both exogenous testosterone and anti-estrogens increase serum testosterone levels, testosterone replacement products suppress LH release. As one would expect, suppression of the pituitary secretions leads to detrimental effects on spermatogenesis in a relatively short period of

time. This data represents 16 weeks of treatment.

On the other hand, raising endogenous testosterone via anti-estrogen therapy shows no negative effect over the same period. Not surprisingly, testicular size is also negatively affected when topical testosterone is used for the same period of time. And yes, this is important to some of the men that I treat.

So what kind of studies should be conducted to test the anti-estrogens in men with secondary hypogonadism who wish to preserve spermatogenesis? The population should be overweight or obese with secondary hypogonadism confirmed by measuring a morning testosterone and LH. Sperm concentration should be over 15 million. Subjects should be randomized to placebo or active treatment and treated for at least 12 weeks to ensure a complete sperm regeneration cycle.

The study should have co-primary endpoints. The first one should be responder analysis using a composite endpoint of the percentage of subjects ending treatment with normal morning testosterone

and sperm concentration. The second endpoint should be a noninferiority comparison to placebo of the percentage of subjects who end the study with a sperm concentration lower than 15 million.

In conclusion, we can accurately identify this population of secondary hypogonadal men. Today, they're getting testosterone. They deserve treatment that avoids the detrimental effects of testosterone replacement products. Maintenance of spermatogenesis is an important clinical benefit. When I took the Hippocratic oath, I was charged to do no harm and possibly do good. Isn't it time that we change the paradigm for the treatment of secondary hypogonadism? Thank you.

I'd like to give the podium to Mike Wyllie for the concluding remarks.

Presentation - Michael Wyllie

DR. WYLLIE: So I've got the largest task of bringing all this together and staying within the time, which shouldn't be a problem, under the agreement, which shouldn't be a problem either. So I'm just going to try and encapsulate what

hopefully we've learned or heard at least from the previous speakers. The formal presentations are finished, and I've only got two slides.

I'm going to start with the negative view on this, what it isn't, what we're talking about. Hopefully, we've seen, as demonstrated, it isn't idiopathic, there isn't any great age relationship, and it certainly isn't associated -- and I'm sure we'll come back to this with one specific sentence, pretty diffused symptomatology. There's a feeling it might be undiagnosable, but I'm certainly influenced by the clinicians in the room that the clinicians feel in general they can diagnose the condition.

The only thing is there's the temptation to say, well, it's not really an issue for us, but it's all around about us. Given my BMI and age, it's very close to home, and certainly listening to the clinicians, there's quite a lot out there in the real-life situation. So we can't duck the issue, and I don't think we intend to duck the issue. It's here and known and happening.

So what is it? It's often seen and diagnosable by clinicians. It's definable. It's commonly body mass dependent, and it's often estrogen dependent. There's a need for effective therapy, particularly in men wishing to preserve their fertility. So I'm just restating what the objectives of the meeting were. The reason we're all here is the need of a definition of a track for regulatory approval. We don't expect that necessarily today or even tomorrow, but I think this is an important part of the process, is to actually walk our way forward from where we are now.

So thank you very much for your attention, and hopefully what we've done is provide you with information that you the panel need to address the FDA's question in an educated fashion. Thank you.

Clarifying Questions to Industry

DR. LEWIS: Thank you. We'll now take clarifying questions for industry. We'll start with Dr. Howards.

DR. WYLLIE: If it's okay with the chair,

can I move to that podium there? Because I don't know who's going to respond.

DR. LEWIS: Sure.

DR. HOWARDS: I have a few comments, sort of editorial, relating to some of the discussion of semen quality. And I'd like anybody on the panel to respond as they deem appropriate.

First, I have a real problem with the term "normal." The World Health criteria do not define what's normal and what's not normal, and yet we've had that word over and over. Second, I happen to know from direct discussions with the leadership of World Health -- a leader of World Health, when the 2010 criteria were developed, that they were extremely unhappy with the methodology used by the chief scientist in charge, and they were very unhappy with the outcome. So I have a problem with the great emphasis on World Health criteria as the defining parameters.

I also have some problem with sperm concentration. Let me just give a little example. If a man had a volume of half a mL and had a

concentration of 15 per milliliter, that would be "normal." If a different man had a volume of 5 mLs and had 10 million per milliliter, that would be defined as abnormal. But which would you rather have in your army, 15 million soldiers or 7.5 million soldiers? I think it's absolutely intuitive that the more sperm you have, the better off you are.

And finally, clinically, although I was interested in the data that doesn't seem to substantiate this, I'm significantly influenced by the number of total motile sperm. So I think we need to talk about total motile and total number rather than sperm count. That is not in agreement with what we were just told, so I'd like your response.

DR. WYLLIE: I suggest the most appropriate person to address your issues is Dr. Kim.

DR. JOFFE: Please be sure, folks, to speak into a microphone.

DR. KIM: That was certainly a loaded commentary, and there are so many aspects of it to

cover. I think that we would all agree that male reproductive biology is fascinatingly complex. And when it comes to looking for one perfect test for fertility, it's certainly not out there.

So when I was tasked to try to put this all together, I remember a slide that was shown many years ago, and that's backup slide number 3, the one that you had up there. But we can -- I just have two slides to show on this topic.

One is on evidence-based medicine, and I think that -- I certainly don't make up the rules for sperm concentration, but I do rely on the guidance that's given to me. And putting everything together -- relevant scientific evidence, clinical judgment, patient values, and preferences -- I really had to fall back on the WHO criteria because I think it does represent the best level of evidence-based medicine that we have to date.

I would also go back to one slide, slide number 32 in the main presentation, and that addresses the topic of total motile sperm count

versus concentration. I'm very interested in hearing the discussion amongst the panel on total motile sperm count versus concentration. And again, when I went back to evidence-based medicine, this is the table that I came up with, and that is that 15 million sperm per milliliter is still the benchmark. But I certainly agree with the comments that if you have somebody with low volume, there is an issue checking concentration. However, show me a better marker than sperm concentration.

When it comes to total motile sperm count, the numbers are all over the place. And one of the biggest points I'd like to make is that what is hoped with the MSS product is to increase fertility by spontaneous methods, not by artificial methods. And total motile sperm count is excellent for -- or it's good for IUI/IVF, but it doesn't correlate that well with spontaneous pregnancy. I think we could discuss this for two hours or longer, but hopefully those bring up the salient points.

DR. LEWIS: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: This question is for

Dr. McCullough pertinent to this slide 75. So Andy, you did a very nice job of presenting what you'd recommend as a phase 3 trial. What I'm struggling, is we are conflating fertility and male sexual function a bit. And your proposed indication is for overweight, obese men with secondary hypogonadism who wish to maintain spermatogenesis.

So perhaps you or your colleagues can answer this question for me. What percentage of men who are middle-weight obese and have some symptomatic hypogonadism in terms of erectile dysfunction or some of the other issues associated with that, that we've seen as sort of the male andropause, what percentage of that population wishes to maintain fertility?

DR. McCULLOUGH: Excellent question. All I can say is if I have a younger obese patient who comes in, he may or may not in that moment desire fertility. But if I tell him that he has an option of taking a treatment that's going to impair his fertility or have a treatment that is not, 9 times

out of 10, he's going to choose an option, especially if he's married and his wife is sitting in the room, that's not going to impair his fertility.

So it's not that they're coming in and they're saying, well, I need fertility. It's like do you want a treatment that's going to cause a detriment to your fertility or not? Again, 9 times out of 10, they're going to choose a treatment that won't impair their fertility.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. Glen Braunstein. I actually have several questions, but I'll just ask one to start with. This is for Dr. Kim on slide 34. This is your clinical trial design for men who have oligospermia and secondary hypogonadism as a cause for male infertility.

If the goal of these patients is actually to appropriate, to have a child, that's why they're coming in, they're infertile, and they want to have a child, why just use a surrogate marker? Why not use pregnancy as the endpoint? We know that in a

randomized, placebo-controlled trial, the female factors and the couple factors should be randomly distributed. So if your drug is effective in improving fertility, not just sperm count, we should be able to see that in an adequately designed trial.

DR. KIM: Pregnancy outcome is certainly very important in the real world when it comes to addressing what our patients actually want. However, real-world biology is very complicated. I think in Dr. Oehninger's talk, he mentioned that female factor can be very complicated, as well as male. And when you put them together, you have a very complex phenomena.

So I would say that analysis of pregnancy rates results in the introduction of female factors, which can really make our analysis of what's going on for the male extremely difficult to weed out. When it comes to fertility, we have to factor in female age, female pathology such as polycystic ovarian syndrome, or tubule factors. Treatment biases always creep into this discussion

to say the least. And certainly, a lot of infertility, especially female factor -- and male factor, too -- is simply unknown.

So I think that if we're focusing on a medication that can improve spermatogenesis and lead to fertility, I would love to have pregnancy, but I think that spermatogenesis is perfectly appropriate because of bullet point number 2. And bullet point number 3 just shows that hypogonadism does include a number of spermatozoa in the definition.

DR. BRAUNSTEIN: Let me just reiterate. You can certainly look at both the male and the female and try to reduce as much as you can the female factors. But irrespective of that, if you have an adequately sized trial, and if it's truly randomized, the female factor and the couple factor issue should also be randomized. And therefore, if the male factor is taking care of by your medication, you should see a significant increase in pregnancy rate in that type of trial.

DR. KIM: So point is extremely well taken

in terms of randomization and placebo-control. I think I would go back to just a little bit of history in terms of the medications that have been approved for male fertility so to speak. When I was researching this, I asked the question, well, of the products that had been improved for male infertility, what criteria were used as their endpoints?

So I actually learned from the briefing document from the FDA that Gonal-F and Follistim, basically FSH type of analogs, are approved. And the endpoint that was used at the beginning of Dr. Joffe's presentation really looked at spermatogenesis. To make that leap from spermatogenesis to pregnancy outcome was based on a bridging study essentially, but for the current approval of Gonal-F and Follistim, it's based on spermatogenesis, sperm concentration, not pregnancy. So I would really go back to what's already been established and vetted out in the past.

DR. LEWIS: Thank you. Dr. Thomas?

DR. THOMAS: Abraham Thomas. This is for Dr. McCullough. It's back to the study design on slide 75. First, it says "total testosterone of 300," and I was wondering why they decided to use that because we know in this group, people who are obese, people who potentially are diabetic or insulin resistance, their total testosterones may be low because their sex-hormone binding globulin is low, and their free testosterone is probably normal.

So what are we really treating, and LH that's not low or very high; a sperm count that is at least above the 5th percentile? It's not clear to me what disease you're treating other than a number. And to bring it to something else, I would never treat a woman on oral contraceptives for a high total T-4 unless she has elevated T-4 and symptoms that match that.

So this study design, without some assessment of true hypogonadism, seems to be, to me, just treating a testosterone value, but may not be relevant to the situation. So it's a little

confusing to me why you would use these criteria.

Did you understand the question?

DR. WYLLIE: I'm sorry. I couldn't hear what you were saying. You're too far from the microphone.

DR. THOMAS: Sorry. I'll just say it briefly. Total testosterone is not a good measure using people who are obese, people who are insulin resistant because the sex-hormone binding globulin is low. So what are we actually treating because all the other parameters, even though they may be lower in terms of the sperm count, they are still considered above the 5th percentile. LH is not abnormal necessarily in this case.

And examples I'd say in other clinical diseases, if I put a woman on an oral contraceptive, their total T-4, thyroxin levels go up. But I wouldn't treat them for that unless they're truly hypothyroid. Their free levels are elevated, and they're symptomatic from that.

DR. WYLLIE: Thank you. I'm going to let Dr. Wu answer the question about the testosterone

issue in the obese men since that was the study that he designed.

DR. WU: Dr. Thomas, I think you're absolutely right that in the obese population with the decline in SHBG, it is important to take that into account, and using total testosterone is a starting point for recruiting potential subjects. But I think it would also be important to take into account either measured or calculated free T to take out the SHBG effect. And I think we have done recent studies, which was published earlier this year, showing that if you take the free testosterone into account, then you can define a much accurate group of hypogonadal patients who have hypogonadal symptoms.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I have a question for Dr. Kim and for Dr. Khera. The first is for Dr. Kim. This is returning to this question of fertility in men with low sperm count. We have a normal range, and we know that for fertile men, they tend to fall within this normal range. But we also know that

men under the range can be fertile.

You have this slide, slide 31, that looks at sperm concentration within the normal range and shows a correlation with time to pregnancy. But I'm not sure I can gather that all together and go from there to say that if you take men who fall below the normal range and bring them into the normal range, that that will have an impact on fertility.

So I was wondering if you could summarize, if you could, your case for that, that argument. And you mentioned the bridging study, and maybe you can talk more about that as well.

DR. KIM: Sure. I think there are two points that I'll address over here. One is whether bringing somebody into a sperm count of greater than 15 million, how does that correlate with pregnancy. Again, I would go back to the WHO Cooper study, and what that 15 million mark means is that 15 million is not so-called normal; it's not average. Fifteen million represents a cut-off point where 95 percent of fertile men will have a

count of greater than 15 million. So if you're less than 15 million, you're in the bottom 5 percent.

So can you establish a pregnancy if your count's less than 15 million? Yes, but it's not so easy. If you're more than 15 million, are you guaranteed to be fertile? As we all know, certainly not, but 95 percent of these fertile men had counts of more than 15 million. So as a benchmark, compared to any other metric that we have, morphology, total motile count, short of pregnancy, it's really the most established benchmark that we have. Everything else is still really controversial and investigational.

The second point I'd like to make is Dr. Oehninger in one of his slides -- I can't remember the exact slide, but it was a graph slide. And it showed that pregnancy over 15 million sperm per milliliter was used as that benchmark for sperm counts. And I think in Dr. Oehninger's slide that he used, 15 million was an appropriate benchmark for fertility, at least for natural conception.

Did I answer your question?

MS. SORSCHER: Yes.

DR. KIM: Thank you.

DR. LEWIS: Thank you. Dr. Gillen?

MS. SORSCHER: Oh, I'm sorry. I had a question for Dr. Khera, briefly. You talked about the outcome measure that you had proposed for your clinical trial, and I was just wondering -- because your focus was on classic hypogonadism -- whether you planned to restrict enrollment to that group?

DR. KHERA: So for these endpoint trials, I'm going to have Dr. Kacker answer that question.

MS. SORSCHER: Sure.

DR. KACKER: Hi. Good morning. My name is Ravi Kacker. I'm the CEO of MHB Labs and also a clinical instructor at Harvard Medical School. Our clinical trial's protocol is intended to follow the clinical trial protocol for testosterone products. So our inclusion and exclusion criteria would be the same as for testosterone products. We would have a rigorous screening with two morning testosterone levels, and we would restrict it to

patients with well-recognized causes of hypogonadism.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: Thank you. This question goes back to Dr. Kim and builds on Dr. Braunstein's statements, which I wholeheartedly agree with, about the hard clinical endpoint of live births. I think another way that you could think about the proposed trial design, though, is that one goal of therapy might be able to give patients that don't have options for artificial pregnancy, for example, more viable options.

So we have guidance that says that IUI is significantly more probable in terms of success if we have 5 to 10 million, for example, total motile sperm count. And the proposed trial design, just looking at total sperm concentration, will be mixing those individuals that may have a viable option in IUI, for example, that don't.

So I guess the question to Dr. Kim is should we be treating all of those patients the same in terms of an inclusion criteria for a study and then

thinking about that same outcome at the end of the day, or if we have individuals for which there is a threshold that we can get them to spontaneous pregnancy, should we be looking at live births in a trial as an outcome versus individuals that, for example, do not have the option even of a likely successful IUI treatment, for example, through artificial pregnancy?

Should we try getting them to a threshold that meets that likely successful IUI treatment? And in that case, should we be looking at total motile sperm count rather than, for example, concentration where we have more guidance?

DR. KIM: Yes. The question really relates, again, to total motile sperm counts, it relates to sperm concentrations, and it also relates to spontaneous versus assisted reproductive techniques. There's no question that there are certain thresholds below which if you have a total motile sperm count of less than 1 million sperm per milliliter, certainly spontaneous pregnancy, certainly IUI is not going to have a very good

chance of working.

The way I'm going to answer this question is to state that the hope with the MSS-722, the clomiphene, is that by raising sperm counts to a certain threshold -- and you have to draw a line somewhere, and that line was drawn at 15 million -- that spontaneous pregnancy would be much more feasible. But there are a number of men whose sperm count is so low.

So one of the questions that was being brought up in the questions that you are asked to consider is whether -- like for example, men with azoospermia and non-classical secondary hypogonadism should be included in the study. I would say that for those men, the likelihood, based on the published literature today, which is case series of those men actually establishing a pregnancy, is actually relatively low. That probably would not be the target population of the study, men with azoo. But men with oligozoospermia, maybe even severe oligozoospermia, can certainly be considered for a trial.

So again, it's really going back to the discussion of IUI, total motile, and we can show this slide. One of the studies that has been quoted is by Ombelet and Kruger, and it looks at total motile sperm count. Their conclusion -- and this is one that was referenced actually in the briefing document -- is that total motile sperm count urgently needs trial for predictive value of IUI. They talk about a lack of prospective studies and lack of standardization in semen testing methodology.

I don't think the time is quite here yet for total motile sperm count. And the next slide, another paper I had come across, was by Hamilton. And this is actually a relatively recent, a year or two ago, single, non-validated study, a spouse total motile sperm count. But again, motility is not a direct measure of spermatogenesis, and there's no consensus regarding a normal total motile sperm count.

If I ask the question, give me guidance as to what is a total normal sperm count, I think

there would be no consensus because there is no consensus in the published literature. It's a big gray zone right now.

DR. LEWIS: Thank you. Dr. Nahum?

DR. NAHUM: Thank you. This is a question that's going to be directed again to Dr. Kim. And specifically what I'd like to do is I'm going to try and wrap some numbers around some of the qualitative arguments that have been raised so far.

If you can bring up slide 31, I think that will be useful for everybody to see when I make the points I'm going to try and make here. Basically, I'm going to go back to the idea of this threshold of 15 million being normal as far as WHO is concerned, and this representing about a 5th percentile rank in a normal population of men.

My question relates specifically to this slide. You've made the point that raising sperm concentrations above 15 million would be a good thing to do because it would fall into a normal range. However, when I look at this slide, if I were to look at the 50 million mark, I'd come up

with about a 23 percent chance of pregnancy per cycle, whereas if I look at about the 5 to 10 million mark, I come up with about a 17 percent chance of pregnancy per cycle.

If I then go ahead and look at what 0.83 to the 12th power is for instance, which we'd come up with about a 90 percent chance of pregnancy if these are independent events over the course of a year for somebody with a sperm count of 5 million per cc, this to me is not that far outside of the normal expected range that most authoritative organizations would cite, which would be for normal fertile men having a 95 percent chance of pregnancy over the course of a year.

So the delta there is between 95 percent for the normal range versus 90 percent, or thereabouts, over the course of a year for people with sperm counts of 5 to 10 million, which to me calls into question the 15 million criterion for normalcy because it doesn't seem that different. And this goes back to the idea of clinical meaningfulness. I mean, how different does it need to be for it to

be clinically meaningful?

Now, you've alluded to the fact that you'd like a trial design with a responder analysis looking at those men who are enrolled in the trial, who have sperm counts of less than 15 million, and who make it over the 15 million threshold. This may not be clinically meaningful given what I've just outlined. And in addition, if you take people with sperm counts initially of 14.999 million and have them exceed the 15 million threshold after treatment, that may not be clinically meaningful.

So please address the idea that there's only a 35 percent difference on a per cycle basis for attaining pregnancy at 50 million per cc versus 5 million per cc, and address the questions I've outlined.

DR. KIM: So I think much of the question really relates to this particular study; numerous aspects in this question. But in this particular study -- and this was a European study. The primary author was from Paris, a Danish study also. And what they did was they queried I think about

900 women who were pregnant. They asked their husbands to provide semen specimens and then looked at the time to pregnancy.

This study is actually relatively frequently quoted in terms of being an accepted study for time to pregnancy and the examination of morphology and sperm concentration as predictive factors of pregnancy. And again, what they found in this study is that there was a relationship between the sperm concentration and probability of pregnancy per cycle when the sperm counts went from let's say the bottom, close to zero, to 55 million. Beyond that, the curve seems to flatten out.

I think that my message from this slide is that sperm concentration is a measure of time to spontaneous pregnancy. This slide itself doesn't address the 15 million, and I think it's important to realize that normal pregnancy per cycle in a supposedly fertile couple is in the range of about -- here's the benchmark, about 20 percent, maybe 20-22 percent. But it's certainly not 40 to 50 percent. So hopefully to directly answer that,

this slide really shows that there is direct correlation with sperm concentration and time to pregnancy up to a certain limit.

Now again, going back to the 15 million, which is a different part of the question but one that is certainly coming up quite a bit, what number does one pick? Fifteen million, to address Dr. Howards' point -- and I hope I didn't use the word "normal." I used the word "15 million" but that's where fertility, again based on the WHO criteria, comes into play.

Fifteen million is not normal. It's where 95 percent of fertile men have their count at least. So again, if you're less than 15 million, you're in the bottom 5 percent, but that is a cut-off that was used by WHO, despite the problems with the methodology of the study, to define where fertility really becomes more likely, not guaranteed but more likely.

DR. LEWIS: Dr. Bauer? I'm sorry. Were you finished?

DR. KIM: Yes, I am.

DR. LEWIS: Dr. Bauer?

DR. BAUER: You can stay at the mic for just a second. I don't mean to beat a dead horse, but I think all these values that you've shown us have been untreated in the natural setting. Is there any data to show that men with low sperm counts, who then are treated pharmacologically, or with weight loss, or whatever, what is the relationship between their change in sperm count and their likelihood of having a normal pregnancy?

DR. KIM: With regard to obesity and pregnancy -- the question was brought up beforehand -- for your morbidly obese patient who has let's say gastric bypass surgery, T levels will increase; sperm counts will increase. Those studies are reasonable, but they're not real high levels of evidence.

In terms of pharmacologic therapy for increasing sperm counts, the best studies that were approved were the Follistim and Gonal-F studies for FSH, and they took men who were azoospermic and took their concentrations to over 1 million as

their endpoint. But beyond that, there are no other approved medications for male fertility, and part of that is that there is still a vast gap in our knowledge base with regard to pharmacologic therapy and male infertility.

So no, this is just --

DR. BAUER: Just to clarify then, so there are no data that take infertile men with low sperm counts, provide a treatment to them, look at their pregnancy outcomes, and then relate that to the change in their sperm counts; is that correct?

DR. KIM: Dr. Schlegel, a question, or a response, or should I answer that?

DR. SCHLEGEL: Do you want to respond to that [inaudible - off mic].

DR. KIM: Oh, okay. I will respond to that. So the answer is, if the question is does improving sperm count improve fertility, the answer is of course it does; not for everybody. But my answer was specifically based for pharmacologic therapy. Other than our Gonal-Fs/Follistims, it's still a big gray zone.

Now, I mentioned a meta-analysis by Chua published in 2013 that looked at clomiphene on the best level of evidence. They did see an increase in sperm concentration. They did see an increase in pregnancy rates. But those are a meta-analysis of studies, not for regulatory approval of a medication.

So yes, there's an abundance of evidence that raising sperm counts improves fertility, but for the purposes of getting a drug to market for male infertility, I think that's what Veru would like to show.

DR. LEWIS: Dr. Curtis?

DR. CURTIS: Kate Curtis. So yes, I think the clinical endpoints for sperm may be different for men with low sperm infertility versus for men with normal sperm and the goal is to preserve spermatogenesis. So I wanted to talk about that group of men, and we've heard that this 15 million cut-off is not normal; it's the low point. So for this group of men who have normal sperm, I was wondering if you could talk about the proposal to

use that 15 million as your endpoint rather than using some meaningful difference from baseline.

DR. KIM: Right. Excellent question. So if we switch gears and look at men who have let's say an average sperm count, normal if we use that term -- let's say they have a sperm count of 80 million sperm per milliliter, and we say, well, going down to 15 million sperm per milliliter, that's a pretty big decrease, but is that really meaningful? Should we look at let's say a percentage decline?

So the history of this is that when Cialis was approved, sperm issues, sperm concentrations were a question because of PD11 in the testis. And the paradigm that was used back at that point was to look at the decrease in sperm concentration. And the benchmark that was accepted by the FDA at that time was a 50 percent decline in sperm count. Where did that come from? It was purely arbitrary. There were really no studies on that, but that was the endpoint that was used in the past.

So when the thought of 15 million, how does

this come along, or in the ZA-304 and 305 studies, how is 10 million or 15 million selected? Initially when the studies were proposed, the benchmark was going to be 15 million per milliliter. That was the initial proposal.

The feedback from the agency was, well, we don't know whether 15 million is really appropriate. We should consider looking at 10, or maybe 20, or maybe consider total motile sperm count. But my understanding was that when everything was said and done, a sperm concentration was felt to be reasonable, and 10 million was selected. But actually, when you looked at the data between 10 million or 15 million sperm in the 304 and 305 studies, it really didn't make that much of a difference in terms of final analysis.

So to answer your question, a percentage decline has been used once in the Cialis studies, but it was purely arbitrary. So to pick a number, 15 million was felt to be reasonable based on WHO criteria as the best evidence. I think that was more supported than looking at a percentage

decline. We're kind of charting new territories, but I think that's what we're all here for, is to hear the proposals and to determine what may be the most reasonable route to endpoints.

DR. LEWIS: Thank you. Dr. Hanno? Dr. Chai?

DR. CHAI: I have a question for Dr. Wu on slide number 59, the Rastrelli study, just two questions. One is can you comment about the age group greater than 70? It looks like there's actually a protective effect against development of secondary hypogonadism. I pulled up the abstract of a paper, and they found in this study that biochemical reversal of secondary hypogonadism to eugonadism was not accompanied by significant symptomatic improvement. Can you comment about why you think that is?

DR. WU: Yes. We have actually just done further analysis on this. May I be allowed to show some backup slides for that to answer your question?

DR. LEWIS: Yes.

DR. WU: Yes. We have divided that group of 140 men into those that have not only low testosterone but also low free testosterone, which is addressing Dr. Thomas' earlier point. And the low free testosterone in this case is less than 170 people, which is about 5 picograms per mL. And you see that in these men, when they develop secondary hypogonadism, there were significant symptomatic worsening or incident symptoms.

Actually go to the side before. If we looked at those people who had low testosterone but actually normal free T, there are no symptoms. They did not develop any symptoms. So our interpretation is that in that original Rastrelli paper, which only used total testosterone, this is the group of people who reversed. And in fact, that turns out to be the case, that the reversal rate in this group is much higher, in fact exclusively in this group, and that's why there were no symptoms change after apparent reversal. It's because their free testosterone is actually normal either at baseline and also during

follow-up.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: Question for Dr. McCullough. There's been increasing recognition I would say over the past decade or so that estradiol levels specifically play a significant role in skeletal health, not just in women but also in men. And there's a recent paper -- there's been epidemiologic data published from Minnesota, also from Sweden, and then a recent interventional study actually from MGH from Joel Finkelstein and the endocrine group, which showed that when they blocked the conversion of testosterone to estrogen, and then replaced back with testosterone, over the course of 16 weeks, men lost about 1 percent of bone mineral density, just over 16 weeks. And importantly, they add about a 10 percent increase in cortical porosity, which we think is an important part of fracture risk.

So how do you reconcile that with plans to antagonize estrogen actions?

DR. McCULLOUGH: I'm going to let Joe talk

on that issue, on the osteoporosis.

DR. DRAKE: Sure.

DR. WERNICKE: Thank you. I'm Joe Wernicke, chief medical officer of Repros Therapeutics. We have some data that -- and I'll explain how we got that. But first I want to just remind everybody that drugs, and even SERMs, are not all the same. They're all in the same big bucket, but each of them is unique in its binding capacity and its properties. It's a little bit like saying all antibiotics are the same, and obviously that's not the case.

Repros is developing enclomiphene pure estrogen receptor antagonists, and we did a one-year study because of that very question that came up. And if I could put that slide up. We did a one-year study looking at bone marker by DEXA, and we see that there is really no effect. If anything, there was a statistically significant improvement with a low dose of enclomiphene, but we think that's noise. So at least for this drug -- and I can't speak to others -- there is no

effect on bone.

DR. LEWIS: Thank you. We'll take a couple more questions before the break, and then there may be some more time -- during the discussion, there will definitely be more time to bring up other points. Dr. Schlegel?

DR. SCHLEGEL: If we can go back to slide 75 just to clarify. In the scenario of patients who have a low testosterone and an elevated LH, which is what's shown on this slide, that would be primary hypogonadism. I believe you mean LH less than 9.4, which would be secondary hypogonadism. Is that correct?

DR. McCULLOUGH: That is correct, and that's the criteria for secondary hypo, and that is a typo.

DR. LEWIS: Thank you. Mr. Bishopric?

DR. BISHOPRIC: Dr. Bishopric. Thank you. A general question, there's a lot of emphasis obviously on pregnancy and fertility as an outcome, but are the men being considered for treatment coming in because of sexual function and general

health, or are they specifically coming in for a desire to generate a pregnancy? I think that is important.

DR. WYLLIE: Would you like any particular physician to answer that?

DR. BISHOPRIC: No, a general question.

DR. WYLLIE: A general question? Perhaps Ed, Ed Kim first of all.

DR. KIM: I think that what's being presented in this forum are actually three different companies that have three different patient populations. For Repros, these are men who are coming in with symptoms not of fertility, but these are men who are coming with symptomatic hypogonadism, or low Ts, that want to potentially be fathers in the future, but they are not actively seeking to have children.

Veru's product, the MSS-722, is looking specifically at men, regardless of symptoms of fatigue or whatever -- they are looking at men who have low sperm counts and are infertile. That's the specific group. HCG is looking at men who have

classic secondary hypogonadotropic hypogonadism who are interested in having children. So three different groups, three different presentations.

DR. LEWIS: Thank you. One last question, Dr. Sandlow. We'll be able to get additional questions later.

DR. SANDLOW: Sure. Just a quick one, Ed, before you sit down. You had mentioned in your study these are all going to be men with both infertility and hypogonadism; correct?

DR. KIM: Yes.

DR. SANDLOW: So why wouldn't you want to use testosterone as another primary endpoint because that is one of their -- that's part of the inclusion criteria.

DR. KIM: Right. The question is for infertile men, for the MSS product, why not use testosterone as a primary endpoint. It would not be a primary endpoint because the primary goal of the study is to raise sperm concentrations. Raising testosterone levels, I certainly feel that it will. It will probably be a secondary endpoint,

but I think the concern is that simply raising T is -- one of the concerns that's been brought up by the agency is that simply raising T is not good enough as a marker.

We're trying to tie in the specific problem, low sperm counts, to the effect of the medication. So that's why sperm concentration has to be the primary endpoint, not the testosterone level. But I think that from clinical experience, anyone in here that's used clomiphene to treat men who have hypogonadotropic hypogonadism knows that, yes, of course it raised testosterone levels.

The question is what else does it do, and that's what we're trying to figure out here. Veru says maybe it can improve fertility. Repros says it preserves spermatogenesis, which is important because what we have out there right now are FDA-approved products fail us in that regard.

I think that one of the reasons that clomiphene use has increased throughout the years is that we realize the shortcomings of testosterone therapy on men who desire to preserve their

fertility. We all know that testosterone therapy is bad for fertility, maybe in this room, but I'm telling you, in the general population of physicians, it's still not really out there. I see patients every week that come into me on testosterone therapy that are trying to have kids, and would go, "Whoa. Somebody missed the boat over here."

DR. LEWIS: Thank you. We will take a break until 11.

(Whereupon, at 10:49 a.m., a recess was taken.)

DR. LEWIS: At this point, we'd like to proceed with the FDA presentations.

FDA Presentation - Olivia Easley

DR. EASLEY: Good morning. My name is Olivia Easley, and I will be discussing the FDA's clinical perspective on the development of non-testosterone products to treat male secondary hypogonadism, so another overview of male hypogonadism basically the condition characterized by low serum testosterone with associated signs and

symptoms.

It can be primary if it results from an intrinsic defect of the testes, or secondary if it's due to problems in the hypothalamus or pituitary gland. The two are differentiated by serum levels of gonadotropins, which are elevated in primary and low or normal in secondary hypogonadism. Both primary and secondary hypogonadism can be due to congenital abnormalities or acquired disease.

The Endocrine Society recommends a diagnosis of hypogonadism in men with a confirmed morning serum total testosterone that is below the lower limit of normal, typically less than 300 nanograms per deciliter on two separate occasions. In addition, the patient must have consistent signs and symptoms, which can include incomplete sexual development, decreased libido, and gynecomastia, among others.

Hypogonadism can be further categorized into classic and non classic. Classic refers to a condition that is caused by intrinsic pathology of

the hypothalamic pituitary axis due to specific well recognized medical conditions, such as Klinefelter syndrome, Kallmann syndrome, or a tumor, or resection of the pituitary gland. In these patients, testosterone replacement is necessary for development or maintenance of secondary sexual characteristics.

In contrast, non-classic hypogonadism refers to situations where serum testosterone is low and patients have associated symptoms that may or may not be related to the low testosterone, and these men have other conditions. Examples include age associated hypogonadism and hypogonadism that is attributed to obesity. In these cases, there is no definitive evidence that raising testosterone into the normal range for healthy eugonadal men leads to clinical benefit or is safe.

The usual treatment of hypogonadism in clinical practice includes first addressing any reversible causes. Next, it's to determine whether the patient desires fertility in the short or intermediate term. If the patient does not,

testosterone replacement therapy can be initiated.

This slide summarizes the FDA approval paradigm for testosterone replacement therapy. Typically, one phase 3 trial is conducted in support of a marketing application, and these trials enroll, quote/unquote, "hypogonadal men with --" and I say quote because while serum testosterone is confirmed to be less than 300, signs and symptoms of hypogonadism are not required for trial eligibility.

These trials are designed to show that the product can reasonably increase serum testosterone into the normal range for young, healthy, eugonadal men. These trials however do not provide substantial evidence of improvement in hypogonadal signs or symptoms. And for these reasons that I've outlined, this current paradigm cannot establish efficacy or safety of a testosterone product in men without classic hypogonadism.

Recently, FDA held an advisory committee meeting about use of testosterone, off label uses in age-related hypogonadism, and as a result of

that meeting and consistent with the advice received from the panel, FDA required that all sponsors of testosterone products revise the indication section of their labeling to clarify that the intended population of testosterone users is men with classic hypogonadism.

The indication statement in labeling is shown on this slide, and I'll point you to the second under hypogonadotropic hypogonadism. "Idiopathic" was removed from that portion of the label, again, to clarify that men with classic should be the ones that are treated. In addition, a limitation of use was added that states that the safety and efficacy of the respective product has not been established in men with age-related hypogonadism.

In hypogonadal men who desire fertility, we've seen this slide several times. There are iterations of this slide already. But basically, this demonstrates the negative effect that exogenous testosterone has on spermatogenesis, and it through negative feedback inhibits release of

GnRH and gonadotropins, resulting in less spermatozoa production and less testosterone production.

For men who do desire fertility, in clinical practice what's done is -- well, it depends on whether the patient has primary or secondary hypogonadism. In primary, hormonal intervention is not really indicated because, in general, these patients won't respond, so donor sperm, assisted reproductive technology, or adoption are means of fathering a child. In secondary hypogonadism, however, gonadotropin therapy can be used to stimulate endogenous testosterone production and spermatogenesis. And that can be used alone or in concert with assisted reproductive technology.

As I said, in men with secondary hypogonadism who desire fertility and who have a low sperm count, LH deficiency is typically corrected first with urinary derived human chorionic gonadotropin or hCG. hCG has pharmacologic activity that is nearly identical to LH. It has been available since the 1930s and is

approved for "selected cases of hypogonadotropic hypogonadism in males."

This product is used to simultaneously raise testosterone and simulate spermatogenesis, and in some men, it alone may be sufficient. If however no sperm are detected after 6 months of hCG treatment -- an FSH products can be added to the regimen, there are several recombinant FSH products that are approved by the FDA for induction of spermatogenesis with the first product being approved in 2000.

In open-label trials involving men with hypogonadotropic hypogonadism and azoospermia, these products were shown to increase the percentage of men having no sperm at baseline to achieving a sperm concentration greater than at least 1 million per mL during treatment. The million per mL threshold at that time was selected as the target because this value had been reported in the literature to permit pregnancy in approximately 90 percent of partners of hypogonadotropic hypogonadal men who were treated

with hCG and gonadotropins that had been derived from the urine of post-menopausal women.

So although that million per mL threshold was considered worthwhile back in 2000, one thing we want to ask the committee is whether that threshold still makes sense, as technology has changed.

Finally, for men who do not respond to hormonal manipulation, assisted reproductive technology is also available for the treatment of male infertility. These modalities include intrauterine insemination, which can be used for mild male infertility; in vitro fertilization; and then intracytoplasmic sperm injection, or ICSI, which has enabled men with even very, very low sperm concentrations to father a child.

As you've already heard this morning, because testosterone replacement therapy can impair spermatogenesis, there has been an interest in developing non-T alternatives to treat men with secondary hypogonadism. These products could either preserve fertility in men who are already

fertile or improve fertility in men who are infertile at baseline.

Candidate drug classes include gonadotropins like hCG, estrogen receptor agonists/antagonists products, and aromatase inhibitors. As we already mentioned, gonadotropins are approved for use in men with secondary hypogonadism, but their long-term use is limited by their cost and necessary injectable route of administration. So preparations with alternate routes of administration that are more affordable would be of interest in clinical development.

The first class of drugs I want to talk about is the estrogen receptor agonists/antagonists. These products competitively bind to estrogen receptors in the hypothalamus and pituitary gland. This results in less estradiol being recognized for negative feedback at these two places. You get greater secretion of gonadotropins and an increase in testosterone production, and these drugs may not suppress spermatogenesis. You need an intact hypothalamic pituitary testicular

axis for these products to be effective.

One member of that class is clomiphene citrate. This has been investigated both as an alternative to testosterone replacement therapy and as a treatment for male infertility. Clomiphene is approved for the treatment of ovulatory dysfunction in women who desire pregnancy.

The majority of published trials involving clomiphene have been uncontrolled with small sample sizes and involving a short duration of treatment, and they have involved men with hypogonadism associated either with age or obesity. And in these small trials, clomiphene did appear to increase serum testosterone to some extent, but there is no definitive evidence that that increase in serum testosterone led to any clinical benefit.

There was one small study involving three men with hypogonadotropic hypogonadism and azoo or oligospermia, and in this small study, clomiphene did raise sperm concentration from a baseline of zero, or close to zero, to greater than 10 million per mL after 3 months of treatment. But again,

because the benefit of increasing serum testosterone in men without classic hypogonadism has not been established, a clinical endpoint that shows that this drug improves how the patient feels, functions, or survives is needed in future trials.

Enclomiphene is an isomer of clomiphene citrate, and it has also been investigated as a treatment for raising serum testosterone into the normal range while also maintaining sperm concentration in men with secondary hypogonadism. Two published trials in obese men with secondary hypogonadism -- which in this case, in these trials was defined as a serum testosterone less than 300 nanograms per deciliter, and these patients also had a baseline sperm concentration greater than 15 million per mL -- compared the effective enclomiphene to placebo and to exogenous testosterone and increasing testosterone and maintaining sperm concentration. At 16 weeks, the composite endpoint was the percentage of men with a normal serum testosterone and a sperm concentration

greater than 10 million per mL at 16 weeks.

So the intent of these trials and of this product is to raise serum testosterone and maintain sperm concentration in obese men with secondary hypogonadism. The problems that the FDA has with this goal is that there is no definitive evidence that raising testosterone in these men leads to clinical benefit. Furthermore, sperm concentration is only one marker of normal spermatogenesis and does not assure fertility.

The clinical utility of thresholds, whether it be 10 or 15 million, is unclear. And furthermore, maintaining sperm at or near pretreatment levels, even if it was shown to be meaningful, isn't relevant if the treatment has not been shown to provide clinical benefit for the underlying condition, in this case hypogonadism; otherwise, why wouldn't you just let the patients be and not intervene at all. They don't need therapy.

The last class of drugs I will discuss are the aromatase inhibitors. These include drugs such

as tamoxifen and letrozole. They have been investigated as an alternative to testosterone therapy in men with secondary hypogonadism. This class of drugs is approved for the treatment of breast cancer and inhibits the aromatase enzyme that is responsible for converting testosterone into estradiol. The result is you have -- as to how it may work in men with secondary hypogonadism, you have less estradiol available for negative feedback at the hypothalamus and the pituitary gland, so you have increased release of gonadotropins and then increased testosterone production.

These products have been studied primarily in men with hypogonadism attributed to obesity. In published small open-label trials in obese men with secondary hypogonadism treated with an aromatase inhibitor, testosterone is increased and estradiol levels do go down. But again, the clinical benefit of changes in these hormone parameters has not been demonstrated.

So as with the other classes of drugs, a

clinical endpoint that shows that the drug improves how the patient feels, functions, or survives is needed to show that these drugs are beneficial in treating men with secondary hypogonadism.

This background now leads us to a discussion of FDA's perspective on the development of non-testosterone products and the regulatory challenges that we face. I'm going to go over some questions that we would like the committee to consider in their deliberations.

The first issue is, for products intended to treat secondary hypogonadism that is not classic -- for example, that associated with obesity -- while preserving testicular function, the clinical benefit of raising testosterone in this patient population has not been established.

One approach could be to show that the product improves the signs or symptoms of hypogonadism, but that approach is challenging because many of the signs and symptoms of hypogonadism are non-specific. Furthermore, there are no patient-reported outcome measures currently

available that assess hypogonadal symptoms that meet the FDA validation criteria, which you're going to hear in our next presentation.

If the goal of the product is to maintain testicular function, how should that be defined and assessed? I want to note again that maintaining testicular function is not treating the underlying condition and cannot establish that increasing testosterone in these patients leads to clinical benefit.

With regards to treating secondary hypogonadism while improving testicular function, we have the following questions. Can clinical benefit be established based on raising testosterone and increasing sperm concentrations above a specific threshold? If not, what endpoints should be required? If yes, if that is a reasonable goal, what sperm concentration threshold should be used, and should other semen parameters be considered?

This brings us to the limitations in using semen analysis in assessing testicular function.

Analysis doesn't definitively distinguish fertile from infertile men because there is extensive overlap in sperm concentration, motility, and morphology in these two populations. Furthermore, there are other factors that may affect male fertility that are not detectable on a standard semen analysis, which include oxidative stress and sperm DNA fragmentation.

So even if your semen analysis was normal, it doesn't necessarily determine that you are still fertile or that you have been fertile.

If sperm concentrations, as I said, don't guarantee fertility, would fertility outcomes make sense? For classic hypogonadism, because there are such a small number of patients affected, fertility outcomes may not be feasible.

Another question we have is should the same approach in terms of clinical endpoints be applied to men who have no sperm compared to oligospermic men? As we've discussed, you don't need tons of sperm necessarily to conceive a child. So should

men who have oligospermia have a diagnosis of infertility at baseline? And then should the same approach be applied for classic hypogonadism as for non-classic hypogonadism?

Thank you for your time. I'll turn it over now to Selena Daniels, who will discuss the clinical outcomes assessment development.

FDA Presentation - Selena Daniels

DR. DANIELS: Good morning. My name is Selena Daniels, and I am a reviewer and a team leader on the Clinical Outcome Assessments Staff and the Center for Drug Evaluation and Research. For those who aren't familiar with our group, our role is to provide advice to Office of New Drugs review division in CDER, as well as our offices and centers upon request on matters pertaining to the development of clinical outcome assessments and related endpoints.

We just heard from Dr. Easley in terms of some of the challenges in measuring clinical benefit and secondary hypogonadism and a potential opportunity to explore a symptom measurement

approach. To measure symptoms, you need a clinical outcome assessment, specifically a patient-reported outcome assessment. So today, I'll be presenting the regulatory approach and how we review clinical outcome assessments and drug development.

The patient perspective is an important part of the drug development process, and FDA values the use of patient input to help foster the development and availability of safe and effective drugs. There was an article published in JAMA by Hunter et al. in 2015 highlighting the importance of engaging patients across the spectrum of medical product development from the agency's perspective

Some of the key takeaways from that article were that FDA is working to give patients a greater voice. And with these efforts, this could lead to advances and transforming patients' experience of health care. It further noted that including meaningful clinical outcomes to patients can ensure that the patient's voice is captured. And one way to do this is to use patient-reported outcome assessments. Now, patient-reported outcomes

assessments are not always required for drug development programs, but they are preferred to be used in most symptomatic conditions.

There are multiple phases in the spectrum of drug development where a patient can be engaged beginning as early as the discovery phase and all the way into post-approval phase. This graphic illustrates some potential areas where patient input could be considered. At the discovery phase, patients can be engaged to identify unmet needs in diseases. Patients can inform clinical trial design at the clinical phase as well as inform clinical outcome assessments such as patient-reported outcomes, which can be used as endpoints of regulatory trials, and I'll discuss further in subsequent slides.

Lastly, at the post-approval phase, patients can be engaged to provide input on communications on benefit-risk. Patient-centered outcomes can also monitor post-approval and are often of interest to payers, providers, and of course patients themselves. However, the subject of

today's presentation will focus on the use of patient-reported outcome assessments in the clinical phase.

So what is an outcome assessment? An outcome assessment is essentially an assessment of an outcome that results in one or more recorded data points. FDA utilizes outcome assessments to determine whether or not a drug has been shown to provide clinical benefit to patients. Clinical benefit can be defined as a positive clinically meaningful effect of an intervention on how an individual feels, functions or survives. When clinical benefit has been demonstrated in registration trials, that description of that benefit can be provided in a label in terms of the concept or outcome that it measured.

There are different types of outcome assessments. There are clinical outcome assessments and there are surrogates. Within clinical outcome assessments, there are four different types. There is performance outcomes in which a subject is performing a specific task or an

activity such as 6-minute walk tests. And then you have outcome assessments that are reported by clinicians. These are generally disease severity rating scales. You have assessments reported by observers such as parents or caregivers who are assessing signs, events, or behaviors for patients who cannot self-report reliably such as young children and the cognitively impaired.

Most importantly, you have patient-reported outcomes. And a patient-reported outcome is a direct report from the patient on their health status without any interpretation from a clinician or anyone else for that matter, and they're reporting on their symptoms and their functioning, et cetera. Surrogates are often a biomarker that is intended as a substitute for how a patient feels, functions, or survives. Some examples of those could be blood pressure, hemoglobin A1c. The subject of this presentation is focused on clinical outcome assessments and specifically patient-reported outcomes for consideration of use in secondary hypogonadism.

It's very apparent that FDA is interested in how a patient feels, functions, or survives, but what does that mean? We do know that drugs have safety risks, therefore some general reasons that a patient might want to take a drug would be either to improve survival, improve symptoms, improve functional capacity, or decrease the probability of developing a complication, for example, a stroke. For secondary hypogonadism, a reason might be for treatment is to improve symptoms.

In saying all this, trial endpoints should be considered to measure at least one of these elements. Trial endpoints will generally not measure something that is not important to the patient. And at the end of the day, the goal of the therapy should make the patient feel better in how they feel or function.

This graphic metaphorically depicts the roadmap to patient-focused outcome measurement in clinical trials. It's important at the first step to have an adequate understanding of the disease under investigation. There are multiple elements

to explore in a disease area, which includes, but is not limited to, understanding the natural history of disease, patient subpopulations, real-world clinical practice, patient perspective, or caregiver perspective depending on the population that is being studied.

Once you have a firm understanding of disease, the next step is to conceptualize clinical benefit, which can entail identifying measurement concepts that are clinically important. Clinical important outcomes might include the core signs and symptoms of a disease or it could be aspects of functioning attributed to the disease, for example, physical function.

In addition to identifying measurement concepts, the context of use for an assessment -- in other words, the target population -- should be clearly defined for the assessment since the assessment would need to be appropriate for that study population and appropriate for the clinical outcome assessment type that's selected.

Once the measurement concepts and the context of use are known, it's important to consider how the assessment is going to be incorporated into the plan trial endpoints and how it fits into the endpoint hierarchy. It's often mistaken that the clinical outcome assessment is the endpoint, however, that isn't the case. The clinical outcome assessment is, again, the assessment that measures the outcome, and the endpoint would be the variable that is going to be statistically analyzed. In the case for clinical outcome assessments, the variable would be the score for an assessment, and the endpoint would be how you plan to analyze that score; for example, change from baseline.

Once you tackle these first two steps for disease understanding and clinical benefit, you're in a good position to start selecting or developing a clinical outcome assessment, whether it be searching for an existing assessment, modifying existing assessment, or developing an assessment de novo. To date, we are not aware of any

patient-reported outcome assessments designed for secondary hypogonadism that meets regulatory standards.

So this is the wheel and spoke diagram, and it represents the general iterative process of developing a clinical outcome assessment. The five spokes in the diagram represent the five key stages of clinical outcome assessment development, which is anchored by the hub or the core, the measurement concept which the assessment is intended to measure. As a reviewer, we look to see if that clinical outcome assessment has gone through these stages, which I'll elaborate a little bit more on the next slide.

This table goes a little bit more in detail in terms of the spokes in that previous diagram. Essentially, I'm not going to go over every single bullet, but essentially as a reviewer, we're looking for documentation of how that assessment is developed. And most importantly, we like to see if patient input has been incorporated, and if the concepts that are being measured are the most

important and relevant to the patient, and that the patient can understand and interpret the assessment appropriately. We refer to this as content validity of the assessment, and that is spoke 2.

Once content validity has been established, you can evaluate the other measurement properties of the assessment cross-sectionally and longitudinally, and that is spoke 3 and spoke 4. Some of those assessments could be reliability, validity, and sensitivity.

One thing to note is that the process to develop an instrument can be lengthy. It can take a few years, and the amount of time is dependent on where you're starting after developing an instrument de novo or if you're modifying an existing instrument. Regardless, it's critical that you seek FDA advice throughout the development process to avoid having an instrument at the end that does not meet regulatory standards. It's also wise to get experience with this assessment in earlier cases of drug development before registration trials.

As a reviewer, when we come into contact with an assessment, we have multiple questions that flow through our mind. We want to know is the instrument appropriately used in the trial; is it developed in the study population; does it measure what's important to the patient; and if there are multiple concepts or domains being measured, do they overlap? Is there redundancy?

Is the instrument reliable? Is it measuring what it's supposed to measure? Is it sensitive to detect change over time? Is there one question that is driving the results? If there's score improvement, what does that score improvement mean? If it's a 2-point change, what does that 2 points really mean?

So the FDA issued guidance on patient-reported outcome assessments in December 2009 for industry. As a reviewer, we also refer to this guidance because it defines good measurement principles. In addition to this guidance, there are also evidentiary standards for us to follow. And within these standards, there are regulations

for clinical outcome assessments that require the methods of assessment of a subject's response to be well defined and reliable in an effort to avoid labeling statements that may be false or misleading.

When FDA evaluates clinical outcome assessments, it looks for characteristics that are consistent with these regulations. Although this guidance was developed for patient-reported outcome assessments, there are many principles that are applicable to any clinical outcome assessment type. This guidance provides an optimal approach to patient-reported outcome assessment development, but it's understood that flexibility and judgment are needed to meet both regulatory standards as well as the practical demands of drug development.

So we acknowledge that there is no perfect instrument, however, we do try to provide advice to sponsors to improve their measurement strategy and maximize the opportunity for successful use of assessments. And as such, we look for the following imported measurement characteristics of a

clinical outcome assessment.

We look to see that the assessment is appropriate for its context of use. It measures the most important concepts to the patient for that disease. Its contents or concepts are well defined. It generates consistent and reproducible data, so it's reliable. It measures what it's supposed to measure; it's valid. It's sensitive to detect change. And lastly, the score change is interpretable and reflective of meaningful changes.

I know I've presented some pretty generic information, and you're probably wondering how this is applied to drug development programs for secondary hypogonadism. So I wanted to take some time just to tie everything up together and make it specific to this condition of walking through this hypothetical case example.

When developing a measurement strategy, it's best to start with the end in mind. At the end of the day, what would you want to say about the product? In this case example, let's just say that we're seeking a labeling claim on symptom

improvement. With this you would want to select or develop a symptom assessment. The endpoint could possibly be changed from baseline, which this would measure symptom improvement throughout the clinical trial.

In terms of what symptoms to measure, this should ultimately be driven from patient input, but an example of one symptom might be reduced sexual desire and activity. The context of use might be male adults with symptomatic secondary hypogonadism. The clinical benefit would be resolution of clinical signs and symptoms. The concept of interest could be the severity of symptoms or maybe even the frequency of symptoms. And again, it would be a symptom assessment, but it would be a patient-reported symptom assessment since symptoms are only known to the patient.

As we've noted, there are some endpoints that involve clinical outcome assessments that could possibly be trial endpoints. There could be endpoints related to sign and symptom improvement and maybe even endpoints related to physical

functioning. Some considerations for measuring sign and symptom improvement are to prioritize concepts to include core signs and symptoms. You would want to select signs and symptoms that would be responsive to treatment, and we refer to those as proximal concepts. So in other words, you would want those concepts that could be modified by treatment.

We caution against using concepts that might not be non-responsive or unrelated to treatment effects, or concepts that might be affected by other external non-drug factors, and we refer to those as distal concepts. So again, you would want to enrich your trial with symptomatic patients because you would want to know if you're seeing improvement, and you would want a sufficient score at enrollment so you could observe a meaningful response throughout the trial.

Some of the same considerations in measuring sign and symptom improvement would follow suit for functional improvement. So again, you would want to prioritize concepts to include core aspects of

functioning attributed to disease. And again, you would want a sufficient score at enrollment with that assessment.

In concluding, I just wanted to share some pathways that are available to receive advice on clinical outcome assessments. There are three pathways. The first pathway is within the context of an individual drug development program. Again, we encourage drug sponsors to begin these discussions as early as the pre-IND stage so that if any work needs to be done on the proposed assessments, there is time to do so before phase 3.

The second pathway is outside of the drug development program, and this is through our drug development tool qualification process. In this program, we work with instrument developers to develop and qualify assessments for use across multiple drug development programs. We work with many stakeholders, including consortia, patient groups, individual academic investigators, and drug developers, to develop and qualify publicly available assessments.

The final pathway, or the third pathway, is the critical path innovation meeting pathway, also known as CPIM, and the goals of CPIM are to discuss a proposed methodology and technology and provide general advice on how that methodology or technology might enhance drug development. We've tried to identify some larger gaps in existing knowledge that requesters might consider addressing in the course of their work.

That concludes my presentation, and I've left here some helpful links to guidances on our patient-reported outcomes, the drug development program, as well as the drug development clinical outcome assessment web page. Thank you.

Clarifying Questions to the FDA

DR. LEWIS: Thank you. We'd like to now take some questions for the FDA. Please remember to state your name for the record before you speak. If you can, direct your question to a specific presenter, and please be sure that you're close to the microphone. Some people are having a hard time hearing around the panel. Dr. Braunstein?

DR. BRAUNSTEIN: Glen Braunstein. A question for Dr. Easley and possibly Dr. Daniels, the same question. And while they're coming up, there's a minor error in slide 19. Tamoxifen is not an aromatase inhibitor. It's actually a blocker at the estrogen receptor. So I think that should have been anastrozole rather than tamoxifen.

DR. EASLEY: Yes. Thank you.

DR. BRAUNSTEIN: The question is this. In the February 2016 issue of the New England Journal of Medicine, Dr. Snyder reported on the results of the testosterone trial in age-related hypogonadism. He studied 790 males at 65 years of age or older and randomized them in receiving testosterone gel or placebo. They were all symptomatic. They all had testosterone at baseline, less than 275 nanograms per deciliter.

They studied sexual function, physical function, and vitality, and they found in that trial, which was a yearlong trial, that there is increased sexual activity with desire and function increasing, and there is an improvement in mood and

depressive symptoms, but no improvement in vitality or walking distance.

So my question is this. There is evidence that treating individuals who have non-classical hypogonadism with testosterone in an adequately powered, double-blind, placebo-controlled trial does result in improvement, at least in sexual symptoms, which would go along with Dr. Wu's EMAS studies, which showed that the best correlates of symptomatic hypogonadism are with sexual findings, erectile dysfunction, thoughts and desire, and things like that.

So my question is, what was wrong with that trial? Why can't those measures be used to look at endpoints?

DR. LEWIS: For obesity I assume you mean.

DR. BRAUNSTEIN: Well, for obesity or for age-related hypogonadism. I mean, we're still talking about non-classical hypogonadism.

DR. EASLEY: Well, even though that trial may have found an improvement, we have really strict criteria that we -- any questionnaire can't

just be submitted and said, yeah, this shows an improvement. We have a very rigorous methodology by which we evaluate questionnaires. They have to be prospectively studied and shown to evaluate the treatment response in the population that you're looking for.

So if you wanted to use a sexual by whatever, increase sexual function questionnaire in men with obesity-related hypogonadism, you need to do validation studies in that population first and show that this measures the concept you want to measure objectively. We can rely on the results. We know how much of an improvement we should find.

So it's not as easy as it sounds. Just because that study showed that in the New England Journal, the measures they used may not pass the muster of the COA staff here at FDA.

I don't know if Selena wants to add on to that.

DR. DANIELS: So just to elaborate a little bit further, in terms of the steps that I've shown in my presentation, we look for certain criteria in

terms of were those questionnaires developed in that study population. That would be one context. Not to say that they couldn't do additional work with those instruments in the secondary hypogonadism or in general, but you would also want to look to see if patient input has been included in those assessments and if those concepts spur the same relevance to this population as well.

DR. HIRSCH: I am Mark Hirsch, medical team leader in urology in this division. Two comments, Dr. Braunstein. Dr. Snyder's trial was consistent with the Institute of Medicine's advice to us, to the community at large, that we explore different areas of benefit in hypogonadism. So it was a series of small trials that composed one larger trial. And we view it in light of a phase 2 sort of exploration of benefit. That's one comment.

The second comment is those differences in sexual function were actually rather small, although statistically significant, and still require further discussion of their clinical meaningfulness.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: Yes. I'm going to preface my question with a comment that I use this type of drug quite a bit in infertile obese men, so I actually use these drugs. But I do have a question for the FDA, probably Dr. Joffe.

As I'm sure you recall, when we had the meeting in 2014 regarding testosterone labeling, we met for a whole day, and we came out with these labeling concepts, which have been mentioned already today. But the next half-day, we had a review of an oral androgen preparation that had been widely used in Europe, and there was extensive data showing its efficacy and safety in the short term; actually not in a real short term, up to 10 years. And yet, we disapproved that drug because of the discussion of the previous day about testosterone and testosterone labeling.

Now we're being asked to approve drugs that elevate serum testosterone. It seems to me that decision in 2014 goes in clear opposition to even having this hearing. So I'd like the FDA's

clarification on that.

DR. JOFFE: This is Hylton Joffe. First, I'd like to clarify that the second day advisory committee was unrelated to the first day. The second day was really a discussion of a specific drug and whether the benefits of those drugs outweighed the risks using the typical FDA approval paradigm for the standard testosterone indication.

Now we're a little different. We're talking not about the standard testosterone indication, but we're talking about these men who have these conditions where we're not sure if you raise testosterone, what benefit are you conferring to these men.

DR. HOWARDS: But I voted not to approve that drug, but I also voiced the opinion that it was very unfair to that company because we totally changed the standard because of the discussion the day before. A similar drug before that day would have been approved easily. So we had a complete -- the day before affected the decision the next day.

DR. JOFFE: Yes. I don't want to go too much off on a tangent. But really, if you look back at the transcripts and the issues with that specific drug, you'll see that there were issues that are unrelated to what happened on the first day, titration issues, food effect issues. So I beg to disagree on that. But let's go back and see if anybody else has any other questions.

I guess the question here is, is testosterone an adequate surrogate for clinical benefit? The FDA's view is if you take men who have classic hypogonadism -- so they clearly have low testosterone, and we know they shouldn't; you take a Klinefelter's patient, Kallmann syndrome, we know that testosterone should not be low -- replacing testosterone in those patients make a lot of sense.

When you take someone who has obesity-related hypogonadism, who really have an intact testicular hypothalamic pituitary testicular axis because otherwise they wouldn't respond endogenously when you give these other agents, how

do we know those patients benefit when their testosterone is raised?

That's the question. It kind of reminds me a little bit of the hormone therapies for women, where everyone said, oh, it's obvious. If you're post-menopausal, your estrogens are down, give it back, and everybody's going to benefit and it's going to be safe. But that turned out not to be the case. So it's akin to that kind of example.

DR. LEWIS: Anybody else from FDA?

DR. JOFFE: And let me add just one more thing. There's a difference between real-world use of drugs and an FDA indication. FDA doesn't regulate the practice of medicine. So if a doctor in his or her practice wants to prescribe testosterone for a patient with obesity-related hypogonadism, that's in their patient-doctor relationship, and that's fine. But to have an indication where FDA says this drug is specifically approved for this condition requires substantial evidence of effectiveness, and those benefits have to outweigh the risks. So we're coming at it from

a different angle.

DR. LEWIS: Thank you. Dr. Adler, did you have a question?

DR. ADLER: Yes. Robert Adler. I want to preface my remarks by saying --

DR. LEWIS: Can you speak closer to the microphone?

DR. ADLER: I want to preface my remarks by saying that I see patients in Veterans Medical Center, but the opinions that I will express are my own and not necessarily those of the Department of Veterans Affairs.

I'm a little concerned about the blurring of functional secondary hypogonadism between older men and younger men. And I see men in their 20s and 30s with one of several, and sometimes more than one of several, conditions, including obesity, but also post-traumatic stress disorder, chronic opiate analgesic use, and even mild traumatic brain injury where we cannot see a specific abnormality on any kind of imaging of the pituitary and the hypothalamus.

I'm a little concerned that what we talked about at the 2014 session is coming into this, and I have a lot more trouble saying I don't want to restore the testosterone level in a 30-year-old man versus a 65-year-old man who wants to get his testosterone boosted. And I think it's really important that age be considered in any review of a given drug. Thank you.

DR. LEWIS: Any comment from FDA?

DR. JOFFE: I think it comes back to what benefit are men getting by having their testosterone increased. We think it makes sense to increase, but if you go from a 290 to a 390, are those men getting any benefit from having the testosterone go up to that degree, and what are all the safety concerns that come along with that?

DR. ADLER: Sure. I don't disagree with you, and I think the studies need to be done. I mean, we do have all the literature that in younger men, for example, testosterone replacement does increase bone density. It's not quite the same thing that Dr. Drake was talking about, but at

least we have some earlier data suggesting that there are some potential measurable hard endpoints that could be used.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Thank you. I have some of the same concerns Dr. Adler just mentioned. I have trouble getting my head around why classic hypogonadism uses one set of endpoints and non-classic uses another. And what is the issue we're really looking at? And I think that it's probably the age of onset rather than the etiology. And maybe that's what we should be focusing on, and that would really change how we look at endpoints and what endpoints are important. That's my comment.

DR. GASSMAN: Dr. Hanno, I guess my follow-up question was if we're going to look at age of onset, one of the things that we're struggling with is what cut-offs would you use? Is 50, 55?

DR. HANNO: I think that's a very good question, but that changes the whole focus of what we're talking about. And I think it's important to

perhaps focus this in a different way so that we're looking at the real issue that seems to be bothering everybody rather than the fact that -- why should the etiology make such an important difference in trial endpoints in and of itself? Is it something else that we're really looking at?

DR. EASLEY: I have another question -- this is Olivia Easley -- related to that. To me, it seems that the etiology's important because if someone's in the ICU and their testosterone is low because they're acutely ill, you wouldn't want to replace it. If someone has a reversible cause or they're obese even -- you know what I mean? I feel do those men really --

DR. HANNO: I totally agree. I think we should try and determine the etiology because some etiologies are treatable directly. But if we have someone with hypogonadism that has had mumps orchitis, and you can't change that, or they have idiopathic hypogonadism later in life and it's not classic by definition, what is the difference? I

think it's the age of onset that you're most concerned about.

DR. LEWIS: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: Well, I guess this dovetails into what both Dr. Adler and Dr. Hanno have said. I've been really struggling with what we're trying to accomplish today because -- and in contradistinction to Phil, I'm not so sure it's an age-related thing.

I was looking at Dr. Easley's presentation and her slide 21 and slide 2, which just simply -- she has chosen to really drill down on non-classic, secondary hypogonadism, e.g., associated with obesity. And the question is, I can see developing a PRO for that condition. I can't see developing a PRO for a condition that is predominantly the patient is seeking care for infertility.

So perhaps it's not age. And again, in appreciation of the FDA's JAMA article, which basically said what do the patients want, maybe this is what the patients are asking. Is this an

infertile presentation or is this a hypogonadal symptomatic presentation? Two very different things in my mind.

Now, they may conflate and overlap. The Venn diagrams are not mutually exclusive. I think if we're going to give guidance to industry about how to successfully develop a trial, it makes no sense to say take a PRO and give it to a 21-year-old who's infertile and may have some component of hypogonadism but is absolutely asymptomatic from every other standpoint.

So I think we're trying to really -- we're taking the proverbial square peg and trying to ram it into the round circle by trying to make everything fit. I don't think this is a one size fits all. And I think Dr. Easley very nicely said, okay, let's take an area of focus, overweight men who have some hypogonadal, quote/unquote "symptoms" and are infertile, or not, and then use that.

So use the patient to help us guide this because I'm not sure we're going to be -- listen. I live in a world of incontinence episodes and PROs

related to that, and I'm listening to you guys who know everything about semen functional quality, and for years you're using a number that probably is remotely predicted but not very much so. So how are we going to give good advice today? So I guess that's my point.

DR. LEWIS: Any comment from FDA?

DR. JOFFE: This is Hylton Joffe. That's a good point. And Dr. Dmochowski, what you were saying is consistent with what I had in my opening remarks, where I said if you're a drug that's intending to improve fertility in men who have secondary hypogonadism, and that's all you want for an indication, then go after a fertility endpoint. And then we have to have discussion on what that endpoint should be so we're assured reasonably that we're actually leading to positive fertility outcomes; whereas if you want a broader indication, then you need other endpoints as well.

DR. LEWIS: Dr. Bauer?

DR. BAUER: I just want to weigh in a little bit on this conversation about age cut-offs. I

suspect it would have been ideal if we actually didn't separate classic secondary hypogonadism from what we've been talking about today. But in fact, I think the tradition is and also because the patient numbers are so small, it would have been extremely difficult, if not impossible, to do clinical outcome studies looking at the proper dose of testosterone in Klinefelter patients.

So I don't think it's really any different; it's just a matter of what's historically. Now we're talking about a huge, huge number of middle age and older men that are obese and that potentially are at risk for this.

But I actually did want to get back to the infertility issue. And Dr. Easley, I'm going to ask you to comment on slide 12 because maybe you or someone at FDA can remember with some historical detail about the decision to use a cut-point of greater than a million sperm per mL for the recombinant FSH.

Was that based on the concept that this was a surrogate outcome based on data that showed that

among treated men, if you got to a million, that increased pregnancy outcomes, or was this a number that was generated otherwise? Do you know?

DR. EASLEY: Yes. This was based on data at the time that men treated with hCG and menotropin -- so gonadotropins derived from the urine of menopausal women -- that 90 percent of the partners of these men achieved pregnancy if the sperm count was at least a million. So that's why they chose that endpoint.

DR. BAUER: I see. So why is it that now we are talking about different cut-points and different things for this drug? Is it because it's a different intervention, or is it not thought to be an overall effect? Can you explain that to me?

DR. EASLEY: Yes. That's a very good question.

DR. JOFFE: This is Hylton Joffe. Those drugs were studied in a very select patient population. So those are men who had no sperm at baseline, nothing on their semen analysis.

I don't know if Dr. Hirsch wants to comment.

No? So raising sperm concentrations in those men may be different if you have a man who's subfertile and his sperm concentrations are 9 million and you're talking about raising it to about 15 million or whatever. It's not exactly an apples to apples comparison.

DR. BAUER: Right. I just wanted to ask the FDA the same question that I asked the industry representative earlier. Is it true that there are no clinical data that look at the efficacy of sperm counts as a surrogate measure for pregnancy outcomes in the population that we are talking about today? Are you aware of any studies that looked at that?

DR. GASSMAN: Well, this is from a regulatory perspective. From a regulatory perspective, the studies that have been done are the recombinant FSH that are for a sperm concentration of greater than 1 million per mL. But I do want to point out this was done in 2000.

Obviously, one of the things that we're doing by coming here is saying do we need to change

the paradigms for clinical trials? Are we looking at the right endpoints, the wrong endpoints, the right cut-offs, the wrong cut-offs? Are we thinking about this? Should our thinking change?

That's why we're coming to you as the committee because what was done in 2000, we've got more data, different assays, different information, and more literature. So we're coming to you as the experts to say we've been doing -- that was 2000. Now we're in almost 2017. How should we be framing the discussion? What endpoints should we be looking at?

DR. LEWIS: We'll take a couple of more clarifying questions, and I want to emphasize we do have time for discussion. A lot of this is discussion that we can go to later. Dr. Weinfurt? You're okay. Dr. Thomas?

DR. THOMAS: Just a quick question for Dr. Joffe. If a drug were to appear that would improve fertility, yet for some reason didn't increase testosterone and you couldn't give testosterone, would that be acceptable? I'm

thinking of the fact that having a low testosterone has its consequences.

DR. JOFFE: Right. I guess it comes down to what's the intent of the drug. If the drug says it's intended to improve fertility and it shows that it improves fertility barring any safety issues and, again, benefit outweighing the risk, we'd approve it for what it's intended to do.

I think we shouldn't get hung up on numbers here, because at the end we're not treating a number. We've got to treat a patient with the intent that any improvement in number leads to some kind of clinical benefit.

DR. THOMAS: The thing is, unfortunately, these agents also raise testosterone, so you get the benefit of testosterone repletion and things like bone health, et cetera, not all of them. But theoretically then you would just say if a drug improved fertility and you couldn't address the testosterone because giving testosterone might impair that, how long would you treat someone for where the risks start to become increasing from a

testosterone deficiency?

The reason I bring this up is there are differences in the issues of fertility versus testosterone treatment. I think that's kind of the crux of these other agents. If it's just testosterone replacement, it's a much harder argument of why you would use other agents than testosterone. But fertility's really what drives you to using agents other than testosterone.

DR. JOFFE: And also I think it's this issue of are you improving fertility or trying to maintain sperm, testicular function, and what does that mean to maintain testicular function.

DR. LEWIS: Thank you. Quickly, Dr. Nahum, and then we will be breaking for lunch.

DR. NAHUM: Gerard Nahum. I have a question for FDA. We've heard some discussion about evidence that's in the literature. Clearly, you've asked us as a committee to address some of the issues that come up with clinical trial design and clinical endpoints for those trials. But I wonder in the current setting, with FDA changing its

thinking perhaps a little bit about real-world evidence, what sort of evidence could be gleaned from the real world that might be able to supplement the labeling and augment the indications for drugs that are already on the market and being used off label for some of these indications. The one that jumps to mind is clomiphene citrate, but aromatase inhibitors as well, and potentially other drugs.

What level of evidence could be brought to bear from evidence that comes from the real world to try and influence at a regulatory level what the labeling looks like and what indications might be?

DR. JOFFE: Real-world evidence is a hot topic these days, and there is interest in trying to leverage real-world evidence in the regulatory sphere. I think the devils are in the details in terms of how good that real-world evidence is and what is it exactly showing.

You've heard issues, for example, with published studies using patient-reported outcomes that really aren't validated, that we don't think

are fit for purpose in measuring what they're supposed to measure. So it comes down to quality of evidence, what those results look like, how the data were generated, are they trustworthy data and things like that, which is hard and abstract. So that's why I said the devil's in the details.

We're open always to hearing proposals if companies had an idea of how they could leverage some existing data, and then those data would undergo and in-depth review at FDA to determine whether they would be of utility or not.

DR. LEWIS: Thank you. We will now break for lunch. We will reconvene in one hour, 1:05 I guess, in this room. Take your personal belongings, please, when you leave. And committee members, remember, please do not discuss the matters at hand during lunch. I think the committee members also have a conference room -- they do -- right across the hall where we will have lunch. Thank you.

(Whereupon, at 12:03 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

Open Public Hearing

DR. LEWIS: I'm going to ask everyone to take their seats so we can resume. We're going to start the open public hearing session in just a moment.

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, FDA believes it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information might include the sponsor's payment of your travel, lodging, or other expenses in connection with your

attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial 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 this open hearing process 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 only speak when recognized by the chair. Thank you for your cooperation.

Would speaker number 1 please step up to the podium and introduce yourself? Including stating

your name and organization.

DR. TEAL: My name is John Teal. I am an adult psychiatrist and faculty member of McLean Hospital and a clinical instructor at Harvard Medical School. The views and opinions expressed are my own as a member of the public and do not reflect any affiliation with any academic institution or industry sponsor. I do not have any financial disclosures.

The aim of my talk is to ask the advisory board that if patient-reported outcomes, necessary for approval for new treatments for secondary hypogonadism due to obesity in these reproductive-aged men, are required, that low mood, low energy, and amotivation are included as distinct patient-reported symptoms and recommended in all current and future trial designs.

An anecdote, in my office I frequently do consultations for depressed men who have failed or only gotten partial responses from conventional treatments like SSRIs. Clinically, these men have low mood, low energy, diminished interest in sex,

and low motivation. They're typically sedentary and inactive.

I always perform metabolic screening, specifically testosterone screening, which is not a standard feature of traditional psychiatric diagnostic assessment. I frequently find these treatment-resistant men share similar characteristics in addition to their obesity such as low testosterone and low to normal luteinizing hormone. So they all meet most largely criteria for secondary hypogonadism.

It's my opinion that this cohort of men, who are familiar to all of us because they present in our psychiatric, urology, and primary care clinics, represent a specific subtype of depression patients; more specifically, a subtype due to an endocrinologic etiology rather than major depressive illness. I believe that because of the epiphenomenon of low mood, these men are effectively misdiagnosed often with major depressive disorders leading to ineffective and expensive psychiatric treatments with significant

iatrogenic potential.

This population of men was further characterized in a recent study by Michael Irwig at George Washington University, where he screened 200 hypogonadal men, 91 percent meeting criteria for secondary hypogonadism with low or normal LH. Of this cohort, 81 percent were overweight and 56 percent presented with clinically significant depressive symptoms and associated neurovegetative features, including low motivation and low energy. Twenty-five percent of these men were already on one conventional antidepressant, thus suggesting limited effectiveness of the psychiatric treatments.

In my clinic, anecdotally, after beginning testosterone replacement therapy under my care, many of these men exhibit profound improvements in low mood and low motivational states. I've observed many cases where upon treatment of these depressive states, many of these men are more able to engage in better self-care, increased physical activity, improved work performance, and ultimately

decreased levels of obesity essentially leading to reversal of this syndrome. A large percentage are eventually able to get off all medications, including psychiatric medications.

A 2014 study by Hamid Amanatkar at Saint Louis University conducted a meta-analysis reviewing the impact of testosterone replacement therapy on mood. While this review did not draw distinction between primary and secondary hypogonadal states, it clearly highlights a relationship between restoring testosterone levels in men and improvement in mood.

Interestingly, during the subgroup analysis, they showed that younger men, presumably of reproductive age under 60 years old, had greater treatment effects than older men with presumed age-related hypogonadism. The analysis also revealed that dysthymia, otherwise known in DSM-V as persistent depressive disorder, had greater treatment effects in major depressive disorder suggesting a further means of differentiation between these two conditions.

While TRT is currently our only viable treatment for this particular cohort of men, I believe selective estrogen receptor modulators such as enclomiphene represent a much safer alternative. SERMs are not abusable, thus limiting induction of aggressive or manic mood episodes at supraphysiologic doses, which is a concern for psychiatrists.

SERMs also avoid the problem of severe suppression of the hypothalamic axis, which is different from TRT, which we know that after cessation leads to its own unique depressive syndrome and can sometimes facilitate need for long-term chronic dependence, which is a phenomenal study by my colleague Skip Pope at Harvard Medical School.

Last and perhaps most importantly, to many of my young patients, particularly ones between the ages of say 20 and 40, selective estrogen receptor modulators maintain normal spermatogenesis, thus giving these men the possibility of starting their own families, a possibility that's sometimes

diminished if TRT and its inhibition of spermatogenesis remains the only viable means of restoration of testosterone in these particular group of men.

In conclusion, I'd like to ask the advisory board that if patient-reported outcomes are required for approval and new treatments, please consider low mood, low energy, and amotivation as distinct patient-reported symptoms of secondary hypogonadism due to obesity in reproductive-aged men in current and all future trial designs. I believe that with the FDA's support and guidance, we can as a field better understand this distinct cohort of men and one day approve safe and effective treatments, avoiding both ineffective psychiatric medications and the iatrogenic risk of exogenous testosterone replacement therapies. Thank you.

DR. LEWIS: Thank you. Would speaker number 2 please approach the podium?

DR. HELLSTROM: My name's Wayne Hellstrom, and I'm a professor of urology at Tulane. I'm the

immediate past president at the ISSM, the SMSNA, and the American Society of Andrology. And I speak on behalf of the first two societies, which paid for my taxi and plane here today, and back tonight, hopefully.

Just a brief background, it was 1931 that testosterone was first isolated, in the mid '30s, it was synthesized, and by 1939 it was actually introduced into clinical practice. I bring this article here. This is over 75 years old by a fellow name Aub in the New England Journal of Medicine.

You can see in his introduction, he talks about testosterone being powerful and a considerable value, and is one of those post-drugs recently introduced, and its effects are so definite and widespread, and its use should be regulated with careful judgment and understanding. He also states that the pituitary at higher doses is basically inactivated and causes the testes to shrink. This is remarkable because this was 75 years ago that this is written in, and it seems

like we're still talking about it today.

Looking at a number of different studies across different continents, you can see that testosterone deficiency occurs anywhere between 2 and 38 percent. This variability is attributed to the heterogenous population through study, the different instruments that are used to identify this subject to be studied, and the different biochemical thresholds that are used.

Testosterone sometimes gets a bad rap. It's thought as a sex drug, but it's very ubiquitous. It affects many cells and organs of the body and has very positive effects in different areas where all recognized. I won't agree with this, but these are the typical signs and symptoms of male hypogonadism, in particular, a decreased libido and erectile dysfunction.

As a definition, mild hypogonadism is the failure of the testes to produce sufficient testosterone and maintain spermatogenesis. The causes are primary, which may be testicular failure; secondary, which is the higher centers,

mainly the hypothalamus and pituitary. The third category I include here is mixed, which is a combination of both above, and it's been labeled by different names, late onset hypogonadism or adult onset hypogonadism. This is not necessarily age dependent, but it seems to be related to comorbidities and chronic diseases and usually occurs in men of adult middle age and late age.

We're all familiar with the pathway with the negative feedback from the higher centers, the testes. As shown before in the middle here, primary hypogonadism basically has a failure of the testes to work, so you have elevated gonadotropins on the far right. When the testes do work, they're low levels of gonadotropins from higher levels that do not permit the testes to work properly.

A study by Guay looked at different age groups of men, and by far, secondary hypogonadism outnumbers primary hypogonadism as the cause. This study I gather was presented this morning probably. It's the European Male Aging Study. And you can see, 3400 men from 8 different countries,

community-dwelling men, and they looked at both the testosterone and the LH levels. The vast majority of patients fall into the category of having normal levels. There is a compensated group. Only 2 percent fell into the primary group and about 11 percent fell into the secondary hypogonadal group.

Of note here, when we look at the age groups by decades between 40 and 80, there's no increase with age in secondary hypogonadism. This past summer in 2015, the Sexual Medicine Society of North America convened a conference to study the issue of men who present with the clinical scenario of low testosterone and associated signs and symptoms and either have low or normal gonadotropin levels. This is termed adult onset hypogonadism, and it's clinically distinct from the classical primary and secondary hypogonadism but is not necessarily an age dependent phenomenon.

We know that when it comes to obesity and the different components of the metabolic syndrome that all these relate to a lower total

testosterone, and the greater number of components that are involved in the metabolic syndrome, or obesity, the more likely that testosterone will drop.

If we look at one study from Italy, 4200 men who came to an ED office looking for identification of the causes, you can see only 11 percent of the patients were able to attribute the cause of their hypogonadism to these different conditions listed. Ninety percent didn't have any etiology. Now, if we look at that 90 percent, you can see that almost three-quarters had the typical metabolic syndrome type of components for obesity included in there, signifying the issue that may be involved with obesity and these different issues.

Just as an aside, there were two papers that came out in the last few years. Both of them were retrospective, not controlled, and didn't have really follow-up studies, but they caused a lot of media stir about testosterone causing cardiovascular events like heart attacks, strokes, and death.

The FDA advisory board convened and did suggest that the FDA should impose strict limitations on the T drug industry. And with regards to cardiovascular risk, they suggested that the T therapy was inconclusive at this time, but they required the manufacturers to do more comprehensive studies.

We do know looking at a number of prospective studies with tens of thousands of men followed anywhere between 6 and 20 years, there is increase of all-cause and cardiovascular disease when men have low testosterone. Looking at some of the literature in the American Heart Association, it's been comprehensively looked at and shown that any of the components of a metabolic syndrome -- coronary artery disease, congestive heart failure, type 2 diabetes, and obesity -- all these men have been shown to have endogenously low testosterone production compared to healthy controls.

In a meta-analysis of 20 different studies by Corona that came out and published two years ago

looking at major coronary events that may occur, there was no difference in those groups being treated versus those not being treated. His assessment was that testosterone supplementation was not related to any cardiovascular events if patients are properly diagnosed and treated.

Looking at the Baillargeon study that came out in the last year, 19,000 patients, Medicare users or non-users, and 6300 who were treated during this period of time, between 1997 and 2005, there was no association with increased risk of MI. A matter of fact, they looked at the high group for MI. These patients were more likely to have a reduced risk MI.

The FDA has cautioned asking for a labeling change when it came to informing patients of a potential risk for heart attack and stroke with its use. The European Medicines Agency was not involved in this, but they said there is no consistent evidence that an increased risk of heart problems occur with testosterone medicines.

The AUA, the governors have said this is

very contradictory, some of the results, and long-term studies need to be done to understand this better. The American Association of Clinical Endocrinologists likewise stated there's no compelling evidence for testosterone therapy to increase or decrease cardiovascular risk.

Recently, the T trial came out in publication. It looked at 900 men who were greater than 65 years of age and treated for one year. They showed that there was an improvement, a significant improvement, when it came to sexual function and some benefits with respect to mood and depressive symptoms when it came to vitality and walking distance. There was no difference in at-risk events, but this study was not powered to look at long-term conclusions related to treatment.

There are a number of different options. All of them employ the molecule when it comes to testosterone. There are just different delivery modalities that allowed this to be delivered to the system. But the question at hand is that we do treat primary and secondary testosterone deficiency

with one medication. And unlike primary testosterone, secondary hypogonadal men still have functional testes, but the pituitary or the hypothalamus doesn't secrete properly to stimulate the testes.

So secondary hypogonadal men are generally still fertile, and hormone replacement, if anything, worsens the pituitary function and may make men azoospermic. So secondary hypogonadism is potentially reversible with treatment and listed here at the primary causes.

In my practice -- and I'm one of the people -- I see 4,000 to 5,000 patients a year; 20 to 25 percent of my patients who have hypogonadism are fertile, but this is typical of what I would see of a symptomatic, hypogonadal male who wants to preserve his fertility. Namely, he wants to still be able to have a family. An infertile male who presents is already on TRT either illicitly or by his PCP, or a subfertile male who is prescribed TRT to improve his fertility because of the lack of knowledge by the prescribing physician.

If we look at the normal pathway, we're all familiar that the anterior pituitary basically secretes the gonadotropins, FSH, and LH, and that there's a negative feedback if there's a high level of testosterone produced. If you give exogenous testosterone, what happens is that there is basically a negative feedback that causes less LH or FSH to occur because this closes off the anterior pituitary.

Importantly to recognize is that exogenous testosterone basically decreases intratesticular testosterone concentrations, and this in turn reduces spermatogenesis and may result in azoospermia. Intratesticular testosterone is an absolute prerequisite for normal spermatogenesis.

We looked at some of the unmet needs when it comes to separate secondary hypogonadism. Key among these are the potential for cardiovascular risks, infertility effects, and the possibility of testosterone replacement therapies, which are key issues in this.

This is a group of international experts

from around the world, 19 that met in Prague in 2015. They came to 9 different questions, and a consensus resolution came on this. Both the EMA and the FDA were invited to attend this meeting. A representative of EMA did show up. The FDA did not show up. But the resolutions that came up of significance were that testosterone deficiency is a significant medical condition, and it does affect male sexuality, reproduction, general health, and quality of life.

The symptoms and signs of TD result from low levels of testosterone, and there is benefit from treatment regardless of whether there's identification of an underlying etiology. Testosterone deficiency is a global public concern. Likewise, there's no scientific basis for any age specific recommendations against the use of testosterone therapy in men, and the evidence does not support increased risk of cardiovascular disease and prostate cancer with testosterone treatment with the evidence that we have today.

In conclusion, secondary hypogonadism, which

includes adult onset hypogonadism, which is really not an age dependent phenomena, is much more common than primary hypogonadism. Testosterone replacement therapy decreases intratesticular testosterone concentration and thereby inhibits sperm production.

SERMs stimulate endogenous testosterone production and have become an accepted off-label treatment for secondary hypogonadism in men desiring to preserve fertility. The potential benefits of SERMS include that they're no supraphysiologic levels of testosterone that are produced, and for this reason, there's a lack of potential for abuse by people using this. There's no transference risk, and there are beneficial effects when it comes to spermatogenesis, namely fertility and maintenance of testes volume. There's a distinct need for rigorous studies of SERMs in a clinical practice for the treatment of male hypogonadism.

Thank you for your attention.

DR. LEWIS: Thank you. Speaker 3 I believe

has changed their mind. Speaker 4?

MS. RAHIMI: My name is Leila Rahimi, and I'm a project manager with the American Urological Association. The AUA represents more than 90 percent of the practicing urologists in the United States and strives to promote the highest standards of clinical urological care through education, research, clinical practice guidelines, and healthcare policies. The AUA thanks the FDA for this hearing and welcomes the opportunity to take part in this discussion.

We summarize our position with respect to the potential clinical trial designs being discussed today. Number one, it is the opinion of the American Urological Association that the subjects in the clinical trial should be deemed a success if they have a normal end of study testosterone of 400 nanograms per deciliter rather than 300 nanograms per deciliter as suggested in the industry briefing documents.

Number two, we suggest that the subject endpoint in patient-reported outcomes also be

measured using a validated questionnaire before and after the use of the drug for the plan time duration. We thank the FDA for its ongoing work to promote the efficacy and patient safety on health care, and we look forward to opportunities to both work collaboratively with and serve as a reference for the FDA. Thank you.

DR. LEWIS: Thank you. The open public hearing portion of the meeting has now concluded, and we will no longer take comments from the audience. The committee will shortly turn its attention to the task at hand. Before we do, I think that industry wanted to add a few clarifying comments.

DR. WERNICKE: Thank you. There's been a lot of discussion about the importance of sperm and sperm count and other parameters of sperm, so I wanted simply to clarify that the whole issue of sperm is different for different drugs. I know there's been some confusion, but the agency has quite rightly segmented these questions.

For drugs like enclomiphene, which have a

separate estrogen receptor antagonist, sperm is not really affected. The whole issue is that it's not diminished, whereas for drugs that want to treat infertility, this is a crucial point. So if I could have that slide up.

These are outcome measures, the study design population and outcome measures that we have proposed. You'll see that there's a sperm concentration of 15 million, and that was, frankly, just because of the WHO recommendation. I understand there's a lot of controversy, but that number for us is fairly arbitrary, whereas for a drug that wants to treat infertility, this is a key feature. That could easily be -- I don't know. But the point is that this drug has not decreased spermatogenesis, and to illustrate that, if I could have the next slide.

These are baseline sperm concentrations for -- the bar graph, please. These are the baseline sperm concentrations from two clinical trials of men -- actually obese men, overweight men with secondary hypogonadism. You'll see that

except for a few, they're in a fairly high range. The point is that one -- this is a distribution by sperm concentration with millions in the X axis. They were actually disqualified if it was less than 15, so there aren't any less than 15, but they're all much higher than that. What we have shown is that, overall, there is no reduction in sperm concentration, which you see.

Can I leave that up there for a moment, please? I would like to use this to illustrate why 50 percent, or some other percent, reduction is really not helpful, because if you take a person from let's say 100 million to 50 million, that probably has no consequence, but if you take them from 20 million to 10 million, that's much different.

So I just wanted to make these points because you're going to be charged with addressing all that, then you have to kind of refocus your mind-set. Thank you.

Clarifying Questions (continued)

DR. LEWIS: We're going to go to additional

clarifying questions. Before we begin this process, I just want to mention that Dr. Oehninger I believe has to leave early, so I think if you have specific questions for him, please address those first. I think we'll begin now for any additional clarifying questions for the guest speaker, industry, or FDA, starting preferably, preferentially, with Dr. Oehninger. Dr. Schlegel?

DR. SCHLEGEL: Just to follow up on those proposed inclusion criteria for patients, for inclusion, why would you exclude patients who have a sperm concentration of less than 15 million per mL? We've certainly seen drug effects -- for example, the effects of finasteride, that are actually much more dramatic for patients who are oligospermic to begin with. So why would you exclude the patients who are at greatest risk, for example, of becoming azoospermic?

DR. WERNICKE: In the enclomiphene clinical trials, that was done because the whole intention was to maintain spermatogenesis in a range that most people -- and this is the WHO -- would

consider as fertile. Well, if you start people that already are below that, you would have to increase them to get into that range because the intent of a drug is not to increase spermatogenesis; it's to maintain it. Well, if you maintain 12 million, what does that mean?

That's why it was done, because it's a whole different approach. The focus of this drug was to increase testosterone while not affecting spermatogenesis, but not to raise it because that's very fundamentally -- totally different.

DR. LEWIS: Dr. Dmochowski?

DR. DMOCHOWSKI: This is a question for Dr. Oehninger. That was an excellent presentation this morning. Being that you have the purview that you do, can you give the panel some sense of this numeric controversy regarding absolute numbers versus relative numbers and whether a number is adequate from the standpoint of a regulatory trial to determine effect on the testis?

DR. OEHNINGER: I think a number is important. I think that one has to clarify -- a

point that I tried to make in my presentation -- that the studies that show a beneficial effect of gonadotropins, in men with secondary hypogonadism with Kallmann syndrome and other idiopathic causes, are men with intact testes. So you may start achieving pregnancies with 1 million, 2 million sperm, that may be absolutely totally different from the 40, 50, or 60-year old population where obesity, aging, et cetera, et cetera. And some degree of subfertility may be present, and therefore those numbers should not be applied in my humble opinion.

Now, whether it's 15, as WHO recommends is the cut-off, or some other, or total motile sperm count, which I think probably should be somehow included, I think that's a number. But the concept is that number at least manifests what over 95 percent of fertile men have in the sperm, in the semen.

DR. LEWIS: Dr. Sandlow?

DR. SANDLOW: This was actually a follow-up to Dr. Schlegel's question about not including

patients with sperm concentrations less than 15 million. If those patients were never examined, they can't be treated because as the treating physician, we won't be able to tell our patients what the potential impact will be because they were never included in the original studies. I think it's very important that they are included, even if this study is only looking at raising testosterone levels and maintaining sperm production.

DR. WERNICKE: Well, theoretically, in a perfect world, that's right, but we can't answer every question. I mean, if they're already below normal, what can -- they can only stay below normal or they can get better. So maybe they go from 12 to 8 million, but that's not what this drug is about.

I mean, there are a lot of things one could explore, and we would like to do that, but the goal of a drug development program is to focus on the issues that this drug is supposed to treat. And yes, you're right, we can't answer every question and we can't tell that person -- we certainly would

never say, well, we're going to raise your sperm. All we can say is this. They haven't been studied. That's not what this drug is about. And hopefully one of the other teams will develop a drug that can raise sperm concentration.

DR. LEWIS: Dr. Adler?

DR. ADLER: I have a question for Dr. Khera. And that is, do you have any preclinical data showing that long-acting hCG preparations have the same effect on the testis as intermittent short-acting hCG?

DR. KHERA: That question I will defer to Dr. Kacker.

DR. KACKER: We're currently in a very early stage of development, so we have primarily in vitro data. We will have some -- and more pharmacokinetic data, but at this point do not have effect on the testes. We will have that prior to IND, however.

DR. LEWIS: Dr. Braunstein? I'm sorry. Did you want to say something, Dr. Joffe?

DR. JOFFE: This is Hylton Joffe. I'd like

industry to clarify one thing for me because it sounds like the enclomiphene company and clomiphene company have very different objectives with their drugs, but they both are working as estrogen antagonists. So why does the enclomiphene company say their drug can't really be developed to increase sperm counts, whereas the clomiphene company is saying that's what their intent is?

DR. WERNICKE: Well, they are really two different drugs. Clomiphene is a mixture of enclomiphene and zuclomiphene. They have quite different pharmacological properties. These drugs can work differently under different circumstances. The clomiphene mixture that's being proposed, they have reason to believe that it increases sperm concentration, and I would like to ask them to address that. But for enclomiphene, it's a pure antagonist, and our data, animal and human, has clearly shown that there is no effect.

So one has to get into the relative pharmacology, but these drugs -- if you would put that slide up, please -- are really very different,

and not just different. One is a subset of the other. But zuclomiphene is not a pure estrogen antagonist. So the pharmacology is clearly going to be quite different. And actually, that was shown -- if I can have that next slide -- in an ovariectomized mouse model.

Here, what they're -- I know we were talking about animals now, but this illustrates that estradiol and tamoxifen, which of course have estrogen agonist activities and cause an increase in endometrial glands in the lumen of the uterus of ovariectomized mice, whereas enclomiphene has much less of an effect, and that's thought to be due mostly to glandular swelling. We're going to do a study that actually uses dry weight.

Can I have the other slide that goes with this one? Do you have that? Let me just say, the drugs are different. And if you would allow, I would like to -- I'm sorry. This shows hyperplasia and edema of the uterus in these mice. But if you would allow the other company to address why they think their drug will increase spermatogenesis.

DR. KIM: So speaking on behalf of Veru, different drugs, different populations, it's all how they present. And for the MSS-722, the mixed, fixed-dose clomiphene, while it's theory, the thought is that you do need some of the estrogen to help out with spermatogenesis; again, a theory but something that needs to be proven.

I think one of the points that probably didn't come across as strongly beforehand was with regard to MSS-722. It's a very small, fixed population, 16 to 56,000 men annually in the United States, orphan drug type of status. And with this, I think that the performance of coming baby studies would be probably not the best use of resources given the technical complexity -- science is not easy -- but for such a very small focused group of men, for a very short defined period of treatment. That is why sperm concentration is being focused on as an increase rather than as a maintenance; so different drugs.

DR. LEWIS: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. I have two

clarifying questions. The first concerns a question that actually Dr. Bauer had asked before lunch of Dr. Kim, and I just wanted to clarify the answer. And the question really was about giving gonadotropins, hCG and hMG or hCG and folliculostatin to patients with secondary hypogonadism and finding an increase of sperm count.

It's my understanding that where you see the increase in sperm count in those studies is really of patients with Kallmann syndrome and other structural defects in the hypothalamus or pituitary, and they basically have normal testes, and you're able to directly stimulate the testes with hCG and hMG and get an increase in sperm count.

Does that also apply to patients with the secondary hypogonadism without structural or congenital functional defects, the type of patients that we're talking about, the obese patient, patients with depression, or any of those other problems that may lead to a lowering of the

gonadotropins?

DR. KACKER: So you're right. Some of the studies on hMG with or without -- sorry, hCG with or without hMG have focused on patients in terms of abnormalities. However, some of them do include patients, a small subset, with idiopathic hypogonadotropic hypogonadism. They're somewhat older studies, and it's unclear how that would fit into our current understanding of the patient groups that we've discussed today. But I'd like to make a point that our indication is primarily for classical secondary hypogonadism and may at some point, with additional data, be extended to maintenance of fertility.

DR. BRAUNSTEIN: I would agree that that drug would be best for patients with classical hypogonadism. Just sort of a comment. You do have an experiment of nature that sort of addresses one of the previous questions with long-acting hCG, and that is men with hCG secreting tumors, either testicular tumors or extra gonadal germ cell tumors.

Now, they may not have normal testes, but nevertheless what happens is they get an increase in testosterone, and oftentimes there's down regulation, but there's also an increase in aromatase enzyme that develops in the testes, that results in increased estrogens with prolonged hCG stimulation, continuous hCG stimulation that leads to gynecomastia for instance. So it will be interesting to see what the data is on a long-acting hCG versus the intermittent injection protocol.

DR. KACKER: So they will be looking at that. I would point out that the one randomized controlled trial, which has examined hCG versus placebo, involved injections of hCG every other day. That actually reaches a pharmacokinetic steady state, and serum hCG levels are maintained in a level that we intend to approximate with a extended-release formulation. And in that group, there were no cases of gynecomastia.

DR. BRAUNSTEIN: Second clarifying question? Okay. This goes back to, again, a previous

discussion that we had, but I'd like to get a little bit more clarify on this. And this would be to Dr. Wu and maybe Dr. McCullough. And it concerns the effect of weight loss on sperm parameters. Dr. McCullough did mention that if you take morbidly obese men and give them a gastric bypass type of surgery, they lose weight. Their sperm counts, which were low, then come up.

What about the non-morbidly obese men? And then perhaps Dr. Wu has some of that data since they have data on testosterone. Do you have data on sperm parameters in your patients that lost weight and had reversal of the secondary hypogonadism?

DR. WU: Data on non-obese sperm count. I don't know of any good studies in the literature that would give that information. I think most of the literature refers to the small number of patients that's gone through bariatric surgery.

DR. LEWIS: Thank you. Dr. Brannigan?

DR. BRANNIGAN: This is a question for Dr. Khera. You refer to the concurrent use of hCG with

testosterone. You refer to a couple small series with patients who are on this therapy. And a couple of slides later, you mention using both concurrently. Can you discuss the rationale for that, please?

DR. KHERA: So there's one study that was out of Baylor looking at concomitant use of exogenous testosterone with concurrent hCG. That's the only study that I know that's looking at preservation of fertility. And in that study, there was no decline in fertility. Again, it's a small series. These patients were young men who wanted to continue to use exogenous testosterone but still wanted to preserve their fertility, and the study was clearly to see if that was possible.

The impetus for that study was based on the Caviola study, which showed that if you give exogenous testosterone with low-dose hCG, there was no decline in intratesticular testosterone, and that's why these studies were done in fertility.

DR. LEWIS: Dr. Chai?

DR. CHAI: So this question is for industry,

whoever wants to answer this. I would like to have a summary of how you would help me vote on the first vote about whether -- you guys know what the first voting question is. Why should I vote yes? Because in looking at the proposed trial for looking at overweight, obese men with secondary hypogonadism who wish to maintain spermatogenesis, your inclusion criteria do not include any symptomatic based type of inclusion criteria. So you're just looking at sperm count, if you will, whatever the numbers you guys want to talk in testosterone level.

But in hearing everything I'm hearing today, patients don't come in and say I have a low testosterone. They don't say my sperm count's X. So why should I vote the way I think you guys want me to vote for number 1 without coming out and saying why don't we include something that the patients are complaining about in the trial so we can answer that question?

DR. WERNICKE: Well, that has been discussed extensively. And as you've heard from the agency

and others, there are no validated patient-reported outcome measures. That's one point. And to develop those, as has very nicely been explained, takes years. If it has to happen, then you just wait years. But in the meantime, people are being treated with testosterone and Clomid.

The other point is that we think that testosterone is really the key feature. There's such a diversity of complaints people come in with. I think the clinicians can tell you better. If a patient feels bad, he's kind of low mood, well, is he depressed? He doesn't have energy. Well, he's obese. He doesn't get up off the couch.

These are such non-specific features. Yes, we could include those, but then to show that they improve in a time that's reasonable for a clinical trial, it just doesn't -- with the tools we have today, it just doesn't seem possible. But in the meantime, these people are being treated either with an off-label drug or a drug that probably isn't appropriate for this population.

DR. McCULLOUGH: Dr. Chai, I want to speak

as a clinician. We've heard from Dr. Joffe that men with classic hypogonadism should be treated because of clear benefit of testosterone replacement in these men. Dr. Braunstein and Dr. Dmochowski on the other hand expressed confusion about the distinction between the classic and non-classic hypogonadism. The man presents to me, with a testosterone of 140 and symptoms, and he and his wife want to maintain fertility, I'll treat him, whether his BMI is 20, 30, or 40, or whether he's 20, 40, or 60. I, like Dr. Howards, will treat him with SERMs.

Now, the FDA does not dictate medical care, but many physicians don't feel comfortable using a medication that's not FDA approved. In fact, we heard 25 percent of urologists treat hypogonadal infertile men with testosterone, which further impairs their fertility. So as a clinician, I don't see utility of the PRO when we are trying to correct the testosterone to treat the symptoms and maintain fertility. It doesn't make any sense to me as a clinician.

DR. LEWIS: Thank you.

DR. BRAUNSTEIN: May I correct a misconception?

DR. LEWIS: Oh. Okay.

DR. BRAUNSTEIN: I'm not confused over individuals with classical or non-classical hypogonadism. Classical hypogonadism, such as patients with Klinefelter's syndrome, such as patients with Kallmann's syndrome, et cetera, have defects that are not reversible spontaneously. They need to be treated to avoid osteoporosis, osteopenia, all the sexual issues, muscle issues, developmental issues. And if those that have normal testes, not the Klinefelter's so much as the patients with hypothalamic hypogonadism, they can be treated to increase their sperm count and achieve fertility.

That's a different kettle of fish than acquired secondary hypogonadism that we're talking about, obese patients, depressed patients, et cetera. So that's the group that we're talking about now. I'm not talking about classic, so I

don't have that confusion. But the second group is a group that are potentially reversible. We've seen the data with obesity. You have patients who are obese with low testosterone. They lose weight; the testosterone comes up.

With depression, we heard from the psychiatrist during the open session. I'd venture to say that depressed patients get low testosterone. You treat the depression, testosterone comes up; chicken versus egg. I'm sure patients with low testosterone will get depressed also, so it can go both ways. But I have seen a number of patients who are depressed, have low testosterone, and it comes up. You put a patient in the ICU, as was mentioned earlier, their testosterone plummets. They come out of the ICU, they get better, it goes up. Those are reversible causes of hypogonadism.

Now, you wouldn't treat a patient in the ICU with testosterone. Why would you treat a patient whose ambulatory with testosterone, unless for having symptoms, and you haven't found out a reason

why they have a low testosterone? So that's a different kettle of fish than classical hypogonadism.

DR. WERNICKE: Could I address that? I mean, you're right. But just to be sure we all understand, even in classical hypogonadism, it hasn't been shown that increasing or restoring the testosterone has a clinical benefit. All the things you say are medically true, but if I could have the slide from 0205 that shows the baseline characteristics?

Actually, to further the previous question from Dr. Chai, have we included people with these baseline conditions, if I could have that slide up? This is from an ongoing study of people with obesity and secondary hypogonadism, and it shows in fact that they do have many of these features, lack of energy, 96 percent. They do have them. But then the next question you're probably going to ask, which I would ask, is, okay, well then show me that you can make them better, and that's where the problem comes in.

You say, well, these things are so diffused, and you say, well, you can measure fatigue. Well, we just heard a very fine lecture why you can't just ask are you fatigued. You have to develop and validate various rigorous outcome measures, and that's true for all of these things. So yes, these patients do have these characteristics, very clearly. There's no doubt about that.

DR. LEWIS: Thank you. I have a quick, straightforward question. Could you please clarify the difference between MSS-722 and clomiphene?

DR. KIM: Yes. MSS-722 will be fixed ratios of the trans- and cis-isomers in clomiphene. The presently available clomiphene that's used right now is generic, and the relative concentrations of the cis and trans are quite variable and really not very well known. So the benefit of MSS-722, what makes a difference, is a very fixed ratio. Whether it's 70, 80, 90 percent, that still has to be determined.

DR. LEWIS: Thank you. Dr. Schlegel?

DR. SCHLEGEL: Can we just go back to -- I

think I've got two different pieces of information of the endpoints for hCG formulations and what indications you're talking about using with this agent, because you list treatment of infertility. Is that still a potential indication?

DR. KACKER: So this advisory committee, we were asked to talk about a drug class rather than the specific indications for a drug. So representative of MHB Labs, we are developing an extended-release hCG formulation for the indication of classical secondary hypogonadism or secondary hypogonadism related to well-known medical causes later in development. And we are in a very early stage of development. We will likely potentially seek an additional claim for maintenance of fertility. At this point in time, we have no plans to seek approval for an indication for improving fertility.

DR. SCHLEGEL: Okay. If you do seek an indication for improvement of fertility, I would caution that a lot of the azoospermic men who have been treated with hCG have had a decrease in FSH,

and therefore their fertility may be harmed. Since they're azoospermic to start with, it would be difficult to detect that potential damage, so to consider that carefully in your trial design.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: So I understand the argument for having a product like enclomiphene is that it would have improved safety over existing testosterone options, but what I'm confused about is I believe the testosterone products are currently only approved for classic hypogonadism, which involves some level of impairment to the pituitary or gonads, and enclomiphene would not work in that group of patients.

So I was wondering if you could provide -- is there any subset of patients who are currently using testosterone on label who could benefit from switching to this product with its improved safety but similar ability to raise testosterone levels?

DR. WERNICKE: well, to answer that last question, no, we know of no subset of this

classical hypogonadism. But I know this isn't about safety, and it's not clear that enclomiphene is safer than exogenous testosterone.

I want to be very upfront about that. These drugs, they have two -- one of the biggest issues is venous thromboembolism, and that probably relates to two potential mechanisms. One is these drugs increase hematocrit, which of course can be a risk factor. But you can have thromboemboli even in the absence of increased hematocrit. In fact, the agency has put that in the labeling. We have had some cases, and there's no claim, at least on our part, to suggest -- and no data to suggest that the drug's actually safer, but it's not less safe.

MS. SORSCHER: With safety, I was just referring to the reduced sperm count as a safety feature.

DR. WERNICKE: Oh, I'm sorry. Okay. That's fine, yes. So did I answer your question then?

MS. SORSCHER: Yes, you did.

DR. WERNICKE: Okay. Thank you.

DR. LEWIS: Thank you. Dr. Weinfurt?

DR. WEINFURT: I just wanted to go back to Dr. Chai's question about the first vote question. And I guess I'm still really struggling with this because I haven't seen any information that anyone's presented that gives me even the slightest idea of the magnitude of the association between testosterone and any clinically meaningful benefit.

So I understand that qualitatively we can say, well, it should be associated with those. There's some suggestive evidence of it. We also hear, well, it would be a big pain in the neck to develop a patient-reported outcome. But there's still a tremendous amount of uncertainty that true correlation was 0.2. I think that's a problem. If it was 0.99, I think we'd feel differently.

I just want to confirm, is it the case that we don't have any information that gives us an idea of the magnitude of that association?

DR. WERNICKE: The reason that hasn't been presented is because this discussion is not about testosterone. But there's actually very extensive literature that shows beneficial effects of

restoring testosterone, but that's beyond the scope of this advisory committee. And I believe we're seeing some of that in the EMAS study. There have been other studies.

The problem is one study shows it, the other one doesn't; well, they're measuring a little bit different; it's a different population. But if you look at it in its totality, there is substantial evidence that after a long time -- and it may take years -- that increasing or restoring testosterone is a good thing. And we would have to review the literature extensively, but that's beyond the scope of this discussion, really. But it's out there. Maybe some of you that have done this can comment. I can't go through all of it right now. We'd be here until tomorrow, but it's there.

DR. LEWIS: Dr. Gassman?

DR. GASSMAN: There is a body of literature about the benefits of testosterone, but from our perspective, I think everyone at the table would say we don't feel that it's substantial enough labeling claims. We don't feel that it's

substantial that there's an instrument or a benefit that we can point to for testosterone beyond what we have in labeling right now.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: Just a comment and really a rephrasing of things from my perspective being a statistician. One of the comments kind of seems to confuse the role of testosterone and its acceptability as a primary endpoint in primary hypogonadism. Really, the discussion today comes down to the utility of surrogate endpoints, and truly three settings is really what we're talking about. There is primary hypogonadism where we have a clear -- at least reasonably clear of the mechanistic pathway that we're intervening on, and it's clear where that mechanistic pathway needs to move. And that is increasing testosterone levels because of testicular dysfunction.

When we get into secondary hypogonadism, we need to think about the Prentiss criteria. I mean, that's a well accepted criteria for surrogate endpoints as we think about them. The Prentiss

criteria basically says that you have an ideal surrogate if that surrogate marker is correlated with the clinical outcome of interest in that the entire net effect of the treatment on that clinical outcome runs through these surrogates of interest. Again, that argument becomes much easier to make in the primary hypogonadism case. That argument becomes extremely cloudy in my mind as you get to the secondary hypogonadism case.

In that setting then, we are left with thinking about what are the clinical outcomes, patient-reported outcomes as we've talked about, as Dr. Weinfurt just talked about. What is the effect of raising testosterone levels on these PROs?

There's a separate thing. So now you're there, and it's thinking about, okay, in obese individuals with secondary hypogonadism, what is the surrogate that's going to come into play? If it's infertility, that's a different outcome that you're trying to treat, and you need to think about what the surrogate impact is there of looking at sperm cell count, either concentration or other

measures.

In some sense, the fertility becomes easier because you have a very objective, in my mind, clinical outcome. How many pregnancies are occurring? What are the proportion of individuals that are becoming pregnant? And I realize there are logistical constraints in terms of numbers of patients and the time to collect that event, but you have an objective measure that is sitting there.

There is room for debate on the PROs, whether you want an objective measure plus, for example, a subjective measure that's coming in. But I believe that that is to frame the question. That's where etiology comes into play. That's what the discussion really needs to be about. So I just wanted to make that comment.

DR. LEWIS: Thank you. Dr. Thomas?

DR. THOMAS: I just decided to look on the -- the power of the internet. I don't know if you have time to look at this article in great detail, but it's been asked many, many times during

this meeting about weight loss. So there's at least one study -- there could be more -- Reproductive Health 2011, a study in Denmark looked at people with BMI from 33 to 41, residential weight loss program. They lost 15 percent of their weight, they increased their sperm count, and other hormonal parameters. Suggestion is they also improved some aspects of sperm function, but probably not clear.

So there's at least one showing weight loss. They lost 15 percent of their weight. And some people might think that's excessive or hard to do, but just remember phentermine and topiramate. The mean average weight loss for that drug is a little over 10 percent. It's not too far off. So at least there's one paper out there.

DR. LEWIS: Thank you. Briefly, I wonder if maybe Dr. Oehninger, and I don't know of industry also could comment on the public hearing person who said that they thought the threshold for total testosterone should be raised to 400. Have you any information about that or experience? No? I get a

clear no from Dr. Oehninger.

Anybody over here? No comment on that.

DR. WERNICKE: We've discussed different levels with the agency. Actually, the number 400 hasn't come up. We could discuss that, whether it's 350 or 400. You have to distinguish between entry criteria and what's called a success. So I think speaker was talking about what is a success. I think that could be discussed. We don't have any --

DR. LEWIS: Dr. Gassman?

DR. GASSMAN: The other thing when you're talking about testosterone levels is you have to look at the assay and the assay performance. There are a lot of issues beyond just picking a number. So I think that's something that would depend heavily on what assay you were using, what the cut-offs are, what your normals are. So we take the recommendations, and we'll consider it.

DR. LEWIS: Anybody else? Any other clarifying questions?

(No response.)

DR. LEWIS: Okay. So before we go to the discussion of the discussion questions and the voting questions, we'll take a short break. Let me remind you that there's no discussion among panel members, please, of the topic at hand during your break either amongst yourselves or with any members of the audience. We will resume in 15 minutes, 2:20 let's say.

(Whereupon, at 2:05 p.m., a recess was taken.)

Questions to Committee and Discussion

DR. LEWIS: We will now proceed with the questions to the committee and for panel discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We have two questions for discussion and three for voting. We'll start with the first question for discussion to the committee. For drugs intended to treat secondary hypogonadism

while preserving existing testicular function -- that is, maintenance of sperm parameters or demonstration of fertility -- discuss, A, the patient population that should be enrolled in clinical trials; B, how preservation of testicular function should be defined and assessed; C, acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and for those who do not have classic hypogonadism; and D, any other trial design features that should be considered.

So the process for this, we'll handle it the same way we've handled the other questions. Raise your hand, and Dr. Bonner will take your name down. I'll try to get everyone in. When it comes to the voting questions, each person will need to weigh in.

Would anyone like to go first? Dr. Braunstein?

DR. BRAUNSTEIN: I'll start. For drugs intended to treat secondary hypogonadism while preserving testicular function -- so these are not

patients who are infertile to begin with -- the patient population should be enrolled in clinical trials. I would want to see patients with documented low testosterone, preferably low free testosterone because we're talking about potentially reversible secondary hypogonadal individuals; more than one testosterone measurement because we know that about 30 percent of individuals with a low testosterone from acquired secondary hypogonadism or non-classical hypogonadism, when you repeat the testosterone measurement down the road, oftentimes it will be normal.

So I'd want to see at least two preferably free testosterone to take into account the SHBG alterations, especially in obese patients where it may be leading to a low total testosterone, but some of those patients will have a normal free testosterone, as Dr. Wu has pointed out.

In addition to the low testosterone, those patients need to have symptoms. I think the companies should work with the FDA to develop good

symptom screening tests. I know that there are some that have been developed. For instance, New England Research Institute, NERI, has one that has come out recently. EMAS has one that they validated. So there are those tools out there, and I think that the companies should work with the FDA to do that.

We do know that a lot of people will have a low testosterone, but many of them won't have symptoms. So that combination will lead to maybe 6 percent or less of the adult male population after filling the criteria.

B, how preservation of testicular function should be defined and assessed, again testosterone and this time also adding sperm count with normal morphology.

C, acceptable endpoints for demonstrating clinical benefits for men with classical hypogonadism and for those who do not have classical hypogonadism, the endpoints for men with classical hypogonadism, first of all, have been well defined in a number of studies, which we I

think discussed, things such as bone mineral density improvement, as well as sexual function improvement, and in those level of sperm counts, improvement of sperm counts with appropriate gonadotropin stimulation.

But for the patients who do not have classical hypogonadism, I would clearly want to see an improvement of symptoms by questionnaire or any objective measurements. So if there's low bone mineral density, showing an improvement in bone mineral density for instance.

Finally, other trial design features that should be considered, all these patients should be entered into a registry to look at pregnancy outcomes and fertility issues down the road since these are patients who not at the time are requesting fertility treatment, but they want to maintain sperm counts for potential fertility in the future. I'd like to see that proven, although registries can hardly prove things. But I'd like to see through a registry that there at least has been no increase in infertility reports from those

patients.

DR. LEWIS: Thank you. Dr. Thomas?

DR. THOMAS: Dr. Braunstein I think outlined very well what needs to be done. I just wanted to add a few things. Twelve-week studies are probably okay to look at short-term efficacy, the response to the drug in terms of raising testosterone and preserving spermatogenesis. However, I really suspect or doubt that this is going to be a short-term treatment, so 12-week trials should not be sufficient to assess a drug that probably will be taken for at least a year or two. So we have to have a longer trial.

I would actually also suggest that we go a little beyond what Dr. Braunstein suggested about a registry. The whole point of using these drugs to me in these classes are you want to preserve the chance of having a child. And if that's the outcome, that's the intent of these drugs potentially, then we should actually look at that. And yes, I've heard from the industry side, oh, it's difficult. There are lots of complications.

It's hard to do science. Well, that's life.

On the PCOS side, which I also see a lot of patients, there are two very well-designed trials that have been published. One in 2007 that looked at metformin versus clomiphene, and the result was live births. Before the study, if you asked most endocrinologists who take care of PCOS women, probably predicted that metformin was the better drug. The actual reality is clomiphene is far superior to metformin.

The same trial essentially was replicated in 2014 with letrozole of metformin. And letrozole is far superior to metformin -- I mean, letrozole to clomiphene, and letrozole was far superior to clomiphene in that study. They enrolled about a thousand subjects in these trials, and they looked at the male partner as well.

So the same can be done. It does cost more money. It does require time. But the reality is that's seen for an answer [indiscernible] because if I'm treating a man who wants to eventually father a child, I'd like to be able to say,

option A gives you a 20 percent chance of having a child, but if you select option B, maybe it's 40 percent. Option C is going to be very unlikely that you father a child even if you preserve spermatogenesis.

I think these are important clinical endpoints. We use surrogate endpoints in diabetes all the time, A1c, but now we're looking more and more at the value of these long-term outcomes like cardiovascular disease. The FDA requires trials in that.

The last thing I was just going to say is one thing that has not been brought up at all in this, especially it will be important in the study of obese men, is sleep apnea. Sleep apnea causes hypogonadism. And in some, but not all studies, treatment of sleep apnea worsens -- sleep treatment with testosterone worsens the sleep apnea. So I think an important part of the screening should be some measure of -- at least a questionnaire screening tool for sleep apnea and potentially even using the overnight pulse oximetry, which is now

the first test before you do a sleep study.

DR. LEWIS: Anyone else? Dr. Curtis?

DR. CURTIS: I think most of my thoughts have been mentioned, but one thing that hasn't been mentioned under the section of "Other Trial Design Features" is I was wondering a little bit about some of the control arms. And this first point gathers a lot of our specific examples together.

For example, for obesity associated hypogonadism, we've heard that weight loss clearly resolves some of these symptoms, and would it be worth considering an arm, in addition to the treatment with a placebo, of a weight-loss intervention. Similarly, with the hCG proposals, would we want an arm that would include the current approved hCG formulation. So just a little more thought about what those control arms should be.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: Thanks. Again, I think as we look at the patient population, low documented testosterone, multiple measurements, frankly whether we use free or bioavailable is a little bit

tricky. I think in clinical practice, relatively few people actually get to free or bioavailable, so it's challenging but at least total testosterone. I think we do need to include patients with all levels of semen parameters. The patients who are at greatest risk may very well be those who are oligospermic to start with.

In terms of preservation of testicular function, I think sperm number as well as quality at some level need to be considered, so sperm concentration. Total motile sperm could be outcomes even though the numbers are not routinely validated in terms of what the best outcome is. I think clinically that's what most physicians use.

I think it's tricky when we look at pregnancy outcomes. I was on the DSMB for the Reproductive Medicine Network. Those couples are all really selected to be patients who can get pregnant. When you're dealing with a male alone and highly variable females, potentially females not interested in pregnancy, it's going to be very hard to look at pregnancy. I think the long-term

effects certainly would be nice to get from a register, but having pregnancy as a primary outcome I don't think is appropriate.

DR. LEWIS: Dr. Burman?

DR. BURMAN: Yes. Thank you. I agree with all the comments that were made, and they were excellent. The question is for treating secondary hypogonadism, and as we've spent the whole day discussing, there are different types of secondary hypogonadism. And I wouldn't want everyone in the trial to have obesity-related secondary hypogonadism, and there should be some characteristics or some clear delineation of how many are going to have secondary hypogonadism that is classic and what percentage are going to have other types like obesity, which of course has to be defined more definitely and have to give a lot of thought to who would be included in that.

Just a minor point, osteoporosis is an important endpoint. It takes a long time for bone densities to change. So I agree with Dr. Thomas the studies have to be relatively long, but I would

also add in bone markers periodically as well.

DR. LEWIS: Dr. Gillen?

DR. GILLEN: I agree with pretty much everything that's been stated. I just wanted to make a couple points from thinking about primary or co-primary endpoints. I definitely agree with Dr. Braunstein that PROs are necessary in this case, again thinking about the clinical outcome of patients, what patients are actually feeling, and to be quite honest, the lack of evidence that's been presented on any kind of correlation between affecting testosterone levels in those clinical outcomes in this patient population.

The only other thing I wanted to say, though, is when we think about preserving existing testicular function, I agree with total sperm count and possibly motile sperm counts. The way that we treat those is going to be slightly differently, though, thinking about superiority, for example, and the PRO, and then possibly choosing sperm concentration, for example, and noninferiority design, and treating those as co-primary endpoints

that have to be met in that study setting.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: Everybody's brought up some excellent points. I guess I'm just a little worried about this, about how do you define some of the ones to preserve existing testicular function. Because my guess is if you ask the vast majority of men, their answer to that is yes, of course, even if they really have no active plans for childbearing.

So I'm not totally sure how one would actually operationalize this, and I think it might rate back something that Phil talked about earlier, which is younger men versus older men. In fact, I think the patient population of most interest for this question is really the younger man who in fact has a high probability where fertility is important, and not middle age or older men where in fact the most likely phenotype is more what was discussed I think in 2014, which was following androgen level secondary to age alone.

So I don't have a good answer for that, but

again I'm worried about how you would actually operationalize men wanting to preserve testicular function.

DR. LEWIS: Dr. Adler?

DR. ADLER: I know that we're not supposed to be talking about safety today, but I think we have to think about it, at least in terms of the length of the trial. And I agree that a 12-week trial, while it would be very helpful in giving us information, many patients, whom we are going to consider some sort of testosterone replacement via testosterone directly or through some other means, will be treated for years, if not decades. And therefore, I think we have to consider that in the trials now. Thank you.

DR. LEWIS: Anyone else? Dr. Thomas?

DR. THOMAS: Just a few things in follow-up. I think because of the duration of treatment, there are two other things I'd like to mention. One is these are people if they want to preserve potential for parenting, however, we should probably also be comparing to see if there's noninferiority to the

standard treatment if you're not interested in parenting, which is testosterone, and then you could actually do the comparison with the different tools that will have to be developed.

The second thing is for weight loss. I think that's a great idea to use weight loss. The only problem will be knowing from the weight loss studies is the dropout rate for most weight loss studies is about 50 percent, and the enrollment of men into weight loss studies is usually somewhere between 5 and 20 percent. So it may be hard to accrue enough people to do that in a reasonable trial with not enough follow-up.

But I think it's an excellent idea and adds to a certain issue, is if you were to treat obese men this way to raise their testosterone, it would be important to look at what are the benefits of that in terms of we know the benefits of weight loss for diabetes prevention and other risk factors. We don't really know what the benefits of this will be for long-term use.

Just to give you an example, if you take

data, which has been done in women who were transitioning to be men, when they take testosterone, they have improvement in their cardiovascular risk factors; they lose visceral fat. However, that's short term. That's in a few months. If you look at it a year, most of visceral fat loss actually reverts back to where they were at baseline. So it's the importance of having a long-term study for follow-up as well.

DR. LEWIS: Dr. Nahum?

DR. NAHUM: Hi. Jerry Nahum. I guess I'm a little confused about one thing. And perhaps I can just bring it up, and others here who understand it better than I do can explain it. I saw the slide where it was presented that for people who are obese and they lose weight, their testosterone levels increase, and I also saw that for people who gain weight, their testosterone levels decrease. And I assume, just thinking about that slide, that it was total testosterone that was being measured.

I'm having trouble bridging from that -- at least conceptually, without going to the idea of a

PRO and referring and bridging from testosterone levels to symptomatology -- how we go from that to if you take obese people who have low testosterone levels and you replace them with testosterone or boost their testosterone levels, that that will, ipso facto, make them more normal in some way or make them equivalent to the way that people would be if they lost weight and had their testosterone levels increase.

So I guess what I'm talking about here is I'm not sure where the causality here is and whether things are not just flipped around, or whether we're just looking at an association here. I'd like to be able to see something that said that the testosterone levels in and of themselves were well enough correlated with a complaint, or clinical outcome, or something else; that confidence that replacing testosterone or giving a drug to increase testosterone would have the same effect, ipso facto, as losing weight and having testosterone increase.

If anybody understands that better than I

do, and maybe I don't get it, please, I'd love to hear the explanation.

DR. LEWIS: Dr. Howards?

DR. HOWARDS: I just have a comment about selecting the men who want to preserve fertility. First of all, I'm very old, and I want to preserve everything.

(Laughter.)

DR. HOWARDS: But secondly, a lot of lay people, if you ask them if they want to preserve fertility, will interpret that as potency. So I think in selecting this group, you have to be very careful to get men who really want to preserve fertility and have a realistic situation where they might really need to preserve fertility. Otherwise, you're going to get a lot of people who have no reason to preserve fertility.

DR. LEWIS: Thank you. Dr. Schlegel.

DR. SCHLEGEL: Sorry. Just to follow up on two prior concepts, certainly there are interventional trials that have observed progressive weight loss and decrease in waist

circumference for men who are hypogonadal and receive testosterone. Probably the best known of these is libido trials from Europe, which showed that progressively over time; not a randomized control trial, so certainly not causation, but some suggestion that testosterone can result in that decrease in weight.

Just to clarify with Dr. Thomas, I wasn't sure what control comparison he was looking at in terms of maintenance of spermatogenesis. I assume that you're not looking at drug intervention versus testosterone for maintenance of spermatogenesis. I assume you're looking at that versus controls with testosterone as at least a third arm?

DR. THOMAS: For the testosterone, it's really more looking at some patient-reported outcomes. So if you were to look at some of the quality of life measures, that might be worthwhile doing, not for spermatogenesis preservation.

DR. LEWIS: Dr. Hanno?

DR. HANNO: Commenting on what Dr. Howards said, if pregnancy is not going to be your

endpoint, it really doesn't matter whether they want to have children or not, or whether they want to preserve fertility, if you're going to do the study. And that would make it a lot easier to recruit patients if you're going to look at semen parameters and that kind of thing as an endpoint rather than pregnancy rates.

DR. LEWIS: Dr. Dmochowski?

DR. DMOCHOWSKI: Yes. Just to dovetail on what was just said by both Stuart and by Phil, I do think that this is not a primary outcome in the trial. I think a registry is a good idea for this study or a study related to this indication. It's critical for number 2.

So again, from the standpoint of making even a primary or secondary outcome, no, I wouldn't -- from a regulatory standpoint, that could be a long-term follow-up kind of criteria. But that's where I think we're getting very close to -- I mean, I find the wording of the question quite interesting in terms of the nuances here. One is about continued fertility and one is the

amelioration of infertility on improved [indiscernible] sperm parameters. So you're flipping the question, and that's where I think the importance of a registry becomes very important in item number 2.

DR. LEWIS: Dr. Gillen?

DR. GILLEN: Just to follow up on that, the response to having co-primary outcomes where you're thinking about sperm count, for example in a noninferiority design there, comes exactly from the wording of the question. So if the wording of the question is to preserve existing testicular function through these mechanisms, then I think you need to have it as an outcome in your trial.

DR. LEWIS: By it, you mean pregnancy or you mean just --

DR. GILLEN: For example, maintenance of sperm parameters.

DR. LEWIS: Maintenance of sperm parameters. Right. Thank you. Oh, I'm sorry. Dr. Weinfurt?

DR. WEINFURT: I agree with everything. I sort of feel somewhat compelled, though, to just

comment a bit. It sounds like a lot of us definitely feel that symptoms need to be measured as the outcomes. And I feel that way very strongly, but I also have a deep appreciation of what we're asking here. And it's a pretty significant undertaking because of multiple symptoms, the heterogeneous presentation of people, the need to define what would count as a clinically meaningful change or a clinically normal range for any of those measures, and an analysis plan that would allow a sensitive detection of those, noting that some people might have one symptom; some people might have three.

So it will take a lot of thought I think to figure out the best way to do that and is there some value in doing a trial on a more restricted population, the most prevalent symptoms first and then going out from there. So it's not a very constructive comment, but I felt like we should just acknowledge we all just sort of glide over that; yeah, we need symptoms. And I agree, too. And in this particular setting, this will be a

scientifically challenging situation.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: Sorry. Just to follow up on that, and not to stir the pot, but Dr. Daniels gave a great presentation on PROs, but frankly, I was flabbergasted that the Snyder study was not an example of adequate PROs. So this is a study initiated by the IOM, sponsored by the NIH, supposed to address those issues directly, and the FDA doesn't agree with the outcome measures they used?

DR. EASLEY: I don't know that we can say we definitely don't agree, but they would require review. The process by which they were developed would require review, so we can't say right now really one way or the other.

DR. JOFFE: This is Hylton Joffe. Often for practical reasons, these large companies just pick off-the-shelf instruments that are out there in the public domain, but those instruments haven't necessarily undergone a thorough review and evaluation according to FDA standards for making a

regulatory decision. Just as you heard, these instruments can take years to develop, which sometimes comes into conflict with practical needs.

DR. LEWIS: Dr. Weinfurt?

DR. WEINFURT: Just to say something positive about the same topic, the good news is for most of the symptoms that are listed here, there are already measures that are a really good start. And it's not the case that for all of these, one would have to start from scratch and build a brand new PRO and take two years and a million dollars per symptom or something.

There are hybrid approaches, and engagement with the staff at FDA can help find ways to very efficiently understand whether -- or make sure the way the symptom is conceptualized in this existing measure is the way it's conceptualized for this disease, and that patients with this disease understand the items as they were intended to be written, and that there's basic performance of the item. So there's quite a range of development approaches that can be taken here, and many are

reasonable and don't have to be completely hellish.

DR. LEWIS: Dr. Nahum?

DR. NAHUM: This is Jerry Nahum. I had a similar comment, which is I'm wondering how the agency would feel -- because there are, as you said, some off-the-shelf quality-of-life measures in SF36 and things like this that have not necessarily been targeted to the particular populations that are being studied and were not particularly developed for them. But there are quality-of-life instruments that often the secondary endpoints can lend some credence to primary endpoints that are more objective and more easily measurable.

So I wonder if, without incorporating specific quality-of-life indicators within labeling, having a primary endpoint, for instance, of a total testosterone or free testosterone level, or something like this, or some change in it that would be clinically meaningful, with the support of secondary endpoint of an off-the-shelf SF36 type of quality-of-life measure, might be sufficient and

whether the agency would consider those types of study designs.

DR. DANIELS: Thank you for your question. The issue I guess with quality-of-life scales is sometimes it's challenging to measure just because some of the concepts can be affected by non-drug factors. And that's why when I was presenting that -- you might want to stick to concepts that would be modified by treatment. We believe that health-related quality of life is important, but it might not move with treatment. So that is some of the challenges that I think sponsors would have to consider.

DR. LEWIS: Okay. Anyone else?

(No response.)

DR. LEWIS: No. Okay.

So as far as question 1, drugs intended to treat secondary hypogonadism while preserving testicular function -- that is maintenance of sperm parameters or continued fertility -- what is the patient population that should be enrolled in the clinical trials, there was general agreement that

several testosterone levels would be important to document at the baseline, including preferably some measure of free testosterone as well, and that agreement should be sought on symptoms that would also define this patient population using some existing instruments and perhaps published data from studies about men with hypogonadism; for example, age-related hypogonadism.

Preservation of testicular function, generally should be defined, assessed, with semen parameters, probably the sperm concentration, but certainly a lot of sentiment voiced that having a measurement of motility as well would be beneficial, total motile sperm count. Even if that's not the primary thing that's assessed, it needs to be included.

Demonstrating clinical benefit, here we get back to symptoms and all the controversy surrounding a PRO type instrument; a lot of thoughts expressed around the belief that it's not necessary to work from scratch but use existing instruments.

Other trial features that should be considered, certainly a trial needs to be longer than 12 weeks; a lot of controversy about what it means to actually preserve fertility, considering that it's probably a young population who we would be looking at, and that patients should have a clear understanding that this is different than preserving sexual function; not that they're two different things, but that's not the outcome that people are looking at.

Let's move on to question 2. For drugs intended to treat secondary hypogonadism while improving testicular function -- that is improved sperm parameters or amelioration of infertility -- discuss, A, the patient population to be enrolled in clinical trials; B, how to define and assess improvement in testosterone function; C, acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and those without classic hypogonadism; and D, any other trial features.

So very similar wording, but in this

question we're asked to talk about improving semen parameters for treating infertility. Dr. Braunstein?

DR. BRAUNSTEIN: I'll start it off again. So A, the patient population that should be enrolled in clinical trials, those would be either low testosterone with oligo- or azoospermia, or just oligo- or azoospermia with normal LH and FSH. Again, the issues about low testosterone that we previously discussed would hold here.

B, how improvement of testicular function should be defined and assessed, it would be through normalization of testosterone and increase in the sperm and semen parameters without a change in morphology.

C, acceptable endpoints, again for those with low testosterone, improvement of symptoms. And obviously in order to enter the trial, if it's low testosterone that they have in the beginning, they should have symptoms with low testosterone, too, although, with oligo- or azoospermia and low testosterone without symptoms, I would accept that

in this trial, but improvement of symptoms if they had symptoms. Sperm count should go more towards normality. And if the patient's coming in because of infertility from abnormal sperm parameters, then I want to see fertility as an endpoint. So that's different from the first question.

If it is that the patients have abnormal sperm parameters and that they're interested in future fertility, which is a little bit different from the first question, but they are not interested in fertility at the present time, then I would tend to go with the sperm parameters, but make sure if they're entered into either a phase 4 trial or a registry, to follow up on pregnancy rates. But for those that are actively complaining of infertility, I'd like to see the endpoint being fertility, that is pregnancy rate, taking into account all the couple parameters and female factor parameters as best as one can. That's got to be the bottom line because that's what their complaint is.

DR. LEWIS: Thank you. Dr. Thomas?

DR. THOMAS: Once again, Dr. Braunstein said I think all the important things, and many of what was discussed for the previous question applies. The only things I would add is clearly you're looking at people who have low sperm counts or sperm that's not functioning well. So that should be looked at in terms of even going above that 15 million threshold and whether you have improvement, so fertility has to be an important part of that.

I would look at a subset of people who have low sperm counts who are using assisted reproductive technology to try to conceive because even though they're not going to get into the normal range, or low normal range, if it improves their success of then being able to harvest sperm or use it to make their partner pregnant, I think that would be an important outcome to know. That might be also something that would be clinically useful in the indication.

DR. LEWIS: Dr. Dmochowski?

DR. DMOCHOWSKI: I think the question before us is really focused on infertility, so I think

that's the population you're looking at, realizing that a substantial percent of those patients may actually not have the hypogonadotropic symptom. So I don't think you can put symptoms into this equation unless you want to just look at a subpopulation that may have symptoms that also is in this population, again, because primarily of their infertility.

Again, as I said on my prior comments, I do think a registry is important, but as a follow-on criteria, not as an aspect of the trial. And I do think you should focus on seminal parameters with motility being the key.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: With these trials, we're dealing with sperm concentration as a surrogate endpoint essentially for fertility. I think I would treat the population with azoospermia differently than with a low sperm count, for two reasons.

One, we already have -- well, there's the common-sense rationale that if you don't have any

sperm, then you're not going to reproduce, the sort of soldier's argument, an army of one is better than an army of none. But then also you have the follitropin products that have been approved already for azoospermia for inducing spermatogenesis, and the population tested there was an azoospermia population.

I might even consider for this endpoint a lower threshold than 15 million if it's been shown that you can have fertility at 1 million. But for the other population, you haven't really validated this endpoint to show that it really correlates with fertility when you increase sperm count from below 15 million to above. So I would want to see different endpoints for that trial, real clinical endpoints, fertility, reproductive outcomes.

DR. LEWIS: Dr. Brannigan?

DR. BRANNIGAN: I didn't have a comment. You saw Dr. Schlegel.

DR. LEWIS: Sorry. Dr. Howards?

DR. HOWARDS: I would like to see a requirement that the partner has been screened by a

reproductive endocrinologist. Obviously, that is a problem to instrument, but at least we'll know that somebody, a well-trained person, fellowship-trained person has said that this partner is probably fertile. And that would make it a much more purer study with pregnancy as an endpoint.

DR. LEWIS: Dr. Gillen?

DR. GILLEN: I agree with that last comment, and I think that, again, what's been stated before is that if fertility is truly the target of inference here, then fertility should be the outcome. It's a measurable clinical outcome. Again, it's logistically difficult. It's hard to run these studies, but we have to look at it as this is the one time where we have a controlled setting, and we can actually assess this particular treatment, whatever it may be, in that setting where we can actually look at clinical benefit in these patients. Once it's gone, it is gone, from my perspective. You can do the phase 4's. I think they're important to do the follow-up studies and the active surveillance, but it's nothing compared

to a controlled clinical trial.

I think an interesting point was brought up. If one is thinking about improving maybe chances for fertility in the future, then maybe focusing on sperm concentration or total motile sperm count might be a possibility. If it's sperm concentration, the only thing that I would say there is it was a little dissatisfying today, to me anyway, where the 15 million threshold comes up.

That's based purely upon a retrospective comparison; in other words, fertile individuals, and then looking at the 5th percentile of those individuals. There's no concept of also what the sperm counts are and concentrations are in non-fertile individuals, and it's purely retrospective. There has got to be more work, more data on this, in order to be able to link and say that sperm counts or sperm concentrations are a reasonable surrogate for increasing truly fertility.

So if that is the route that it's gone down, I think, for lack of a better word, the generic

threshold that's been posed, based upon the WHO 5th percentile among fertile males, needs to be refined or at least defended.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: Most clinical guidelines and most trials are based on a definition of male infertility being one or more abnormal semen parameters, so sperm concentration, motility, or morphology. Some would even consider indications for intervention being other measures of sperm function like DNA fragmentation.

But I think if we're looking at an infertility intervention, you should have one or more abnormal semen parameters. I think following those changes over time is a little more challenging in terms of what the cut-point should be because the reality is couples do not try to conceive simply by natural intercourse. There is no couple who is going to agree to a 12-month trial of natural intercourse if there are other opportunities that are available.

How does the Reproductive Medicine Network

look at this? It looks at month-by-month intervention. So a couple signs up basically for one month evaluation, and if you look at male infertility interventions, you'd be looking at a year. So fertility is obviously the most important endpoint, but you're going to have fertility without intervention. You're going to have fertility with IUI. You're going to have fertility with IUI and gonadotropin stimulation; IVF on top of that. And Dr. Gillen could probably tell me what size study we need, but that's pretty darn large.

So I don't think fertility can be your primary outcome. Improvement in semen parameters has documented the meta-analysis of SERMs as being associated with an increase in fertility. We get that as a secondary outcome. That would be very helpful. But I think a trial that has abnormal semen parameters and follows the way that patients are actually treated would be much more useful.

DR. LEWIS: Dr. Adler?

DR. ADLER: Yes. To follow up on that, I think the duration of the trial is really important here, and I think the practical point Dr. Schlegel just brought up is really very important. So one could conceive of a trial where a change in sperm parameters was the primary outcome, and that could be a short-term trial.

To have a couple sign up for a longer-term trial would require the different interventions, and obviously there's a whole smorgasbord of interventions now. So that really makes it a very difficult trial to accomplish. So I think for the simplest version of this, just a change in sperm parameters would be most important. And that brings up a question that I have as a non-expert in this, and that is, are there data on the day-to-day changes in sperm count and what the least significant change is for, say, sperm number?

DR. LEWIS: Dr. Sandlow?

DR. SANDLOW: Great segue. For those of us who have done any kind of research in male infertility, one of the toughest challenges is the

fact that the semen parameters change on a day-to-day basis, and you cannot do studies off of one semen analysis either before or after intervention. We all know there is regression to the mean. So you could have a sperm concentration of 12 million prior to treatment and 20 million after treatment, and you think you've made this great improvement, and you really haven't done anything.

So I think it's going to be very important that there are multiple semen analyses prior to and after treatment, and then they'll have to decide both statistically and clinically are those meaningful changes.

DR. LEWIS: Dr. Nahum?

DR. NAHUM: Thank you. Jerry Nahum. I guess I have another question, which is I think we're talking about -- when we talk about infertility, we're talking about spontaneous pregnancies. And given that everybody's talked about this at least peripherally, and some people directly, given that we have so many good interventions, including ICSI, I'm wondering what

the relevance is of being able to improve sperm parameters by a little, or even by a substantial amount, if all we need is one sperm in the right place, and during ICSI we can get people pregnant.

Now, of course this depends upon resources. It depends on a lot of other things. But just improving semen analysis, to me, in the face of all of the competing technologies that currently exist, to be able to get people with inadequate, or semen would be inadequate, semen analyses to obtain pregnancies, I'm wondering if we're missing the boat here, whether we're not computing what we should be.

DR. LEWIS: I'll just answer it as a practicing reproductive endocrinologist. I think it's very important. People are going to both want to take advantage of every treatment that's available, but not everybody has the resources to have every treatment available. Not everyone wants to undergo ICSI. Some people feel like that if the man's issue is the reason -- some couples -- that I'm not getting pregnant, then let him take his

drug, and why should I undergo, as the woman, all the things that I have to do to get to IVF, and why should we as a couple spend all the money.

So both are important, what would be the outcomes with assisted reproduction and what is the shorter easier thing to measure the semen parameters.

Dr. Brannigan and Dr. Sandlow?

DR. BRANNIGAN: I wholly agree with that. That concept of downstaging a level of assisted reproductive techniques is a really important concept, and it's something that our male partners ask about all the time. When they don't have enough sperm to facilitate efforts with intrauterine insemination, and then their partner's looking at going through IVF, that's a big deal, physically, financially. So I think that it is an important point. Even if the numbers don't go to normal, to open the door for IUI is really important to couples.

DR. LEWIS: Yes, Dr. Sandlow? Dr. Bauer?

DR. BAUER: Just to clarify, though, if the

goal is a live birth and you're randomizing participants, why does it matter how they get there, whether it's naturally or with assisted techniques? To me, that should be taken care of by the fact that you are doing things in the placebo group as well. It does complicate the analysis, and as someone who would want to use a large clinical endpoint trial to understand how well the surrogate works, for example, sperm count, it probably precludes that. But the most important thing is what's the likelihood of having a live birth.

So I guess I don't quite understand why a randomized trial with fertility as the outcome, it still couldn't be done with just a larger number and more complex analysis.

DR. LEWIS: Dr. Sandlow?

DR. SANDLOW: So to respond to that, a couple of things. First of all, while live birth is the desired outcome, I think, as we've all heard, pregnancy's a two-person thing, and even if the woman's been fully evaluated, you cannot take

her out of the equation. So the whole point about this drug I would think is does this improve sperm production and hopefully subsequent fertility. And I think to use actual live birth as a primary outcome would be very difficult.

The second thing is sitting in front of these people day after day, they want to know what can they do to improve. And if their only option is IVF, so be it. Just yesterday, I had a patient say, "Isn't there a pill you can give me?" We hear that all the time.

So we know that the improvement in semen parameters will make pregnancy more likely. We can't say by how much. But I think that's very important for us to know when we're treating these patients clinically, that we're going to be able to say to them, yes, this pill may improve things or, no, it really hasn't been shown to improve things.

DR. LEWIS: Thank you. Dr. Thomas? Brannigan?

DR. THOMAS: I'll wait for Dr. Gassman.

DR. LEWIS: Sorry. Dr. Gassman?

DR. GASSMAN: I have a quick question for Dr. Sandlow and maybe Dr. Brannigan. Would you consider avoidance of IVF and ICSI, for example, bringing someone who's oligospermic, if you could bring them up to a count that would allow them to do IVF, would that be a clinically meaningful outcome for you?

DR. SANDLOW: Sorry. You mean to go from IVF to IUI, correct?

DR. GASSMAN: Right.

DR. SANDLOW: Yes.

DR. GASSMAN: In other words, if you convert them, would that be an example of -- I mean, I'm just trying to figure out what's your --

DR. SANDLOW: Yes, for me, it would be because, again, in a state where there isn't a mandate for insurance coverage of IVF and it's all out of pocket, for many of my patients it's not a reality. So if I can take somebody who right now can only do IVF and I can treat them however it is, whether it's surgically, medically, lifestyle changes, and they can then do IUI, that would

be -- in my mind, that's a win.

DR. GASSMAN: So what cut-off would you use?

DR. SANDLOW: For my lab, they would need 10 million motile sperm.

DR. GASSMAN: Okay. Thank you.

DR. LEWIS: So I would say it isn't that you couldn't do IUI below that, but the likelihood is very much lower.

DR. GASSMAN: Right. But again, we're trying to come back to something clinically meaningful. So one of the questions, as we're discussing here, is to try to get to some clinically meaningful outcome that could be explained to patients. That's why I'm asking the question.

DR. SANDLOW: Which also, going back to what Dr. Howards had said, I'd push very hard to use total sperm count as opposed to sperm concentration, which is totally dependent on the volume. I mean, I would love to use total motile, but we know that there isn't data. I mean, it's intuitive that if there's a certain sperm

concentration that's associated with fertility, then total sperm count would be as well. It's just you taking the volume out of the equation.

DR. GASSMAN: And would the cut-off for that be --

DR. SANDLOW: It's either 40 or 50 million. If you look at WHO, it would be 40 million.

DR. GASSMAN: Thank you.

DR. LEWIS: Thank you. Dr. Thomas, you had another --

DR. THOMAS: I just wanted to add, I think actually what was just said makes the argument stronger for looking at live birth. There is so much emotion and investment around this that we make an assumption that if you improve the sperm count, we'll get better, but we don't know for specific patients how that works.

You have multiple products that are potentially coming to market. What if one of them is much better at this than the other? You'd hate to say use product A that's approved without knowing the outcome. You could have wasted a year

or longer. Product B might have a great outcome, and that would be your first-line therapy.

So I think in practical use clinically for people making a decision about which drug potentially should happen, the live birth rate really is important, for exactly the reasons that were mentioned: cost, emotional burden.

DR. LEWIS: Thank you. Dr. McCammon?

DR. McCAMMON: And I agree a hundred percent with everything that's been said, especially the live birth rates. But I wonder if -- and I'm sure that industry would love to say that we can improve live birth rates, but would it almost be better to change the question and just say improve testicular function? I know that's kind of common sense, but then we're not actually having this argument if we just go, can we improve testicular function going forward and not necessarily say ameliorate infertility.

DR. LEWIS: Thank you. Dr. Brannigan, you have another question, comment? No. Anyone?

(No response.)

DR. LEWIS: Okay. So for drugs intended to treat secondary hypogonadism while improving testicular function -- that is improve semen parameters or amelioration of infertility -- discuss the patient population, everyone agrees that abnormal semen parameters with normal or low LH would be important.

There is some also sentiment that the patient population should include people who are in a relationship where the woman is being worked up or has been evaluated by a reproductive endocrinologist, or at least according to certain standard criteria, and certainly that more than one semen analysis would be required for entry into the trial because of the variability of levels.

DR. BRAUNSTEIN: Excuse me. In addition to LH, FSH also.

DR. LEWIS: Oh, sorry. Yes, FSH also, yes.

Improvement in testicular function, define and assess, most of the discussion centered around semen parameters. Certainly there's the WHO sperm concentration, but many felt that total sperm count

or total motile sperm count would be perhaps more aligned with what's looked at clinically.

Acceptable endpoints for demonstrating clinical benefit, everyone wanted to see something related to pregnancy, although it's recognized that that presents certain challenges. Perhaps there could be -- or not could be, but there should be not only some change in semen parameters that's meaningful, but also a demonstration of pregnancy with the recognition that that can be complicated because lots of things cause infertility. Lots of different treatments are available with differing expectation in terms of pregnancy rates and in terms of live birth rates, things that can complicate pregnancy.

Other trial designs that should be included, registry was cited to be really important in this population especially because they are actually actively seeking fertility unlike the prior population where the registry could be a little bit vague if somebody's not in a relationship or is not really interested in fertility.

The duration of the trial is also important. You might see a difference in the semen parameters on a very short-term basis, but that 12-week timing is not going to be necessarily adequate to look at other things, and also what kinds of infertility treatments the couple undergo.

I think that's about it. Okay. Let's move on to, then, the voting questions. We have the buttons for voting. I'll read the questions, and then you'll vote yes or no. And we'll go around the room and talk about why we voted that way.

First voting question. For products intended to treat men with hypogonadism attributed to obesity, is raising the testosterone concentrations into the normal range for young, healthy, eugonadal men, and preservation of spermatogenesis as assessed by maintenance of sperm concentrations, sufficient for establishing evidence of clinical benefit?

If you vote no, describe what endpoints would be needed to provide sufficient evidence of clinical benefit, and if you vote yes, specify how

preservation of spermatogenesis should be defined based on sperm concentrations and explain your definition.

(Pause.)

DR. LEWIS: You want everyone to press the button one more time? Is that correct? Okay. And then will continue to flash afterward Don't worry about that.

(Pause.)

DR. JOFFE: I guess we want to make sure everyone's really sure about voting on this question.

DR. LEWIS: I know. I was going to say let's just go old school and raise our hands. How many people vote -- no?

DR. JOFFE: We used to do this the old way, and now we much prefer electronics. We may have to revert to this if they can't fix it. Give us one moment. The hope is that everybody enters without seeing how other people are voting because we really want an independent assessment from each person and not to feel pressure if they see a lot

of other hands go up with the opposite vote.

(Pause.)

DR. LEWIS: Five minute break.

DR. JOFFE: We'll take a five minute or so break. Folks stretch, bathroom if you need to, and we'll be back.

DR. LEWIS: Okay. Got it.

(Whereupon, at 3:21 p.m., a recess was taken.)

DR. LEWIS: This time I will re-read the question. For products intended to treat men with hypogonadism attributed to obesity, is raising the testosterone concentrations into the normal range for young, healthy, eugonadal men, and preservation of spermatogenesis as assessed by maintenance of sperm concentrations, sufficient for establishing evidence of clinical benefits?

If you vote no, describe what endpoints would be needed to provide sufficient evidence of clinical benefit. If you vote yes, specify how preservation of spermatogenesis should be defined based on sperm concentrations and explain your

definition.

So we'll register our votes, and then we'll go around the room so that everyone can explain their vote.

(Vote taken.)

DR. LEWIS: Okay. We have 5 yes, 16 no, zero abstentions. Let's start with Dr. Brannon [ph]. Can you tell us how you voted and why? Sorry.

DR. BURMAN: Dr. Burman?

DR. LEWIS: Brannon. You voted, yes?

DR. BURMAN: Dr. Burman.

DR. LEWIS: Burman. Sorry. I can't see it so clear.

DR. BURMAN: No problem. Thank you. Yes. I voted no. First I want to say that the discussion was fantastically good. It illustrates the complexity of the issue, and I know that's why the FDA brought this up for consideration.

To the specific question, the question was too general. They didn't say what age of men. They didn't say what kind of hypogonadism

specifically. They didn't define obesity, which are all things we've talked about throughout the day. Maintenance of spermatogenesis to me means it's within 10 to 20 percent of the original value, probably.

They also talked about serum concentrations, sperm concentrations, and that's not enough based on the conversation we've had. But it's not only concentration, but total sperm count as well as motility that seem important. We talked about the obesity.

There's a question of what the endpoints should be beside sperm concentration and motility and total amount. Should it have anything to do with symptoms? In this case, probably not, but we don't know why the individual is coming in. Are they coming in because of infertility? Are they coming in because of just hypogonadism and symptoms? I assume it's for infertility in this circumstance. And shouldn't we prove that they're actually infertile. And as mentioned earlier, the woman should be checked as well.

Other endpoints that aren't necessarily primary would include measurement of free testosterone, total testosterone, SHBG, and bone mineral density. But I think major points are related to the definition of obesity. Thank you.

DR. LEWIS: Thank you. Dr. Adler?

DR. ADLER: I think this illustrates the difficulty of writing questions because while I voted yes, a lot of what Dr. Burman just said I agree with. I interpreted the question that a person who would fall into the category about whom you would ask these questions had come in because of symptoms of hypogonadism. And that was the major question, not infertility because you're talking about maintenance of his sperm situation with hypogonadism.

So I'm not talking about going out on the street and grabbing a hundred men and looking for those who have low testosterone, but otherwise somebody with hypogonadism and presumably symptoms of hypogonadism who would come into a study this way. And therefore, I thought as a minimum, or as

a primary endpoint, it was reasonable to bring the testosterone up into the normal range and maintain sperm at whatever level it is, and that was a reasonable set of endpoints.

DR. LEWIS: Dr. Sandlow?

DR. SANDLOW: I voted no, although I have a lot of the same comments just because the question itself does not specify that these are symptomatic men. And we know that at least primary care providers check testosterone for no reason. And that's not to bash primary care docs, but they do, which is how we got into trouble with testosterone in the first place.

So these patients have to be symptomatic. There needs to be symptom assessment prior to and after treatment so that you can show if it really is working that with normalization of their testosterone levels, their symptoms improve as well.

I also haven't heard anyone mention measuring estradiol levels, especially in obese men. Maybe it's just where I come from, but

everybody's got elevated estradiol levels, and I think that's a very important function with these obese men, especially. A lot of their secondary hypogonadism is due to aromatization with high E2 levels. And when you normalize those, they feel better and they get better. So while this drug is not intended to do that, I would want to know the impact of the drug on estradiol levels.

DR. LEWIS: Thank you. Dr. Brannigan?

DR. BRANNIGAN: Yes. I voted no. I would want to measure the improvement in symptoms that he presented for treatment of. There are patients who presented with no complaints but low testosterone, as Dr. Sandlow was saying. I think we don't treat those patients routinely. So I think that the testosterone would not be a sufficient measurement in my mind.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: I also voted no, and again, with the understanding that hypogonadal men who are going to be treated would be symptomatic, and a follow-up of their specific symptoms would be

needed as a measure.

DR. LEWIS: Thank you. Dr. Weinfurt?

DR. WEINFURT: I voted no for the same reasons as the previous three reviewers.

DR. LEWIS: Dr. Gillen?

DR. GILLEN: I also voted no for similar reasons. I believe that they should have clinical symptoms at baseline, and change in clinical symptoms should be evaluated as the primary endpoint. And has been discussed, possibly low mood and/or low energy should be included in those PROs for symptoms.

DR. LEWIS: Dr. Thomas?

DR. THOMAS: I agree with everything that was said. And the only other comment is I think we have a better idea of what happens with testosterone treatment. We'd want to make sure in terms of outcomes. I know we're not supposed to talk about safety, but bone health, et cetera, insulin resistance, lipids, what happens, because these will be people who are at high risk for these who are going to take it for a long time

potentially.

DR. LEWIS: Dr. Bishopric?

DR. BISHOPRIC: I voted yes simply because of the way the question was worded. I assumed that the patient had already been diagnosed as having hypogonadism, and this is a simple, quick measure that would demonstrate response. But I certainly agree with the other comment as well.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I voted no for essentially the same reasons stated by Dr. Joffe at the start of this meeting. Raising testosterone in men into the normal range is a surrogate endpoint. And there wasn't a lot of evidence presented at this meeting that for this population, raising testosterone produces clinical benefit. So it's not really a validated endpoint. And certainly we don't have testosterone products approved on this basis for other populations, for age-related hypogonadism for example.

Maintaining sperm concentrations, again, that's a safety measure, and it can't be used to

establish efficacy because you're maintaining them in the same state.

I acknowledge that there's a desire to get enclomiphene or other products out there that don't reduce sperm count, but you're comparing them to off-label testosterone, and I'm not sure patients should be taking that product in the first place if it hasn't been proven to show benefit for this group.

So those are essentially my reasons for voting no, and I would require a clinical benefit to be shown. In trials, I understand it's hard to design a quality instrument, but there have been other tests run, testing libido, erectile dysfunction, and osteoporosis. I think it can be done, and I think it ought to be done for this approval.

DR. LEWIS: Dr. Curtis?

DR. CURTIS: Kate Curtis. I also voted no for all the reasons already said. But I would echo Dr. Weinfurt and other's comments earlier that we do definitely need the PRO outcomes. We heard the

onerous process of developing those earlier, but we also heard that there are things we could possibly use. So I would really encourage us to figure out how to reasonably and feasibly develop those measures if we're going to recommend them.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I voted no. I assume from the wording that this does not include men with infertility, but if it did, I'd want pregnancy. As to the other men who were not complaining or having infertility, I would want outcome measures of their symptoms.

DR. LEWIS: I voted no for basically the reasons that were cited. I think it's important to settle on a group of symptoms that are important. But I would also include maybe weight loss in there or some measure of body composition as a possible outcome.

DR. CHAI: I voted no for the same reasons that the panel members ahead of me said no to.

DR. DMOCHOWSKI: I voted yes, and share Dr. Adler's consternation with question construct.

(Laughter.)

DR. BAUER: I voted no, and again, it's been well articulated. I would just add that I think an entry criteria ought to be as failed at least one good attempt at medically supervised weight loss for men that are obese.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: I also voted no basically because I treat patients for clinical endpoints. I treat the patient. I don't treat the numbers. So for that reason, I couldn't not vote no.

DR. BISKOBING: I voted no as well for all the reasons already stated. But I also want to make sure we would be treating hypogonadal men, and so I'd want to measure free testosterone rather than total.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: I voted no because in the beginning, I'd like to see, for entry in the trial, low, free testosterone; need clinical symptoms, normal LH, and improvement during the trial with a PRO or any objective measure that one can have. I

would strongly advocate for a double-blind, placebo-controlled trial of obese men desiring treatment, and that the placebo group, as well as the active group, undergo weight loss instruction and monitoring and diet in order to see if there is improvement over and above weight loss alone.

DR. LEWIS: Dr. McCammon?

DR. McCAMMON: I voted yes, and I have to concur with Dr. Adler about the question. But I would also agree with everything that everybody said about everything.

DR. LEWIS: Dr. Hanno?

DR. HANNO: I voted yes. And the reason, I thought that it should be reflected in the label -- that I assume these men were all symptomatic in the question. And I thought that voting yes would be reflected in the label as saying that this drug increased serum testosterone to normal levels, not that it treats male menopause or that it treats any specific symptom. And if the companies wanted to go for that indication, they would have to prove it. But I think there is value

in letting the physician decide when to use a drug like this and just showing that it does move testosterone into the normal levels.

DR. LEWIS: Thank you. Let's move to our next voting question. For products intended to treat men with classic, secondary hypogonadism and azoospermia or oligospermia, is raising the sperm concentration above a specific threshold sufficient evidence of clinical benefit?

So here we have four choices, A, B, C, or D. So you'll see four flashing buttons: A, yes, but only for azoospermia; B, yes, but only for oligospermia; C, yes, for both azoospermia and oligospermia; and D, no. And include a rationale for your answer.

Again, if no, what endpoints would be needed to provide sufficient evidence of clinical benefit for such products? If yes, specify the threshold for sperm concentration that should be exceeded to establish evidence of clinical benefit and explain why you select that threshold.

(Vote taken.)

DR. LEWIS: Thank you. So 2 votes yes, only for azoospermia; no one voted only for oligospermia; 13 voted yes for azoospermia and oligospermia; and 6 voted no, and there were not abstentions.

So let's go around the room and describe our rationale. Let's start this time on this side with Dr. Hanno.

DR. HANNO: Okay. I voted no. I was in favor of pregnancy rates as an endpoint for these drugs.

DR. LEWIS: Thank you. Dr. McCammon?

DR. McCAMMON: I voted no because I'm not really sure how we define, really, clinical benefit. So if there's no good definition, then I would think pregnancy would have to be the definition, and that's why I voted no.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: I voted C, yes, for azoospermia and oligospermia for the following reason. This is classical secondary hypogonadism, and I would accept -- I ideally want to see

pregnancy as the outcome. But as a surrogate before we get to pregnancy, I would look at the data with hypogonadotropic hypogonadism from a common syndrome with anosmia/without anosmia; but purely a well-defined congenital hypogonadotropic hypogonadism, those patients who have been treated with chorionic gonadotropins and menotropins or follicular statin to see what sperm concentration was achieved that also achieved pregnancy.

So I would take the 95 percent confidence limits around that and say get above that lower level, and that would be the level that I would choose to initiate the study. But ideally, I'd like to see pregnancy as an outcome.

DR. LEWIS: Thank you. Dr. Biskobing?

DR. BISKOBING: I actually meant to vote no. I read the no and not the C. I wanted to also see testosterone levels -- and I guess I'm thinking more long term. If it's just going to be used for treatment of infertility, yes, that's sufficient. But again, the question was kind of worded vaguely. If you're going to use it long term, I want to see

that testosterone levels are being maintained as well. So I thought the question was not clear.

As far as sperm concentration, I guess I would accept the WHO criteria of 15 million, but I'm not a urologist, so I think that question is better left to them.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: I voted for C, yes for azoospermia and oligospermia. When I read this, I really confined myself to the fertility issue as opposed to the long-term testosterone issues because the issue of maintenance of long-term testosterone replacement can maybe better be done with testosterone, but specifically around the period when pregnancy is considered, I thought C was okay.

I actually don't have a specific threshold. I'd defer to respective endocrine urology. If they want 30 million total or if they want 10 million total, whatever they think is a reasonable number to achieve some sort of favorable outcome, whether it be by ICSI, or IUI, or any of these things.

Whatever it is, that would be the number that I would choose as my baseline.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: I actually wanted to vote for no, but I pushed C instead, so I apologize. But actually, I voted this because I think the live births should be the outcome of interest.

DR. LEWIS: Could you repeat that?

DR. BAUER: I think live births should be the outcome of interest.

DR. LEWIS: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: I voted C for both, and my comments would echo Dr. Drake's comments. I think the thresholds might vary between the two conditions. And we already have a prior regulatory threshold and an approval in 2000 of 1 million. So maybe that raises the -- may be a higher target for oligo such as 10. But again, the oligo assumes that they start out below 10, and if they're starting out above 10, it's sort of a useless number.

DR. LEWIS: Thank you. Dr. Chai?

DR. CHAI: I voted C also, and I read this question completely as an infertility patient not worrying about the testosterone level. So I think having a medication that has been tested that has a measurable change will give these patients something valuable, and for healthcare providers, something to offer these patients.

I thought pregnancy -- I heard the debate. I tended to fall on the side that I think it's a very difficult outcome to power a trial or do a trial for, although I realize and I can understand why that is the ultimate outcome. But I chose C.

DR. LEWIS: Thank you. I chose C also. I agree that it's very important to have different thresholds for people who would enter as in azoospermic and those who enter with oligospermia because if you're azoospermic, then the couple -- if you're oligospermic, the woman has already been exposed to at least a million sperm, so that is not a relevant number to say that you could achieve a pregnancy that way. It also assumes that those sperm are relatively normal,

which a lot of times they're not with oligospermia. So I think that that's important, that threshold level.

I think pregnancy is also important. I think, yes, it's complicated, but certainly it's an outcome for a lot of female infertility studies, and you just define the population that you're going to study and try to make the women as uniform as possible. I think that's the best clinical outcome to go for. Certainly, semen parameters are an important surrogate marker.

Dr. Howards?

DR. HOWARDS: I voted for azoospermia because if you take a patient who's azoospermic and raise him to have some sperm, and if the patient and the partner agreed that they wanted to do ICSI and they can afford it, then you've made them eligible for ICSI without a surgical intervention. So that to me is a clear yes.

I would have voted for C if it hadn't said "sperm concentration." If it had said "total motile sperm," then I might well have voted for C.

DR. LEWIS: Thank you. Dr. Curtis?

DR. CURTIS: I voted no. The question asked about clinical benefit, and to me, clinical benefit is pregnancy or fertility. However, I did hear there are clear difficulties with doing that. Sperm concentration alone to me probably isn't enough and would be -- as we've heard, total sperm count is important and other measures, semen analysis.

Finally, I think whatever the outcome is, that's what the indication should be. So if the outcome is only raising sperm concentration, then that's the indication. The indication should not be treating infertility.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: So I voted A for azoospermia only. I was a little thrown by this question because as far as I could tell, none of the products being considered for the presentations today were for this indication, so we didn't have a lot of discussion around it. Generally, I think that there wasn't a lot of evidence presented that

moving a patient out of the oligospermia range is going to increase fertility and specifically how that's defined, as 15 million, or 10 million, or what have you; whereas for azoospermia, you can make a pretty clear case that that makes an important clinical difference for patients.

DR. LEWIS: Thank you. Dr. Bishopric?

DR. BISHOPRIC: I voted for C. I think it's because I'm a pathologist, and I don't see patients coming in with reproductive problems.

DR. LEWIS: Okay. Dr. Thomas?

DR. THOMAS: I voted no for many of the reasons that were already said. I think fertility is really the ultimate outcome in this type of patient. Also, the issue about what the count should be I think varies depending on the goal, that you can get someone to assisted technology or are you going to do without assisted technology. And I agree with what Dr. Braunstein said, is since we use hCG for this now, that really should inform what we do in terms of the other agents.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: I voted no because I believe that the live birth rate is the true clinical outcome here. I think for reasons that were stated earlier, randomization will take care of it. I believe it should be spontaneous pregnancy or artificial pregnancy. Either way, if it's a randomized controlled trial and well controlled, then that should balance out.

DR. LEWIS: Dr. Weinfurt?

DR. WEINFURT: I got confused by the buttons. I actually meant to abstain, which is sad in itself. And then I hit the wrong button --

(Laughter.)

DR. WEINFURT: -- which may be evidence that I shouldn't be voting.

DR. LEWIS: Dr. Schlegel?

DR. SCHLEGEL: I voted C. A concern with treatment of this entire population of patients is that you could treat any of them, and pregnancies would occur independent of the medical intervention. The medical intervention may have a substantial benefit and certainly would be the most

cost-effective treatment that you provide for couples, but you could take an azoospermic man, biopsy, and get sperm and use IVF, and it's just a very different burden of treatment.

So the clinical benefit is really changing the burden of treatment. The outcome of interest for azoospermia is enough sperm for ICSI, which would be more than 100 motile sperm per ejaculate certainly. For oligospermia, it's moving you up at least one stage in terms of treatment. So if you're less than 5 million motile sperm per ejaculate, going above that or potentially another higher threshold for men who had 5 million motile sperm per ejaculate to start.

DR. LEWIS: So you're saying basically getting to some point where you could do IUI.

DR. SCHLEGEL: Correct.

DR. LEWIS: Dr. Brannigan?

DR. BRANNIGAN: I voted C, and I echo the comments, especially what Dr. Schlegel just said. I don't have anything to add.

DR. LEWIS: Thank you. Sandlow?

DR. SANDLOW: I'll stay in lock-step with the other urologists. I do want to just make a quick editorial comment about the live birth rate. And while that is the ideal, for those of us who work in this field, it's not doable. So to put that kind of burden on anyone, we'll never get live birth rates for the treatment of male infertility. It just won't happen.

I would not want to hold back a potential treatment because we put too high of a price on it. I think it's a great thing to look at, and I think it makes a lot of sense. But I think asking couples to participate in studies where live birth is the outcome, we'll never get it done.

DR. LEWIS: Dr. Adler?

DR. ADLER: I voted C. Dr. Schlegel said it a lot better than I could. But I think the point is that if you're dealing with infertile couples here, getting the sperm count up, because obviously there's no unanimity about what the levels should be, I think increases the chance of live birth, and therefore is a reasonable endpoint.

DR. LEWIS: Thank you. Dr. Burman?

DR. BURMAN: I'd just echo the same comments, and I voted C as well for azoospermia and for oligospermia.

DR. LEWIS: Okay. Thank you. So last question. For products intended to treat men with secondary hypogonadism and azoospermia or oligospermia, but who do not have classic hypogonadism, is raising the sperm concentration above a specific threshold sufficient evidence of clinical benefit? A, yes, but only for azoospermia; B, yes, but only for oligospermia; C, yes for oligospermia and azoospermia; and D, no.

Then the same. We'll go around with a rationale for your answer. If no, what endpoints would be needed to provide sufficient evidence of clinical benefit? Yes, which is either A, B, or C, what's the threshold for sperm concentrations to establish evidence of clinical benefit, and why?

(Pause.)

DR. LEWIS: We have some people who have a question about abstention. It doesn't appear that

that's available. FDA, can you give us some guidance here? Somehow that didn't get put in the mix. Should we just record that as we go along?

(Pause.)

DR. JOFFE: Unfortunately, it isn't built into our system to abstain. So probably I guess if someone wants to abstain, they shouldn't answer the question, and then they could verbally say that they abstained and the reasons why.

DR. LEWIS: That makes sense. Okay. So let's register our votes, please.

(Pause.)

DR. JOFFE: So right now we have that one person has abstained. I just want to confirm that's correct before -- okay.

(Vote taken.)

CMDR BONNER: For the record, 2 voted yes for A; B, zero; C, 8; and D, 10, and 1 abstain.

DR. LEWIS: Okay. Let's start on this side with Dr. Burman, please.

DR. BURMAN: Thank you. Dr. Burman, and I voted no. Many of the same issues we've talked

about on previous questions arise here, but I think for the record, it's worthwhile to discuss them or mention them briefly.

What is the goal of the patients who are coming in with secondary hypogonadism? Is it infertility? I assume it is. Secondary hypogonadism that's non-classic of course is an issue we spent all day on, and it's a heterogeneous group that is not well defined, especially the obesity aspect. There are so many inchoate issues with regard to that, that I think that should be separated from classic hypogonadism in any study.

With regard to long-term studies, at the moment, there are no long-term prospective randomized, controlled studies assessing this issue, but it would be very important for the committee or for us to recommend that that be performed because this group represents probably the largest group of patients with hypogonadism, as we saw earlier.

The same endpoints that we talked about earlier in terms of FSH, LH, free testosterone,

SHBG, sperm motility, as well as concentration and total amount, should be examined as well. But I do think it's a very important group that we should investigate, but at the moment, we don't have enough information.

DR. LEWIS: Thank you. Dr. Adler?

DR. ADLER: Again, I agree almost completely with my friend Dr. Burman, except that I voted C, yes. I interpreted this, again, as patients with infertility. And frankly, the fact that we don't have a demonstrable lesion that we can show is the cause of their problem, they have azoospermia or oligospermia, those are pretty hard endpoints.

So to help their fertility -- and that to me is the objective here -- short-term use of a drug to raise the sperm number or concentration seems to be a reasonable goal, and not talking about long-term management, which I think is a completely different topic. I think for short-term management for infertility, it makes sense that these patients should be tried on what is a reasonable way that we may be able to improve their fertility.

DR. LEWIS: Thank you. Dr. Sandlow?

DR. SANDLOW: I voted C for similar reasons from the previous question, although it is a different patient population. This is probably half of the patients that I see, where they don't truly have a real endocrinopathy. This is more empiric treatment. They may have slightly low testosterone with oligospermia. And I still voted yes because I think we do want to see the impact on the oligospermic patients. My only caveat would be a total sperm count as opposed to a concentration.

Then as Dr. Schlegel alluded to in the previous group of patients, this group as well that are azoospermic, if you can convert them even to severely oligospermic, you have demonstrated clinical benefit.

DR. LEWIS: Thank you. Dr. Brannigan?

DR. BRANNIGAN: I voted C, and I agree with what Dr. Sandlow said. I look at these patients. They are a different cohort for sure, but I think the clinical outcomes apply to this group as for the previous question.

DR. LEWIS: Thank you. Dr. Schlegel?

DR. SCHLEGEL: I also voted for C. This is a substantial proportion of patients who could be benefitted. And again, the burden of treatment is of concern. The burden of treatment for a couple that has a child with assisted reproduction is a little bit different from a natural pregnancy also because there are risks of multiple gestations, there are risks of complications from that, and potential burden on the family as well.

DR. LEWIS: Thank you. Dr. Weinfurt?

DR. WEINFURT: I had abstained because I felt more comfortable deferring to my clinical colleagues among whom there was disagreement, and I didn't feel I had enough time to ferret out who was right or wrong.

DR. LEWIS: Thank you. Dr. Gillen?

DR. GILLEN: I voted no primarily for the same reasons as the last question. I believe live birth rate is the true clinical outcome here. I agree with the statements that were made about getting patients past the threshold and making IUI

a viable option. But again, I think if you looked at all live birth rates, you will capture that as well in your randomized clinical setting.

DR. LEWIS: Thank you. Dr. Thomas?

DR. THOMAS: I voted no. And similar to the other comments and also from the previous question, if this was restricted to just those who were looking at fertility, I think everything that was said is very appropriate. My concern is that this is going to be treated for people who are not looking for fertility but will be using this instead of testosterone or for non -- even for reasons that really aren't hypogonadal, but just an afternoon total testosterone measured at the wrong time in someone's office.

So I think there are a lot of other things that would have to be looked at to make sure that it's effective to cover what we would usually do for a true hypogonadal person.

DR. LEWIS: Thank you. Dr. Bishopric?

DR. BISHOPRIC: I voted C, and it's just in keeping with my previous answers and the other

comments I've been in agreement with.

DR. LEWIS: Thank you. Ms. Sorscher?

MS. SORSCHER: I voted A, largely for the same reasons as I voted A for question 4. I think if you include oligospermia, you're going to have some real problems determining what is a meaningful threshold there, and the case is much simpler for azoospermia.

DR. LEWIS: Thank you. Dr. Curtis?

DR. CURTIS: I also voted no for the same reasons as I did on that earlier question and the reasons that have been stated, although I have been persuaded by some of our colleagues' discussion around the azoospermia group that measuring the sperm concentration or increasing sperm concentration in that group probably is of clinical benefit.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I voted C in error because I thought it was worded differently from question 2. So I really would like to change my vote from C to A for the same reasons I just cited for 2.

DR. LEWIS: Thank you. I have nothing to add.

Dr. Chai?

DR. CHAI: I voted for C. I did not hear any discussions why we would treat -- again, I read this question as an infertility question, short-term treatment. I didn't hear anything that would scientifically justify why we would treat a classic secondary hypogonadism for infertility differently than someone with a secondary hypogonadism. There was no discussion -- I don't think there's any evidence, therefore I was consistent with my answers between this vote and the previous vote.

I didn't add about which concentration you would -- I would defer -- I hear the arguments of total count versus concentrations. I think the total count would make more sense for this and the previous.

DR. LEWIS: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: I voted D. And I have to perhaps say in a misguided thought that this had

something to do with also the patient who might have symptoms, therefore I was looking for a symptom appraisal as well.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: I voted for D, for the same reason before, which is I think live births ought to be the outcome of interest.

DR. LEWIS: Dr. Drake?

DR. DRAKE: I also voted for D for any of the same reasons that have been stated already.

DR. LEWIS: Dr. Biskobing?

DR. BISKOBING: I voted C this time with the assumption that this is just for infertility, then I think it's reasonable. If it's going to be used long term, then I think other measures should be recorded.

DR. LEWIS: Okay. Dr. Braunstein?

DR. BRAUNSTEIN: I voted D, and that's different from how I voted for 4, which was C, because there is a difference between -- I feel there is a difference between patients with classical secondary hypogonadism and the acquired

hypogonadism that we've been discussing, in that there is data that patients with classical hypogonadism respond to gonadotropins with an increase in sperm count and increased pregnancy rate. There is not that data for this group of patients. And until that data is presented, I think that fertility should be the outcome that we look at.

These drugs have the potential for being used very widely, and I think it's incumbent upon the pharmaceutical companies who develop these drugs to show they actually have the clinical benefit that they're going to be marketed for, which is not to -- I mean, nobody really cares about increasing sperm count if they're complaining of infertility. What they really care about is getting a pregnancy. And if that means getting enough for ICSI, fine. If that means getting enough for IUI, that's fine, or for the good, old-fashioned way of getting pregnant, that's fine, too. But fertility really should be the endpoint in this unknown area.

DR. LEWIS: Thank you. Dr. McCammon?

DR. McCAMMON: I voted D for the previous comments that were already mentioned.

DR. LEWIS: Dr. Hanno?

DR. HANNO: I changed my vote this time to A for the reasons Dr. Howards and Ms. Sorscher noted already.

DR. LEWIS: Thank you.

So that brings the meeting to a close. I want to thank the presenters from the FDA and the industry, and of course all the panel members for your time and attention this afternoon. Dr. Joffe has some comments for us.

Adjournment

DR. JOFFE: I'll just say a big thank you to the panel. I don't know about you all, but I'm pretty tired right now. Thank you for all the wise advice that you shared, and we'll take this back and internally think about it.

I'd also like to thank Dr. Lewis who's our excellent chair for orchestrating a very good meeting; the presenters both on FDA's side and

industry. Industry had the challenge of bringing three different companies together, and I thought that was well done.

I'd like to also thank our AC advisory committee staff, LaToya, Kalyani, Yvette, and then also all these other AC support staff who do things like transcription and make sure votes get captured. So I want to thank everyone and hope you all have safe travels back home.

(Whereupon, at 4:10 p.m., the meeting was adjourned.)