FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF BONE, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE (BRUDAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Wednesday, September 17, 2014

7:58 a.m. to 5:04 p.m.

The Marriott Inn and Conference Center

University of Maryland University College (UMUC)

3501 University Boulevard East

Hyattsville, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. JOHNSON: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other device if you have not already done so. I would also like to identify the FDA press contact, Morgan Liscinsky.

Morgan, could you please stand? Thank you.

Now, I would like for all of the participants in the advisory committee going around the room and, starting with the FDA, to introduce yourselves and state your name into the record.

Julie?

DR. BEITZ: My name is Julie Beitz. I'm the director of Office of Drug Evaluation III in CDER.

DR. HIRSCH: I am Mark Hirsch, medical team leader in urology in the Division of Bone Reproductive and Urologic Products.

DR. NGUYEN: Good morning. I am Christine Nguyen. I am the deputy director for safety with the Division of Bone Reproductive and Urologic

Products.

DR. IYASU: Good morning. My name is Solomon Iyasu. I'm the director of the Office of Pharmacovigilance and Epidemiology in the Center for Drugs.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the director of the Division of Epidemiology II and the Office of Pharmacovigilance and Epidemiology, CDER.

DR. MOENY: Good morning, David Moeny, team leader for epidemiology, Office of Surveillance and Epidemiology.

DR. TYLER: Good morning. I am Linda Tyler. I'm administrative director of pharmacy services at University of Utah Hospitals and Clinics and associate dean of the College of Pharmacy.

DR. GERHARD: Tobias Gerhard. I'm associate professor of pharmacoepidemiology at Rutgers University.

DR. PHILLIPS: Marjorie Shaw Phillips, pharmacy manager for clinical research and education at Georgia Regents Medical Center and

clinical professor at University of Georgia College of Pharmacy.

DR. ERSTAD: Brian Erstad, professor and head, University of Arizona College of Pharmacy.

DR. HOWARDS: Stuart Howards, professor of urology at the University of Virginia and Wake Forest University.

DR. CURTIS: Good morning. I am Kate Curtis. I'm a health scientist at the Centers for Disease Control and Prevention in Atlanta.

DR. CHAI: Good morning. I am Toby Chai. I am from Yale University, where I'm professor and vice chair of research in the Department of Urology.

DR. JOHNSON: Good morning. I'm Julia Johnson. I'm a reproductive endocrinologist and professor and chair of OB-GYN at the University of Massachusetts.

MS. BHATT: Good morning. I am Kalyani Bhatt. I'm with the Division of Advisory Committee Consultants Management.

DR. HERRING: Good morning. I am Amy

Herring. I'm professor and associate chair of biostatistics at the University of North Carolina at Chapel Hill.

DR. ADLER: I'm Robert Adler, endocrinologist at the VA hospital in Richmond and professor of medicine and epidemiology at Virginia Commonwealth University.

DR. ALEXANDER: My name is Richard Alexander, professor of urology at the University of Maryland.

DR. LINCOFF: I am Michael Lincoff. I'm an interventional cardiologist and clinical trialist at the Cleveland Clinic and current chair of the Cardiac and Renal Drugs Advisory Committee.

DR. BURMAN: Good morning. Ken Burman, chief of endocrinology at the Washington Hospital Center and professor in the Department of Medicine at Georgetown University.

DR. BRAUNSTEIN: Good morning. I am Glenn Braunstein. I'm a professor of medicine and endocrinologist at Cedars-Sinai Medical Center in Los Angeles.

DR. DMOCHOWSKI: Good morning. Roger Dmochowski, professor of urology, Vanderbilt University Medical Center and also chief of patient quality and safety for Vanderbilt Health Systems.

DR. SHEHAB: Good morning. Nadine Shehab, CDC, Atlanta, Georgia, medication safety program.

DR. DOMANSKI: I'm Mike Domanski. I'm professor of medicine at Mount Sinai Medical School in New York and a cardiologist.

DR. GARNICK: Marc Garnick. I'm professor of medicine, Harvard Medical School in Beth Israel Deaconness Medical Center in Boston.

DR. THOMAS: Abraham Thomas, endocrinologist in Detroit, Michigan.

DR. BOINEAU: I'm Robin Boineau. I'm a cardiologist at the National Institutes of Health, National Heart, Lung, and Blood Institute.

DR. GORDON: And good morning. I am Keith Gordon. I am the medical affairs strategy lead for women's health at Merck, and I'm the industry representative here.

DR. JOFFE: I'm Hylton Joffe, director of

the Division of Bone Reproductive and Urologic Products at FDA.

DR. JOHNSON: Thank you, everyone, for your introductions.

For topics such as those being discussed today, there are often a variety of opinions, some of which can be strongly held. Our goal is for today's meeting to be fair and have an open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record, but only if recognized by the chair. We look forward to a very 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 to constrain their discussions of the topic at hand to the open forum at this meeting. We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, the FDA will refrain from

discussing topics of this meeting until its conclusion. Also, the committee is reminded that we shall refrain from discussing the meeting topics at breaks or at lunch. Thank you very much.

Now, let me pass it on to Kalyani Bhatt, who will read the conflict of interest statement.

Kalyani?

Conflict of Interest Statement

MS. BHATT: Good morning. The Food and Drug Administration is convening today's joint meeting of the Bone Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

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

The following information on the status of

these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., 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 these committees are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts, when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of these committees 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 U.S.C. 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 the appropriate indicated population for testosterone replacement therapy and the potential for adverse cardiovascular outcomes associated with its use. 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, a conflict of interest waiver has been issued in connection with 18 U.S.C. Section 208(b)(3) to Dr. Marc Garnick. Dr. Garnick's waiver involves stock investment in an affected firm. This aggregated value of the investment is between $25,001 and $50,000.

The waiver follows this individual to participate fully in today's deliberation. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on the FDA

website at www.FDA.go/advisorycommittees/committee meetingmaterials/drugs.

A copy of the waiver may be obtained by submitting a written request to the agency's Freedom of Information Division, 12420 Parklawn Drive, Element Building, Room 1029, Rockville, Maryland, 20857, or a request may be sent via fax to 301-827-9267.

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 representatives, we would like to disclose that Dr. Keith Gordon is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by Merck and Company.

With regards to FDA's guest speakers, the agency has determined that the information to be

provided by these speakers is essential. The following interest is being made public to allow the audience to objectively evaluate any presentations and/or comments made by the speaker.

Dr. Peter Snyder has acknowledged that he is an investigator for the testosterone trials, which are partially funded by AbbVie.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which 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 participants to advise the committee of any financial relationships that they may have with the firms that would be affected by the committee's discussion. Thank you.

DR. JOHNSON: Thank you very much.

Now, we'll proceed with Dr. Joffe's introductory comments. Dr. Joffe?

FDA Opening Remarks - Hylton Joffee

DR. JOFFE: Good morning, everybody. Thank you for coming today. Before I get started, I just wanted to take one moment to acknowledge two outstanding human beings and excellent scientists who worked at FDA, both of whom died unexpectedly within the past few weeks. The first is Dr. Eric Andreasen, who was a non-clinical pharmacologist/toxicologist in our division. And the second was Dr. Hyunjin Kim in the Office of Clinical Pharmacology. Both of those young men had worked on countless testosterone products, and they'll be sorely missed.

What I'd like to do in the next 10 minutes or so is provide an overview of the objectives and scope of today's meeting. And I'll give some background and overview of today's agenda. And then I'll give a preview of the topics for discussion and voting questions that we'll be posing to the advisory committee.

So we have two objectives today. The first is that we need help from the committee to identify

the appropriate indicated population for testosterone replacement therapy. And the second is to ask the committee to provide an assessment of whether there's a potential risk for major adverse cardiovascular events associated with testosterone use. And here we're talking about arterial events, so things like heart attacks and strokes.

To make sure we have appropriate expertise for this meeting, we've populated our joint advisory committee with additional individuals with expertise in endocrinology, cardiology, epidemiology, and urology as well.

Today's scope is on the class of testosterone products. The objectives that I presented on the previous slide did not apply to a particular specific product. Here, we're talking about class issues, so please keep that in mind with today's discussion.

Also, some of you may be aware that FDA is reviewing abuse with testosterone products, for example, in athletes who use testosterone for performance. And that review is still ongoing and

is not included in today's scope, either.

So two slides on background, first, the indicated population. In men, testosterone is produced in the testicles under the direction of the hypothalamus and pituitary in the brain. And all FDA-approved testosterone products are indicated for replacement therapy in men who have low testosterone with an associated condition.

Now, benefit is clear in those men where the associated condition is a specific medical condition such as those who have had damage to their testicles from chemotherapy or those with specific genetic abnormalities like Klinefelter syndrome. And no one would question the use and benefit of testosterone in that population.

However, the predominant use of testosterone in the United States is in men who are between the age of 40 to 64 years of age and have what is so called age-related hypogonadism. So these are men who have testosterone levels measured that are considered low. They have signs and symptoms that could be consistent with low testosterone, but they

don't have an obvious medical course for this condition. The only thing that possibly explains this is increasing age. And as you'll hear from presentations over the course of the day, benefit is unclear in this population. There is no conclusive evidence of benefit here.

Despite that, the predominant use is occurring in this population where benefit is unclear, and that's prompted FDA to question whether our labeling accurately reflects the appropriate indicated population for testosterone.

With regard to cardiovascular risk, we started looking at this back in 2010 with the publication of the TOM trial, which is a trial of testosterone use in elderly men with limited mobility. That study reported a possible cardiovascular risk.

At the time FDA reviewed that, those data, and all other available data, and concluded that any cardiovascular risk was inconclusive. But there have been some more publications that have come out since then, and that's prompted FDA to

reassess whether there could be a potential cardiovascular risk with these therapies. And we'll share our findings and conclusions with the panel today. And we will seek advice on next steps.

So this is our agenda. We're going to have two guest speakers who will each speak for about 25 minutes. We'll then have an hour industry presentation, an hour FDA presentation, the open public hearing, and then, towards the end of the day, committee discussion and voting. There will be opportunity throughout the day for the panel to ask clarifying questions of the speakers.

Because the issues we're discussing today affect all testosterone sponsors, we invited all testosterone sponsors to collaborate on a presentation for today and also on a background document for the committee. And some of them chose to do so, and those are the folks you'll be hearing from during the open public hearing and also during the industry presentation. And some additional ones might decide to speak in the open public

hearing.

Our guest speakers, we have two. We have Dr. Peter Snyder, an endocrinologist who is a professor of medicine at the University of Pennsylvania, and Dr. Mark Sigman, who is a urologist, professor and chief of urology at the Warren Alpert Medical School at Brown, as well as Rhode Island Hospital and Miriam Hospital.

We asked both of these experts in testosterone to provide their independent expert views of hypogonadism, how do you diagnose it, and who should be treated based on their interpretation of the existing data.

For industry, we have asked industry to talk about who are the patients that are currently getting testosterone products and what are they receiving testosterone products for.

We have asked industry to summarize the evidence which would support benefit with its current use and also the evidence for potential cardiovascular risk. And we have asked industry to end with whether the approved labeling for these

products, including the indication, currently reflects the appropriate population and reasons for testosterone use.

From FDA, you'll hear four presentations today. Our first one will be our view on drug utilization. You'll then hear a presentation on prescription drug promotion. You'll then hear about our current approval paradigm for testosterone replacement therapies and how that impacts the indicated population.

Lastly, you'll hear from the Office of Surveillance and Epidemiology regarding the potential for cardiovascular risk.

Towards the end of the day, the committee is charged with two discussion questions and two voting questions. The first discussion question asks the committee to describe the specific patient populations for which approval is supported based on data generated from the current regulatory approach for testosterone replacement therapies. And we'd also like to hear what the committee thinks would needed to be changed with this current

paradigm to support an indication for the so-called age-related hypogonadism.

We'll then ask the committee to discuss the totality of the cardiovascular data and whether the data indicates a cardiovascular safety signal. We are interested in hearing how strong the committee thinks the signal is, whether the committee believes the signal applies to all testosterone users or a subset such as older men.

Then we're also interested in hearing whether the committee thinks the available evidence to date is sufficient enough to rise to the level of inclusion of risk in labeling for these products.

There are two voting questions. The first one asks whether FDA should revise our current indication for testosterone therapies, and you'll see more later on in detail what the current indication is. And we'll also ask the committee to provide a rationale for their vote. And for those who think we should change the indication, we're interested in hearing the specific changes you're

recommending that we make.

For question 2, we would like to hear whether the committee thinks FDA should require sponsors of testosterone products to conduct a cardiovascular safety study to further assess cardiovascular risk.

This is a multiple-choice question. There are three answers. A is no, a study is not required. B is yes, but only for certain indications for testosterone therapy. And if you vote for B, we're interested in hearing which specific indications you think should prompt a need for a cardiovascular study. And C is, yes, a study is needed regardless of what the indication is for testosterone. And we're interested again in hearing the rationale for your vote.

If you do think a cardiovascular safety study is needed for some or all testosterone indications, we are interested in hearing what type of study you think is needed to answer a risk, should you decide that one exists. Can an observational study do this, for example, or do you

need a controlled clinical trial?

We're also interested in hearing what type of study population should be enrolled into this study if you say one is needed and also how much risk needs to be excluded.

With that, I will end. I want to thank everybody for coming, and I look forward to a reasoned and thorough discussion of these important issues.

DR. JOHNSON: Thank you very much, Dr. Joffe.

John, if you could just quickly introduce yourself, we'd appreciate it. Thank you, sir.

DR. TEERLINK: Happy to do so. I'm John Teerlink, professor of medicine from the University of California in San Francisco and director of heart failure and director of echocardiography at the San Francisco VA Medical Center. And I apologize that the vagaries of transcontinental travel intervened and caused my late arrival, so thank you.

DR. JOHNSON: We're so glad to have you

here. Thank you for coming.

Now, we'll proceed with our guest speakers. Dr. Snyder?

Guest Presentation - Peter Snyder

DR. SNYDER: Good morning. Thank you. My thanks to the FDA staff for the invitation to present to this very important meeting. My charge from the FDA is to discuss male hypogonadism, specifically what is it, who has it, who should be treated, and what are the consequences of treatment.

So I'd like to consider those questions with regard to three categories of men, men who have unequivocally low testosterone with a diagnosed pituitary or testicular disease; men who have unequivocally low testosterone concentrations, but for no discernible reason other than old age; and men who have symptoms that could be caused by low testosterone levels, but actually have normal levels.

Now, current discussion of the questions of who has hypogonadism and who should be treated,

those discussions, both in the lay press but also professionally, have generally not made the distinction among these three categories of men. And yet, the diagnosis, and the treatment, the possible benefits, and the possible risks, I think, depend on which group a man belongs to.

So I'd like to start with the first group, men who have unequivocal hypogonadism due to known disease, and I'd like to start with the guidelines of the Endocrine Society, last published in 2010, with regard to diagnosis and treatment of frank hypogonadism.

Those guidelines say that one should make the diagnosis of hypogonadism, based on, first, symptoms and signs consistent with hypogonadism and unequivocally low morning serum testosterone concentration confirmed, unequivocally low meaning less than 300, and the lower, the more certain, morning, best at 8:00 to 10:00 a.m. Total testosterone is usually sufficient, although not always, and confirmed, meaning at least two values consistently low.

Then known causes of hypogonadism, there's primary hypogonadism due to testicular damage and secondary due to pituitary and hypothalamic disease, and there are some others.

Now, if a male is hypogonadal, and unequivocally hypogonadal, there are certain known consequences. Before pubertal development, it results in incomplete pubertal development. And after puberty, frank hypogonadism results in decreased energy, libido, muscle, body hair, increased fat, osteoporosis, decreased hemoglobin, even anemia, and possibly impaired glucose tolerance.

Treatment is based on the endocrinologic principle that replacing the missing hormone with what is missing in a fashion to mimic the normal serum concentration of that hormone will result in restoration of normal function.

There are several preparations available for testosterone treatment. And that treatment of men who are unequivocally hypogonadal, that increases their testosterone from severely low to normal,

reverses the abnormalities associated with low testosterone, as shown by this study that was conducted in severely hypogonadal men, who were treated for three years.

You can see that they were severely hypogonadal. Their pre-treatment testosterone was less than 100, and when they were treated, the value is increased to normal and was maintained for the three years of treatment.

That treatment increased bone mineral density of the lumbar spine by 7 to 8 percent. It increased fat-free largely muscle mass by 3 kilograms; decreased fat mass by 3 to 4 kilograms; increased hematocrit from anemic to mid-normal; increased energy on a Likert scale; increased from 50 to 70, as maintained for three years of treatment; increased sexual function by questionnaire, also on a Likert scale, 25 to 55 percent and maintained for three years.

So I think it's fair to conclude that testosterone testimony of severely hypogonadal men, due to known disease, dramatically improves bone

density, fat-free mass, fat mass, erythropoiesis, energy, and sexual function.

But what about the second group of men, men who have below testosterone for no discernible reason other than increased age? This slide shows data from the European male aging study and shows that as men get older from -- this is a cross-sectional study -- 40 to over 70, their total testosterone concentration decreases a little, but explained by the increase in SHBG with increasing age, their free testosterone decreases even more.

But then of course, the question becomes, is this decrease in testosterone with increasing age, is it a physiologic phenomenon, perhaps adaptive? Or is it pathologic, resulting in disease? The terms that we hear used for men who are older and have low testosterone, male menopause, andropause, late onset hypogonadism, all of those terms assume that it's pathologic. But is it really?

Well, one reason to think that the decrease in testosterone with increased age is pathologic are the parallels between the consequences of male

hypogonadism and the consequences of what you could call normal aging. Both are characterized by decreased energy, libido, muscle, body hair, increased fat, osteoporosis, decreased hemoglobin, hematocrit, and possibly impaired glucose tolerance.

But when clinical trials have been conducted of elderly men with slightly low testosterone levels, the results have been equivocal. I'll give but two examples.

One example is the effect of testosterone in elderly men with testosterone concentrations that are a little low, the effect on bone, two studies on bone. In the first study, bone mineral density of the lumbar spine in men who are treated with testosterone, with or without finasteride, increased substantially and significantly more than men treated with placebo. But these men were treated with doses of testosterone that were approximately twice physiologic replacement dose.

In another study, also in elderly men, also testosterone versus placebo, there was an increase

in bone mineral density of the lumbar spine, but the difference between the testosterone-treated men and the placebo-treated men was not statistically significant.

Another example is on physical performance. In this study, elderly men who are mildly frail were randomized to receive either testosterone or placebo for six months. Testosterone treatment, shown in read, increased muscle strength but did not significantly increase several different tests of physical performance.

In a very similar study, also conducted in men who are mildly frail, testosterone had a suggestive effect on a couple of tests of physical performance, but no suggestion of an effect on other parameters of physical performance.

Now, one could say, "Well, maybe testosterone improves some parameters in elderly men with low testosterone. Well, why not try it? Why not treat them with testosterone?" Well, one reason not to do so is that elderly men are prone to several conditions that are testosterone

dependent, including prostate cancer, BPH, and erythrocytosis.

Now, prior trials of testosterone in elderly men have not shown an increased risk of these conditions, but the total number of men in these trials added together has been far too small to draw definitive conclusions. And, as Dr. Joffe mentioned, there have been recent studies indicating the possibility of increased cardiovascular risk in men treated with testosterone. There have been both observational studies and clinical trials.

Here, we see summaries of three of the observational studies. One in VA patients showed that 1229 men who were treated with testosterone had an increased risk of combined MI, stroke, and death compared to 7,000 who did not; the hazard ratio, though, only 1.29.

But another study, also in VA patients, although a smaller number, the hazard ratio was only 0.61. And then a third study of men who were given prescriptions for testosterone showed an

increased risk of nonfatal MI after testosterone than before. But again, the overall rate ratio was relatively low.

All of these studies, of course, have the limitations of observational studies in that the diagnosis was not controlled, the treatment was not controlled, the monitoring of treatment was not controlled.

Then there were testosterone trials. This is the same one in elderly moderately frail men that was stopped by its DSMB because 23 men in the testosterone-treated group developed cardiovascular adverse events, but only 5 in the placebo-treated group.

But in a very similar trial, a similar number of men, similar age, also mildly frail, there was no reported imbalance in cardiovascular adverse events. And then there were two meta-analyses. One of 51 trials showed no significant effect on mortality or cardiovascular outcomes, but the other did show an increased risk of cardiovascular events with an odds ratio of

1.54.

So my conclusion is that if we think about all of the trials, although there have not been that many and the numbers have not been that large, if we think of all of the evidence so far about testosterone treatment of elderly men with demonstrated low testosterone, I conclude with regard to efficacy that the evidence that testosterone treatment is beneficial is tantalizing, but it's inconclusive. And with regard to risks, the evidence that testosterone treatment increases risk is concerning, but inconclusive.

Now, a decade ago, the Institute of Medicine constituted a committee that evaluated the evidence concerning the effects of testosterone in elderly men, and in 2003, it made the following recommendations.

The committee recommended that the NIA conduct clinical trials of testosterone therapy in older men with low testosterone. And specifically, the committee said that the initial trials should

be designed to assess efficacy, but that studies to assess long-term risks and benefits should be conducted only if clinically significant benefit is documented in the initial efficacy trials. They thought that a large long-term trial to determine risk was premature because they weren't convinced that testosterone was efficacious in this group.

So the NIA followed the recommendation of the Institute of Medicine committee, and it sponsored the testosterone trials, which are seven coordinated, randomized trials to determine if testosterone treatment will benefit elderly men who have low testosterone levels and conditions that low testosterone may cause.

Seven hundred ninety men enrolled in these trials. The treatment was testosterone or placebo in a randomized, double-blind fashion for 12 months. The primary endpoints for each of the seven trials were all powered at 90 percent so that negative as well as positive results would be meaningful. And there were multiple secondary and exploratory endpoints for each trial.

So where does it stand? The last enrolled participant completed treatment this past year, and the initial results are expected to be made public by the summer of 2015.

Here, you see the seven trials. There's physical function trials, sexual function, vitality, cognitive function, anemia, cardiovascular, and bone. Here, you see the primary endpoints for each of these trials as I mentioned are numerous secondary and exploratory endpoints for each. And here you see the number of subjects in each trial. Subjects could participate in one or several trials, and that's why the total here adds up to more than 790.

So what can we expect when we finally see the results of the testosterone trials? Well, I think we can -- and maybe it's premature to say this. I may regret saying this. But I think we can expect definitive answers, positive or negative, about the efficacy of testosterone in each of those seven areas. But we cannot expect definitive answers about adverse effects of

testosterone in this population because the study was not large enough or long enough to give such answers.

Now we come to the third group of men, men who have symptoms of low testosterone, but who actually have normal testosterone concentrations. And this group is illustrated by a recent cover story in Time magazine about men who are taking testosterone because they don't feel like they used to feel.

This story describes many things, but I was especially interested in the description of a group of clinics in the United States that diagnoses 50 percent of its attendees as having low testosterone. Now, I was struck by that because in the testosterone trials where the men were over 65, and to qualify, had to have a testosterone less than 275 early in the morning twice, only 14 percent of men were diagnosed as hypogonadal. And these men were generally under 65.

So that led me to speculate -- and of course this is only speculation because I haven't been to

these clinics. That led me to speculate that they are diagnosing men not based on, say, the Endocrine Society Guidelines for diagnosis of hypogonadism, and led me to conclude that diagnosing low testosterone on the basis of symptoms alone, or tests not done early in the morning, or a single test, will result in over-diagnosis.

So I summarized the state of this field as follows. And, again, with regard to these three groups of men. For men who have low testosterone due to pituitary or testicular disease, those men experience severe multiple consequences of this deficiency, and those consequences can be prevented or reversed by testosterone treatment.

For men who have low testosterone, documented low testosterone, but for no discernible reason other than age, I conclude that the efficacy of testosterone treatment of these men has yet to be established. The results of the testosterone trials will likely provide better evidence, positive or negative, than in prior studies. I also conclude that the testosterone trials will not

provide sufficient evidence about risk in this group of men.

Finally, for men who have symptoms of low testosterone but actually normal values, they may be inappropriately diagnosed as having low testosterone if the testosterone concentration is not measured early in the morning, or only once, or not at all.

So finally, I wish to make some proposals. For men who have low testosterone due to pituitary or testicular disease, these men should be treated with testosterone, with the expectation that they will improve and that the current discussion about cardiovascular risk does not apply to these men because there is no reason to think that they should be at increased risk of any condition if they are physiologically replaced, no increased risk above what it would be if they made their own testosterone.

For men who have low testosterone, clearly documented by two or more low levels early in the morning for no discernible reason other than age, I

propose that until the efficacy of testosterone has been demonstrated with more certainty, a higher standard should be used to make the diagnosis. By a higher standard, I mean lower testosterone level, say, less than 250 or less than 200.

Second, if the testosterone trials demonstrate sufficient efficacy of testosterone, then I propose that federal agencies and industry should consider funding a larger, longer trial to determine risks.

Finally, for men who have symptoms of low testosterone but normal serum concentrations, I propose that federal agencies, professional organizations in industry, should educate physicians better how to diagnose hypogonadism. Thank you very much for your attention.

DR. JOHNSON: Thank you very, very much, Dr. Snyder.

Now, we have the privilege of hearing from Dr. Sigman.

Guest Presentation - Mark Sigman

DR. SIGMAN: I'd like to talk about

hypogonadism as well. We were both given some questions, and there will be some overlap and maybe a little bit different perspective, but he has made my job a lot easier by explaining many of the things.

First, I want to go over what is male hypogonadism and how do we diagnose it; what is age-related hypogonadism, as you've heard about. What's the difference between the two, age and classical hypogonadism? Why should we even diagnose it, and why should we even treat it? And then we're going to touch on some of the risks of treatment, although much of the cardiovascular risk is going to be dealt with later on, I've been advised. We don't need to go into too much detail with that.

I want to make clear some definitions because this is often confused both among doctors, patients, and even some of the publications. There is low testosterone level, androgen deficiency. And that just means a low testosterone level. It has nothing to do with symptoms. We can also call

that biochemical hypogonadism, but it is often referred to as hypogonadism, but we're going to refer to it differently.

Then there's clinical hypogonadism, which is really what we're talking about. And that means you have to have some clinical symptoms that happen to be associated with low testosterone and inadequate testicular function. Testicles do two main things, make testosterone and supposed to make sperm. And in theory, you would have a decrease in both of those, although in practice, most people are more concerned about the testosterone production unless it's the fertile age group.

We classify these into two general categories. Primary hypogonadism, we mean the testicles don't work properly. You have adequate gonadatropin, FSH, and LH stimulation. The testicles don't respond, so these levels tend to increase.

You have secondary hypogonadism, where in fact the testicles are working perfectly normally, except they don't have adequate hormonal

stimulation, so you have low levels of gonadatropins. This is a defect in the hypothalamus or the pituitary. And then you can have mixed, and that's you have patients with a combination of both primary and secondary hypogonadism.

Now, we've also grouped patients into two somewhat artificial categories. And based on our medical knowledge over the years, we have classical hypogonadism. And as you've heard, that's low testosterone due to a known underlying medical condition. And you can have primary hypogonadism causes and secondary. Some of the primary ones -- Klinefelter's syndrome, mumps, orchitis, orchiectomy, when we surgically remove the testicles, and there are others. You could have secondary hypogonadism, causes including pituitary pathology, Kallmann syndrome. Chronic opioid use is another one.

What I think is very important to understand is we're taught in medical school that these patients present early and as young patients and

have very, very low testosterone. And that is true for some of them. It is absolutely not true for everybody. And we often see some of these patients showing up as adults, and that's the first time they're diagnosed.

Then you have age-related, also called andropause and a variety of other things, where the low testosterone is due to decreased testosterone production, and the best we can tell, the only thing causing it is aging. And many of these patients have a mixed primary and secondary pattern.

This is a level of testosterone throughout the male life cycle. In utero, you'll see there's a testosterone surge. It quiets down during childhood, and then, unfortunately, as adolescence comes along, the testosterone levels tend to increase. They go through puberty into the adult levels. And then as the male ages, they'll gradually go down.

If you have a defect early on during the fetal period, you're going to have somebody show up

with some abnormalities, micropenis and cryptorchidism, for example. If they have that normal surge, but they fail to have their pubertal surge, you'll have patients that we diagnose as absent puberty. They don't go through puberty. You can have patients that start to go through puberty, and then their testosterone drops off, so they'll have partial puberty.

Then they have the big group that everything is normal up to adulthood somewhere, and then the levels may drop whether abruptly or slowly with age. And they may show up with a variety of other symptoms, erectile dysfunction, infertility, and other hypogonadal symptoms.

When we talk about measuring testosterone, it's important to keep the various names in mind. Total testosterone refers to all of the various protein-bound forms plus free testosterone. Free testosterone is the testosterone not bound to anything. There's bioavailable that consists of basically albumin and free testosterone.

There's no complete consensus about those

who work in this business. However, most studies and most guidelines first rely on total testosterone, and then they'll use free testosterone and sometimes bioavailable when your total testosterone is in the borderline region to help settle the difference.

It's important to keep in mind that testosterone is secreted in a pulsatile fashion. It's higher in the morning than it is in the evening, and older men will tend to have a variation that's less than younger men. So what do we mean by a normal testosterone level? Well, usually, it's defined as the 95 percent confidence interval of the testosterone in young, healthy men.

It's important to understand that what you define as your reference population is going to affect your confidence interval. And certainly, for some of the laboratories, they don't query the men, what's your sexual function or do you have these other gonadal symptoms? And that may impact your local reference range.

The other thing to keep in mind is because

you're defining it statistically, by definition, 2 and a half percent of healthy men will have low testosterone, indicating that low testosterone doesn't make you unhealthy necessarily.

If you look at one of the guidelines, well, there again, there are no universally agreed-upon guidelines. These are some of the most common ones. You've got the Endocrine Society. You've heard about those. And they recommended treating patients with classic hypogonadism, but they were very much conflicted on whether you should treat and diagnose age-associated hypogonadism.

They defined it as symptoms plus a low testosterone, ideally below the reference range, and these are some of the ranges if you don't have one or a low normal with a low free testosterone. The American Society of Andrology and a variety of other organizations published in 2008, and you can see they have a little bit of a different range, but they also require symptoms. The European Male Aging Study, interestingly, published, and they recommended that you need three sexual symptoms,

not just one symptom, three sexual symptoms, plus a low testosterone and a low free.

So while these are different, all of them recommend you have to have symptoms. A low testosterone alone is not adequate. The other thing to keep in mind is that the prevalence of a biochemical low testosterone is always going to be higher than the prevalence of clinical hypogonadism.

These are some graphs from the BACH study, and you can see there's the prevalence of low testosterone, biochemical. And you can see it increases with age; that's this line here. If you look at free testosterone, that's going to increase with age a bit more rapidly, as you've heard.

However, this starts -- over 20 percent have low testosterone. But if you then say well, what about the patients who actually have clinical hypogonadism, you can see the prevalence is much lower and then it increases with age. And as you've already heard, both free and total testosterone decrease with age.

So how do we diagnose it? Well, you start with a morning testosterone level. Not everybody agrees with this, but most of the recommendations involve that because of the variation. If it's low, it should be repeated. Why do you want to do that? Well, about 15 percent of young healthy men will have low testosterone at some point during a 24-hour period. Secondary, about 30 percent of men who have a low testosterone will have a normal one on a follow-up level.

You then want to get some other studies to make sure you're not missing some significant disease, gonadatropins, prolactin in many cases, and sometimes pituitary MRI.

So let's talk about symptoms. These are some of the most common symptoms. The Endocrine Society grouped them into specific and those ones tend to be more prevalent with low testosterone. Many of these are sexual symptoms. These are certainly not all of them, but you can see things like decreased libido, decreased spontaneous erections, loss of body hair, small testes, low

sperm count, low bone density, and so on. There are other symptoms such as decreased orgasmic intensity that you could also query your patients for. When I lecture to medical students, I tend to refer to these as shrinkage symptoms. Things sort of get smaller and lower as the men go along.

There are less specific symptoms and signs. And this is where it gets to be very difficult. You have a lot of things like depression, lethargy, poor concentration and memory, sleep disturbances, reduced muscle strength. A lot of these occur as men age anyways, and it's clearly going to be multifactorial.

This is some very interesting data from the European Male Aging Study. And in the blue, you'll see total testosterone levels of asymptomatic men. In the red, you'll see total testosterone of symptomatic men. And you've got a variety of symptoms here. This is total. This is free. But what you see is that the two populations almost overlap completely.

What that points out is testosterone levels

do not separate symptomatic and asymptomatic men. So far, there is no study that's defined a level of testosterone that consistently separates those that will respond to treatment from those who will not. And I think that's very important. We don't have a lot of data on that. Each symptom may be caused by things other than low testosterone. The other thing that I think is confusing is that the testosterone level at which symptoms develop may vary by symptom and by patient.

This is some data again from the EMAS study, and you have a variety of symptoms here. And I'll point you to this black line here, spontaneous erections. This is testosterone levels. This is the percent of men having those symptoms. And they define a threshold where, clearly, the slope starts to increase here with testosterone below this level. And for each of the various sexual symptoms, you can come up with different or other symptoms as well. You come up with different thresholds.

So what they then do, as you can see, is you

can say, well, here's a symptom and here's a threshold. Here's another symptom and here's a different threshold.

So you get different thresholds for different symptoms. And what the interpretation is, the chance of symptoms being present are greater if your testosterone level is below that threshold than if it is above it. But patients still may have those symptoms even if the testosterone is above that threshold. Different symptoms clearly have different thresholds. However, most of the thresholds are roughly in the range around 300. They are not jumping from 300 to 900, for example.

This is some other data that points out some interesting facts. These are younger men. These are older men. If you look at this, this is patients who have low testosterone. These ones have symptoms. This group here doesn't have symptoms. As you look at the older men, more patients with low testosterone are in this symptomatic group. So older men are more likely to

have symptoms with low testosterone than younger men. However, still about 47 percent of the older men who have low testosterone have no symptoms.

Now, that brings us to why we should even diagnose it. Well, as you've heard, there are some significant medical issues that can go along with it, so you don't want to miss a significant medical condition. Also, ideally, you'd like to identify patients who are going to benefit from treatment.

Why should we treat? Well, if treatment will relieve symptoms, that'd be a really good reason. And there's certainly a lot of interest. Does treatment protect against future pathologies? And I don't think we have the answer to that.

What kind of conditions are associated with low testosterone? Well, a whole lot of the most common ones that plague the western civilization currently: obesity, noninsulin dependent diabetes, hypertension, COPD, and so on.

There's clearly an association between these kinds of comorbidities and hypogonadism, late onset hypogonadism, here. This is a meta-analysis. And

you can see, for a variety of these kinds of things -- obesity, diabetes, chronic diseases, increased cardiovascular risk, metabolic syndrome -- there is a greater incidence of hypogonadism in patients with these conditions than in patients without them.

From the EMAS study, you'll see again that hypogonadism incidence increases with age, increases with BMI. Most interestingly, the more comorbid conditions patients have, the greater the prevalence of hypogonadism.

It's important and this unfortunately continually gets confused as a causation or association. And I think we really don't know in many of the cases at this point does low testosterone cause disease or is it due to the underlying disease? Does treatment for hypogonadism improve the underlying condition? There is a lot of interest in this.

If we're going to treat, what is the goal? How high should you get your testosterone? Well, it's important to understand, when we have

guidelines, those are consensus guidelines and not evidence-based guidelines. The Endocrine Society, as you heard, recommends treating classic hypogonadism patients, aiming for a mid-range of 400 to 700 nanograms per deciliter of testosterone.

As I said, they are a little bit divided on the age-associated, but said if you're going to treat, you should probably aim for a little bit on the lower side there.

Now, when you think about this, it's a little bit inconsistent. If you have a patient who has symptoms and a clearly low testosterone, you should get their testosterone not above the 300, but you should get it above 400, to the 400 to 700 range. If you have a patient who has got the same symptoms, but his testosterone is 310, for example, and his free testosterone is normal, you're going to leave him at 310, and you're not going to get him above 400.

Well, why do organizations recommend that kind of approach? And as you've heard, it's because we really don't know the long-term risks of

testosterone therapy, so they felt they'd rather be conservative than treat patients who have clearly low testosterone levels.

You have already heard about the Institute of Medicine report, so I am not going to go over that. But basically, you need short-term studies, which require smaller populations, as you see in the T-trial. But they recommended that you're at some point going to need bigger studies with thousands of patients. And the problems with the current data we have is much of it is observational, which has caused problems in interpretation.

What happens to symptoms? You have heard some of that already. There is relative evidence that many of the sexual symptoms do increase in hypogonadal patients, libido, sexual thoughts, attention to erotic stimuli, erections. Interesting, erectile dysfunction, while it does increase in some patients, it's less so in older men. Why would that be? Well, older men have a whole lot of other reasons why they may have

erectile dysfunction, like vascular disease.

What about effects on body composition? There is evidence that you have decreased fat mass in patients, increased lean body mass, increased muscle strength, but that is somewhat conflicted, and you've heard about that as well. And the effects generally are modest.

Bone density. There's good evidence that hypogonadal men have decreased bone density and an increased fracture risk. Interestingly, in one study, it was best correlated with estrogen levels. Treatment does seem to increase bone density, particularly lumbar. One study suggested maybe not the femoral neck. I think we clearly need better studies, and hopefully we'll have that next year. Ideally, we want to know what's the effect on fracture risk. We don't. There are no studies on that currently.

Psychological symptoms. There is some evidence for improvement on a variety of psychological symptoms, but the data is inconclusive at this point in time.

What about comorbidities? What happens to some of these in patients that are treated with testosterone? Well, in type 2 diabetes, there's evidence in a variety of these biomarkers. This is a meta-analysis, and you can see that the overall effect size favors treatment. Again, this is a meta-analysis not of perfect studies.

What about metabolic syndrome? One of the more common things we have today. Again, if you look at the various biomarkers, the meta-analysis tends to favor treatment.

So there seems to be evidence that does exist for a benefit and a variety of signs and symptoms and comorbidities. Those with very low testosterone levels -- and those often the ones with classical hypogonadism, but not always -- likely show the bigger benefit. But as you also heard, that's not the majority of patients now that are getting these prescriptions.

Many classical hypogonadal patients are older. Those of us in urology and adult urology tend to see that. They do not have extremely low

testosterone levels, and the levels tend to be similar to the age-associated patients. And it's unclear to me that, necessarily, we have two identical patients.

Is it really different? We don't have a lot of data on how the response is. But evidence seems to suggest an improvement for both groups. Clearly, I think that's very important, you've heard we really lack large randomized controlled trials.

What are the risks? These are some of the more common risks related to testosterone. I'm just going to hit on these a little bit. Increased red blood-cell mass -- pardon me. Before we get to red blood-cell mass, let's talk about spermatogenesis because that's a real problem.

Exogenous testosterone is a contraceptive, a pretty good one, not a great one. It suppresses gonadatropins, so these patients become azospermic. They stop making sperm. If you have patients who need testosterone that are in the reproductive age, you need to look at some alternative methods listed

here. These are all off label, but they should be considered in these patients.

Increased red blood-cell mass, one of the most common side effects. It's more common with IM injections, less common with transdermal, and more common in older men. The concern there is thromboembolic events, although the data on that is primarily from polycythemia patients. It's relatively easy to manage. If that happens, you can reduce the testosterone dose. You can stop therapy if indicated, or you can have the patients donate blood.

Prostate, benign prostatic hypertrophy. Most of us urologists feel that the data suggests that it does not increase symptoms of BPH. What about prostate cancer? We're taught that it's a very concerning thing. We don't have a definitive answer. The data that's there suggests it probably doesn't, but we don't have a large study which we're going to need to answer that. We have epidemiologic data we can look at, and that shows that testosterone levels are not related to the

risk of prostate cancer. And there's two trials here.

There are treatment studies, and this is a meta-analysis that shows no increase in prostate cancer rates or clinically significant PSA in patients that are on testosterone treatment, and the effect size overlaps one.

Cardiovascular, I'm only going to briefly touch on because you're going to hear about that later. But the big concern is does it increase cardiovascular events and mortality. There is data suggesting it's safe. There's also data suggesting it's not safe.

The problem is this. The studies are primarily observational. They have uncorrected bias. And no matter what you do, you can't correct for it. We don't know why someone was treated and why somebody was not treated. And despite the manipulations you can do, you can't turn it into a randomized trial. In addition, these are often interpreted as causation as opposed to association. These are really hypothesis-generating studies, and

we are going to need a very large study to determine safety over the long term for this.

So in conclusion, clinical hypogonadism is common. There are many symptoms and comorbidities that are associated with low testosterone. The criteria for who to treat is controversial. We cannot clearly separate out those who benefit from those who do not benefit, and that's likely because the signs and symptoms are multi-factorial.

There seems to be reasonable evidence that testosterone is beneficial for some patients, for some signs and symptoms. And I think what we see is for some classical and some age-associated hypogonadism. I'm talking about patients with low testosterone. But again, we're going to need long-term safety studies to answer the safety question. Thank you.

Clarifying Questions to Guest Presenters

DR. JOHNSON: Thank you very much to both of our speakers for your excellent presentations. Now, if I would ask you both to be up for potential questions. And now I am bringing it to the

advisory committee.

Do you have clarifying questions for the guest speakers? If you do so, please raise your hand. And when you present your question, please state your name for the record before you speak, and if you can directly ask your question to the specific speaker. Thank you very much.

Dr. Dmochowski?

DR. DMOCHOWSKI: Roger Dmochowski. Dr. Snyder, two questions. One, you clearly use the term "unequivocal" for 300. So Dr. Sigman's present clearly had some other numbers. So one of your conclusions was, we need to do better education, especially for this group of men with massive levels. So where are we with absolute numbers and how do we do a better job with education?

Then secondarily, related to your overall review, did you control for method of administration of testosterone, or did that include both transdermal and parenteral in terms of the results that you presented?

DR. SNYDER: With regard to number, I used the term unequivocal, but as I mentioned at the outset -- and I used the number 300, which is the lower limit of normal for most testosterone assays. But the diagnosis of unequivocal depends, as I mentioned, not just on the absolute number, but on the time of day and the number of times that the measurement is made. And clearly, just with regard to diabetes, even though we may use a specific number, it's likely that there is no one number.

I also mentioned, and I should emphasize now, that the lower, the more certain. So just for practical purposes we have to pick a number. But if we picked 300, and we found someone with a value of 298, even if it was measured early in the morning, three times, and was always 298, that person wouldn't necessarily be hypogonadal.

So clearly, the lower, the better. And if it's associated with a disease known to cause low testosterone, then that makes it more likely that it's real. So someone who has a value of 100 and has a large pituitary adenoma, there's no question.

But you could say, well, what about 150? Sure, still no question. But you get over 200, and it's less certain. But the same of course is true in all areas of medicine.

This of course has to be part of our education. You asked about education, and part of our education relates not only to specific numbers, but to time of day, number of times, and associations. And there are many other complexities that probably we don't have time to go into now, obesity, for example, other illnesses, and those all have to be considered.

Your second question was about did I present studies that were of transdermal testosterone preparations or intramuscular preparations, and the answer is yes. So some of the studies I presented used intramuscular preparations. For example, I showed the example of the effect of testosterone and bone mineral density.

The first of the two studies I showed, the one that used amounts of testosterone that were approximately twice physiologic, that study used an

intramuscular preparation. The second one used a transdermal preparation.

DR. JOHNSON: Thank you very much. Dr. Boineau?

DR. BOINEAU: Dr. Snyder, this question is for you. I noticed that you're suggesting treating based on laboratory value and not including symptoms. And I was interested in hearing why you hadn't suggested including symptoms.

DR. SNYDER: The Endocrine Society Guidelines certainly include symptoms. The Endocrine Society Guidelines recommend treatment on the basis of symptoms that are consistent with those of hypogonadism and of laboratory values: a certain level, time of day, number of times.

So all physicians who treat men, who see men who are hypogonadal, do experience men who are severely hypogonadal and don't admit to symptoms until they're treated, and then they feel better.

So I think symptoms are important, and I think they are appropriately part of the guidelines. But there are men who are severely

hypogonadal and don't admit to symptoms.

DR. JOHNSON: Dr. Teerlink?

DR. TEERLINK: I will preface this with I'm just a cardiologist.

DR. SNYDER: Oh, no, not just a cardiologist.

DR. TEERLINK: I know. So in our field, we have NT pro-B, and P, and different biomarkers, and neurohormones that we measure. And when we measure those, we try to use age-adjusted and BMI-adjusted values for what we consider to be normal. And it's interesting to me that in this field, it seems that normal is being compared to a young male and does not seem to be age-adjusted levels.

So is that true? And if so, why? Help me understand that.

DR. SNYDER: So you remember in discussing the fall in testosterone with increasing age, I tried to say that we don't know if this fall is a physiologic phenomenon or a pathologic phenomenon. Now, if the fall is a physiologic phenomenon, we should use age-adjusted values. But if it's a

pathologic phenomenon, we should use constant values.

So my answer to your question is we don't know whether we should use age-adjusted values now or not.

DR. TEERLINK: So something that seems to happen in the human race as a whole over age would seem to be suggestive that it's a biological process, kind of like. And it's interesting that you seem to have -- there's a parallel between menopause and andropause. And I am wondering also if we have a parallel here between estrogen replacement therapy, which we said this just obviously makes sense because estrogen is dropping, so we should definitely replace them, and whether that's going to be the same thing we find out with testosterone therapy.

The last part was speculation, but the first part seems to be -- and, once again, as I said, I am only a cardiologist in that regard. But it does seem like this is a population effect.

Is that not correct? I mean, in a human

population of males, the testosterone over time decreases.

DR. SNYDER: Yes. It does, but it's very gradual. It's also very variable. In studies where we recruit elderly men and we want their values to be less than 300 or less than 275, we have to reject most men who volunteer. We reject the large majority because their serum testosterone concentrations are too high. So this fall with increasing age is very variable.

DR. TEERLINK: Then the final thing with regards to your trial, which I am looking for the results of, were there pre-specified cardiovascular event definitions? And if so, are they being adjudicated as we would normal cardiovascular events in other studies?

DR. SNYDER: Yes and yes.

DR. TEERLINK: Thank you.

DR. SNYDER: They're not being adjudicated as quickly as I'd like.

DR. JOHNSON: Thank you very much.

Now I have the opportunity to ask a question

of Dr. Sigman. You brought up the topic that, indeed, with obesity, diabetes, and other health factors, that there is a lowering of testosterone levels. How do you look at cause and effect in this? And is this an appropriate group if they have low testosterone levels and symptoms to treat, or because of their cardiovascular risk, are they a group that should be closely considered before putting them on testosterone replacement?

DR. SIGMAN: The short answer is I don't know. Clearly, there is an association. There is some evidence that some of the biomarkers do improve, and there are physicians out there who think strongly that these patients should be treated if it's low. There are other physicians that think no, and there are many in the middle.

The data is just not conclusive. I think it's intriguing. Does this really improve the underlying comorbidity? And I think there's some evidence that it may, but I don't know. Some people think that you start out by giving them testosterone. They then start losing weight

because they have more energy. And then the disease goes away because they are doing a better lifestyle, not necessarily testosterone. We don't know the answer to that.

DR. JOHNSON: Thanks. Dr. Erstad?

DR. ERSTAD: Brian Erstad. My question is for Dr. Sigman. And I wanted you to talk a little bit more about free testosterone concentrations. On the one hand, it's appealing in sense of not having some of the binding problems of total testosterone levels, but then on the flip side, it's still a surrogate marker.

Presumably, it's a more technically difficult procedure to perform and not widely available. And so it seems like it, again, has a couple of advantages, but then some disadvantages from a practical standpoint, interpretation standpoint.

So if you could give your thoughts on free testosterone concentrations.

DR. SIGMAN: Sure. I think free testosterone is excellent if it's done

appropriately. Unfortunately, there have been commercial tests that are inaccurate. While they may correlate with free testosterone measured by the classical gold standards, they give different values. While there's some disagreement about the use of that, most people feel that those are not the best assays to use, the analog assays. Ultracentrifugation dialysis works great, probably just as good as bioavailable, and there's some ways of measuring that.

All of these are available nowadays. I think, historically, they have not been available. But if you request your lab, send them to a place that does that appropriately, you have no trouble getting them.

So I think free testosterone is fine. For most people, total testosterone will suffice. Some people feel that you should, right off the bat, get a bioavailable, or free T, or get all of them. I'm not sure it makes a huge difference as long as the assays are done appropriately. The government has taken on a standardization program for total

testosterone because that's been a huge issue, and I think that's getting better, too.

DR. JOHNSON: Dr. Adler?

DR. ADLER: I have two questions for either speaker. The first one is to ask you to comment upon the study from Australia that suggested that highly successfully aging men had relatively normal testosterone up until age 80 or so, suggesting that comorbidities associated with getting older were the causes of low testosterone found in other studies.

The second question relates to the competing effects of obesity and aging on sex hormone binding globulin and how that has an impact on measurements by the best methods even of free or bioavailable testosterone. Thank you.

DR. SNYDER: Several studies have shown that comorbid conditions have a significant effect on testosterone with increasing age. The European Male Aging Study showed that. And I think the Massachusetts Male Aging Study showed that also. So I think the data supporting that idea is quite

good now.

Tell me your second question again.

DR. ADLER: It has to do with the competing effects on SHBG by obesity and aging.

DR. SNYDER: Sure. So as you may remember from the slide I showed from the European Male Aging Study, SHBG goes up with age. And so if we used the total testosterone concentration for assessing testosterone production and effect, then we will be misled to some degree because the free testosterone will be lower than we would otherwise suspect.

Obesity has the opposite effect, and I think that's what you're driving at, that men get more obese as they get older, which tends to lower their SHBG, but age alone increases the SHBG. So one could use that reasoning to support the more frequent use of measuring free testosterone. And I'll add that if it is measured, it should be done by equilibrium dialysis.

But I do agree with Dr. Sigman. Under most circumstances, I don't think that's necessary.

DR. JOHNSON: We are going to go a little bit beyond because we have some great questions. We'll have five more of our committee members with questions. Dr. Domanski?

DR. DOMANSKI: One can see that you can, with treatment, get levels of testosterone that are in a normal range. I just wonder whether it makes any -- you can recapitulate the normal range total, but you don't recapitulate the time course of the release of testosterone. It would happen in somebody who's normal.

Does that make any difference or do you think that's a red herring?

DR. SNYDER: With the transdermal preparations, the serum concentration is relatively -- I was about to use the word steady, but steadier than with intramuscular preparation.

DR. DOMANSKI: I'm not looking for steady, though. I'm looking for physiologic and --

DR. SNYDER: I was about to get to that. But it doesn't reproduce the higher values early in the morning and the lower values in the early

evening. That is physiologic. And so your question is, does that make a difference? And I think the answer is that nobody knows.

DR. JOHNSON: Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. This is a question, actually, both to Dr. Snyder and Dr. Sigman, and it has to do with efficacy. The briefing book shows that the average duration of use of testosterone after prescriptions are given is about six months with a median of about three months.

Does that suggest that perhaps there's a large placebo effect, and that it wanes, and that the patients are voting with their feet, that they do not think that the therapy is efficacious?

DR. SNYDER: I didn't read the briefing book thoroughly enough to -- but my understanding is -- and whoever prepared that can correct me if I'm wrong -- that that's based on all testosterone preparations given in the United States. And my impression is, based on the journal of Time magazine, that many of those prescriptions are

written for men who are not really hypogonadal. If that's the case, then those men will not likely experience any benefit and will, as you say, vote with their feet.

But in my practice, men who are hypogonadal due to known disease, by and large, I'd say the very large majority, more than 90 percent, take testosterone as prescribed. And I bet that's the case in your practice, too.

So I think that the data that we're seeing about how long the average man in the United States takes testosterone is based on the class of men. In going back to my three classes of men, I would say, those data are based largely on men in class 3, those men who have symptoms that could be due to low testosterone but don't really have low testosterone.

DR. BRAUNSTEIN: I just wonder how many of those are also in class 2. I agree with you on the class 1, with the clear-cut primary hypogonadism and the structurally-induced secondary hypogonadism, that those patients stay on

testosterone and benefit from it.

The question is, do patients with late onset hypogonadism with testosterone levels in the 250 to 300 range really benefit? And they, along with the class 3 group, are probably accounting for the vast increase use of testosterone in the United States.

DR. SNYDER: I think that's quite possible.

DR. SIGMAN: Could I add just a couple comments to that? And I think you're right. When we have patients with really low testosterone, they will stay on it. You have the patients, maybe 250 to 300, that present with these symptoms, which could be due to something else, they often may go on a trial. But if they don't have any clear bad disease going on associated with it, and if their symptoms don't get better, some of these patients will stop it.

The third thing that I think complicates the data is what we're seeing with the insurance companies is the patient will go on testosterone. Three months later, the insurance company says, "You can't have that anymore." They come off of

it. And then the company makes a deal with another company, and they may go back on something else. We're seeing a lot of that, and I don't know how the data cleans that up. But all three are involved.

DR. JOHNSON: Thank you. Two more questions. Dr. Garnick?

DR. GARNICK: Thank you. My first question is directed to both Dr. Snyder and Dr. Sigman. Should we be concerned about which assays are being utilized in the initial diagnosis of hypogonadism? And my second question is to Dr. Sigman. What is your recommendation to the general practitioner or the primary care physician in terms of urological history and urological evaluations prior to administering any of the testosterone formulations?

DR. SIGMAN: You're referring to should be mandating free testosterone versus total or something like that, or the actual assay?

DR. GARNICK: The actual assay, is one assay from one laboratory different than the other of the normal range? Is it comparable? I mean, what are

the issues of assay quality in making the initial diagnosis?

DR. SIGMAN: Well, there's now a federal program to validate testosterone assay machines, so that variation that we used to see is less of an issue. And I think, certainly, any lab you're getting at should use a machine that's been validated to give accurate levels. So now, the total testosterone shouldn't be a big issue.

Your second question was urologic evaluation. Yes. I do think these patients should be evaluated. You've heard that while we're not so concerned about BPH symptoms, we certainly don't want to treat somebody who's got undiagnosed prostate cancer. While many of the urologists may put patients who have prostate cancer on it, they're doing it while they're being very closely monitored, and there's very clear reasons why they may want to do that.

But I think there is a concern amongst us when a lot of patients get testosterone with no evaluation, that some of these other conditions

that are hormone sensitive will be missed. It doesn't have to be done by a urologist. I just meant the urological system should be evaluated.

DR. JOHNSON: Finally, Dr. Gerhard?

DR. GERHARD: I guess my question was to both Dr. Snyder and Dr. Sigman. And most of my questions actually have been posed by Dr. Braunstein and already been answered. Just one quick follow-up.

In the clinical trials and in the trial specifically for the late onset hypogonadism populations, so your class 2 patients, how does compliance look long-term in these trials?

DR. SNYDER: I can address that question with regard to the testosterone trials. Compliance was measured by weighing the bottles of gel before and after they were returned. All bottles were required to be returned. And so compliance in that regard was quite high.

But of course, that's not a typical clinical situation. Those subjects were - badgered -- would be a mild term -- to use their gel every day. They

were seen once a month for the first three months, and then every three months. They were called in between. So even then, the compliance wasn't perfect, but it was quite high.

DR. GERHARD: Could you be a little more specific, put a number on it?

DR. SNYDER: The weight of the bottles was -- people were taking different doses, so the weight was compared to what it should have been, and it was what it should have been about 95 percent of the time.

DR. JOHNSON: Thank you very much to both of our speakers for your presentations as well as answering all of our clarifying questions.

Now we have an opportunity to hear from our industry representatives. Allow me to start off by saying that 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, the FDA believes that it is important to understand the context of the individual's

presentation.

For this reason, all participants are encouraged, including industry, non-employee presenters, to advise the committee of any financial relationship that they may have with the firm in regards to issues such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those that may depend on the outcome of this meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you have any of these financial relationships. Also know that if you choose not to address these financial relationships at the beginning of the presentation, it does not preclude you from speaking.

Now, we have the opportunity to proceed with industry's presentations. Thank you.

Industry Presentation - Kraig Kinchen

DR. KINCHEN: Good morning. I'm Dr. Kraig Kinchen, senior director of global urology at Eli Lilly. We would like to thank the advisory

committees and the FDA for the opportunity to share the industry perspectives on the discussion topics. Although AbbVie and Lilly have taken the lead in preparing the briefing material and presentation, this presentation reflects the input of the group of 12 sponsors listed on the slide.

Some sponsors have marketed products that are highlighted in yellow. As this presentation is on behalf of the sponsor group, we are not prepared to discuss product-specific data.

In the Federal Register of July 14th, discussion topics were proposed by the FDA for the advisory committee's consideration. Our goal for this presentation is to provide information to assist the advisory committee in addressing these topics and the more recent questions posed by the FDA.

For approval, registration trials enroll men with a deficiency of endogenous testosterone. Registration study populations have been enrolled without regard to etiology and included men with age-related hypogonadism.

The primary efficacy endpoint of most phase 3 registration studies is to demonstrate that at least 75 percent of patients achieve an average serum concentration testosterone level within the normal range, between 300 and 1,000 nanograms per deciliter.

The lower bound of a 95 percent confidence interval must also be greater than 65 percent. Studies usually have several secondary endpoints. The most recent registration trials have included three Cmax thresholds as critical secondary efficacy endpoints. The Cmax must be at 1500 nanograms per deciliter or less in at least 85 percent of subjects, between 1800 and 2500 nanograms per deciliter in no more than 5 percent of subjects, and no subjects can have a Cmax greater than 2500 nanograms per deciliter.

Some registration studies have included measures of body composition and symptomatic improvement as secondary or exploratory endpoints. Historically, improvement in some of these measures were included in product labeling. Specifically

the psychosexual daily questionnaire, or PDQ, was used to measure symptomatic improvement in sexual function and mood.

In December 2009, the FDA finalized guidance for industry on patient-reported outcome measures, or PROs, to support labeling language. The PDQ, which was previously sufficient to support labeling language prior to the FDA guidance, was no longer considered a valid instrument after the issuance of the guidance, and this left no validated PROs for TRT to support labeling language for symptomatic improvement.

In response to this guidance, some sponsors initiated work with the FDA to develop and validate new PRO measures. Dr. Jain will discuss some of our current efforts in this area later in the presentation.

To support the current indication, FDA has not required randomized placebo-controlled trials, demonstration of improvement in signs or symptoms of testosterone deficiency, or delineation of the etiology of low testosterone. Also, with the

exception of safety labeling to reflect unique formulations or modes of delivery, the FDA has preferred class labeling.

This information is important to keep in mind as we discuss the evidence in regards to the clinical benefits and the potential for cardiovascular risk presented later in the presentation.

Regarding labeling, the current class indications for TRT are in adult males with a deficiency or absence of endogenous testosterone. The first indicated condition is for congenital or acquired primary hypogonadism, which is testicular failure due to several conditions listed here. The second indicated condition is congenital or acquired hypogonadatropic hypogonadism, also known as secondary hypogonadism, characterized by idiopathic gonadatropin or luteinizing hormone, releasing hormone deficiency or pituitary hypothalamic injury. I should note that selective labeling for pediatric use is also in place for some products.

The FDA makes clear in its briefing document that it is considering revising the indicated patient population. In the summary of Section 2 of the FDA's briefing document, they acknowledge that the current label does not clearly differentiate between specific etiologies of hypogonadism, such as men with Klinefelter's syndrome, and less defined etiologies such as age-related hypogonadism or obesity.

Sponsors have interpreted the approved indication to include men, adult men with less defined etiologies of hypogonadism. Given this, we look forward to input from the FDA and the advisory committees today.

In addition to the labels, clinicians also inform their use of TRT based on expert guidelines such as those of the Endocrine Society, last updated in 2010.

Given the design and objectives of registration programs, these data are not the primary basis of our review. Rather, the data informing the discussion of benefits and

cardiovascular safety of TRT are based on the body of available literature. Also, to be discussed in our presentation are utilization data, which will be based on available information from various sources.

The objectives of the sponsor presentation today are to review available data regarding TRT for clinical benefits, cardiovascular safety, and utilization, and to provide our assessment. The sponsors will focus on product labeling, promotion, and education. We will also discuss ongoing and future research to study the benefits and risk in less defined populations such as patients with age-related hypogonadism.

I will now review our agenda and introduce our presenters. Dr. Adrian Dobs will present a clinical perspective on the benefits of TRT and the current approach to patient selection and management. Dr. Shalender Bhasin will discuss the data on cardiovascular risk and TRT. Finally, Dr. Rita Jain will summarize utilization data and close with the sponsor's assessment and proposals

for next steps.

When we turn to the question and answer period, we have other experts with us today, and their names are listed here. All non-industry speakers and invited experts have been compensated for their time and travel.

I would now like to invite Dr. Dobs to the lectern.

Industry Presentation - Adrian Dobs

DR. DOBS: Good morning. I'm Adrian Dobs, professor of medicine and oncology at Johns Hopkins University in the Division of Endocrinology and Metabolism. I treat adult males who have sex hormone disorders and conduct research in the area. Here are my disclosures. I am not speaking on behalf of Johns Hopkins University.

I will address three topics this morning. I will first give a brief overview of male hypogonadism, discuss the benefits of testosterone replacement therapy, and then present a clinical approach to the use of testosterone therapy in hypogonadal men.

Male hypogonadism is an endocrine disorder that is characterized by decreased testosterone secretion with or without decreased sperm production from the testes and signs and symptoms associated with androgen deficiency.

The causes of hypogonadism are classified as either primary or secondary. With primary hypogonadism, the cause is testicular defects when there's been some damage to or problem with the development of the testes. Secondary causes are due to hypothalamic or pituitary defects in which there is a deficiency or problem with gonadatropin-releasing hormone secretion from the hypothalamus or FSH and LH secretion from the pituitary gland. Thus, there is not the proper stimulation to the testes.

With combined hypogonadism, there is a problem in both the hypothalamic pituitary access and also in the testes. Examples of this include age-related decline in testosterone production. With aging, there is both a reduction in Leydig cell number and a problem with the responsivity of

the pituitary gland to hypothalamic stimulation by gonadatropin-releasing hormones.

Classical hypogonadism can be due to either congenital or acquired causes that lead to generally irreversible testosterone deficiencies. Examples of primary hypogonadism would include Klinefelter's syndrome, testicular trauma, and mumps orchitis. Examples of secondary hypogonadism include Kallmann's syndrome and pituitary tumors.

This slide lists conditions that can be associated with testosterone deficiency. Let us begin by discussing conditions where an evaluation for hypogonadism is merited with or without symptoms. For example, this would include men with a sellar mass, men receiving medication such as glucocorticoids or opioids or infertility.

On the other hand, there are some conditions that we have learned are also commonly associated with a reduction in testosterone levels. This includes men with end-stage renal disease on dialysis, type 2 diabetes, and moderate to severe COPD. In these situations, the pathophysiology is

not clearly defined, and an evaluation is merited in the presence of signs and symptoms consistent with hypogonadism.

The signs and symptoms of hypogonadism can be specific or nonspecific. On the left are those signs and symptoms that are generally considered more specific. These include impaired sexual development, reduced libido, and regression of secondary sexual characteristics, among others. Also specific for hypogonadism is an increase in fragility fractures and hot flashes.

The nonspecific symptoms of hypogonadism include reduced energy and vitality, low mood, and a reduction in muscle mass and performance. Increased body fat can be seen with hypogonadism as well.

The prevalence of symptomatic hypogonadism has been studied in various populations. Here is a summary of prevalence rates in three populations, starting from the 40-to-49 age range and going up.

In blue is the European Male Aging Study. They define hypogonadism as someone with a total

testosterone less than 320 nanograms per deciliter and three specific sexual symptoms. Because of the specificity of sexual dysfunction, they reported the lowest rates.

The BACH study defined hypogonadism as a testosterone level less than 300, a reduced free testosterone and at least one sexual symptom or two or more nonsexual symptoms, including sleep disturbance, depressed mood, lethargy, or diminished physical performance. Since nonsexual symptoms were included in the definition, prevalence rates were higher than the European Male Aging Study.

The Massachusetts Male Aging Study, in green, used criteria of testosterone less than 200 with three sexual or nonsexual symptoms. Some generalizations can be made. The first is that the prevalence of hypogonadism increases with age. The second is that the prevalence is variable based on the population study and the definition used. A very ill hospitalized population would have even higher prevalence rates.

Age-related decline in testosterone is a topic of great interest. The Massachusetts Study of Aging shows that in longitudinal studies, there was a decrease of 1 to 2 percent in testosterone per year after the age of 40. The Institute of Medicine, in 2004, concluded that there were insufficient data about giving testosterone replacement therapy to elderly men. This position is shared by the Endocrine Society, which has also recommended caution in treating this population due to the paucity of data.

Dr. Snyder has already discussed the T-trial, an important ongoing study to evaluate the potential benefits of testosterone therapy in elderly men with age-related decline in testosterone.

There are important limitations of the data on clinical benefits of testosterone therapy. There have been no large, long-term randomized clinical trials. The outcome measures in the trials to date are not hard clinical endpoints. For example, there is data on bone mineral density,

but none on fracture reduction.

Trials are heterogeneous in terms of inclusion and exclusion criteria, the indications for treatment, definition of low testosterone levels at baseline, and the symptoms of hypogonadism. The endpoints and study designs are also variable. The studies I will now review contain the best available data on the benefits of testosterone therapy, despite these limitations.

The potential benefits of testosterone therapy include improvement in bone mineral density, improvement in lean mass, reduction in fat mass, improved muscle strength and physical function, improved sexual function, improved mood, and the amelioration of fatigue. I will speak to key data from each, focusing primarily on meta-analyses of randomized trials.

Isidori looked at a meta-analysis of the five trials reporting changes in bone mineral density after testosterone therapy. Results that fall to the right of zero indicate an increase in bone mineral density due to testosterone therapy.

The overall treatment effect, shown in blue, was a significant 3.7 percent increase in lumbar spine bone mineral density. The meta-analysis also looked at femoral neck bone mineral density, but the observed difference was smaller and not statistically significant.

Isidori examined measures of body composition in a meta-analysis. This is of interest in that there is a decline in muscle mass as men age and also as men develop chronic diseases. So body composition may be an important variable for overall health and prognosis. The data on the top are those studies in which the average baseline testosterone was less than 288 nanograms per deciliter. The studies in the middle were those in which the average baseline level was greater than 288.

Then there are two studies at the bottom with glucocorticoid-treated patients. The overall pooled estimate is at the bottom. The effect was generally consistent across the three groups. The pooled treatment effect showed an increase of

1.6 kilograms from baseline or 2.7 percent of lean body mass. Isidori also reported a significant decrease in total fat mass of a similar magnitude to the increase in lean mass.

The important question that's asked when we discuss muscle mass is whether or not it translates to a functional improvement. The testosterone in older men with mobility limitations, or TOM trial, was a randomized, double-blind, placebo-controlled trial in frail, older, hypogonadal men to determine the effects of testosterone therapy on lower extremity strength and physical function.

The first measure, shown here, is change in leg-press strength. The mean increase was significantly greater in the testosterone group. There was also an improvement in chest-press strength in the testosterone group, but not in the placebo group. And next is a loaded stair climb power test. This was a statistically significant greater improvement in power in climbing stairs in the TRT group. This data would suggest that not only does testosterone increase muscle mass, but

that this translates into a functional effect.

Several randomized controlled trials have investigated the effect of testosterone therapy on erectile function. A meta-analysis of results are presented as the standardized mean difference. Benefits favoring testosterone therapy are to the right of zero. The hypogonadal population showed improvement on erectile function and there was no benefit in giving testosterone to a eugonadal or a mixed population.

The overall improvement was 0.8 in terms of the standardized mean difference between the testosterone and control, which is considered a large effect. Similar effects were also observed for libido and orgasmic function, but I will not cover these for the sake of time.

A meta-analysis of 16 randomized trials on the effect of testosterone therapy on mood suggests that TRT has a moderate overall effect on improving mood.

The observed effect was significant in hypogonadal men, but not in eugonadal men. It was

significant in studies where the mean age was less than 60, but not in studies where the average age is greater than 60. In an observational study of 799 men treated with testosterone, there was a 22 percent reduction in fatigue scores over six months. In a placebo-controlled study of HIV-infected men, a similar reduction was seen in fatigue scores over a period of 12 weeks.

While these data have limitations and are not conclusive, they suggest a potential benefit of testosterone therapy treatment in several areas in hypogonadal men, but not eugonadal men. Additional benefits data in men with non-classical hypogonadism is desirable.

This is the algorithm for evaluating hypogonadism that's been recommended by the Endocrine Society. For men with symptoms, the critical steps are to measure a morning testosterone and, if it is low, to exclude reversible causes, to obtain FSH and LH levels, to determine whether hypogonadism is primary or secondary, and to repeat the testosterone level to

confirm the low testosterone state.

The algorithm, which is commonly used, emphasizes the need for symptoms, repeat validation, and attempts to determine the etiology. Follow-up is crucial for anyone who is started on testosterone therapy. These are the treatment guidelines from the Endocrine Society. Symptom response and adverse events should be evaluated at three to six months and annually.

Testosterone levels should be measured at baseline and at three to six months. Hematocrit should be measured at baseline and be repeated three to six months and annually. This is particularly important in anyone who is treated with injectable testosterone since this mode of testosterone therapy administration is associated with erythrocytosis.

A bone mineral density measurement is recommended after the first one to two years. A digital rectal exam and a PSA should be performed at baseline and then again at three to six months.

In conclusion, testosterone therapy is well

accepted and indicated in men with classical hypogonadism. There is increasing appreciation that certain chronic diseases that may suppress the hypothalamic pituitary gonadal access might warrant consideration for treatment. The data on the benefits of testosterone therapy in patients with other chronic diseases, such as age-related hypogonadism, is limited and requires further study. Thank you very much.

Allow me to turn the lectern to Dr. Bhasin.

Industry Presentation - Shalender Bhasin

DR. BHASIN: Good morning. I am Shalender Bhasin, professor of medicine at Harvard Medical School and director of the research program in men's health, aging, and metabolism at the Brigham and Women's Hospital.

I have studied androgen biology for over 25 years and mechanisms of testosterone's actions in men and women. My remarks today will focus on my assessment of the relationship of testosterone therapy to the risk of cardiovascular events in men.

Here are my disclosures. I am not speaking today on behalf of the American Board of Internal Medicine, the Endocrine Society, Brigham and Women's Hospital, or Harvard Medical School. I have been compensated for my time and travel.

The risk/benefit ratio associated with testosterone therapy varies with the context of use. In young men with classical hypogonadism, due to known diseases of the testes, pituitary, and the hypothalamus, testosterone improves many symptoms of hypogonadism and is associated with low frequency of adverse events. In contrast, neither of the risks nor the benefits of testosterone therapy have been demonstrated in older men with age-related decline in testosterone concentration, or in elderly men with frailty, mobility limitations, or critical illness.

I will discuss the biologic plausibility, observational studies, and intervention trials, including meta-analyses of intervention trials. I will then synthesize these data and offer my concluding thoughts.

A number of pre-clinical and clinical observations support the biologic plausibility of a relation between testosterone administration and risk of cardiovascular events. Testosterone increases hematocrit. The increase in hematocrit is related to on-treatment testosterone concentrations and age.

Older men experience greater increase in hemoglobin and hematocrit than younger men. Testosterone administration reduces plasma HDL cholesterol. The reduction in plasma HDL cholesterol is related to dose and route of administration that is greater with oral administration than with parenteral administration and greater with non-aromatizable androgens than with aromatizable androgens.

Testosterone induces platelet aggregation, presumably by a stimulation of thromboxane a2. Testosterone administration is associated with salt and water retention, which could cause edema formation. In pre-clinical models, testosterone has been shown to promote smooth muscle

proliferation and increased vascular adhesion molecular expression.

Testosterone also has been shown to have potentially beneficial effects on the cardiovascular system. For instance, testosterone acts as a vasodilator by inhibition of L-type calcium channels, resulting in increased coronary and penile blood flow. Testosterone consistently decreases whole body, subcutaneous, and intraabdominal fat. Testosterone has been reported to reduce vascular reactivity and improve endothelial function. It also shortens QTc intervals.

Testosterone has been reported to increase both prothrombotic as well as antithrombotic factors. It has neutral effects on myocardial infarct size in pre-clinical models of myocardial infarction. Some pre-clinical and clinical observations are inconsistent across studies.

Testosterone has been shown to retard atherogenesis in some pre-clinical models, but not in others. Testosterone induces myocardial

hypertrophy in some mouse strains, but not in others. Some randomized trials have reported increases in blood pressure, but these data are not consistent across trials.

The effects of testosterone on insulin sensitivity are inconsistent across trials in severe models of androgen deficiency such as in men receiving androgen deprivation therapy, or in men experimentally rendered hypogonadal by administration of GnRH agonists or antagonists, there is an acute worsening of insulin sensitivity. However, the effects of testosterone on measures of insulin sensitivity in intervention trials have been inconsistent.

Thus, testosterone's effects in pre-clinical and clinical models are diverse. Some of these effects may be considered beneficial and others potentially deleterious. In aggregate, the association of testosterone with cardiovascular events seems biologically plausible.

I will now review observational studies. The relation of testosterone and coronary artery

disease in cross-sectional and prospective cohort studies has been inconsistent. Half of the cross-sectional studies have shown low levels of testosterone to be associated with increased risk of coronary artery disease, while others have shown no association.

The relation between serum testosterone levels and cardiovascular events has been inconsistent in prospective epidemiologic studies. A small number of epidemiologic studies have reported an inverse relation between testosterone concentrations and common carotid artery intima-medial thickness, a measure of subclinical atherosclerosis.

For example, in the Rotterdam studies shown here in this slide, the men in the lowest tertile of testosterone levels had greater progression of intima-medial thickness than men in the highest tertile of testosterone levels.

The relation of testosterone and mortality has been heterogeneous across studies. A meta-analysis of 11 studies by Araujo, et al. found

that, in aggregate, lower testosterone levels are associated with a higher risk of all-cause mortality, particularly cardiovascular mortality.

Epidemiologic studies can only show association, but cannot prove causality. Reverse causality cannot be excluded. It is possible that testosterone level is a marker of health. And those who are at high risk of dying have lower testosterone levels.

A rapid induction of severe androgen deprivation has been associated with development of insulin resistance and cardiometabolic risk. For instance, in this observational study of 37,000 men with prostate cancer in the VA, androgen deprivation therapy was associated with increased risk of diabetes, incidence of coronary heart disease, myocardial infarction, stroke, and sudden cardiac death.

Two recent studies performed a retrospective analysis of the association of testosterone administration with either mortality or cardiovascular events.

Vigen et al. conducted a retrospective cohort study to determine the association between testosterone therapy and all-cause mortality, myocardial infarction, and stroke in middle-aged and older men with low testosterone levels who underwent coronary angiography.

In the adjusted analysis, there was an increased risk of the composite endpoint for men receiving testosterone therapy after adjusting for the presence of coronary artery disease, but unadjusted analysis did not reveal this risk.

In contrast, Molly Shores and colleagues evaluated another subset of men within the VA system with low testosterone levels who received testosterone therapy during routine clinical care. After adjusting for age, body mass index, baseline testosterone, and other comorbidities, testosterone-treated men had a lower risk of death than untreated men.

Two additional studies have looked at the association of testosterone administration and cardiovascular outcomes. Finkle, et al. reported

on a retrospective cohort study of men before and after receiving testosterone therapy. They reported an increased risk of nonfatal myocardial infarction in the three months following a testosterone prescription than in the year prior to receiving testosterone prescription for patients who were 65 years of age or older and in patients younger than 65 who had a history of heart disease.

Baillargeon, et al. however found no increase as to myocardial infarction in a sample of male Medicare beneficiaries on testosterone therapy who were matched to beneficiaries not on testosterone therapy. In this study, testosterone use was found to be modestly protective, marginally protective, albeit, against myocardial infarctions among men at higher myocardial infarction risk.

These studies suffer from many limitations that are inherent in epidemiologic studies and in retrospective analysis of electronic medical records data. These studies included heterogeneous study populations and differed in the duration of intervention and study design. They used various

definitions and ascertainment of cardiovascular outcomes, treatment indications, treatment regimens, on-treatment testosterone levels, and exposure differed and was somewhat unclear from the publications.

These studies also suffered from a potential for residue or confounding and the patients assigned testosterone therapy differed from comparators in baseline cardiovascular risk factors. Because of these inherent limitations and inconsistency of finding across trials, across these studies, they do not permit strong inferences about the relation between testosterone therapy, and mortality, and cardiovascular outcomes.

I will now review the intervention trials and the meta-analysis of intervention trials. There are no published or ongoing trials that were specifically designed or powered to determine the effects of testosterone therapy on cardiovascular events. Two trials, however, deserve specific mention.

The testosterone's effects on

atherosclerosis progression in aging men, the TEAAM trial, is a three-year placebo-controlled randomized trial to determine the effects of testosterone administration on subclinical atherosclerosis progression using common carotid artery intima-medial thickness and coronary artery calcium scores. The T-trials that Dr. Snyder described have also been powered for efficacy, but not for safety outcomes or cardiovascular events.

Randomized clinical trials are inherently limited in their ability to determine the adverse events associated with drugs in clinical practice because the populations that are included in randomized clinical trials, by virtue of careful selection, often differ substantially from the individuals in whom the drug is actually prescribed after its approval.

The testosterone in older men with mobility limitation trial, the TOM trial, was an NIA-funded, double-blind, randomized, placebo-controlled trial to determine the effects of testosterone administration on measures of muscle performance

and physical function. The trial included 209 men, 65 years of age or older, with mobility limitation and total testosterone less than 350 nanograms per deciliter or free testosterone less than 50 picograms per mL.

These men were randomized to receive either testosterone or placebo for a duration of six months. Testosterone dose was adjusted to maintain testosterone levels between 500 and 900 nanograms per deciliter while maintaining blinding.

The trial was stopped early by its data and safety monitoring board due to a higher frequency of cardiovascular-related events in the men assigned to testosterone arm of the trial compared to the placebo arm.

The divergence in cardiovascular events continued throughout the six-month intervention duration and abated after treatment was discontinued. Overall, the cardiovascular events were small in number and variable in their severity and significance.

The TOM trial was not designed for

cardiovascular events. Accordingly, cardiovascular events were not pre-specified, were not collected in a standardized manner, and were not adjudicated prospectively. Also, there was some imbalance at baseline between the groups in cardiovascular risk factors.

We looked at the attributes of participants in the TOM trial that might have rendered them susceptible to cardiovascular events. There were trends toward higher free testosterone and estradiol levels in men with cardiovascular events. However, differences in hematocrit, blood pressure, plasma lipids, and other cardiovascular risk factors did not explain the difference between study arms.

A number of meta-analyses of randomized controlled trials have examined the association between testosterone therapy and cardiovascular events, major cardiovascular events, and death. There is considerable overlap in the studies included in each meta-analysis. Note that many of these meta-analyses show point estimates greater

than 1. However, most meta-analyses, with the exception of that performed by Dr. Xu, have not shown a statistically significant association between testosterone and cardiovascular events, major cardiovascular events, or death.

These meta-analyses are limited by the heterogeneity of randomized trials included in these analyses. The trials were heterogeneous with respect to eligibility criteria, testosterone dose and formulation, and intervention durations. The variable quality of adverse event recording in clinical trials has been well-documented and was particularly apparent in these trials, which reported a very low frequency of all adverse events as well as cardiovascular events.

The small size of many trials and the inclusion of pilot studies with very small sample sizes was another constraint. Cardiovascular outcomes were not prespecified. They were often defined post hoc and were of varying clinical significance. The major cardiovascular events were not adjudicated, not specified prospectively, and

the total number of major cardiovascular events was too small to draw strong inferences.

Therefore, the available data from randomized clinical trials are insufficient to establish a causal link between testosterone therapy and cardiovascular events.

Conclusion. It is important to distinguish classical hypogonadism in young men with known diseases of the hypothalamus, pituitary, and testes from age-related decline in testosterone concentrations. In young men with classical hypogonadism, due to known diseases of the testes, pituitary, and the hypothalamus, testosterone therapy improves some symptoms and the frequency of adverse events is low.

In older men with age-related decline or in elderly men with mobility disability or frailty, neither the benefits nor the risks of testosterone therapy have been clearly demonstrated. To more clearly understand the risks of testosterone therapy in these populations, we will need larger randomized clinical trials and prospective

mechanisms for tracking of adverse events, particularly cardiovascular events and major cardiovascular events.

Both approaches will be necessary, as they provide complimentary information, and because populations that are included in randomized clinical trials often differ from those in whom the medication is used in clinical practice.

Thank you. I will now turn the podium over to Dr. Jain.

Industry Presentation – Rita Jain

DR. JAIN: Thank you, Dr. Bhasin.

Good morning. My name is Dr. Rita Jain, and I am the vice president of Men's and Women's Health and Metabolics at AbbVie. Dr. Dobs and Dr. Bhasin have reviewed the available information on the potential benefits and cardiovascular safety profile of TRT.

I would now like to turn to a discussion of utilization data for TRT, and then provide a summary of the sponsor's presentation, and then make proposals for next steps. Let me begin with

the utilization data.

A review of the total number of TRT prescriptions dispensed annually, from 2000 through 2013, shows an approximately ninefold increase over this interval. In 2013, the last full year of data, a total of 7.5 million prescriptions were written and 2.3 million individuals received TRT.

An analysis by a prescribing physician in this interval indicates a modest increase in the number of prescriptions written by endocrinologists and urologists and a more pronounced increase among primary care physicians.

In 2013, endocrinologists and urologists combined wrote approximately 20 percent of all prescriptions. Primary care physicians wrote approximately 60 percent of all prescriptions and a mix of other specialties together make up the remaining 20 percent.

We also evaluated the use of TRT in 2013 by age group. Men age 45 to 54 and 55 to 64 combined received the highest portion of TRT prescriptions, constituting approximately 60 percent of the total.

Men younger than 45 years old received approximately 20 percent of all prescriptions and men over 65 accounted for the remaining 20 percent.

Use of TRT by age group over time was also evaluated from 2009 to 2013. In this interval, increases in the number of prescriptions were seen in men age 35 to 44, 45 to 54, and 55 to 64. Increases in the number of prescriptions was also observed in men under 35, however, the total number of prescriptions in these men was small. For men over 65, there was a modest change in the number of prescriptions over the last several years.

There is limited direct information of the specific etiology of men's hypogonadism before beginning TRT. However, to improve our understanding of these etiologies, we used a large U.S. medical and pharmacy claims database to identify the most frequent diagnoses in men receiving TRT.

This review included data from 2006 through May 2014 and evaluated close to 3 million diagnostic codes. These diagnostic codes are not

unique to an individual patient, and, therefore, an individual may have more than one code. The top diagnostic codes are presented here.

Of this list of diagnostic codes, the term "other testicular hypofunction" directly identifies hypogonadism. Of the remainder, the diagnostic code of malaise and fatigue may represent a symptom of hypogonadism. Other common diagnoses included hypertension, hyperlipidemia, routine exam, and unspecified chest pain.

The sponsors reviewed available data on the frequency with which pre-treatment serum testosterone levels are obtained. Our findings show a range of values but generally agree with the 72 percent figure reported by FDA in their briefing document.

Specifically, in approximately 10,000 patients treated with TRT in the Kaiser Permanente system, 91 percent of patients had baseline levels of serum testosterone prior to starting therapy. Additionally, two large U.S. medical claims databases, Truven Marketscan and Clinformatics Data

Mart, reported that 60 and 75 percent of men respectively had a serum testosterone measurement prior to treatment.

Of the men who had a baseline testosterone levels determined, we do not know what proportion of the men had their testosterone levels collected in the morning as recommended or had a second confirmatory test of testosterone. Furthermore, we were unable to determine the proportion of men who had post-treatment testosterone levels evaluated.

Lastly, in a separate analysis of treatment duration, the data indicate that the median length of treatment for testosterone products is between three and four months.

In summary, utilization data for TRT shows a consistent increase in use from 2000 through 2013, with PCPs accounting for a majority of prescriptions. Men aged 45 to 64 years old received 60 percent of all prescriptions. And the median duration of use is three to four months.

The data are variable on the frequency of testing for certain testosterone levels prior to

therapy, and there is insufficient data to characterize post-therapy testing of testosterone levels. Lastly, the reason for initiating TRT is not well characterized.

Now that we've discussed utilization data for TRT, I will provide a summary of the sponsor's presentation and proposals for next steps. To date, in order to gain approval for a testosterone replacement product in the U.S., registration trials have been required to show that a product raises testosterone levels to the eugonadal range and that it is safe for use in hypogonadal adult men.

These studies generally include 100 to several hundred men. Given the design of the registration programs, the body of data on clinical benefits and cardiovascular safety is primarily derived from the literature. Also, the Endocrine Society clinical practice guidelines synthesize available information and offer guidance on appropriate use to inform clinical practice.

For classical hypogonadism, a favorable

benefit/risk profile for TRT is well accepted. For less-defined populations such as age-related hypogonadism, the data is insufficient to support a consensus for the benefits of TRT.

As I discussed, the use of TRT has increased, and we assume that increase includes these less-defined populations. As for the reasons for the increased use of TRT, we can't quantify the contribution of each factor, but some of the factors that we believe have contributed to this increased use are approval of multiple new products, sponsor promotional activities, including direct-to-consumer advertising and disease-state awareness, non-pharmaceutical promotional activities such as low-T clinics, and potentially the availability of professional guidelines.

The cardiovascular risk profile in hypogonadal men receiving TRT was discussed by Dr. Bhasin and was also reviewed by the sponsors. The sponsors recognize that there are limitations in available data to address the potential association of TRT use and cardiovascular risk.

However, based on the review of the available literature, we find insufficient evidence to support a causal association between testosterone use and an increased risk of cardiovascular events.

Before turning to proposals for next steps, I want to review some ongoing activities that may facilitate and inform future research. Several sponsors, including AbbVie and Lilly, have ongoing efforts to develop validated patient-reported outcomes instruments. If validation efforts are successful, these instruments may be useful for future studies of benefits.

Over the next two slides, I will review some ongoing randomized controlled trials and epidemiologic studies. There are three ongoing randomized placebo-controlled trials I would like to highlight. The T-trial is an independent conducted one-year study, partially sponsored by AbbVie.

The study is designed to characterize the benefits of TRT in men over the age of 65 with age-

related hypogonadism. This trial is expected to add considerably to our understanding of the benefit of TRT in age-related hypogonadism, although we recognize it will not address all of the open questions.

Eli Lilly is conducting a study to measure the effects of TRT on sexual function and energy over a three-month period with an additional six-month open-label extension. The study is evaluating men with confirmed low testosterone and at least one symptom of androgen deficiency.

The TEAAM trial is an independently conducted study sponsored by AbbVie that will examine the effects of TRT on subclinical atherosclerosis progression in older, hypogonadal men over a three-year period. All of these trials are completed or close to completion and reports are expected by the first half of 2015 or sooner.

There are also three large ongoing NIH-funded epidemiologic studies of TRT and cardiovascular risk. The studies are being conducted in various large healthcare databases,

including medical e data, and are expected to be completed in mid-2015.

These studies are not expected to resolve the question of TRT and cardiovascular risk, but the results may add to our understanding of the potential association between TRT, and cardiovascular events, and MACE in particular.

Finally, I would like to turn to proposals for next steps. The sponsors can only provide directional responses today. This is due to a number of reasons, including the fact that only some of the sponsors currently have marketed products. Also, specific actions on label changes or future research activities will need to be discussed by individual sponsors with FDA.

In the near term, sponsors are committed to individually working with the FDA to discuss modifications to product labeling, promotion, and education. AbbVie and other sponsors, including Auxilium, Endo, and Upsher-Smith propose working with FDA to change specific areas of the label.

These proposed label changes include

addressing the limitations of data for TRT in less defined populations, including age-related hypogonadism and incorporating elements of professional society guidelines for testing and monitoring of testosterone levels into the label.

Lilly will engage with FDA to re-assess the label, including the proposals above, in the context of the forthcoming Lilly clinical trial data. The sponsors will modify promotional and educational activities according to any changes introduced into the label. Also, individual sponsors will further educate healthcare providers, especially primary care physicians on selection, diagnosis, and management.

We anticipate that future research designed to address the topics considered by these committees would include consultation with FDA, external experts, and individual sponsors. The objectives of any study would need to be carefully defined. This would include consideration of the appropriate study population and experimental design.

Data that would bear on these questions, such as results from the T-trials and the other studies I mentioned are expected to be available by the first half of 2015 or sooner. These results will influence the research approach to further studies on benefits and cardiovascular risks of TRT in men with age-related hypogonadism.

In closing, the sponsors remain committed to working with FDA and other stakeholders such as professional societies to provide relevant information regarding TRT to clinicians and patients so that they can make informed treatment decisions.

Thank you for your attention. We are now prepared to respond to questions.

Clarifying Questions to Industry

DR. JOHNSON: Thank you for your presentations. Now, we can present clarifying questions to our guest speakers. Please state your name for the record and, if you can, direct the question to a specific presenter. Dr. Braunstein?

DR. BRAUNSTEIN: Glenn Braunstein. Two

questions. First one to Dr. Bhasin. Since testosterone is aromatized estradiol, let's turn to the example that we have from the Women's Health Initiative Study. There is a timing hypothesis that has been demonstrated in animals and also in reanalysis of the WHI data that says that if you give estrogens to a woman at the time of menopause, it may have either neutral or protective effects from a cardiovascular standpoint, whereas if you give it to an individual who already has established atherosclerosis, let's say, after the age of 60, that may bring about some instability of the atherosclerotic plaque and may lead to an increase in the number of coronary events.

Since testosterone is aromatized estradiol, is it plausible that individuals with well-established atherosclerosis are going to be more susceptible to the effects of testosterone via aromatization as far as causing cardiovascular events through increasing plaque instability?

DR. JAIN: Dr. Bhasin?

DR. BHASIN: Thank you, Dr. Braunstein.

It's certainly plausible that men with preexisting coronary artery disease, or with certain comorbid conditions, or very old individuals may be more susceptible to cardiovascular events than younger men or middle-aged men. We don't have data to sort this out clearly from the available randomized trials, but it's certainly plausible.

DR. BRAUNSTEIN: Dr. Jain, since the industry sponsors have agreed that there is very little data as far as efficacy and late onset of testosterone for treating late onset hypogonadism, and certainly there's confusing data as far as safety. Until this gets sorted out, are they willing to stop directly consumer advertising of this?

DR. JAIN: Ms. Rockney will address that question.

MS. ROCKNEY: Tracy Rockney, AbbVie regulatory affairs. The sponsors concluded direct-to-consumer advertising, sponsors that were doing direct-to-consumer advertising in June of this year. Until we have the opportunity to

clarify product labeling with FDA, sponsors will work with FDA, specifically the Office of Prescription Drug Promotion, as we currently do, to decide on any new direct-to-consumer promotion.

DR. JOHNSON: Dr. Burman?

DR. BURMAN: Thank you. Just a point of clarification for Dr. Bhasin. On slide CO-46, where you're discussing lower testosterone levels associated with higher all-cause mortality in a meta-analysis, can you make a general comment about the populations studied? Were those patients with a bona fide hypogonadism with pituitary tumors primary or secondary hypogonadism, or did they include the patients with age-associated decrease in testosterone?

DR. JAIN: Dr. Bhasin?

DR. BHASIN: Dr. Burman, these meta-analyses included epidemiologic cohort studies, so these are community-dwelling men. These were not patients with specific disorders. We do not know whether the men included in these studies had specific disorders of the testes, pituitary, or the

hypothalamus.

DR. JOHNSON: Dr. Lincoff?

DR. LINCOFF: Thank you. Michael Lincoff. For Dr. Bhasin or others, relating to the cardiovascular safety, you acknowledge that the data is insufficient -- or you state that it's insufficient evidence to support a causal association, but I think it's fair to say that it's also insufficient to refute or rule out.

As a point, the one randomized trial and the meta-analyses, most, at least have a signal. Their numbers are small and you wouldn't expect them to be statistically significant, but the larger of the meta-analyses had the signal in support of a cardiovascular risk.

The number of events, if you recall, for the endocrine guidance, for diabetes, for example, to rule out a 1.8 hazard ratio would be 122 events and 600 events to allot the 1.3. So none of these are anywhere near the number of events.

So the upcoming trials, the T-trial and the TEAAM trial, appear to be followed for one year or

three years, which might develop as something of a database of events, but I don't know -- first of all, the numbers of patients in the two, 788 and 309, a thousand patients, except in the most ultra-enriched population for cardiovascular risk, would not be sufficient to even get you 122 events over these time periods.

Can you give us some characterization of what the populations are in those trials with regard to what their cardiovascular risk is, and also whether or not there's a systematic ascertainment and adjudication of cardiovascular outcomes in those trials, beyond the calcium score and the IMT, in a manner similar to what's been required for the diabetes drugs from the endocrine guidance?

DR. JAIN: I'm going to ask Dr. Mohler to talk to the T-trials, and then Dr. Bhasin to talk to the TEAAM trial.

DR. MOHLER: Thank you. I'm Emile Mohler. I'm a cardiologist at the University of Pennsylvania and current investigator on the

T-trial. So to answer quickly the last question you had regarding event adjudication, absolutely those events are being adjudicated up front and have now been prospectively defined. So hopefully that will eliminate some of the issues regarding some of the other studies.

I totally agree that the T-trial, at least the cardiovascular section, is not geared to looking at cardiovascular events overall. It's not large enough. But we are looking at, with CT angiography, plaque size as well as plaque consistency to see if there's infected testosterone, either beneficial or harm in this particular study.

DR. LINCOFF: And the entry criteria, are they somewhat enriched for patients selected to be at high risk or not?

DR. MOHLER: The entry criteria are the general population of men with low T. So we're looking at patients who would volunteer to be in the cardiovascular study as part of the larger study.

DR. JAIN: I'll ask Dr. Bhasin to speak to the TEAAM trial.

DR. BHASIN: In the TEAAM trial, the inclusion criteria required men to be 60 years of age or older and have low total or free testosterone concentrations. The trial started in 2004. It predated the findings of the TOM trial. After the findings of the TOM trial became known, the IRB and the DSMB required exclusion of men who had had recent cardiovascular events or were at higher risk of cardiovascular events.

So by virtue of the inclusion and exclusion criteria in ongoing randomized trials, we have excluded men at high risk of cardiovascular events. And this reaffirms my earlier assertion that in addition to randomized controlled trials, which by virtue of what we know at this time are not likely to include people at high risk because of the IRB concerns, we will need observational prospective mechanisms to track adverse events, particularly cardiovascular events and major cardiovascular events. I think we'll need both, the complementary

data from both.

DR. JOHNSON: We are now at the point where we would take a break, but these are important questions, so we're going to continue on. We still have five more questions. Next, Dr. Howards?

DR. HOWARDS: Stuart Howards. We have obviously many unknowns, but there is one unequivocal known, and that is that providers need education. The prescribing providers need education in this area.

So my question for industry is, in other areas, when you've tried to educate providers, how effective has it been, and what are the outcomes of the attempt to educate providers?

DR. JAIN: Dr. Rivas will respond.

DR. RIVAS: In our educational activities, materials, and programs on this topic of testosterone replacement, sponsors have emphasized the identification of the proper symptoms and signs as, for example, captured in the Endocrine Society Guidelines, the proper testing, diagnosis, identifying treatment options, and then

subsequently, as Dr. Dobs pointed out, monitoring.

Some sponsors have conducted assessments such as focus groups, surveys, and other tools of observations of physicians actually in practice to monitor whether there is good understanding of some of these concepts. And at least some sponsors have evidence that, when it comes to doing testosterone monitoring or diagnosis, testosterone level prior to initiation of therapy, there is good receptivity, and in one of the sponsor's data or surveys, about over 90 percent of the physicians that the sponsors are educating are doing at least one testosterone level.

DR. JAIN: I think if I might add to that, the recommendations that we had the sponsors to have a conversation with FDA regarding labeling modifications, partly to include elements of professional society guidelines for testing and monitoring of testosterone, we do think having some of those elements incorporated into the label and then reflected further in other activities could add to these educational proposals.

Also, we've noted that a number of managed care organizations have set up various algorithms within their systems that seem to be effective in some settings, at least to ensure monitoring of testosterone levels. And so we are evaluating those tools to see if we could also, as industry, utilize those to further facilitate proper testing and monitoring of patients.

DR. JOHNSON: Dr. Chai?

DR. CHAI: This is questions for Dr. Bhasin. Oh, I'm sorry. Toby Chai. Minor question for Dr. Bhasin on his slide showing the TOM trial, the trends towards higher testosterone and estradiol levels in men with CV events, I presume these are pre-randomization levels, not post-randomization. Could you please clarify?

DR. JAIN: Dr. Bhasin?

DR. BHASIN: The slide was making the point that on treatment, free testosterone concentrations and estradiol concentrations tended to be higher in men who had cardiovascular events than in men who did not have cardiovascular events. And therefore,

monitoring of on-treatment testosterone concentrations, we believe, can be useful and is necessary.

DR. CHAI: Can I just follow up? I'm sorry. So these were measurements done after randomization, then, at some point after randomization.

DR. BHASIN: That is correct. These were on-treatment testosterone concentrations that were drawn two weeks after initiation of testosterone therapy. And then they were measured at additional time points, and this reflected the average free testosterone and estradiol concentration on treatment.

DR. JOHNSON: Dr. Adler?

DR. ADLER: Robert Adler. I have a question for Dr. Jain. I was struck by the short median duration of treatment from the various reviews of administrative databases. I would think that both -- at least the Kaiser and the Truven databases would be adequate for you to tease out those patients who have classical hypogonadism from

those who have the hypogonadism associated with aging and determine what duration of treatment is for those who have the less-established reasons for their low testosterone levels.

DR. JAIN: Yes. And we can show you data in regards to duration of treatment by individual products. In terms of looking at various databases to understand which patients are being treated for how long, that is certainly a possible exercise to undertake. What we did not do in preparation for this meeting was a patient-level medical record study to really understand what a clinician was doing in terms of evaluating the patient, the diagnoses, and then following the patient over time.

So that is something that can be done, and we're open to considering that. We just do not have that information available today.

In terms of duration of use, this is just a slide indicating duration of use by individual products over 12 months. And as you can see, the median duration of use is three months. There is a

proportion of men clearly that continue on therapy over the 12 months with a range of 10 to 37 percent at the end of 12 months.

So clearly, there is a subset of men that continue on therapy for more extended periods of time. There is limited data on why men discontinue therapy. There is a small study done that indicated that some of the reasons do include cost of therapy as well as lack of efficacy. But clearly, for a subset of men, they are continuing on therapy also.

DR. JOHNSON: We'll have three more questions, and then any other questions from the advisory committee, we will save until our open opportunity towards the end of the meeting.

Dr. Garnick, did you have a question, sir?

DR. GARNICK: Yes. I'm struck by the fact that 25 to 28 percent of men who are initially prescribed testosterone don't have a baseline testosterone value. I've got two questions. Number one, have there been any payers that have refused to reimburse the prescription? And do we

have any data on the percentage of patients who do get a baseline testosterone value? Do we actually have any data on the percentage of patients who actually get a follow-up testosterone value?

DR. JAIN: Yes, very important questions. In terms of follow-up testosterone values, we do not have a good set of data to present to you today. We recognize, though, that, that is a critical activity, ensuring that testosterone levels are measured for an individual while on therapy. It is critical to do to ensure that they are not having excessive levels of testosterone and so forth. And so it's an area that we think we do have to focus on with FDA, possibly through labeling, but certainly education.

Coming back to your first point -- and we can look for further details to provide after the break -- what I am aware of is there are a number of managed-care organizations that do require testosterone levels to be performed prior to the product being dispensed, but I don't have more details than that available at the moment.

DR. GARNICK: One follow-up question. Has there been any effort to look at the individual testosterone values in those patients who have had a cardiovascular event? There was data presented on populations, but do we have actually any individual specific data on those patients that suffered the cardiovascular events to see what their T levels were at the time of the event?

DR. JAIN: I'm afraid we don't have information from those trials on that point.

DR. JOHNSON: Dr. Teerlink?

DR. TEERLINK: I'm John Teerlink, and I have two questions, one for Dr. Bhasin or whoever is willing to address it, and then one for Dr. Jain. So perhaps we'll start.

What's the state of the PRO instrument and where is that in terms of its production stage? And is it being implemented in any of the ongoing trials?

DR. JAIN: Yes. And let's start -- I'll have Mike Miller speak to the AbbVie PRO instrument, and then Kraig Kinchen speak to the

Lilly. Mike?

DR. TEERLINK: So you've developed these instruments independently as opposed to --

DR. JAIN: Yes. These have been ongoing efforts by individual sponsors over several years.

DR. MILLER: Thank you. Mike Miller, AbbVie clinical development. As was mentioned before, the draft guidance for the PRO instruments was released in 2006. It was finalized in 2009. Since that time, we've been working with the FDA to come up with a validated instrument. Essentially, for those of you that don't know the steps of the creation and validation, you go through a certain level of qualitative research where you come up with the questions, and then you make sure those questions accurately reflect the signs and symptoms that patients experience.

Then you go through a phase of quantitative validation where you assess some of the men's symptoms and signs on treatment and see what questions may need to be dropped over time and so forth.

As you can guess, this is an integrated process that's done over time, and several meetings are required along with the FDA that takes the time.

DR. KINCHEN: Kraig Kinchen, Eli Lilly. Based on qualitative interviews with hypogonadal patients, we developed two instruments to look at two of the more important symptoms of hypogonadism. One instrument is the hypogonadism energy diary, to look at patients with energy. And the second instrument is the sexual arousal interest and drive instrument. Both of those instruments are incorporated in our current clinical trial. The last patient visit for that will be next month, and we hope to have the data available in 2015.

DR. TEERLINK: Thank you.

DR. JOHNSON: Dr. Alexander? Go ahead.

DR. TEERLINK: Dr. Bhasin, I was wondering -- or whoever. There seems to be -- I am caught with more cognitive dissonance here. And this is something that we hear in many of these kind of meetings, where there is, "Well, we can't

do this trial because the IRB won't let us do it." And in this case, it's strange because, on the one hand, it seems like the sponsor and industry perspective is that we really don't know whether there is this cardiovascular signal or not. And then there's the -- you're suggesting, I think, that the IRBs would be reluctant to do a trial because they are so convinced that there is a cardiovascular signal in this group, that they wouldn't allow a trial to be done.

So it sounds like the sponsors have equipoise on this point, and usually sponsors and investigators can promote those kind of trials.

DR. JAIN: Dr. Bhasin can add, but to clarify, I think he was referring to a specific trial. We certainly, the sponsors, as we discussed in terms of future research, do think there is additional information to be obtained, and we do think there are ways to design appropriate studies. And part of the dialogue today and following today will include what that may look like.

So certainly, we were not suggesting that

it's infeasible. I think Dr. Bhasin was referring to a specific study in a specific dialogue.

DR. TEERLINK: That addresses it. That's fine. It's up to you if you want to address it. You're welcome to.

DR. BHASIN: The point that I was trying to make was that, in randomized trials, we have excluded, by virtue of our inclusion and exclusion criteria, men who are at risk for prostate cancer and who have had recent cardiovascular events in the last six months.

So the populations in which testosterone is being prescribed will necessarily differ from those in whom the randomized trials are conducted.

DR. TEERLINK: The reason you excluded those patients was?

DR. BHASIN: That in light of -- the reason for that is that we did not know whether testosterone increases the risk of clinical prostate cancer or the risk of cardiovascular events. And in the wake of the TOM trial, in conversation with the DSMBs of other ongoing

trials, and in conversations with the IRB, this was the trade-off that was agreed upon. And we thought this was reasonable, that we should exclude individuals at high risk of prostate cancer, as well as individuals who have had recent cardiovascular events.

But even getting beyond testosterone, I think, in general, the randomized clinical trials are not the most optimum ways of establishing safety. They are designed optimally for efficacy because the populations in which the drugs are used differ necessarily from those in which the randomized clinical trials are conducted because RCT populations are constrained by inclusion and exclusion criteria, which don't always apply to patients in which the drug is used.

DR. TEERLINK: I think we'll have to agree to disagree on that point because I think RCT is probably the only way to actually effectively establish safety. It's just that we have been too conservative in how we've been finding our RCTs and thinking more of efficacy rather than actually

designing RCTs for safety.

DR. JOHNSON: Dr. Alexander, for our last question?

DR. ALEXANDER: Thank you. Richard Alexander. As we consider potentially creating some very large and very long randomized trial, I am curious to know the frequency and the management of dropouts in the studies to date. I can envision that people who believe they're on placebo become frustrated and say I just don't want to continue this. And I'm wondering if that may be an issue in recruitment for a large study, and also if that could be viewed as an endpoint of the so-called informative missingness.

DR. JAIN: I think the challenge we have in responding to that question is we have been talking about a body of literature, multiple studies. And so we could look at dropout rates in a few select studies, but I don't have a good figure to provide you as a general for those studies.

DR. JOHNSON: Thank you again to the sponsors for answering these questions. We can ask

additional questions when we have another opportunity to do so.

We will now take a 10-minute break. Panel members, please remember that there will be no discussion of the meeting topic during the break, amongst ourselves, or any members of the audience, and we will return at 11:08.

(Whereupon, a recess was taken.)

DR. JOHNSON: Thank you again for everyone in your involvement in this meeting. Now, we are going to move on to presentations by the FDA.

Dr. Mohamoud?

FDA Presentation - Mohamed Mohamoud

DR. MOHAMOUD: Good morning. My name is Mohamed Mohamoud. I am a drug-use analyst in the Division of Epidemiology, the Office of Surveillance and Epidemiology. The title of my talk today will be Testosterone Replacement Therapy and Drug Utilization Patterns.

The purpose of this presentation is to summarize recent trends in drug-use patterns of testosterone products. The outline of the

presentation will be as follows. First, we will discuss national sales of distribution of testosterone followed by patient utilization of testosterone with a focus on outpatient retail setting.

We will then present our findings on the concurrent use of cardiovascular medications among testosterone users as well as indications of use for testosterone.

We will also present our analysis of the occurrence of laboratory testing of testosterone and a duration-of-use analysis. We will end our talk with the key findings, limitations, and conclusion. To conduct this analysis, we use several databases with various features. We will describe each database briefly before presenting the results of each section.

Testosterone products are dispensed in multiple settings of care, for example, retail pharmacies, mail-order pharmacies, hospitals, and clinics. For our sales distribution analysis, we use a database that captures sales of testosterone

products from meta-factors and wholesalers into the backdoor of settings of care.

These sales data are nationally projected to all settings of care. However, we have to emphasize that the results you're about to see represent sales of testosterone products from manufacturers to all settings of care, but do not represent actual patient use.

The graph here shows sales of active-ingredient testosterone in kilograms over time. The kilogram of active-ingredient testosterone is shown on the Y axis. We chose to use kilograms as our unit of analysis to account for the variety of formulations and changes in packaging size over time.

In 2013, a total of 14,000 kilograms of testosterone were sold to all settings of distribution. This is a 66 percent increase from 8500 kilograms in 2009. In 2013, topical testosterone products accounted for 71 percent of the total testosterone market, while injectable testosterone products accounted for 24 percent of

the testosterone market.

Topical testosterone products accounted for the majority of testosterone sales throughout the examined time. Both topical and injectable sales increased. However, injectable testosterone sales had the largest relative increase, almost doubling between 2009 and 2013.

Now, we will transition our analysis to the number of patients receiving a testosterone prescription in the outpatient setting. We focus our testosterone patient utilization on the outpatient retail setting because 72 percent of the testosterone sales were distributed in this setting between 2009 and 2013.

For this analysis, we use a database called Symphony Health Solutions, which captures U.S. adjudicated prescription activity across all payment types, including commercial plans, Medicare, Medicare Part D, cash, assistance programs, and Medicaid. These data are nationally projected to the outpatient pharmacy setting from a sample of over 40,000 pharmacies.

The graph shows nationally projected number of unique patients receiving a prescription for testosterone over time, stratified by sex. In 2013, 2.3 million patients received a prescription for testosterone from an outpatient retail pharmacy. Among these patients, men accounted for 97 percent or 2.2 million patients and women accounted for 3 percent or 58,000 patients.

The number of unique patients receiving a prescription for testosterone increased by 90 percent, from 1.2 million in 2010 to 2.3 million in 2013.

Here are the results of our patient utilization analysis, focusing on the male patients, stratified by age. Of the 2.2 million that receive the prescription for testosterone in 2013, 1.5 million were men between the ages of 40 to 64, accounting for the largest proportion of patients at 69 percent. Men between the ages of 40 to 64 also accounted for the largest increase in the number of patients from 850,000 patients in 2010 to 1.5 million patients in 2013.

Men between the ages of zero to 39 also doubled from 150,000 patients in 2010 to 300,000 patients in 2013. And men between the ages of 65 to 74 also increased from 180,000 patients in 2010 to 300,000 patients in 2013.

Men 75 years and older also increased by 38 percent, from 63,000 patients in 2010 to 87,000 in 2013. Please note that the trend lines for the age group zero to 39 and 65 to 74 are superimposed.

We also evaluated the extent of real-world concurrent cardiovascular medication use by testosterone users. We conducted this analysis by determining the proportion of patients receiving a testosterone prescription concurrently with at least one cardiovascular medication.

For this analysis, we use the same database we described earlier, which was used to determine the number of patients receiving a testosterone prescription.

In order to determine the number of testosterone users that are concurrently receiving a prescription for at least one cardiovascular

medication, we first identify testosterone products and a select group of cardiovascular medications by using national drug codes or NDC numbers.

We selected the following cardiovascular medication classes: anticoagulants, antiplatelets, antihypertensives, statins, and nitrates. Patients were considered to be on concurrent therapy with a testosterone product and a cardiovascular medication if there was an overlap in therapy based on the prescription for testosterone and at least one cardiovascular medication.

I should emphasize that our analysis did not assess whether the use of the cardiovascular medication began before or after the testosterone prescription.

The diagram on the slide shows one scenario of concurrent patients, where the cardiovascular medication was started before the testosterone therapy. Another scenario not displayed on the slide could be that the cardiovascular medication started after testosterone therapy.

Here are our results for the nationally

projected concurrent use of cardiovascular medications among testosterone users. Out of the 2.3 million patients who received a testosterone prescription in 2013, about 1.3 million also had a concurrent prescription for at least one cardiovascular medication. This accounts for 57 percent of patients who received a prescription for a testosterone product in 2013.

Now, we will transition our analysis to the reasons for which testosterone was commonly prescribed. To determine this, we use a database that contains data from monthly surveys of 3200 office-based physicians, representing 30 different specialties across the United States. These data are nationally projected by physician specialty and region and are helpful in characterizing the use of drug products in clinical practice.

Our results show that testicular hypofunction was the top diagnosis associated with the use of testosterone in men of all age groups. This is a non-specific diagnosis that does not enable us to determine the specific reason for

which testosterone was prescribed.

We also examined concomitant diagnosis, which are defined as other conditions that may or may not be treated during the visit in which the survey was filled. Hypertension was the top concomitant diagnosis in most patients that were being seen for testicular hypofunction.

In addition, among men between the ages of 40 to 64, which represent the largest number of testosterone users, diabetes was the second concomitant diagnosis.

Now we will transition to another database, which we used to conduct analysis of occurrence of laboratory testing for testosterone prior to and after initial testosterone prescription as well as a duration-of-use analysis. This is a commercial healthcare plan databases, which contains claims for 66 million covered lives under 100 health insurance plans.

This database captures all prescription procedure and medical claim activity covered by insurance. However, in contrast to data provided

in previous slides, these data are not nationally projected and only represent a sample of commercially ensured population in the United States.

To conduct this analysis, we first identified men that received their first prescription for testosterone after January 2008 through 2013. The patient sample after that was limited to those who had six months of insurance coverage prior to the first testosterone prescription and did not have a testosterone prescription filled during that time period.

This was done to limit our analysis to patients who could be considered new users. Laboratory testing conducted before or after the testosterone prescription was identified using the following procedure codes shown on the slide. Here are the demographics of the new male testosterone users identified in our inclusion criteria.

There were 240,000 patients identified in our sample, of which 73 percent or 177,000 were between the ages of 40 to 64, 15 percent between

zero to 39, and 9 percent between 65 to 74. As mentioned before, this is a commercial health plan database and underrepresents patients who are 65 years and older.

Out of the 240,000 testosterone users identified in our sample, 72 percent had a claim for testosterone testing prior to the first testosterone prescription while 21 percent of testosterone users had no claim for testosterone testing before or after the testosterone prescription. And 6 percent had a testosterone test after the initial testosterone prescription.

For patients who had a claim for testosterone testing prior to the first testosterone prescription, the claim for testing occurred at a median of 36 days before the first prescription. Of note, testing reimbursed outside the healthcare plan was not captured in this analysis.

Now we will describe how we conducted our duration-of-use analysis for testosterone. For this analysis, we used the same patient population

we used for our laboratory testing for testosterone. The days of supply, which refers to how many days the dispensed medication will last the patient, was used to define our treatment episodes.

This was done by linking the days of supply across consecutive testosterone prescription. We applied a grace period to account for delays in medication refilling, and our duration of use was determined by the sum of the treatment episodes.

Out of the 240,000 patients that met our inclusion criteria during our analysis time period, between 2008 and 2013, the average number of testosterone prescriptions per patient was 7. The number of treatment episodes were 4. The mean average duration of a single episode was 47 days with a median of 30. And the average duration of use over the five years we examined was 187 days or six months with a median of three months.

The variation between the mean and the median suggests that a small number of patients are using testosterone for a longer time period than

our median of three months.

The key findings from our national-level analysis are as follows. We observed increasing trends in testosterone sales and use. The majority of use was in a topical formulation. Both topical and injectable testosterone product increased over the examined time. And in the outpatient setting, the majority of users were men between the ages of 40 to 64. Large proportions of testosterone users were concurrently taking at least one cardiovascular medication.

The top diagnosis associated with testosterone was testicular hypofunction, and hypertension was the top concomitant diagnosis in patients seen for testicular hypofunction.

We conducted additional analysis in a sample of commercially-insured patients, where we found that 72 percent of testosterone users had a claim for testosterone-level test captured prior to the first prescription and 21 percent of users had no claim for testosterone-level testing captured before or after the first testosterone

prescription. The duration of use of testosterone was an average of six months.

The major limitation to our analysis are as follows. Our patient utilization is only nationally projected to the outpatient retail pharmacy setting and does not include utilization of testosterone in hospitals, clinics, or other settings of care.

Concurrent cardiovascular use, medication use was used as a surrogate for possible cardiovascular disease. And it's unknown if the cardiovascular medication use began before or after the testosterone prescription.

The nonspecific ICD-9 code associated with testosterone use does not allow us to assess the specific reason for testosterone prescribing. There were also limitations to our health plan claims analysis. Our analysis represent a sample of the commercially insured and underrepresents patients who are 65 years and older. And we did not have any testosterone lab values for testosterone testing analysis.

In conclusion, over the past few years, testosterone use increased in all age groups. A majority of testosterone use was in middle-aged men and the majority of testosterone use was for the topical formulation. However, topical and injectable products both increased. Thank you.

FDA Presentation - Trung-Hieu Brian Tran

DR. TRAN: Good morning. My name is Brian Tran, and I am a regulatory review officer at the Office of Prescription Drug Promotion at the FDA. Today, I would like to briefly discuss the regulations in prescription drug promotion, disease awareness communications, and product claim promotional materials.

So to start off, the mission of OPDP is to protect the public health by assuring prescription drug information is truthful, balanced, and accurately communicated. The Federal Food, Drug, and Cosmetic Act, also known as the FD&C Act, gives the FDA regulatory authority over the labeling and advertising of prescription drugs. Under the FD&C act, prescription drugs are considered misbranded

if, among other things, its labeling or advertising is false or misleading.

Prescription drugs are also considered misbranded if, among other things, its labeling or advertising fails to reveal material facts, including material facts about the consequences which may result from the use of the drug as suggested in the labeling.

So next, I would like to discuss about the different type of promotions, starting with disease awareness communications. Disease awareness communications are communications disseminated to consumers and healthcare practitioners and may discuss a particular disease or health condition.

Disease awareness communications may not mention any specific drug or make any representation or suggestion concerning a particular drug. Disease awareness communications can provide important health information and can encourage consumers to seek or healthcare practitioners to provide appropriate treatment. Unlike prescription drug promotion, disease

awareness communications are not subject to the requirements of the FD&C Act and FDA regulations. So next, I would like to show an example of a current disease awareness TV ad for low testosterone available at www.isitlowT.com.

(Video played.)

DR. TRAN: So I'm sorry that there's no audio at the beginning, so I'm just going to play it one more time so you can hear what the full video says.

(Video played.)

DR. TRAN: So just as a reminder, this is considered a disease awareness communication and is not subject to the requirements of the FD&C Act in FDA regulations.

So the next type of promotion that I would like to discuss is about our product claim promotional materials. Product claim promotional materials discuss the name of a drug and its benefits, including the indication and risks associated.

Product claim promotional materials must

comply with the FD&C Act and FDA regulations. Failure to comply with the FD&C Act and FDA regulations may result in, among other things, the issuance of a warning letter. Warning letters identify the violation such as problems with claims for what a product can do.

Additionally, warning letters also notify the company that they must correct the problem and provide directions and a time frame for the company to inform FDA of its plans for correction.

So in the guidance for industry, titled "Presenting Risk Information in Prescription Drug and Medical Device Promotion," language used in prescription drug promotion should be comprehensible to the target audience to be considered accurate and non-misleading.

So for example, promotional materials directed to consumers should convey benefits and risks in language understandable to consumers so that they are clear, understandable, and non-technical.

So next, I will be showing and discussing an

example of an enforcement action regarding the promotion of testosterone replacement therapy.

(Video played.)

DR. TRAN: So this was a video for Testopel pellets that resulted in the issuance of a warning letter on March 24, 2010. So please note that the following being discussed are not all of the issues cited in this warning letter. As you can see in the video, the video presents statements made by Dr. Abraham Morgantaler, in which he promotes the use of Testopel.

In the video, he states, "I specialize in sexual medicine and, in particular, work around testosterone." When we treat them, patients, and we get their levels back to normal, the guys come back and they say, "I feel normal again." Their strength may improve. Their workouts at the gym may get better. They start chasing their wives around the room a little bit. They just feel like guys again.

The totality of these claims misleading implies that Testopel can be used to treat sexual

dysfunction. FDA is unaware of any data to support these claims.

So in addition, the video also presents other statements made by Dr. Morgantaler, as well as a patient's testimonial about Testopel treatment. In the video, Dr. Morgantaler states, "I had a patient just the other day who was a golf professional. And he found he just wasn't hitting the ball as far. He had low testosterone." In the video, the patient states, "I was having trouble doing push-ups. I couldn't do more than five to six. And I tried and it really bothered me."

The totality of these claims misleadingly implies that Testopel has a positive impact on the enhancement of athletic performance of professional and nonprofessional athletes, such that Testopel can improve physical strength in these patients.

These claims are especially concerning because they contradict the Testopel prescribing information or PI. The warning section of the Testopel PI states, "This drug has not been shown to be effective for the enhancement of athletic

performance. Because of the potential risk for serious adverse health effects, this drug should not be used for such purpose."

Lastly, the video presents statements from the patient which include, "My symptoms are really slowing down. I was feeling old. Before this, my brain was slowing down, and I didn't want to do things, but now I've got a lot of get-up-and-go, and I want to do things all the time." These claims from the video imply that an outcome of treatment with Testopel is the ability for patients to resume their normal activities and lifestyle.

FDA is not aware of any studies that measured these outcomes or any other evidence to support such effects for Testopel treatment.

So as a result of these violations, as well as other violations from this video, a sales aid, and webpages, OPDP requested that the sponsor immediately cease the use of these materials cited in the warning letter and all promotional materials with same or similar violations.

OPDP also requested a list of promotional

materials that have been discontinued as a result of the warning letter. Because the violations described in the warning letter were serious, OPDP also requested that the sponsor submit a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in the letter to the audience that received the violative promotional materials.

So in conclusion, disease awareness communications can educate and encourage consumers to seek appropriate medical treatment. OPDP has received complaints regarding disease awareness communications for hypogonadism. However, these communications are not subject to the requirements of the FD&C Act and FDA regulations. Promotional materials for all prescription products, including testosterone replacement therapies, should comply with the FD&C Act and FDA regulations.

Over the past several years, there has been an increase in the submission of promotional materials to OPDP for testosterone replacement

therapy. The next speaker, Dr. Mark Hirsch, will be discussing the indication, target population, and efficacy endpoints for testosterone replacement therapies. I would like to thank the advisory committee panel and audience for their time and attention. Thank you.

FDA Presentation – Mark Hirsch

DR. HIRSCH: Good morning. My name is Mark Hirsch, and I am medical team leader in urology at CDER. And the topic that I wish to discuss today is current issues in testosterone drug development and the indicated population.

This is an overview of my brief presentation today. First, I will show the testosterone class indication. Next, I will discuss the current drug development paradigm for testosterone products. Then I will discuss how the current drug development paradigm impacts the indication and vice versa. Then I will revisit the indication and, finally, I will discuss challenges that we face in the current situation.

The following is the current class

indication and it is stated, "X is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone." Subsequently, specific conditions are listed under primary and secondary hypogonadism.

Under primary hypogonadism are listed cryptorchidism, undescended testicles, bilateral torsion, twisted testicles, orchitis, inflammation or infection of the testicles, vanishing testes syndrome, a syndrome in which the testes dose not manifest, orchiectomy, which is surgical excision of the testicles, Klinefelter's syndrome, a genetic abnormality, chemotherapy-related damage to the testicle or toxic damage to the testicle from alcohol or heavy metals. Under hypogonadatropic hypogonadism are listed specific pituitary or hypothalamic injuries from tumors, trauma, or radiation.

With this indication in mind, the basic premise of testosterone drug development is that testosterone products are to be used as replacement

therapy in men with specific hypogonadal conditions associated with deficient or absent testosterone.

With that in mind, FDA requires sponsors to demonstrate that a T-product reliably increases serum testosterone concentrations into the normal range for healthy eugonadal men. And therefore, the primary efficacy measures are pharmacokinetic assessments of serum testosterone concentrations.

For the current T replacement indication, FDA does not require demonstration of benefit by any clinical efficacy measure, and the rationale for this determination is that testosterone replacement in men with specific hypogonadal conditions is a long-accepted efficacious therapy.

I will now provide an overview in the next four slides of the current drug development paradigm for testosterone replacement therapy products. The foundation for most testosterone applications that we receive is a single phase 3 study with supporting evidence from phase 1 and phase 2 studies.

The phase 3 efficacy assessment is generally

based upon a limited duration of treatment and relatively few subjects. And I will describe those more in a few minutes. The phase 3 trial is often unblinded and uncontrolled.

Phase 3 safety data is usually not collected for more than one year and clinical efficacy endpoints such as measures of sexual desire, body composition, bone mineral density, muscular strength, and quality of life when they are assessed are considered exploratory endpoints and not formal endpoints for analysis.

The following are elements of a typical phase 3 testosterone replacement therapy study. The design is open label, single arm, and usually involves several periods. For a drug that is titratable, there is a dose titration period of 6 to 8 weeks followed by a stable dose period of 6 to 8 weeks and a safety extension period of 12 to 36 weeks. These are typical but not in every application.

The number of subjects is typically around 100, but may be up to several hundred in this

study. The eligibility criteria are adult hypogonadal males. These are the critical eligibility criteria, adult hypogonadal males with an average morning serum testosterone on at least two separate draws below the normal range. And that tends to be less than 300 nanograms per deciliter.

I would point out that, in most subjects, a specific etiology for hypogonadism is not known. Most of the subjects have idiopathic hypogonadism. And again, the efficacy endpoints are serum testosterone concentrations and we use the average serum testosterone concentration and a maximum serum testosterone concentration as endpoints.

Again, these are some additional elements of a typical phase 3 TRT study. The primary and critical secondary efficacy endpoints are listed here. The first is proportion of subjects with an average serum T within the normal range, and that tends to be set as 300 to 1,000 nanograms per deciliter. Success for that endpoint requires greater than or equal to 75 percent responders with

a lower bound of the 95 percent confidence interval of 65 percent.

In addition, we ask for a measurement of the proportion of subjects with a maximum serum T concentration outside of the normal range, and the three categories we have defined are Cmax greater than 1500 nanograms per deciliter, 1800 to 2499 nanograms per deciliter, and greater than or equal to 2500 nanograms per deciliter. And the limits of those are shown beside those.

We also assess secondary efficacy endpoints, including the major metabolites of testosterone, DHT, and estradiol, as well as other hormones listed on the slide. Safety endpoints are routinely collected, and these include clinical adverse events, physical examinations, vital signs, laboratories, such as chemistry and hematology, prostate-related parameters, and where appropriate application site assessments.

Based on the nature of the registration studies, as well as the indication, the intended population for testosterone replacement therapy

products are hypogonadal men with specific disease conditions associated with absent or deficient testosterone, for example, Klinefelter's disease, pituitary injury, and others of the conditions that I read earlier.

Product use data, however, shows a different real-world population, middle-aged men with low T, a condition that we refer to as age-related hypogonadism. Current product labeling does not include age-related hypogonadism or aging. However, current labeling may unintentionally imply such use by including the term "idiopathic gonadatropin" or LHRH deficiency, a physiological condition that does occur in older men.

Here, I am showing again the class indication. And under hypogonadatropic hypogonadism is listed idiopathic gonadatropin or luteinizing hormone-releasing hormone deficiency. To be clear, the current drug development paradigm is not capable of providing data that would support use for age-related hypogonadism. And the current indication is not meant to support specifically

testosterone replacement specifically for age-related hypogonadism.

The two main obstacles to including this use in labeling are the following. It is unclear whether the signs and symptoms in aging men that are purported to reflect hypogonadism, such as fatigue, diminished sexual desire, muscular weakness are a direct result of low T. But perhaps more importantly, the clinical benefit and safety of testosterone replacement for age-related hypogonadism has not been demonstrated by substantial evidence from adequate and well-controlled clinical studies.

Thus, there are both short- and long-term challenges related to this situation. In the long-term, evidence is needed to demonstrate that the signs and symptoms in aging males that are purported to reflect hypogonadism, such as fatigue, diminished sexual desire, and muscular weakness are a direct result of low T.

Again, more importantly, evidence from adequate and well-controlled clinical trials is

needed to show that testosterone replacement therapy provides clinical benefit, that is, improvement in signs and symptoms and is safe in an aging male population.

The designs endpoints, study durations, and sample sizes for these studies need to be carefully discussed, selected, and justified.

In the short term, it appears that current product labeling may not be sufficiently clear. The indication itself may need to be clarified and populations where efficacy and safety data are lacking, for example, in aging males, may need to be specifically stated.

Finally, conclusions based upon the limited data collected in current registration studies may need to be made clearer. Benefits that have not been demonstrated may need to be specifically stated.

Thank you for attention, and I I'll turn the podium over to Dr. Monique Falconer to discuss potential cardiovascular risks of testosterone replacement therapy.

FDA Presentation - Monique Falconer

DR. FALCONER: Good morning. I'm Monique Falconer, an epidemiologist in the Office of Surveillance and Epidemiology. The title of my presentation is "Testosterone Therapy and Cardiovascular Risk, the Evidence from Observational and Randomized Controlled Trial Data." Dr. Hirsch has just presented the current labeling and indications and the study endpoints assessed in clinical trials with testosterone to support approval.

He also presented the limitations of those trial designs in evaluating whether testosterone therapy is associated with cardiovascular events. My presentation will assess that association using postmarketing data as well as describe some of the patient characteristics which might be associated with testosterone therapy.

The objective of this presentation is to critically evaluate the published data, which consists of five observational studies and a meta-analysis of 27 randomized controlled trials.

These studies evolved the association of testosterone therapy and cardiovascular-related outcomes, or all-cause mortality, or both. The observational studies were identified from an FDA search of the literature, and this meta-analysis was reviewed due to the recency of its publication.

Before discussing the published studies, I'll first discuss the role of surveillance data in evaluating this issue. The FDA has been collecting spontaneous adverse drug reports, drug events since the 1960s. And since 2012, mandatory and voluntary reports sent to the FDA have been stored and retrieved via the federal adverse event reporting system database.

Spontaneous adverse event reporting systems are most efficient for detecting rare, clinically serious, and unknown or unlabeled adverse events. Given the high background rate for cardiovascular disease in older men, it is difficult to distinguish the role of testosterone versus other factors such as medical history, lifestyle, genetic predisposition, and reports of cardiovascular

events sent to the FDA in association with testosterone.

So due to these limitations, we would not draw any conclusions about drug-event causality from postmarketing reports of cardiovascular events with testosterone use.

To identify observational studies assessing the association between any testosterone exposure and cardiovascular outcomes, a PubMed search was conducted. The search used the terms testosterone, cardiovascular, myocardial infarction, stroke, mortality, and safety. And to capture all potential observational studies, we searched all article types published in the last 10 years.

The search was limited to the last 10 years because the bibliographies of the recently published studies and the Institute of Medicine's 2004 report on testosterone and aging did not list any relevant observational studies in the 10 preceding years.

The search yielded 1738 articles for further review, most of which were studies or reviews of

the effects of endogenous testosterone in men. There were also drug reviews, editorials, pre-clinical studies, and placebo-controlled randomized controlled trials.

Four suitable observational studies were identified from the literature search, including two that had already been identified. The fifth suitable study was published after this initial literature search.

In addition, an FDA librarian search for relevant observational studies, unrestricted by year, as well as additional searches using testosterone brand names and a search of the M-based database did not identify any additional observational studies.

The question of an association between testosterone therapy and cardiovascular events, and the strength of an association was explored in the reviews of the five observational studies and a meta-analysis of 27 randomized controlled trials. However, the question of a differential risk by age, preexisting conditions, or duration of

testosterone therapy was only explored in the review of the observational studies.

So what is the strength of association? From the five observational studies, the risk estimates were modest and contradictory. It is also important to note that the endpoints measured were also not uniform across the studies.

In addition, the integrated risk estimate in the meta-analysis of the 27 randomized controlled trials was also modest. Two of the observational studies showed an increased risk for cardiovascular with testosterone therapy. The Vigen study showed a 30 percent increased risk for the composite outcome, myocardial infarction, stroke, and all-cause mortality.

The Finkle study had a similar increased risk of 40 percent, but only for nonfatal myocardial infarction. And the confidence intervals barely excluded the null in both studies.

The Baillargeon study showed a 15 percent decreased risk for myocardial infarction leading to hospitalization with testosterone therapy, but that

association was not statistically significant. And finally, two of the observational studies showed a statistically significant decreased risk for all-cause mortality with testosterone therapy.

The Shores study and the Muraleedharan studies showed an approximate 40 percent and 60 percent decreased risk respectively.

This is the forest plot for the meta-analysis of the 27 randomized controlled trials. As you can see, the event rates are relatively low in most of the component studies. And also, there is not a consistent showing with point estimates. Most are spread across both sides of the null and all but one of the confidence intervals include one.

A fixed-effect meta-analysis was used to integrate the results and estimated that testosterone therapy increased the risk for cardiovascular-related events by 50 percent. In addition, to account for possible publication bias or selective reporting, a trim and fill analysis was done. And the revised odds ratio was 1.7, with

a 95 percent confidence interval of 1.2 to 2.4.

Is their risk different by age? We concluded that age might be an important effect modifier with testosterone therapy. In the Finkle study, while the overall risk for nonfatal myocardial infarction was small, age at baseline appeared to be an important effect modifier for therapy, with a doubling of the risk for men over the age of 65 years old.

In the Shores study, there seemed to be a greater reduction in all-cause mortality with testosterone therapy in men less than 60 years old. However, the interaction effect was not statistically significant.

Is there a risk difference for pre-existing conditions? We concluded that preexisting cardiac disease might be an important effect modifier with testosterone therapy.

In the Finkle study, while the overall risk was small, age and heart disease status at baseline appeared to be important effect modifiers with testosterone therapy.

Men less than 65 years old with a history of heart disease and men over the age of 65, irrespective of heart disease have a doubling of the risk for nonfatal MI with testosterone therapy. In the Vigen study, there was no difference in the effect size of testosterone therapy on the composite outcome of myocardial infarction, stroke, and all-cause mortality among men with or without coronary artery disease.

In the Baillargeon study, treated men at highest risk for myocardial infarction at baseline had a statistically significant decreased risk for myocardial infarction with testosterone therapy. This was based on a myocardial infarction prognostic index score developed from medical diagnoses and procedures at baseline. And in the Shores study, there seems to be a greater but non-significant reduction in all-cause mortality in treated men without cardiac disease.

Is there a risk difference for duration of therapy? We concluded that the relationship between duration of testosterone therapy and the

study outcomes is unclear. While the Vigen, Shores, and Muraleedharan studies reported testosterone treatment durations from 10 to 24 months, only the Baillargeon study did a sensitivity analysis of treatment lengths on study outcomes. This study did not find an increased risk for myocardial infarction with increasing cumulative number of testosterone injections in the first year.

As previously described, those estimates of the studies are modest and contradictory, and the confidence intervals barely excluded the null. The next few slides outlined the limitations in interpreting these study results.

It is not possible to make generalizations about these results, as the study populations are varied. For example, the populations included U.S. veterans, men with low testosterone, and type 2 diabetes. And baseline testosterone levels were not available in all the studies. Also, the studies used different testosterone formulations and, as mentioned previously, different study

outcomes were measured.

Also, there were issues with the appropriateness of the comparator groups. Four studies compared men treated with testosterone to none-users of testosterone. Three of those studies included only men with low baseline testosterone. And in one study, the baseline testosterone was unknown. However, factors that determine which men were treated versus untreated were unknown. So confounding by indication might have been introduced in which men at higher risk might be more likely treated.

The Finkle study used two study designs, a self-controlled cohort and a parallel cohort method with the active comparators, the phosphodiesterase-5 inhibitors. While a self-controlled cohort controls for measured and unmeasured time and variant confounders, this design might be inappropriate for drugs used chronically like testosterone, as this design might be more appropriate for drugs with intermittent exposures.

Also, a phosphodiesterase-5 inhibitor as an active comparator might not be appropriate, as it is not a competing therapy. And those drugs are used as needed and not chronically, as with testosterone.

There were also limited data on adherence or the adequacy of therapy. The Finkle study censored follow-up time at 90 days, which is questionable given that testosterone is chronic therapy. In the Baillargeon study, the average number of injections appear to be low given the recommended frequency of that mode of therapy.

On average, there were about four and a half injections in the first year of follow-up. The number of injections expected over a year would be at least 12 depending on the frequency of injections.

In addition, only two studies captured follow-up testosterone labs, and one showed follow-up testosterone level to be within therapeutic range, while in the other study, the testosterone levels were still therapeutic.

The methods of analyses also varied by study due to factors such as testosterone therapy variable, initial time of follow-up, censoring, covariates, and the handling of confounders. For example, using time of diagnosis for low testosterone rather than the initiation of therapy could lead to exposure, misclassification bias in which unexposed time within the treatment group might be misclassified as time on treatment.

Also, there were varying methods for correcting for imbalances in the study groups such as variable adjustments in Cox regression models, matching cohorts on baseline, myocardial infarction prognostic scores, or stabilized inverse probability waiting. However, residual founding might still persist despite these methods.

Despite the limitations of the observational studies, we did learn something about the study populations. Compared to known use, some of the patient characteristics associated with testosterone use were fatigue, hypogonadism, sexual dysfunction, and osteoporosis, as well as,

generally, slightly younger age, increased BMI, or lower baseline testosterone. And testosterone therapy was associated with increased comorbidity load in the largest studies. So generally it appears that men with more comorbidities, or men with lower baseline testosterone, or both may be more likely prescribed testosterone therapy.

The next few slides outline the limitations in interpreting the meta-analysis of the 27 randomized controlled trials. The meta-analysis was a trial-level analysis, and there was heterogeneity of designs of the component studies. Individual trial durations ranged from 12 weeks to three years, participant ages from 18 to 88 years old. Trial sample sizes were as small as 11 and as large as 316. The studies varied widely by publication years and study locations. They were also varied by participant baseline testosterone concentrations and testosterone formulations.

There was also clinical heterogeneity among the component trials. The study populations had varying baseline health status such as healthy

individuals and individuals with various preexisting conditions such as rheumatoid arthritis, end-stage renal disease, metabolic syndrome, and cardiovascular diseases.

In addition, the component studies were not designed as cardiovascular safety studies. Cardiovascular-related events were not prespecified or adjudicated and they were broadly and inconsistently defined.

A major limitation of the meta-analysis was a broadly defined outcome, cardiovascular-related events. In the first two rows, the first two rows show the results of the meta-analysis, which included more than 20 categories of cardiac and vascular events ranging from bleeding esophageal varices, constrictive pericarditis, hypertension, peripheral edema, and syncope. These events were given equal weight to such events as deaths due to myocardial infarction.

While combining these clinically heterogeneous events might provide necessary power to detect a difference between the treatment

groups, the aggregated outcome is difficult to interpret and might mask or distort the signal for the most clinically important cardiovascular outcomes.

The third row shows a re-categorization of the events by the FDA using the major adverse cardiovascular events categories, defined as myocardial infarction, stroke, cardiovascular death. It appears that only 30 out of the 181 events would have met the narrow definition, for an event rate of approximately 1 percent in each arm. The agency did not perform a re-analysis for the original or re-categorized data.

So in conclusion, due to the differences in study design characteristics such as study populations, drug exposures, and outcome measures as well as differences in the methods of analysis, the overall cardiovascular risks and benefits are still unclear.

To more fully evaluate the cardiovascular risk with testosterone therapy, future studies should use data sources available to capture

important baseline and time-varying characteristics such as the diagnosis for testosterone use, cardiovascular risk factors, and laboratory results.

Clarifying Questions to FDA

DR. JOHNSON: Thank you to the FDA for these presentations. Before we begin our clarifying questions, I just wanted to announce for the record that our patient representative, Craig Lustig, is unavoidably absent to today's advisory committee meeting.

Now, we will open to the advisory committee for questions to the FDA. Please state your name for the record when you speak. And if you can, direct your questions towards a specific presenter. And I'm going to take the chair's option to ask the first question to Dr. Hirsch.

Dr. Hirsch, am I correct in hearing you that, indeed, the indication for the use of testosterone replacement is based on testosterone level alone and is not related to any signs or symptoms that may be related to low testosterone?

If this is correct, then the disease awareness information that talks about a treatable condition appears that they are talking about symptoms, not about testosterone levels. So can you clarify that for me? Thank you.

DR. HIRSCH: Yes. It is absolutely correct that the efficacy endpoints that are assessed for approval are serum testosterone concentrations, and efficacy endpoints that are clinical, such as sexual desire, muscular strength, fatigue, when they are assessed, are assessed as exploratory, not formal endpoints, as I mentioned in the presentation.

However, when folks are enrolled in these studies, they are determined to be hypogonadal and have a biochemical hypogonadism by T less than 300. So they are on men with hypogonadism. While it is true that we do not formally assess clinical benefit from baseline to endpoint or require that, although some trials have done that and on an exploratory basis, it is also true that men who are enrolled are hypogonadal in the determination of

the investigator who enrolled them.

I hope that helps.

DR. JOHNSON: Yes. And just to clarify on that, the disease awareness speaks not of testosterone levels. They speak of symptoms. And so that is a different focus point.

DR. HIRSCH: There are currently little evidence in labeling of efficacy endpoints changed from baseline. So what is in labeling is what a sponsor can claim. And in most labeling, there is little or no such mention of change from baseline or clinical benefit on a sign or symptom.

DR. JOHNSON: But the disease awareness that we saw is an exception to that, so that's allowed to use symptoms as a reason to evaluate low T.

DR. HIRSCH: Hypogonadism is a clinical condition. As the speakers have said today, there is biochemical hypogonadism which requires there to be an associated sign or symptom. So hypogonadism has signs and symptoms. And in some labeling, to be frank, these signs and symptoms are listed in one of the sections.

That doesn't mean the labeling describes benefits in those signs and symptoms, but in certain labels in certain sections are described descriptors of hypogonadism.

DR. TRAN: Just to clarify, because that is considered a disease awareness communication, it does not fall under the jurisdiction of the FDA, or the FD&C-implementing regulations, or the FD&C Act.

DR. JOHNSON: Who regulates those disease awareness communications?

DR. TRAN: Right. So the Federal Trade commission or the FTC regulates disease awareness communications.

MS. BHATT: Can you please state your name for the record?

DR. TRAN: My name is Brian Tran, and I am a regulatory review officer at the Office of Prescription Drug Promotion.

DR. JOHNSON: Dr. Gordon?

DR. GORDON: Just for clarification, you mentioned that Cmax is the other parameter that you look at closely. What's the evidence for the

relevance of Cmax to the safety of the products?

DR. HIRSCH: Right. In determining the need for a critical secondary endpoint, Cmax outliers, the underlying premise was that excessive testosterone, excessive, outside of the normal range does not meet the primary efficacy endpoint of repletion to the normal range. So we set up parameters of critical Cmax outliers that would demonstrate excessive testosterone repletion. That's the underlying premise.

DR. GORDON: Can I just follow up with one question, then? So then do you specify time points at which blood draws have to be taken, relevant to the products and their delivery methods?

DR. HIRSCH: Sure. Indeed, these are 24-hour blood sampling. These are results from 24 hours of blood sampling, not from a single draw. So the baseline and the primary endpoints are based upon 24 hours of draws.

DR. JOHNSON: Thank you. I'm just going to let the committee know that we are indeed at the point when we were scheduled to go to lunch. We're

going to allow at least 10 minutes for additional questions, which will shorten our lunch period.

Dr. Adler?

DR. ADLER: Robert Adler. Very quick question for Dr. Mahomoud. Is it possible that you have underestimated the proportion of men getting both testosterone and a cardiovascular drug by not capturing those taking over-the-counter aspirin as an antiplatelet agent?

DR. MOHAMOUD: Yes. We did not include NSAIDs, or aspirin, or such products that are available over the counter. So in that case, yes, we would be potentially underestimating.

DR. JOHNSON: Dr. Lincoff?

DR. LINCOFF: Mike Lincoff. So for Dr. Falconer, I was sort of startled by your last bullet point of your last slide. I recognize you work in a division of epidemiology, but I mean, perhaps I am misinterpreting. But were you suggesting that a non-randomized observational design of any sort, even with collection of covariates, would be sufficient to prove causation

of testosterone therapy with cardiovascular risk, or were you in fact considering a randomized trial as the appropriate approach?

DR. FALCONER: We understand the limitations that come along with observational studies, but we'd never rule out trying to use observational studies to gather additional information about cardiovascular risk in testosterone therapy. And, no, I wasn't trying to make the claim that we would try to prove causality using an observational study.

DR. JOHNSON: Dr. Phillips?

DR. PHILLIPS: Marjorie Phillips, Georgia Regents. Question for Dr. Hirsch. I am still wrestling with your differentiating from the labeling that describes idiopathic hypogonadism and the studies that included a large group of subjects with idiopathic hypogonadism, and your statement that age-related hypogonadism is not addressed in the labeling.

If the only measure is really low testosterone, would age-related hypogonadism and

idiopathic be mutually exclusive?

DR. HIRSCH: One can view the phase 3 study, the single phase 3 study that tends to support these NDAs, as a very large pharmacokinetic study. And the subjects in the study, irrespective of their etiology, are used to determine whether testosterone is adequately repleted. So although there are many middle-aged men in these trials and we do not limit the trials to specific men with specific etiologies of hypogonadism, they serve as a model to determine whether the drug repletes testosterone much like a giant pharmacokinetic study.

DR. JOFFE: This is Hylton Joffe. I just wanted to add on this model idea, it's much more feasible to enroll these types of populations in these clinical studies than to go try and find this much smaller population with these specific medical conditions, such as pituitary abnormalities.

Then the second point is that we wouldn't expect testosterone to behave any differently in the patients that are studied with regard to

raising testosterone to within the normal range compared to someone who had a specific disease. So that also lends some support for why we use patients like that in these trials.

DR. JOHNSON: Dr. Domanski?

DR. DOMANSKI: I just want to make sure, as we troop off to lunch, I am getting this big picture. If I look at all this, it looks as though there is absolutely no demonstration of safety or efficacy of these drugs, with respect to clinical endpoints, for the indication for which they are most frequently given.

In point of fact, the agency has not labeled and said that it's indicated for those purposes. And now we're really talking about labeling. I am just not so sure. And we're talking about big clinical trials, which may in fact be an opportunity cost for perhaps more important science.

But in any event, leaving that aside, the thing that sort of strikes me is that I am not so sure that labeling is going to change behavior very

much. I mean, there's no data now. The fact that you put a label on it and say you don't see any indication for it is not really news. And I just want to make sure I'm seeing this big picture. Maybe the group can answer that.

DR. JOFFE: This is Hylton Joffe. Why don't we have OPDP speak possibly to the effects that labeling changes could have, for example, on promotion?

DR. TRAN: Brian Tran from OPDP again. So as in my presentation, according to the FD&C Act and FDA-implementing regulations, prescription drug promotion would be considered misbranded if, among other things, its labeling is false or misleading. So for example, if the indication were to change, prescription drug promotion should be presented in such a way that it's not false or misleading.

DR. DOMANSKI: That, you see, is the primary outcome of today's deliberation?

DR. TRAN: We would defer to DBRUP for that question.

DR. JOFFE: Yes, I think that's one of the

outcomes here, is how can we most accurately reflect in labeling what the science says in terms of who should be using these products? Physicians can always use things off label, and FDA doesn't really get into that. But what we want to do is, in our labels, accurately reflect the correct patient population, where the science supports it.

DR. DOMANSKI: In fact, that's precisely what's happening now, though. It's being used off label.

DR. JOFFE: Yes. I guess it depends how you define off label. If you flip these patients into that category that Dr. Hirsch showed, the idiopathic gonadatropin population, then someone might say they're actually already included somewhat in the indication.

DR. JOHNSON: Finally, Dr. Herring?

DR. HERRING: I had a question. Dr. Amy Herring, University of North Carolina. A question for Dr. Mahomoud. Just understanding the population size, so in particular, your utilization data showed about just under 1.6 million users in

that age range of 40 to 64. And based on the 2010 Census, I'm thinking we have about 50 million men in that age group. Does that sound right? So roughly just under 3 and a half percent of men in that age group who are using?

DR. MOHAMOUD: I can't corroborate the Census data you mentioned. I think you said 50 million. Is that what I heard?

DR. HERRING: Fifty million.

DR. MOHAMOUD: Right, between the ages of 40 to 64 -- is that correct?

DR. HERRING: That was based on my quick search.

(Laughter.)

DR. MOHAMOUD: Yes. So yeah. We found that patients that have a prescription for testosterone between the ages of 40 to 64 to be the majority of users. Out of the 2.2 million men that had a prescription for testosterone, 1.5 million were between the ages of 40 to 64, which represents the largest majority.

DR. HERRING: But it sounds reasonable that

3 percent of men in that age range are taking prescription testosterone.

DR. MOHAMOUD: I suppose so.

(Laughter.)

DR. JOHNSON: I offer my apologies to Dr. Teerlink and Garnick. We will bring your questions forward after the public presentations. But we want to be able to start those as scheduled.

So now, we will break for lunch. We'll reconvene in exactly 35 minutes at 1:00 p.m. for our open public hearing session. Please take your personal belongings with you.

For the panel members, please remember that we are not to discuss the meeting topic at lunch amongst ourselves or with any members of the audience. I thank you very much. Be back in time to give a five-minute warning before we begin our afternoon session. And again, thank you to everyone for your excellent presentations and your insightful questions.

(Whereupon, at 12:23 p.m., a lunch recess was taken.)

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

(1:07 p.m.)

Open Public Hearing

DR. JOHNSON: Welcome back from lunch, everyone. As we put some slides onto the computer, allow me to do an introductory statement.

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 portion of this advisory committee meeting, the FDA believes it is important to understand the context of every individual's presentation.

For this reason, FDA encourages you, the open public hearing speakers, at the beginning of your written or oral presentation, to advise the committee of any financial relationship that you may have to the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any financial relationship.

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 on the open public hearing process. The insights and comments can help the agency and this committee in their considerations of the issues before them today.

That said, in many instances and on many topics, there are a variety of different opinions. One of our goals today for this open public hearing is that it be conducted in a fair and open manner, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. And I would like to, in advance of your presentations, thank everyone for your participation.

Will speaker number 1 kindly step up to the

podium and introduce yourself? If you would please state your name and any organization that you are representing for the record?

DR. CAROME: I'm Dr. Carome, director of Public Citizens Health Research Group, testifying on behalf of myself and Dr. Wolfe. We have no financial conflicts of interest. The key questions before you are, do the available data indicate a cardiovascular safety signal associated with testosterone therapy and should information about major CV adverse events associated with testosterone drugs be included in the labeling for these products?

The answer to both is a resounding yes. The very large, well-designed cohort study by Finkle, the randomized placebo-controlled TOM trial, and the carefully conducted meta-analysis by Xu provide compelling evidence of a cardiovascular safety signal associated with testosterone drugs as summarized in this table here. And the risk appears to be particularly apparent in the first several months of therapy.

The FDA noted that the TOM trial authors explicitly indicated that the difference between the groups in CVAEs might have been due to chance alone. However, the differences were statistically significant even after adjusting for age and cardiovascular baseline risk factors.

Several effects of testosterone drugs make the link between these drugs and CVAEs biologically plausible, including increased hemoglobin and hematocrit, causing increased blood viscosity, acutely increased platelet thromboxane a2 receptor density and aggregation response, shown in a randomized trial in healthy men, changes in the viscosity and flexibility of RBC membranes, which could impair RBC movement in capillaries, and decreased HDL cholesterol levels, among other things.

The FDA recently required that all testosterone product labels include a general warning about the risk of venous clotting events. The same mechanisms predisposing to these events likely contribute to the increased risk of arterial

CVAEs seen with these products.

A recent observational study found that low testosterone levels appeared to protect patients with a history of MACE events from experiencing additional such events. The authors suggested that low testosterone levels might reflect a naturally occurring protective compensatory mechanism and testosterone use in such men might be deleterious to overall and cardiovascular health.

The available data suggests that older men and men with a history of heart disease may be at greatest risk for CVAEs related to testosterone use. However, there is not sufficient data indicating that this risk is restricted to these subgroups. There is sufficient evidence to warn inclusion of cardiovascular risk information in the testosterone drug labels.

FDA review has repeatedly stated in the briefing document that the available data do not provide conclusive evidence of a causal association with testosterone drugs and CV events. However, the labels of many drugs include warnings, in some

cases black-box warnings, about serious risks based on far weaker evidence for safety signals than that available for testosterone drugs.

Indeed, the FDA's recent action regarding testosterone labels to include general warnings about the risk of venous thrombotic events was based solely on post-market reports. In July, Health Canada, acting appropriately to protect public health, issued a safety alert to patients and healthcare providers about the risk of serious and possibly life-threatening cardiovascular problems associated with testosterone drugs.

The agency reported that it was working with manufacturers to update Canadian drug labels. Health Canada's actions are based on the same evidence available to the FDA.

In conclusion, as in Canada, healthcare providers and patients in the U.S. should be warned about the risk of serious adverse cardiovascular events associated with testosterone drugs, which are widely overprescribed in this country. To protect public health, we urge the advisory

committees to recommend that the FDA require such warnings on the labels of all testosterone products. Thank you for your attention.

DR. JOHNSON: Thank you very much. Now, I head to open public speaker number 2.

MR. BROWN: Hi. Good afternoon. My name is Paul Brown. I am testifying on behalf of the National Center for Health Research. Our nonprofit research center conducts research and evaluates scientific and medical data so that we can provide objective health information to patients, providers, and policymakers.

Our president is on the board of directors of two nonprofit organizations dedicated to providing scientific resources to the FDA. Our organization does not accept funding from drug companies and, therefore, I have no conflicts of interest.

From 2010 to 2013, the number of patients receiving testosterone prescriptions increased from 1.3 million to 2.3 million. That means a large and growing number of patients may be at risk for

adverse events due to TRT. At the same time, it is not clear what percentage of men taking TRT actually need it for medical purposes. In the topics for discussion, I am addressing question number 2, whether the data indicates a cardiovascular safety signal associated with the use of testosterone therapy.

The topic covers four issues. Issue number 1, signal strength. Three studies have shown evidence for cardiovascular safety signals associated with TRT, a 2014 cohort study by Finkle, the 2013 meta-analysis by Xu, and a 2010 randomized placebo-controlled trial by Basaria. In the Basaria study, cardiovascular events were statistically significant after adjusting for age and baseline cardiovascular risk factors, as Dr. Carome just pointed out.

Issue number 2, biological plausibility of the signal. The link between TRT and CV adverse events makes sense biologically. It includes increased blood viscosity, increased micro viscosity of red blood cells, and decreased levels

of good cholesterol, HDL.

Issue number 3. Should the signal apply to all users? Although data suggests that older men and men with a history of heart disease may be at greater risk for cardiovascular events from TRT, there are not enough data to conclude that those are the only men at risk. Having warnings only for older men and men with a history of heart disease will give other TRT patients a false sense of safety.

Issue number 4, warning labels. FDA recently required all testosterone product labels to include a warning about the risk of blood clots. The same processes that place men at risk for blood clots are likely to contribute to increased risk of adverse cardiovascular events due to TRT. FDA should be consistent with this label, warnings and include them for both blood clot and cardiovascular events for all populations that use TRT.

In this August 12, 2014 memo, FDA reviewers stated, "The uncertainty around important factors leading to the use of TRT and the association of

testosterone levels with CV risk are difficult to assess." FDA reviewers have also stated that available data do not provide conclusive evidence of a causal association between testosterone therapy and cardiovascular events.

The evidence may not be conclusive, but it certainly is substantial. These products are already on the market and weren't adequately tested for safety before FDA granted approval. The FDA should now be more cautious and provide these potentially life-saving warnings to the millions of patients using TRT. Therefore, the FDA should include cardiovascular risk information in testosterone product labels for all populations. Thank you.

DR. JOHNSON: Thank you very much. Public speaker number 3, please?

DR. DANDONA: Good afternoon. I am Paresh Dandona. I am representing the American Association of Clinical Endocrinologists and their view on this matter.

These are somebody else's slides. I don't

know how I lost my slides. So anyways, I might as well use my team to speak.

As far as the cardiovascular risks are concerned in the recent publications, a lot of people will be talking about it to challenge the quality of those papers, and I will not spend time on that. But what I would like to talk about is the conditions where it's established that a hypogonadal state exists and, therefore, these people need investigation and treatment on a regular basis.

In our own work, since 2004, it is demonstrated quite clearly that 1 in 3 type 2 diabetics are hypogonadals. That's the male population. And that results in a substantial number, millions of patients, who require testosterone therapy following an adequate investigation.

Similarly, the same work extended, published in 2009, shows that one-fourth of obese non-diabetics are hypogonadal and have low testosterone concentrations. So that adds to the enormous

population base that's waiting to be investigated and to be treated.

Remember also that these two populations carry considerable cardiovascular risk. And therefore, whenever testosterone is prescribed, unless you do a proper investigation -- not retrospective meta-analysis, but carry out an investigation on a prospective basis -- you will then and only then be able to assess actual cardiovascular risk.

I repeat that the two papers that have littered this recent controversy are badly conducted meta-analyses and do not carry the intellectual commitment or excellence with which we can be carried out as the two previous speakers have made it out to be.

Now, finally, the last thing I want to mention -- and again, I wish I had the slides to show you -- and those are our own investigations in the state of hypogonadism in type 2 diabetes. And basically, what those investigations have demonstrated, A, that hypogonadal patients with

type 2 diabetes have 30 percent extra insulin resistance as measured by CLAM techniques, and testosterone administration over a period of six months reverses that.

Furthermore, our analysis has shown that at a cellular molecular level, there is a diminished insulin signaling transduction mechanism in these patients. You get testosterone and that gets reversed. And finally, the other thing that this investigation shows -- and these data were presented at the annual meetings of the ADA and the Endocrine Society -- is that testosterone is anti-inflammatory, including causing a reduction in correspondence concentrations and several other inflammatory markers.

Last but not the least, it also results in changes at a cellular molecular level in adipose tissue and causes a replacement of adipose tissue with lean body mass. These changes are not consistent with an increase in cardiovascular risk. In fact, they are indicative of something in the other direction, i.e. benefits.

But what we still need to do is to conduct a prospective properly conducted randomized trial with testosterone in these conditions to make a final judgment on what happens. And what I would suggest is, just as a women's health initiative was conducted a decade and a half or nearly two decades ago, we need a men's health initiative funded by the NIH to proceed ahead. Thank you very much.

DR. JOHNSON: Thank you very much. And we sincerely apologize for the error with the slides. Thank you for your interesting presentation. We appreciate it. Now, on to speaker number 4?

DR. SWERDLOFF: Yes. My name is Ronald Swerdloff, professor of medicine at UCLA, representing the views of the Endocrine Society that have provided transportation to this hearing. My conflicts also include serving as an investigator for both pharmaceutical company and NIH-sponsored clinical trials for testosterone.

I am a member of the Endocrine Society Guidelines Committee for testosterone therapy in men with androgen deficiency syndrome. And my

testimony is the opinion of the Endocrine Society and was developed by a panel of experts in testosterone therapy.

The Endocrine Society has developed clinical guidelines that provide evidence-based criteria for the diagnosis and treatment of testosterone deficiency syndrome. The diagnosis of male hypogonadism requires both symptoms and signs consistent with testosterone deficiency and consistently subnormal morning serum testosterone levels.

Many of the symptoms that are associated with hypogonadism are not specific to testosterone deficiency. Hypogonadism occurs in men of all ages and can be caused by damage to either the testes or the hypothalamic pituitary access. Some patients are diagnosed after specific injury or disease. However, in many instances, there is no clear precipitating event or identifiable anatomical defect.

Many drugs and medical conditions are associated with the testosterone deficiency

syndrome, which may reversible with treatment of comorbid disease, change in medication, or lifestyle. We have evaluated the quality of the evidence for diagnosis and treatment of testosterone deficiency syndrome, and we recognize that there is a need for more data to better define the thresholds or symptoms and justify treatment.

We also recognize there is a need to standardize and harmonize testosterone assays to reduce the extreme variation in levels, measured by different assays. We are aware of the National Institute of Aging-sponsored testosterone trial, evaluating the short-term efficacy of testosterone treatment in older men with hypogonadism.

The data from this study will better define our thinking on the topic. However, these trials were not designed to determine the long-term efficacy and risks of treatment.

We have reviewed the data on cardiovascular risk from testosterone therapy and have concluded that there are inadequate data from well-controlled interventional studies to determine if testosterone

therapy will result in increased, decreased, or neutral effects on the cardiovascular system. Similar situations would exist with regard to the prostate.

In conclusion, one, we recommend that the treatment with testosterone be limited to men who meet established diagnostic guidelines for hypogonadism and that treated patients be monitored as recommended by the guidelines.

Two, we also recommend that more data be collected on men of different ages to better establish the serum testosterone thresholds for specific organ-related syndromes and to determine which clinical manifestations will benefit from replacement testosterone therapy.

Lastly, we recommend that a prospective long-term, large-scale, well-controlled study be conducted to assess cardiovascular and prostate risks associated with testosterone replacement therapy. Thank you for allowing me to speak on behalf of the Endocrine Society.

DR. JOHNSON: Thank you. We appreciate your

information

Now, to open public speaker number 5?

DR. LIGHT: Good afternoon. My name is Richard Light. I represent my company and have no conflicts to report. We have been providing analytical reporting services to major pharmaceutical companies for over 20 years, and undertook an analysis of the FDA's FAERS database to see whether a safety signal existed for the adverse events of interest.

The testosterone cases we extracted and included only males the last five years. And it was a comprehensive analysis, including all MedDRA categories of adverse events. There were over 8,000 cases and 28,000 adverse event terms associated with them.

The adverse events of interest numbered in the low 100s to mid-100s, as you can see here, we had a control population, two control populations, actually. The first was phosphodiesterase-5 inhibitor cases, which were purged of pulmonary artery hypertension therapy. These numbered

approximately twice as many as the testosterone cases.

Control number 2 were a series of match controls extracted from the FAERS database, matched on five different criteria, age, gender, year of initial report, reporting country, and reporter occupation. Once again, the numbers were in the low to mid-100s for the cases of interest. We use a case reporting ratio, which is similar to a risk ratio, to assess the signal. And this is entirely analogous, computed the same way, as are the 95 percent confidence intervals.

This slide may be of interest to people here. In the last three years, you can see there's been a more than sixfold increase in the number of reported adverse events for transdermal testosterone. And that has, as far as I can tell, from this morning's numbers, far exceeded the increase and the use of testosterone over this period.

We chose to use the last five years of data for our analysis and here it is. MIs, other

ischemic heart disease, hemorrhagic cerebrovascular disease, ischemic cerebrovascular disease, and death all had reporting ratios that were less than 1, meaning that there was not an excess of reports with respect to the control populations.

As you can see, embolism and thrombosis for venous events was in excess of 2 in both populations, that it is compared to both control populations. And thrombophlebitis, pulmonary embolism, and thrombosis, and peripheral embolism, and thrombosis were likewise increased in number, and the reporting ratio reflected this.

This is a demonstration that this ratio can actually corroborate already recognized adverse events in the clinical labeling. The first half, about 8 events here, are adverse events that are in labeling for topical testosterone.

Interestingly, headaches and dyspnea are mentioned, but are not seen in excess in this analysis. Similarly, gall bladder disease and gall stone disease is not recognized to be an adverse event associated with testosterone, but came up as

a possible signal in this analysis.

So in conclusion, there is no apparent safety signal for ischemic cardiovascular disease, stroke, or death from any cause in the data we looked at compared to the control populations we used. And in general, the findings are consistent with current labeling. We did find and corroborated the safety signal for venous thromboembolism. And that's in accord with recent regulatory action. Thank you.

DR. JOHNSON: Thank you very much. Now, we'll move on to open public speaker number 6.

DR. RICHARDS: Thank you. I thank the advisory committee for their excellent questions this morning and I hope to shed a little more light than heat on this topic, but I'm not sure. I'm a plastic surgeon. I have no pharmaceutical financial arrangements. I do lecture internationally on testosterone science, testosterone therapy, and I teach a course to physicians, and such.

As far as testosterone and benefits to the

cardiovascular system, I'd like to say the case is closed. About 75 percent of all journal articles are false in their conclusions. We know this from multiple sources. Most of the remaining 25 percent of the reproducible studies support the protective and healing effects of testosterone on the cardiovascular function and on vascular inflammation.

Here is a few of the double-blind studies on both men and women on the benefits of testosterone therapy for ailing hearts. The likely beneficial biochemical pathways involved in explaining this benefit have been partially defined. Testosterone does increase the levels of anti-inflammatory cytokines and increases tissue antioxidant levels and antioxidant capacity.

It doesn't take much imagination to believe that testosterone therapy can save us some significant amount of healthcare expenditures. Testosterone has been shown in other disease states, such as diabetes, depression, dementia, menopause, and andropause to be of great benefit.

So this brings me to the main part of this discussion, which is, who is the target population. And in my opinion, and in my clinical practice, and then from the thousands of hours of studies I have read, I believe that that is all aging men and women eventually if we live that long.

The Framingham study uncovered about a 30 percent drop in testosterone levels in men of the same age between 1986 and 2006. They admit their data from the previous 20 years indicated a similar drop, but they didn't have enough data for statistical significance. Male and female tissues are biochemically and physiologically identical. We are the same species. We can exchange organ and transplantation.

All male and female intracellular estrogen originates inside each cell from testosterone metabolism. This was shown by Simpson, et al. in both 2000, 2001, and 2003. Both sexes report quality of life and productivity enhancements with testosterone therapy. Testosterone's many metabolites beneficially regulate inflammation and

metabolism, as has been shown in the biochemical literature.

Recent studies have come out, showing substantial reductions in both breast cancer and prostate cancers from testosterone therapy. Testosterone therapy has been proven to improve the health of people with diabetes and heart disease and hopefully would reduce their enormous health costs on society.

So those of us who have been on the forefront of this, reading the literature, treating patients, and teaching, have been fighting the mythology. Mythology has bred the current illogical treatment protocols and ranges for testosterone.

The lower limit of normal for male serum testosterone varies by over 300 percent on the east coast laboratories, with zero being considered acceptable for women. It's tissue levels, not serum levels, that determine symptoms and disease states. Serum levels of testosterone and estrogen do not actually reflect tissue levels.

Dosing is therefore a patient-specific clinical decision. Optimal dosing maximizes improvements while minimizing undesired side effects, such as excessive hair or acne. Testosterone pellets, which contain highly compressed molecularly identical human testosterone in stearic acid, are the only treatment that provides a near-identical steady state availability for months. All other delivery systems are suboptimal for many reasons, including the frequent testosterone peaks and troughs that also create deficiencies or excessive intracellular estrogen. Thank you.

DR. JOHNSON: Thank you. Now, we move on to public speaker number 7.

DR. NANGIA: Thank you. My name is Ajay Nangia, professor of urology at the University of Kansas Medical Center. And I'm representing the American Urological Association and the Sexual Medicine Society of North America, a subsociety within the AUA. They have provided travel funding, no honorarium. I have no other conflicts of

interest and do not represent any pharma companies.

We thank the FDA for their excellent background data and the opportunity to speak today. The volume of testosterone use has increased dramatically recently. Why is this? First, the increase in scientific knowledge and association of testosterone deficiency with several common conditions in men, such as obesity, osteoporosis, muscle wasting, and diabetes.

Second, there are more delivery methods for testosterone which are often preferred by patients. We suspect that this, along with increased public awareness of the possible symptoms of testosterone deficiency, has led to an increased use of testosterone. However, we must not forget that the dramatic increase in obesity, diabetes, and metabolic syndrome in this country over the last several decades is a larger and multifactorial problem and a public health concern independent of age.

The association of these conditions with low testosterone and whether low T is caused by or

occurs as a result of these medical conditions is unclear, but has highlighted that the public health status of men in this nation needs to be studied, improved, and encompasses more than just testosterone replacement. This perspective should remain our overall focus.

In February of 2014, the AUA issued a position statement on T therapy. This document was shared with the committee in our written statement. An important part of this document was, number one, the call for rigorous evaluation and testing before starting testosterone therapy; number two, thorough discussion of potential risks of testosterone therapy; and, number three, appropriate surveillance of patients on T therapy, including ongoing assessment of side effects.

Education may be more effective in guiding the appropriate use of T therapy than labeling changes. We summarize our position with two distinct points. First, T therapy can be effective. It's been on the market for over 60 years with FDA approval and a vast number of

prescriptions and patients treated. If used appropriately, according to the accepted indications, T therapy can improve patients' metabolic and general health.

As such, the AUA believes that T therapy used in this setting of documented low biochemical testosterone levels together with defined signs and symptoms of hypogonadism is appropriate. T therapy for low or low normal biochemical testosterone level without signs or symptoms of hypogonadism or T therapy for symptoms suggesting hypogonadism but without biochemical confirmation is not supported by published literature or the AUA.

The second main point is the AUA shares the FDA's concerns about recently published studies according to T therapy with increased cardiovascular risk. We need to strongly point out, however, as does their own document, that the studies are inconclusive and controversial based on methodological issues.

Given that the preponderance of evidence prior to these few recent studies had suggested

just the opposite, that appropriate T therapy reduces cardiovascular risk, we call for additional larger studies before the FDA decides on any changes in labeling or restricts the availability of T therapy.

As such, we thank the FDA for their ongoing work and hope that the AUA can serve as a reference for this in the future. Thank you.

DR. JOHNSON: Thank you for that information. Now, we're moving on to open public speaker number 8.

DR. MORGENTALER: Good afternoon. I am Dr. Abraham Morgantaler. I'm an associate clinical professor at Harvard Medical School. I represent the Androgen Study Group whose membership is seen here. The Androgen Study Group receives no compensation. I have relationships as a consultant to scientific advisory or research with AbbVie, Auxilium, Antares, and Clarus. And I hope I didn't leave anybody out.

Why are we here? We're here because this past year saw an extreme media response to two

relatively weak retrospective studies that created fear amongst patients who were taking testosterone and potential candidates for it. We saw editorials, headlines, and a brand-new area of medical malpractice.

The FDA appropriately decided to announce that it would investigate this issue, and we have now heard today the FDA's own analysis of these cardiovascular studies of this past year, which concluded there was no evidence of increased risk. The Androgen Study Group agrees.

We have now moved on to several other questions at this meeting, and I wish to address them briefly.

What about overuse? This is a slide taken from the FDA's own website, accessed in 2007, that represents that only 5 percent of men with hypogonadism were treated. This rate doubled or tripled as the data suggested to the present day does not represent over-usage. In fact, there are no testosterone products in the top 20 prescribed according to these data from 2010.

What about direct-to-consumer marketing? In 2010, there was not a single testosterone product in the top 25 most-advertised drugs. This cannot be the reason why prescriptions have increased.

What about inappropriate use? I am going to skip this slide for time. I think one of the issues that's come up at this meeting and has been present in conversations about testosterone since the 1980s is about primary and secondary hypogonadism and the very specific causes that were cited in a label for the entire class that dates to 1981.

Let me suggest that a lot has happened in medicine since 1981, CAT scans, MRI, SSRIs, statins. PSA hadn't been introduced. In fact, the entire AIDS epidemic did not become real until 1982. Why must we today be burdened with a state of knowledge from a prior era?

In fact, we have learned a great deal about testosterone since 1981 when that class label came out. This is what we've learned, that men have symptoms that bring them to the doctor that are

bothersome, that those symptoms are indistinguishable whether they have a specified condition like a pituitary tumor or not, and that in fact, we can induce symptoms in healthy men as volunteers in experiments, as witnessed by the Finklestein, et al. article this year in the New England Journal of Medicine.

Isn't this really what has caused the testosterone hysteria? We have testosterone advertised everywhere, with products of unknown provenance, with claims that are impossible. Feel like a beast, perform like a champion, testosterone max. We have 70-year-old men who have bodies of 20-year-olds promoted everywhere together with testosterone and the use of growth hormone. In fact, we have a black-market situation. It makes no sense to impose restrictions on an approved prescription product because of an unregulated black market.

This is what we see in clinical practice every day. Men come in with symptoms that bother them. Treatment is effective. And physicians are

trying to do the right thing for their patients.

On behalf of the millions of symptomatic men with hypogonadism in this country, we thank the FDA for all your efforts today and in the past for providing us with the tools that in the clinic we use to treat these men successfully. There is no testosterone crisis today, and there is no additional need for restrictions on testosterone products. Thank you very much.

DR. JOHNSON: Thank you for your presentation. Now, we will move on open public speaker number 9.

MR. VATS: Thank you. Good afternoon. My name is Vikas Vats. I work for a company called Tesvgen. I don't have any financial compensation or travel compensation to come to this meeting from any of the testosterone manufacturers.

So I'll get into the presentation, and we want to basically make two key points about optimizing testosterone therapy and the monitoring of on-treatment testosterone levels.

Point number 1. Circulating testosterone,

as you know, is bound to SHBG and albumin. Therefore, total testosterone concentrations are affected greatly by variations in SHBG concentrations. A number of common conditions today, such as obesity, diabetes, liver disease, hepatitis, entire disorder affect SHBG concentration. For instance, obesity and diabetes, two highly prevalent conditions, are associated with low total but normal free testosterone concentrations. Thus, some obese and diabetic patients with low SHBG level may be misclassified as being androgen deficient if only the total testosterone level were measured.

Therefore, we believe that accurate determination of free testosterone concentrations is essential for making a diagnosis of androgen deficiency and in monitoring on-treatment testosterone levels in patients with disorders characterized by adult SHBG levels.

The second point is that we can see from several studies that there is substantial variation in on-treatment testosterone levels with all

formulations. Shown on this slide are baseline and on-treatment testosterone levels from one published randomized clinical trial using topical formulations in older men, illustrating the wide variation in on-treatment testosterone levels.

Almost 40 percent of men with an initial dose have levels below the target range and approximately 10 percent have levels above the target range, as shown here. Careful monitoring of on-treatment testosterone levels is necessary for achieving and maintaining T levels in a therapeutic range and reducing the risk of superior physiologic levels.

As we heard today from several experts, we do not know whether T therapy increases the risk of CV events. There is strong evidence that increments in hemoglobin and hematocrit levels are related to on-treatment testosterone concentration. These data from published studies show that the increments in hemoglobin and hematocrit are greater at higher doses and greater in older men than in younger men.

So in conclusion, I tried to make two points that can help improve the diagnosis of androgen deficiency and the safety of testosterone therapy. First, because of substantial variation in SHBG in men due to obesity, diabetes, genetics, and other common conditions, accurate determination of free testosterone is necessary for reducing the risk of misdiagnosis and unnecessary TRT in these men.

As there is considerable variation in on-treatment testosterone levels, on-treatment free testosterone levels should be monitored and maintain T levels in the therapeutic range to minimize the risk of superior physiologic levels. Thank you for your time.

DR. JOHNSON: Thank you. Now we will move on to open public speaker number 10.

MR. LEONARD: Hi, good afternoon. My name is Brandon Leonard, and I am director of strategic initiatives for Men's Health Network. I have no conflict to disclose. Men's Health Network is a national nonprofit organization whose mission is to reach men, boys, and their families where they

live, work, play, and pray with health awareness messages and tools, screening programs, educational materials, advocacy opportunities, and patient navigation.

Researchers have found that nearly 39 percent of men over the age of 45 may suffer from hypogonadism or low testosterone. Hypogonadism is associated with symptoms including decreased energy and mood, fatigue, loss of muscle mass, decreased libido, and erectile dysfunction. There is also growing evidence of a link between low testosterone and other serious health conditions, including heart disease, diabetes, and metabolic syndrome.

Because the symptoms of low testosterone are often similar to those of other medical conditions, many of those suffering go undiagnosed for quite a while.

Low testosterone carries a significant burden for men both physically and psychologically. During the many community health fairs, screenings, and other events I have attended while on the staff of Men's Health Network, I have heard numerous

stories from men and their loved ones about the impact of this condition.

In addition to feelings of weakness and fatigue, men suffering from low testosterone often feel that they have lost their manhood and that their quality of life has decreased. Depression, anxiety, and stress often accompany hypogonadism.

While the symptoms of hypogonadism may become an impediment to daily life, many men wait months or even years to get treatment because they assume the symptoms will go away or they are too embarrassed to discuss them.

Many of those who suffer from hypogonadism may be reluctant to seek help and treatment due to stigma and their lack of understanding about the condition. Men may also be averse to seeking help because of social norms that teach them to suffer in silence. This dangerous mentality often leads to exacerbation of medical conditions that only grow more severe and costly if they are not managed and treated early.

FDA-approved testosterone replacement

therapies provide hope for those men who are diagnosed with hypogonadism and suffering from symptoms that affect everything from their mental well-being to the health of their relationships. A variety of treatments have been approved in recent years that provide men with more options to restore their testosterone levels according to the most appropriate method for their condition and lifestyle.

We believe the key to any medical decision, including the decision to pursue testosterone replacement therapy, is an informed discussion between the patient and his healthcare provider. With an appropriate diagnosis and an understanding of the patient's symptoms and concerns, the provider and patient can decide together if treatment is appropriate, and, if so, which particular treatment is best for that individual.

To that end, we support improved and ongoing education of both patients and providers regarding TRT. Thank you very much for the opportunity to offer comments.

DR. JOHNSON: Thank you very much for your comments. Now, we go on to open public hearing speaker number 11.

DR. WU: My name is Frederick Wu. I am professor of medicine at the University of Manchester, United Kingdom. It may not be very united by the end of this week, I am afraid.

(Laughter.)

DR. WU: I am speaking on behalf of Repros, who have supported my time and travel to this meeting. I'd like to discuss the diagnosis of hypogonadism in aging men using data from the European Male Aging Study, for whom I am the principal investigator.

You've heard a number of times that, in clinical practice, we categorize patients into primary or secondary hypogonadism. This is for classic hypogonadal disorders. So using the same approach, we can categorize or segregate a general population of aging men, of whom there are over 3,000 from 8 countries, using the same thresholds into those who have normal testosterone to the

right, and abnormal or low testosterone to the left, and those with primary or secondary hypogonadism.

Accordingly, in the general population, you see that approximately 12 percent will have biochemical hypogonadism with secondary hypogonadism being six times more common than primary. In this slide, you see that with increasing BMI or obesity, there is a substantial drop in total and free testosterone irrespective of age, without any increase in LH, suggesting that there is hypothalamic failure, characteristic of secondary hypogonadism. In contrast, you see the age trend for testosterone is relatively minor over four decades. And this is because the age-related increase in LH can compensate for any degree of testicular failure, therefore minimizing the prevalence of primary hypogonadism.

So we can discern two dominant tracts of hypogonadism in the aging male population, secondary hypogonadism associated with obesity, primary with aging. They have different natural

histories, clinical features, and outcomes, and require different management strategies.

So this slide shows you some quasi dose-response relationship between changes in hormones over four years relating to the extent of weight change, decreased weight to the left, increased weight to the right. If you follow this panel and this panel, you see that secondary hypogonadism develops with weight gain, with lowering of testosterone without any change in LH. And then the reverse is that if you lose weight, testosterone increase and LH increase, therefore showing that secondary hypogonadism is reversible.

So you've heard earlier that exogenous testosterone is a very good male contraceptive, inducing infertility, but preserving androgen effects. So if you give testosterone to men with secondary hypogonadism, you will further suppress the gonadatropins, reduce the sperm count, and prevent any chance of recovery of testicular or pituitary function.

So in summary, I have shown you that in the

aging male, secondary hypogonadism is associated with obesity. The underlying hypothalamic suppression is reversible by weight loss. And strategies to reverse the gonadatropin suppression either by lifestyle changes or pharmaceutical means to allow recovery of endogenous testosterone and to preserve fertility are preferable to exogenous testosterone in the treatment of secondary hypogonadism. Thanks very much.

DR. JOHNSON: Thank you. Now, we will move on to public speaker number 13.

DR. CRIPE: Good afternoon. My name is Bob Cripe, and I come here representing myself. First of all, I'd like to thank the committee for taking the time to hear some of the thoughts of people here in the audience. I have come because I took AndroGel back in February of 2011. I took it based on the suggestion of my doctor, who after doing a blood test in the afternoon saw that I was borderline low T and accompanied with my complaint of being tired.

After that, he had prescribed the drug. I

started taking it. And within a day, I started feeling a severe pain in my upper mid-back and soon thereafter developed severe drop foot on the right side of my body. And within a week, I was completely paralyzed from T4 or the chest down. And soon thereafter, based on tests, MRIs, and a number of different studies, he said the reason and cause of this was the testosterone, which caused a blood clot within my spinal cord, which burst. And eventually, I was completely paralyzed.

Prior to that, I was a very active person. I coached soccer for my daughter and for my son, still played all athletics until I was in my late 30s, early 40s, and had a very active lifestyle. And because of this, I am now confined to a wheelchair, will be here for the rest of my life.

So I think it's important that these drugs are studied and that there's an understanding that there can be some very debilitating reactions to them. And I don't know exactly what the right order should be or what the right prescription should be for taking these, but I do think that

extensive blood testing should be at least in order so that we can understand exactly if this blood type could have a type of reaction with the exogenous testosterone causing severe consequences like I have had, and I know there's a number of different cardiovascular and stroke type of incidents.

So in conclusion, I do think it's important that this is studied, that we try to understand what effects this drug has on people. And I promise you that if I would have known about the potential true side effects of AndroGel, that would have included strokes, or heart attacks, or debilitating blood clots, I never would have taken the drug. And I thank you for taking your time today to hear us.

DR. JOHNSON: Thank you very much. Now, we will move on to open public speaker number 14.

DR. WELLS: Hello. I'm Martin Wells, a biostatistician. I have been retained by the counsel for the multi-district litigation. And what I want to talk today about is to further

highlight the excellent presentation we saw this morning by Dr. Falconer about possible sources of heterogeneity in the studies.

So we had a discussion this morning. Dr. Falconer and I had a discussion about the Xu study. And one of the sources of heterogeneity that she did not discuss was funding bias. And so in the original Xu paper, there was a discussion and a funding bias. And he had a paper, essentially a picture of a forest plot that looked like this one. And what I want to do is just re-plot this to give you an idea of how to understand what the magnitude of this funding bias is.

In this forest plot, what happens is that the studies that were not funded by the pharmaceutical industry find a positive relationship between cardiac problems or CV problems and testosterone therapy and those not funded by the pharmaceutical industry do not find one.

So if we look at another type of plot which

is called a forest plot, another forest plot that uses what's called the cumulative frequencies, when you look at this plot, what happens is, you're basically looking at the effect and what the studies are learning over time.

So at the top, you see that there isn't much information and the confidence intervals for the forest plot effects are quite large. And as you go down, you see the confidence intervals get narrower. And what we want to look at is see what's the effect of where the funding kicked in -- and where the studies that were funded, what their effect is in the overall total.

So if we look at a further stratification of this, on the top plot, we see that, in the unfunded studies, you find a quite significant effect, positive relationship, but in other funded studies, you see a quite different model.

So this has implications for if there's going to be further study, you have to decide what the possible heterogeneity is; and whether the funded studies are carried out in a different way

than the unfunded studies, you have to understand what the background is.

So to check the robustness of this, I looked at another set of analyses, another meta-analysis by Corona. It's an extension. It's essentially an extension of the Xu study, and here is the forest plot. And one of the interesting aspects of this is that there's actually a significant difference between these groups. There are some significance tests that one can carry out.

There's a significant difference between the unfunded and the funded studies. And I am using the categorization that was given in the paper. So we can go through and do the cumulative meta-analysis one more time, and almost you see the same story.

Just as we saw in the Xu study, at one point, there is significant information that there is an effect, but then we start looking at the other studies coming in, we'll pull it back over. And we look at the stratification again, and we see the same picture that we saw previously .

We could do this for the MACE events that are another class in the Corona paper. And we see the same story all over again.

Here, we did restrict it to be less, look at where we had more than one event, and we see the same phenomenon. So the conclusion is that, if you're going to design a further study, you need to understand heterogeneity and where that heterogeneity is coming from. Thank you very much.

DR. JOHNSON: Thank you for providing that information. And now we'll go on to open public hearing speaker number 15.

MR. CUNNINGHAM: Hello. My name is Robert Cunningham. I was an AndroGel user. I am 42 years old. When I was 40, I started experiencing the loss of energy and motivation. It bothered me because I was pretty active with the Boy Scouts. I'm a leader with my son's Boy Scout troop. We went on many hikes, backpacking trips, canoe trips.

Around the same time, I noticed ads for testosterone saying that I could get my energy back, so I went and talked to my doctor. He

prescribed me the AndroGel. Three months later, I had a heart attack. I knew I had high cholesterol prior to that, but I didn't think that I was really at risk for a heart attack. I was in denial the whole time I was being diagnosed. I was like, "I can't be having a heart attack."

The doctor told me after my surgery that I had been living with CAD, which is the -- I have forgotten, really nervous here -- thank you, coronary artery disease, and that a clot had caused my heart attack.

I eventually started hearing that there might be a link between taking testosterone treatment and heart attacks, so I went and talked to my cardiologist. And she confirmed that there were studies indicating a higher risk of heart attack. Since I have never really experienced a benefit to taking the testosterone, I didn't think it was worth the risk of continuing the treatment, so I stopped.

My heart attack has had a significant impact on me and my family. There was permanent damage to

the muscles in my heart. Any little pain now in my chest or weird fluttering in my heart kind of freaks me out now and makes me wonder if I am getting ready to have another heart attack.

It's also caused financial hardship. We actually cashed out a life insurance policy to pay the copays and the deductibles, which really didn't cover everything. We're still struggling with the medical expenses for that. Had I known that the testosterone treatment could have caused my heart attack, I wouldn't have taken it. And I really hope that the word gets out to more people who are on the testosterone treatment who don't know that there is an increased risk. Thank you for your time.

DR. JOHNSON: Thank you for your presentation. Now, I'll go on to the 16th open public hearing speaker.

DR. FUGH-BERMAN: Good afternoon. I am Adriane Fugh-Berman. I'm a physician in the Department of Pharmacology and Physiology at Georgetown University Medical Center and also the

Department of Family Medicine. I direct PharmedOut, which is a Georgetown project that promotes rational prescribing.

I'm also a paid expert witness in litigation regarding pharmaceutical marketing, including in testosterone. This is my academic work that I am presenting today and is entirely separate.

You've heard some proponents of testosterone therapy claim that testosterone actually benefits the cardiovascular system. My team at Georgetown has performed a systematic review of randomized controlled trials of testosterone in adult men for various conditions, including cardiovascular health, and that's the section of the systematic review that I am presenting here today.

The evidence supporting the use of testosterone for preventing or treating cardiovascular disease is both inconsistent and unconvincing. Studies of testosterone's effects on angina and brachial artery response are evenly split between positive and negative results. A study on peripheral vascular disease showed no

improvement in any symptoms, any measures. And three studies from the same group found a benefit for congestive heart failure symptoms. One study was stopped early for adverse cardiovascular events.

Lipid effects are mixed. Only 9 of 19 studies showed favorable effects. Two studies actually show unfavorable changes in lipids and 8 studies showed no effects. Some evidence does support an acute and chronic effect of testosterone on increased time to ST segment depression, not a clinical result. Most studies showed no effect of testosterone therapy on inflammatory markers.

Our systematic review found no compelling benefits, cardiovascular or other benefits, for testosterone, which certainly supports the FDA's assessment. We actually analyzed more than 200 studies.

There's growing evidence of cardiovascular risks, and it bears noting that the long-term studies showing no increased cardiovascular risk censored short-term events. Basaria's, Finkle's,

and Xu's studies suggest that risks are highest soon after treatment commences. Omitting short-term results in a long-term study biases the results through depletion of susceptibles. In other words, the surviving cohort appears stronger because of culling of the herd or survival of the fittest. Any studies that examine only prevalent users will suffer from this bias. It's very important to emphasize the studies of new users prospectively.

The use of testosterone among normally aging men is a public health concern. The current labeled indication of testosterone therapy is so broad and so vague that any man with a single low testosterone level can be diagnosed with hypogonadism. Testosterone levels can vary hourly, weekly, and seasonally. Levels are affected by exercise, sexual activity, handling a gun, handling a baby, marriage, divorce, and the performance of one's favorite sports team.

We lack standardized age- and ethnicity-adjusted normal testosterone concentration ranges.

Current assays vary widely and there's no consensus on what constitutes a low level. Although the goal of testosterone therapy is to raise levels into the normal range, what constitutes normal is a hazy and illusive target.

Even a small increased risk may mean thousands of life-threatening cardiovascular events. An absolute increased risk of 0.5 percent means that 1 in 200 testosterone users will have a drug-induced adverse event, and there are 2.3 million men using this drug.

Most patients on testosterone are being treated unsuccessfully for aging. Given that the diagnostics are questionable and the benefits are unconvincing, are the life-threatening risks of testosterone worth taking? I ask the committee to please change the label to limit the use of this drug only to real diseases and real trauma. Thank you.

Clarifying Questions (continued)

DR. JOHNSON: Thank you very much. I would like to thank all of the open public hearing

speakers for your thoughtful comments. I can assure all of you that the advisory committee has heard what you have said, and we will factor that into any recommendations that we make to the FDA.

The open public hearing portion of this meeting is now concluded, and we will no longer get comments from the audience. The committee can now turn its attention to the task at hand, the careful consideration of the data before the committee as well as using the public comments.

So now, we can take the opportunity to add clarifying questions either to our industry representatives and to the FDA. So remember to raise your hand if you have a clarifying question , and please state your name for the record and direct to whom you wish to have your question answered. So to start off with, Dr. Garnick?

DR. GARNICK: Dr. Marc Garnick, Boston. I have a question for Dr. Falconer from your earlier presentation this morning. Is she here? Two questions. One, has the FDA done any compilation of MedWatch reports relating to adverse

cardiovascular effects and any relationship between those and testosterone usage? That's my first question.

DR. FALCONER: I'll defer that question to our Division of Pharmacovigilance.

DR. COTTER: Hi. My name is Samantha Cotter. I'm a safety evaluator with the Division of Pharmacovigilance for the FDA. So despite the limitations of the FAERS database, we did do a descriptive review of the postmarketing safety data. So can I pull up slide 13?

DR. JOHNSON: Which department?

DR. COTTER: The Division of Pharmacovigilance.

DR. JOHNSON: Is this the correct slide?

DR. COTTER: Yes, that's the correct slide. So we did a search of the database. We received 192 reports, of which about 31 of them were eliminated. These are all the reported cardiovascular events that we had in the database. As you can see, there was 65 mild myocardial infarctions, 47 strokes, 13 CABGs, 13 stents. We

had elevated cardiac enzymes, and I think it was 8 patients, angina in 5 patients, 4 transient ischemic attacks, and we had an "other" category that captured patients that had a possible MI, possible stroke. So this was the data that we captured.

DR. GARNICK: They were reported as a result of the physician thinking that there was some relationship between testosterone administration and these events?

DR. COTTER: These were not all reported from the physician. Some of these were direct reports. So as you can see slide 6 for report type.

So as you can see, 13 of these reports were directly submitted to the FDA. 135 came expedited and 13 reports came through periodic. I can't give you an exact number of how many of those were healthcare professionals that provided that data.

DR. GARNICK: In general, do you have any estimate of what's the percentage likelihood of someone reporting an adverse event through the

MedWatch program versus the actual prevalence of that particular product?

DR. COTTER: No. I'm just going to show you the limitations of our spontaneous reporting, which is slide 22. So for disease states with a high background rate like cardiovascular events, where we see 720,000 myocardial infarctions a year according to the CDC and almost 800,000 strokes a year, this is a huge limitation for our FAERS database because we don't have a numerator. There is underreporting. There can be spontaneous reporting due to something that is seen on late-night TV. So we can't come to any causality with this data. We can just do a descriptive analysis of the studies.

DR. GARNICK: Thank you.

May I ask Dr. Falconer my second question?

DR. JOHNSON: Yes. You may.

DR. GARNICK: Dr. Falconer, thank you for that lovely presentation earlier. Did you have a chance or did anyone have a chance to re-categorize the cardiovascular events in either the Finkle or

the Vigen study, similar to what you had done for the meta-analysis? In terms of the actual cardiovascular events, you nicely distilled the ones that seemed to be very, very significant. Was the same analysis done for the two major papers that identified the potential risk?

DR. FALCONER: For those two studies, we didn't need to do that. For the Finkle study, they looked specifically at non-fatal myocardial infarctions, and for the Vigen study, they looked at MI, stroke, and all-cause mortality. Unfortunately, for the all-cause mortality, we weren't able to tell how many were actually related to a cardiovascular death.

DR. GARNICK: Thank you very much.

DR. JOHNSON: Dr. Thomas?

DR. THOMAS: Abraham Thomas. I have two questions, one for maybe Dr. Bhasin and then one for the FDA. The first one is, the problem that we have with this issue is that, at certain levels of testosterone, the benefit is not clear and the risk is not clear, so it's hard to make that

risk/benefit assessment.

But if I look at patients that I see, and I see a certain level of testosterone, usually, if it's in the 50s or less than 100, I'm willing to take that the risk of treatment is less than the benefit of treatment at that range. In the Endocrine Guidelines and other societies' guidelines, they use ranges in the 250 to 300 range, which may be partly contributing to this issue because we don't know what the benefit is.

Is there a number maybe in the deliberations that we were going on originally in these guidelines, where people feel very comfortable that the benefits would outweigh the risks?

DR. JAIN: Dr. Bhasin?

DR. BHASIN: Dr. Thomas, as I mentioned in my presentation, men with classical hypogonadism due to known diseases of the testes, pituitary, and the hypothalamus, and then the risk/benefit ratio appears favorable -- so the patient that you describe, too, has very low testosterone levels of, say, 50 nanograms per deciliter or 100 nanograms

per deciliter.

There, the likelihood that the real testosterone level is really low is high, and the risk of misclassification is lower. But when patients, even those with known diseases of the testes, pituitary, and hypothalamus have testosterone concentrations in the borderline zone, because of a variety of factors, including the diurnal ultradian circannual rhythms as well as variations in testosterone measurements and due to genetic factors.

The risk of misclassification is very high. And I agree with Dr. Snyder that in these individuals, measurement of free testosterone and repeating testosterone concentration several times, especially in the morning using reliable assays, is very essential to reduce the risk of misclassification.

DR. JAIN: I'm sorry.

DR. THOMAS: I'm glad to hear that opinion, but it also is irrelevant in terms of the fact that we know that 21 percent or more people don't even

get a testosterone level. And then, when they do get a testosterone level, we don't know if it's measured correctly or the right time, so that might be something very important as we make considerations for labeling.

The question for the FDA is one of the public hearing speakers showed that the amount of events that's being reported has increased dramatically over the last few years, especially for preparations that are dermally absorbed. The question I had is, there could be reasons for that, a variety of reasons.

One could be, there's just more events. It could be that there is the same rate of events, but more people are taking prescriptions. But I am just curious if there's any information about what happens when publicity occurs regarding a drug or drug class. For example, I know clinically, in practice, for the last few years, I've been getting many, many more patients who want testosterone.

But when the news came out about people maybe having heart attacks from testosterone, I

started to get people, including patients who had been on it, prescribed by their physicians, wondering if they should go off testosterone. So I'm just wondering if there's an impact of either reporting from the FDA or advertising from law firms that suddenly has an impact on the adverse reporting.

DR. NGUYEN: If I may ask Samantha Cotter from the Division of Pharmacovigilance to address that question.

DR. COTTER: Just to show you the reporting trends, if we could show slide 11. This would be the reporting trends for what we have seen since the early '80s to recently. And as we can see -- and this may correlate with drug-use data. However, you see in the block from the early '80s there was only 3 reports that were coming in for cardiovascular events of interest.

However, in the last four years, we've had 89 reports come in for cardiovascular events of interest. So this may correlate with the drug-use increase. And I don't know if you want somebody

else to speak to the rest of your question.

DR. THOMAS: If you have information with someone else, if not, that's fine.

DR. IYASU: Let me try to answer. As you know, these are spontaneous reports, so they are subject to a number of limitations, as has already been stated. When there is publicity around a particular safety issue, we do see what we call a phenomenon, which is stimulated reporting.

Whether that increase represents an increase that it could quantify in terms of an increase in risk versus whether these are reports that are not being reported, but now, because there's an increasing awareness, they are being reported. And remember that spontaneous reporting systems are trying to capture information based on whether there is some suspected association with an event and a drug exposure.

They don't necessarily have to prove before reporting that they are related. So there are a number of interpretation challenges to looking at trends, especially when you're looking at numerated

data, which is subject to a lot of underreporting and also the fact that we don't have any exact denominative data to say this is an incidence rate that we can measure over time to make conclusions about trends.

DR. JOHNSON: We are going to go on with more qualifying questions. I know that the industry wishes to clarify something from earlier something, if you want to do that first. And then we'll go on with Dr. Curtis, and then Dr. Braunstein.

DR. JAIN: Ms. Rockney?

MS. ROCKNEY: Yes. Tracy Rockney, AbbVie regulatory affairs. Dr. Braunstein, earlier, I understood your question earlier today related to direct-to-consumer to be direct-to-consumer television advertising. So sponsors have discontinued direct-to-consumer television advertising as of June, like I stated. If sponsors elect to do new TV ads, we will not run new TV ads until we receive advisory comments from the Office of Prescription Drug Promotion, which has been and

will continue to be our customary practice.

DR. BRAUNSTEIN: I was also referring to print information as well as some of the internet information.

DR. JAIN: Ms. Rockney?

MS. ROCKNEY: As Dr. Jain has indicated earlier, based upon the feedback today, sponsors are committed to working with the FDA on revised labeling as well as revising promotional and educational efforts. So we would anticipate continuing to communicate to consumers based upon the feedback we receive today.

DR. JOHNSON: Dr. Curtis?

DR. CURTIS: Kate Curtis. So this is a general question, but maybe either Dr. Jain or Dr. Falconer would want to answer. We have heard a lot today about the limitations of both the observational studies and the RCTs in looking at safety data. And clearly, I am trying to think about whether the observational studies or an observational study in the future has any advantage over an RCT. Clearly, the one main advantage would

be larger numbers.

Specifically looking at the administrative databases, you can get large sample sizes and a large number of events, but they come with all the limitations of observational studies and sometimes even more lack of confirmation benefit exposure, lack of confirmation of outcome, and lack of some of the key potential confounders.

So, Dr. Jain, I was interested to see that you mentioned three ongoing studies looking at safety using large administrative databases. And I was just wondering whether you or maybe someone from FDA could help us think about the advantages and disadvantages of using those large administrative databases and whether this is something that should be considered.

DR. JAIN: I can start, and certainly I will turn it back over to FDA. And really, the point that we were making earlier today was that, based on our review of the available information, we found insufficient evidence to suggest a causal association between TRT use and increased

cardiovascular risk, but we also acknowledged the limitations of currently available data.

So what we were intending with these studies is to show you three studies that are ongoing that would report by mid-next year. These may face some of the same challenges as previously conducted observational studies, and our intent was not to say that these studies would be definitive. They would just add information to what is currently understood.

I think, in parallel with that, we would anticipate having dialogue with FDA and possibly other stakeholders to think about what the right next steps are. I mean, certainly, as FDA indicated in their briefing document, there are multiple approaches. Each has its own pros and cons and its own timelines.

We're not suggesting that one approach only is the right approach. We're open to the dialogue to understand the best path forward. And it may be that some of these studies may provide nearer-term data for us to better even inform other studies.

DR. JOHNSON: Dr. Burman?

DR. BURMAN: Thank you. This is either for Dr. Snyder or Dr. Bhasin. The serum testosterone level is obviously the cornerstone of the diagnosis of hypogonadism. But we haven't talked yet in much detail about the measurement of testosterone. And there's a large debate even among the Endocrine Society whether testosterone levels should be measured by immunoassay total levels or by tandem mass spec, with some investigators believing that it should only be measured by tandem mass spec because you get so many falsely low values or abnormal values with total testosterone measured by immunoassay or by ELISA. Do you have any thoughts on that?

DR. SNYDER: My understanding is that most investigators in the field of testosterone research think that tandem mass spec is the current gold standard. And not that it's perfect; no test is. And that is the method that is being harmonized by the CDC program.

So I think it's fair to say that is the test

that should be used in all current and future studies of testosterone.

DR. BURMAN: But if I might, isn't it correct that in most of the studies, observational and controlled trials that have been presented to date today, that the measurements haven't been by tandem mass spec.

DR. SNYDER: That's correct because those studies were performed in the past. Yes. That's absolutely correct.

DR. JAIN: Dr. Bhasin will add a comment if that's acceptable, Dr. Snyder.

DR. BHASIN: I agree with Dr. Snyder's comments that LT tandem mass spectrometry has greatly enhanced the accuracy as well as precision of testosterone assays. And with the involvement of CDC's host program to harmonize testosterone assays, the intralaboratory variation between testosterone values that are CDC-certified currently, by labs that are certified by CDC's host program, has come down very, very substantially.

So both the availability of a Nest

calibrator and the CDC's host program, and the advent of LC-MS/MS has greatly reduced the intralaboratory differences that were commonplace just a few years ago. In addition, the other effort that was significant is the effort under Endocrine Society's leadership PATH program. There's an effort to harmonize reference ranges across different laboratories and across epidemiologic studies.

So that effort, I think also, will allow common harmonized reference ranges, which will also reduce the variability and reduce the risk of misclassification.

DR. JOHNSON: Dr. Braunstein?

DR. BRAUNSTEIN: Glenn Braunstein. For Dr. Bhasin and maybe Dr. Snyder, we know that the T-trial is a prospective controlled trial, but it's limited to individuals over the age of 65, looking for efficacy. And even if efficacy is found in that group, the largest group of individuals who are using testosterone are those in the age range of 45 to 64. Do you know of any prospective trials

going on that are going to answer efficacy information in that group, or do you expect that we're going to have to just extrapolate the data from the T-trial and the 65-and-older group to the younger group.

DR. SNYDER: Eighty-five?

(Laughter.)

DR. BRAUNSTEIN: No, 65.

DR. SNYDER: That was a joke. So not only do I not know of any prospective trials in men, say, 45 to 65, but based on the fact that to recruit a sufficient number of men for the testosterone trials, men over 65 who had a testosterone concentration less than 275 on two occasions early in the morning, our yield based on testosterone alone was 14 percent.

Now, the prevalence of low testosterone in men who are younger is much lower than in men over 65. I think it is totally impractical to even think of such a study in men who are 45 to 65 unless one is recruiting from a population of people who have pituitary tumors, in which case,

again, the population would be relatively small and it would be too small to assess cardiovascular risk.

DR. BRAUNSTEIN: I am specifically talking about the late onset group. Yes.

DR. SNYDER: I'd say under 65 is early onset.

DR. JOHNSON: Thank you very much to everyone for answering the questions.

Ms. Nguyen, did you have a question, Dr. Nguyen?

DR. NGUYEN: Christine Nguyen from the FDA. I just want to clarify on an FDA response to a question about the impact of labeling on use behavior. It not only impacts promotional materials, but certainly it helps to guide recommendations to practitioners either through educational materials or guidelines, issued by professional societies.

Last but not least, it certainly can impact insurance coverage. So I just want to make sure that there are other consequences beyond just

changing advertisement.

DR. JOHNSON: Thank you very much.

DR. JAIN: I just wanted to follow up on the last question that Dr. Snyder started to respond to for the T-trials. We did mention earlier today the trial being done by Lilly. It's clearly a different design and a different population, which we will mention.

That said, we also are not suggesting this study or other studies are the definitive studies in this space. We're just trying to highlight some of the research that is ongoing, that may start to add to the body of information. And this is one randomized controlled trial that's being done, that allows inclusion of a younger population.

DR. KINCHEN: Kraig Kinchen, Eli Lilly. Just a quick note on that study. At least on a preliminary assessment of baseline data, that of the 715 men, approximately 60 percent of those are between the ages of 45 and 64.

DR. JOHNSON: Thank you. We do have two additional questions, and then we'll have an end to

our questions. Dr. Howards?

DR. HOWARDS: I have a comment, not a question. Is that okay?

DR. JOHNSON: Yes, sir.

DR. HOWARDS: Twenty-one percent of men, in some of the data shown today, did not have a T before being treated. And one speaker mentioned this, but I'd like to reemphasize it. It depends on the database. For example, if I see a man who has had two or three testosterone levels from an outside provider, I will not necessarily repeat the testosterone. I often would, but would not necessarily.

Therefore, he would go down, if that outside provider was not in our database, the same database, as not having testosterone, but he did have testosterone. So I would say that the 21 percent is an overestimate.

DR. JOHNSON: Dr. Teerlink?

DR. TEERLINK: I thought there was an interesting comment earlier, many interesting comments earlier, one of which was, "Hey, should we

really be bound by what happened in 1981 going forward?" And I think it's pretty clear, to me at least, that there's no way that testosterone would be approved for the treatment of age-related low T by current contemporary regulatory standards.

From my understanding of the data so far, we have absolutely no evidence for any efficacy other than a PK study, which may or may not be relevant to this group. We have no evidence of any clinical benefit to patients. We have questions about clinical safety.

So I am interested in, whoever from the sponsor would like to address this, those of you who prescribe for age-related low T, when you're talking to the patient, what do you tell them in terms of what you're saying, why they are taking this drug?

DR. JAIN: I will start, and then I might ask Dr. Dobs just to comment from a clinical perspective. And if I may, go to the labeling promotion education slide from the main deck, please.

So as we discussed earlier today, we certainly do recognize the limitations of data in less-defined populations, including age-related hypogonadism. And with that, we are seeking very short-term dialogue with FDA as soon as they are available to discuss how to inform on that information within the label to have information that discusses the limitations of data.

DR. TEERLINK: When you say limitations, you mean absence? Is that what you're saying?

DR. JAIN: It's not complete absence, but there are substantial limitations and the reason --

DR. TEERLINK: So you have evidence on clinical benefit that show it does --

DR. JAIN: So my point simply there is that, as was discussed with the benefits data that was presented earlier, many of those studies included heterogeneous patient populations and were not necessarily restricted to classical hypogonadism. Many of those studies enrolled mixed populations of patients, but because they were not designed as

registration-style studies and because it was not systematically studied, I can't provide the type of data that you're looking for, that we would --

DR. TEERLINK: So there's no regulatory standard evidence of clinical benefit.

DR. JAIN: Right. And so we're trying to indicate that information and to reflect it in promotional and educational activities. We also recognize and are planning to engage in further dialogue with FDA on obtaining additional information.

Our point of highlighting ongoing studies was simply to say there's some data that may become available by the first half of next year that could also substantially inform this space, not that it would definitively inform the space, but it might provide some directional information.

DR. JOHNSON: Thank you very much.

DR. JAIN: Then in terms of how people approach this in clinical practice, Dr. Dobs could suggest how that is done.

DR. DOBS: It is always a dialogue in

deciding --

DR. JOHNSON: Kindly make this short. Thank you.

DR. DOBS: It's a dialogue, and we base it on the level. We base it on the symptoms. We base it on the response. We base it on the end organs that might have been affected, meaning someone who has a low bone mineral density at baseline, that would be somebody we might be more interested in discussing that should be treated. But there's oftentimes men that we don't treat and we just follow.

DR. TEERLINK: Do you tell them in terms of what the benefit from that treatment will be, and what's the basis for that, saying that that's the benefit in this low T population?

DR. DOBS: We could certainly talk about bone marrow density very confidently, that it does increase bone mineral density, particularly in the spine. It does change body composition. Whether or not that translates into a function outcome is not clear.

Recall that testosterone was first around with the endocrine paradigm. If it's low, one tends to treat it. And Dr. Snyder certainly showed convincing data in a very hypogonadal population --

DR. JOHNSON: Thank you very much. I appreciate that. Thank you.

We had one comment from Dr. Staffa.

DR. STAFFA: Judy Staffa from Epidemiology. We didn't get a chance to respond to Dr. Curtis' question about epidemiology studies that we're considering. We are actually considering epidemiology studies, and we haven't come to a determination of whether we have the kind of data available to us and administrative data that we would like to see, that Dr. Falconer described in her last slide, the kind of granular clinical data about indication for use, and both baseline and ongoing testosterone-level measurements.

So I'm wondering if the sponsor could share some information about the retrospective studies they mentioned, that are ongoing. Will any of

those have that kind of information included in them?

DR. JAIN: Christian Conradt. And if we could, pull up the slide of the NIH studies.

DR. STAFFA: Actually, it's the observational -- yes, those.

DR. CONRADT: Christian Conradt from AbbVie Pharmacoepidemiology. I am happy to share with you the information, which is available to us, which is the public information we could get about these studies. So these are by no way funded by the industries. They are funded by the NIH alone. So it is to be mentioned that, for example, the Kaiser Foundation database is going to use as well healthcare records and it is going to use as well laboratory data.

So the same is going to be true for the U.K. GPRD study.

Questions to Committee and Discussion

DR. JOHNSON: Thank you very much. Thank you to both the FDA and to our industry sponsors for answering all of our questions. We sincerely

appreciate it.

Now, I'd like to prepare for the panel discussion portion of our meeting. And I am going to warn Dr. Gordon that he is going to be the first one because he's on the end of the table, to be able to bring forward his thoughts.

What we will do now is begin with the questions. We will then do the votes. Is that correct, Dr. Joffe?

DR. JOFFE: Correct.

DR. JOHNSON: Thank you. So although this portion is open to public observers, public attendees may not participate except at the specific request of the panel. So allow me to start with question number 1. And this and question number 2 are really just topics for discussion, so I am asking the advisory committee to give your opinions, your thoughts after all you've heard today in regards to these topics.

I will read to you question 1. The current approach to establishing the efficacy and safety of testosterone products for marketing approval is

based on the pharmacokinetic assessments of serum testosterone concentrations and acceptable safety profile.

The product must be able to reliably raise low serum testosterone concentrations into the normal range for healthy eugonadal men. FDA does not require a demonstration that testosterone products ameliorate or improve any specific hypogonadal signs or symptoms.

So as members of the advisory committee, we are being asked, first, discuss specific patient populations for which approval is supported based on data generated from this current approach. And then secondly, also address the issue of discussion of changes that would be needed in the current development paradigm to support an indication for testosterone replacement therapy in men with age-related hypogonadism.

I have a question from Dr. Lincoff. Great. With both of these questions, we're going to go around the room, and I'll be taking notes as you speak with your thoughts on this topic.

DR. GORDON: So just briefly, I would say that, while ideally you may be able to do these things, I think what we've heard today is that, in practice, that's very hard to achieve. I don't think we've heard very much in terms of the longitudinal monitoring that goes on with patients under treatment to make sure that they stay within these guidelines. So that's one concern that I would raise.

Another thing is, with regards to the fact that, if you just make these changes in labeling, we also fully acknowledge and have seen that, obviously, the labeling that is there today isn't being followed because the treatment patterns are for patients that you have to work somewhat to get into the label. And I think, if that were changed, that would be probably a positive feature.

Those are my two biggest observations. I wouldn't speculate on how you would get the age-related hypogonadism into an indication because I don't think we have any evidence that there is benefit in that indication.

DR. JOHNSON: Thank you very much. And Dr. Boineau?

DR. BOINEAU: I think that we have a huge shortage with the approach that has been taken so far in conducting research to identify patients that will benefit from this therapy. I think we need to know that there is a benefit from this therapy and patients that are treated. I think we have also seen, in looking at the data today, the data, when it's not a randomized controlled trial or an observational study, it doesn't collect sufficient data to indicate the patients that are on the therapy, whether their testosterone level measured is measured on repeated occasions, is low, is using a valid measurement, as well as follow-up.

I think there's a huge problem with not collecting signs and symptoms prior to the conduct and then seeing if there is improvement with those signs and symptoms. And there's a shortage of having a questionnaire that hasn't been validated or approved by the FDA.

So I think there's a huge amount of things

that can be done with classic large simple trials that are randomized to assess who will benefit. But I think with the current indications, we don't have valid information to say that this is a helpful therapy for a large proportion of the patients that are currently using this.

DR. JOHNSON: Thank you. Dr. Thomas?

DR. THOMAS: Abraham Thomas. So for the first part, it's the specific patient population. I think for most of us as endocrinologists and other physicians who treat this, the classic hypogonadal patient, even if it's not specifically from pituitary disease or a testicular problem that has a very low testosterone, less than 100 maybe or even slightly above that, it becomes fairly clear to treat that patient for potential benefits, even though long-term benefits haven't been shown for that group, either, though we assume that there are for bone and other reasons.

The murkiness, as Dr. Bhasin said, it's very hard to classify some of these patients who have testosterone levels above that, but below 300. You

can misclassify.

So as part of question B is, really, if you want to have an indication for age-related hypogonadism, you really have to show benefit on that group because then you don't know what's an acceptable risk because you don't really know what the benefit is.

I think the Institute of Medicine had it right. First, you show that there's a benefit for treatment. And then you should be doing the assessment for risk. If you think about all drug development, initial trials, look at pharmacokinetics, and they look at efficacy and safety. And really, it's the later stages that safety becomes even more prominent, especially in my background, which has been diabetes drugs and obesity drugs.

Clearly, you wouldn't go onto the cardiovascular safety trials until you had some notion that there was some efficacy.

DR. JOHNSON: Thank you. Dr. Garnick?

DR. GARNICK: Marc Garnick, Boston. In

addition to the primary and secondary hypogonadal populations, the aging male andropause patient is an appropriate patient population for consideration. However, the criteria must be much more precise. For example, in my own practice, the long-term effects of the androgen deficiency that is induced pharmacologically are potentially devastating, and large populations who experience transient androgen deprivation therapy are significantly improved when endogenous testosterone values are restored and the HTPXs recovers.

So in the aging male andropause population, I would also include those with the appropriately valued low testosterone, those with erectile dysfunction, loss of libido, loss of nocturnal erections, those with diminution of bone mineral density. But in order to address these populations, it is mandatory that a minimum baseline testosterone be obtained in any population that's studied.

In addition, a detailed cardiovascular history should be obtained and may need to include

a baseline ECG. We also need in any patient population quality-of-life measurements and instruments that need to be routinely monitored. Not uncommonly, as we heard today, replacement of testosterone does not result in any meaningful improvements. So instruments to adequately measure outcomes, both positive and negative, need to be implemented at regular intervals and a call for utility needs to be addressed.

I do believe that under the Madison Avenue catch-all term of low T, it does have some validity, but it has been totally, in my opinion, abused and misrepresented. Moreover, although this meeting has been focused on cardiovascular issues, underlying all of these potential indications is an assessment of prostate health. This cannot be underestimated and information, however flawed and incomplete, relating testosterone physiology to prostate health needs to be outlined and understood.

PSA values on the whole do not rise with T replacement. However, I can cite numerous

occasions where an individual patient did not follow this norm and, either coincidentally or spontaneously, prostate cancer was unmasked in this population. There's just simply not enough level 1 evidence to sort this out.

In my opinion, business as usual cannot go on, given the ambiguities in other matters that need to be addressed in the variation of the definition of hypogonadal levels of testosterone. And we have to have some credible lab certification for those labs performing testosterone testing.

In reference to question 1B, age-related use of testosterone for age-related hypogonadism needs a significant overhaul. It is the marketing of this indication which may in the end be valid that needs more study. Critical aspects that are must-haves include baseline testosterone measurements, the criteria for the presence of symptoms related to hypogonadism, T levels, concomitant meds, cardiovascular history, prostate history, bone density, hemoglobin and hematocrit, and some triggers for the indication, perhaps come

up with a scoring system that identifies the likelihood of T-related symptoms.

Post-initiation of therapy, we need to monitor testosterone levels, hemoglobin, and hematocrit, bone mineral density periodically, PSA periodically, cardiovascular symptoms, maybe lipids and liver function studies. And assessment of these responses should be done periodically.

Given the T replacement, and the benefit, and the doubts have been voiced today. We really need to address these in a much more organized fashion than has been done so far.

DR. JOHNSON: Thank you. Dr. Teerlink?

DR. TEERLINK: There's only so far one can kind of turn the clock back on what's been done. So I think, obviously, the current label as it was intended, I think this is where we can go back to our forefathers and try to go to original intent, and try to see if you can write a label that incorporates that original intent.

So that's the specific patient populations for which approval that we have so far, I think

appropriate.

In terms of the changes need to be current development paradigm to support an age-related hypogonadism. I think the good old standard of, "You need to show us that you make a patient feel better or live longer," and you need to be able to do a study that actually shows that.

I think, when we see 1 million new prescriptions for something, I have a sense that we'd probably be able to get patients for a trial. It seems like it would be feasible with that issue, especially since my patients who are 80 are banging down the door on me who have heart failure, asking for it because they are interested in it.

I think we also need to try to define the disease is a bit separate from the normal process of aging. The sponsor themselves said 1 to 2 percent age-related decrease in testosterones from the age of 40 on. So how do we distinguish the disease from the normal aging process? And I think that's something that's incumbent upon the scientific community and everybody else to help out

with. And I'll stop there.

DR. JOHNSON: Dr. Domanski

DR. DOMANSKI: I think one of the things that's interesting about all this is, the data are as weak as they are. I mean, we really don't know whether these drugs are effective for anything. And we don't have much of a signal for harm, either, so we're sort of starting from scratch.

I would suggest that the FDA stick close to its roots, which is to demonstrate safety and efficacy before they approve a drug for marketing or certainly label it. So I think speaking perhaps specifically to B, I think somebody coming with a drug asking for a label that talks about age-related hypogonadism should be forced to show that the drug is safe -- that it's effective, first of all, for the intended purpose. I think that intended purpose really ought to be something that's clinically important.

I have some doubts about libido, et cetera, and forms for it. I suppose one could include that, but I think osteoporosis, things with

reasonably hard clinical endpoints in terms of effectiveness would be of some interest. And secondly, of course, safety signals -- the trial needs to be suitably powered to show safety signals for a cardiovascular endpoint because there is some signal there.

So I think suitably powered clinical trial, randomized clinical trial showing safety and efficacy of hard clinical endpoints.

DR. JOHNSON: Thank you. Dr. Shehab?

DR. SHEHAB: I concur with the previous speakers that the current drug development paradigm is probably too vague to allow for determining which populations these products are clinically indicated for. And I would encourage the FDA to consider a drug development paradigm or approval process that more closely mimics what we would expect for FDA-approved drugs today, whereby if a product or a sponsor wants to gain a label for a certain clinical indication, they come with the efficacy and safety studies to support that indication.

In that regard, I wondered if the FDA would consider separating classical hypogonadism, such as those two, primary or secondary hypogonadism from age-related hypogonadism and other indications. It's probably fine to continue with the current drug development paradigm and the label for the primary and secondary hypogonadism, where we know that the premise of testosterone replacement is probably very reasonable and there are sufficiently low testosterone levels there to support the use of testosterone products, but it's not the same for age-related hypogonadism and other indications for which there has been no safety or efficacy data.

So in that regard, I would just, again, to reiterate what the previous speakers have said, for any new products that are seeking that indication on the label, the eligibility criteria in those clinical trials reflect the properly-indicated population.

DR. JOHNSON: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: Actually, Dr. Shehab stole my thunder quite a bit. I think the current label

is actually quite well written, with a proviso that there's that one little wiggle room phrase for idiopathic hypogonadism, which maybe could be tightened up. But I do think there's a dichotomization here. And the dichotomization is we clearly have individuals who need to have their testosterone normalized due to either primary or secondary failure, hypothalamic or testicular failure. Then we have this other group that has been introduced, which is this age-related group.

I agree with what has been said by other members of the panel. I am not sure we have ample evidence to support any effect in that population. And so I think a separate developmental strategy, which would involve, again, something maybe more akin to my world of urology, what has been paired with BPH, which is a composite of measurables plus symptoms, whether we do a composite, or we do coprimaries, or whatnot.

This is a plea to industry. PROs are going to be very important in this condition because PROs do impact patient decision-making, which will be my

last point. And there's no point in having 16 PROs, folks. We should have one. So why not get you guys together and develop one as a confluence of resources? It'll save you money and it'll really stop putting a lot of garbage in the literature.

The other thing is that, in my experience as a urologist, patients come in exactly as our public members. They don't come in because of bone density. They come in because they are fatigued or they are concerned about their libido, and that's what they want treatment for.

So obviously, these have to be considerations. And one of the pleas -- and this may be getting a little bit outside drug development, but it does get to the quality-of-care issue -- is the concept of paired decision-making in patient education. And I believe I heard both of the individuals who had had complications from a testosterone formulation saying they were unaware of the complication.

That does place an onus on the provider for

education, but also on the purveyors of these products to do a better job educating. And we can have quite literate individuals who just simply don't get the message. And we've got to figure out how better to have a paired decision-making model for a condition that is clearly not -- which is quality-of-life-threatening, but not life-threatening, per se.

DR. JOHNSON: Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. Glenn Braunstein. For the patients with classical hypogonadism, that is primary hypogonadism due to a testicular disorder or secondary hypogonadism with either structural or infiltrative pituitary hypothalamic disease, clearly, I think the current protocol for using pharmacokinetic assessment to approve a testosterone product is sufficient. There is ample data in the literature supporting the use in the classical group.

For the individuals in group 3 of Dr. Snyder's presentation, those who have symptoms that could be caused by a low testosterone level

have normal levels, I don't think testosterone is indicated in that group and it should be clearly discouraged. It's the group of age-related hypogonadism patients that are the most vexing.

We are going to get some data soon from the testosterone trial. Next year, it should be out. And so I do think that we need to wait for those results to see if indeed testosterone is efficacious in the 65-year-old or older group, with symptoms and low testosterone.

If it is, then I think that the current approach is probably appropriate for that group once you set up a diagnostic paradigm. And until that takes place, I don't think we should change very much except to provide clinicians with a clear-cut algorithm, if you will, of how to approach this.

The approach should be that patients, number one, need to have symptoms. Number two, they need to have low testosterone. It can't be just a single testosterone measurement. It has to be collected in the morning, preferably measured by GC

tandem mass spec.

Then it needs to be confirmed with another sample taken another time. I prefer to also confirm it with free testosterone measurements because there are a number of individuals who are obese and overweight, where their SHBG levels are low. Therefore, their total testosterone would be low., but their free testosterone may be normal.

So you may actually eliminate some individuals who have some symptoms, but a low total testosterone, but have a normal free testosterone. And then I would give very clear instructions on what levels one should aim for and how long one should give a treatment trial before saying that it's either working or not working and making a decision at that point.

All that, of course, should be modified based on the results from the testosterone trial. And if those results are very positive, then I would strongly advocate that a trial be carried out in the 45 to 64 year old group because I don't think -- we can always extrapolate data from

65-and-olders to 45 to 65, even though we are trying to extrapolate data from very young men with a normal range of testosterone to older individuals and say that's the level we should be shooting for.

So basically, I think, at the present time, the current approach is okay for the classical group.

DR. JOHNSON: Dr. Burman?

DR. BURMAN: Thank you. I think the present indications are insufficient and incomplete based on what we know in 2014 and that serum testosterone levels are the cornerstone of the diagnosis of hypogonadism, but as we've seen today, multiple caveats are noted. There's diurnal variation, and we have to be careful to recommend monitoring in the morning and drawing it twice.

As the Endocrine Society recommends, FSH, and LH, and probably testosterone or pulsatile as well. And we have heard today that multiple comorbidities lower total testosterone and maybe free testosterone, but it's difficult to know what's primary and what's secondary. As

endocrinologists, at present, we considered the changes in testosterone with comorbidities to be secondary to the comorbidities and not to be primary.

We talked a little bit about serum SHBG and free testosterone and emphasized that total testosterone has to be measured accurately, probably with tandem mass spec. It is mandatory that all patients have testosterone levels, physical exam, and signs and symptoms evaluated both prior to and during monitoring on several occasions.

There is an active debate, as we've discussed, regarding the measurement of total testosterone, free testosterone, and SHBG. As I asked a question earlier, it sounds like most of the authority recommend measuring total testosterone alone unless there is a specific reason to suggest low SHBG, which the Endocrine Society recommends as well.

I think it's essential that these issues be mentioned in the package insert as well as the

populations studied where the data are insufficient for benefits, efficacy, and safety. And that's specifically the low T and the older men.

DR. JOHNSON: Thank you. And Dr. Lincoff?

DR. LINCOFF: Mike Lincoff. So I certainly agree with my colleagues that the established group of primary and secondary for which there is established pathology, I think this paradigm is fairly well appropriate, as it fits under the endocrine paradigm of replacing a missing hormone. I also agree with much of the sentiment and want to emphasize the idea that we don't really know that this aging-associated low testosterone is in fact a disease at all and that there are very few conditions that have such spontaneous waxing and waning of symptoms, vagueness of symptoms, symptoms that are so subject to placebo, that we would accept this level of absence of data to allow a drug that has potential adverse effects to be used broadly.

So I strongly agree that we need randomized trials using endpoints that really relate to

measurements of patient well-being that can determine once and for all, if there really are, benefits in this population. This is inextricably linked to the safety. I recognize that it is maybe best to move in a step-wise fashion with efficacy determined and then safety.

But whatever magnitude of efficacy, assuming efficacy is shown there is will have to be balanced against safety. And we can dissect the different studies that have been done with regard to the cardiovascular endpoints and say this was flawed this way and this was flawed that way. But the bottom line is, there is a pathophysiologic and biologic plausibility for potential cardiovascular effects, both positive and negative.

We can look at surrogates as much as we want, but all surrogates can eventually fail us. There are signals of clinical harm that may or may not be true, but it needs to be sorted out because this is a population, obviously, that is at high risk for the cardiovascular endpoints, especially with long-term therapy, and it must be sorted out.

And the only way to sort it out is with a properly sized randomized controlled trial looking for cardiovascular endpoints in the population this is going to be tested.

It's always frightening to consider trials of this size, but there's tremendous precedent that this has already been done with populations that have event rates as low as or lower, for example, the drive now to do this with all the obesity drugs.

So these are patients that, if anything, will have lower rates than this population of middle-aged and older men. So to say that it can't be done or that it's impractical is wrong. It can be done. And if we don't do it, we risk repeating the experience of post-menopausal hormone replacement therapy.

There is no amount of experience or registries, or observational data that will overcome the intrinsic flaws of those types of data. And this is such an important question affecting such a large population of patients at

risk that there is no way around this.

I would strongly urge that there be some sort of regulatory requirement of the companies to prove cardiovascular safety.

DR. JOHNSON: Dr. Alexander?

DR. ALEXANDER: Richard Alexander. First, I can't completely agree with the statement that there's no evidence that testosterone has any efficacy in helping any complaints that patients have. The FDA briefing document is full of examples, certainly not definitive, but certainly not zero evidence in support of all of the types of symptoms that men will present with. So I would first say that.

Second, my feeling is that we are treating people who have to have a complaint. They have to have something wrong with them, either subjectively as what they express as a symptom or objectively like bone density, but as someone has said, that's rarely what patients come in with, but at least as an objective measure. And obviously, they must have low testosterone.

Now, we shouldn't be screening for low testosterone, and that's sort of what I'm hearing, that patients have to have something that we can attempt to make better.

For example, many of my patients will say, I have low libido. I have erectile dysfunction. I have lack of erotic stimuli. And none of those make any difference in my life at all. So patients without a problem, in my view, don't really need a solution.

So I agree that the real answer to answering all of these questions is a large-scale something, like the women's health study, randomized trial. The T-studies that have been alluded to will give information about efficacy. And that can be then rolled into the design of a study if T supplementation in aging men can be safe and effective.

It obviously has to be powered to detect the cardiovascular effects and any other potential side effects that may be important, but have not clearly been associated with T supplementation.

We also may consider designing such a trial to look at people with clearly low testosterone, not just borderline low, where patients come in and say, "Look, it's right at the lower limit of normal. Please, can I go ahead and have this?" So patients who are clearly hypogonadal -- if we don't help them, if there's not efficacy in that population, then I think it would be highly unlikely that we would find it in men with higher testosterone.

So I agree that the paradigm of the way this came about was the FDA was interested only in objective findings. And I think they are coming to realize that there's much more to it than that. And the way of the world today is that these drugs are not -- we talk about this primary and secondary hypogonadism. That's got to be incredibly rare compared to use of the drug for age-related hypogonad age-related hypogonadism.

So I think it's time for us to really, as many have said, to design a really large-scale randomized trial that all these stakeholders should

be participating in to finally get an answer that we can all believe.

DR. JOHNSON: Dr. Adler?

DR. ADLER: Robert Adler. I agree with my colleagues about treatment of those men who have classic or what I would call organic causes of hypogonadism. But I'd really like to talk about the aging-associated hypogonadism.

I was one of the people who disagreed with the Institute of Medicine on the desire to do small efficacy studies at first, and even tried to do the kind of study that we're all talking about today because I predicted, quite right, more than 20 years ago, that if we did small studies, we would still be stuck, as we are now. And I wanted to do a study that had hard outcomes, hard cardiovascular outcomes, hard bone outcomes, that is fracture, with prostate and cardiac safety built in. And it would take thousands of men to do it, but unfortunately, I couldn't get funding for doing this and we might have the answer today.

So we really are stuck because of the

paucity of the data. I can tell you, with the patients that I see, many of them have those comorbidities that are associated with low testosterone, obesity, and diabetes, opiate use, PTSD and other kinds of depression, chronic illness. And whenever possible, I try to discuss this with the patient and try to address the comorbidities.

Of course, there's fairly good evidence. For example, with bariatric surgery for obesity, that testosterone levels improve, estrogen levels go down. And I think that's a more natural way, perhaps, to improve testosterone.

I'd also like to say that the evidence that many men use the testosterone preparations for a short time is pretty good evidence, circumstantial to be sure, that it's not a panacea, that many of these nonspecific symptoms are not relieved by the short-term use.

Finally, I'd like to remind everyone that the Endocrine Society Male Osteoporosis Guideline did not advocate testosterone for osteoporosis or a

low bone mass in men, but rather use an osteoporosis-specific drug because there's no evidence that even though testosterone increases bone density -- and I think it does and there's good evidence for that -- there's no evidence that it decreases fracture risk.

So there is now some evidence that this phosphonate does decrease at least vertebral fracture risk in men treated for osteoporosis, including some who are hypogonadal, so I don't think that we can use a low bone density necessarily as a reason not to treat patients.

So I think we dichotomize, again, as has been stated, to those people, those men who have true organic hypogonadism, I have no problem with the present indication. But I do think we have to make changes for those with the associated testosterone lack with aging.

DR. JOHNSON: Dr. Herring?

DR. HERRING: Thank you. I agree with me and colleagues that the current strategy is sufficient for the diagnosis of straight classical

hypogonadism, with a caveat shared by Dr. Braunstein, that it's unclear to me that it's appropriate to restore to the levels in healthy young males instead of to some sort of levels normalized by age. I do have concerns that the products may be used when other therapies might be more appropriate, for example weight loss, as Dr. Adler mentioned.

Regarding age-related declines, I think we absolutely need well-powered randomized clinical trials that can provide us that definitive efficacy and safety data. We need to be able to make causal inferences and the ability of testosterone to effectively address primary patient concerns, including the troublesome and somewhat squishy endpoints like fatigue and sexual symptoms.

These studies need to be able to demonstrate that we can provide safe and effective therapy in important groups, including the majority of users, those men who are 40 to 65 years old, including older men who may have more concomitant conditions, and including men who are at high cardiovascular

risk.

Such a trial would need to be quite large, but the proportion of men age 40 and up who are potential users of the therapy is also quite large.

DR. JOHNSON: Thank you. And I'll take this opportunity to say that my colleagues have said pretty much everything I'd say, so I'm going to pass it along, except of course I have to say at least two things. One is to clarify that, indeed, the diagnosis is based on low testosterone levels, not on symptoms. And therefore, the appropriate testing from the Endocrine Society has to be communicated very, very effectively to those who are prescribing this medication. And they are missing other causes for the low testosterone level by not doing adequate endocrine testing.

The second thing I would bring forward is what happens if the T study does not show improvement in symptoms. Are we then going to come back and change? And I think we need to be ready for that possibility. At least some of the symptoms that are going to be examined, and the 65-

or-older group are not going to be improved by testosterone.

If that is the case, we need to be ready to make a significant change in how these medications are used. And of course, I agree with the large study looking at risk after the initial small study is done.

DR. CHAI: The problem with sitting on this side of the table is everything is getting less and less original n this side. So I'll try to limit my comments to maybe address these two points, which is a specific point of discussion, and then add some caveats.

Regarding the specific patient population, it's obvious what's the current indication for the population is not what is being treated right now. I would agree with my predecessors and their comments. I appreciate how the FDA wanted a hard objective parameter to look at initially when they were looking at using testosterone and looking at a pharmacokinetic study, if you will. So I think that first point A is pretty straightforward.

In terms of B, about the need in the current development paradigm to support indication for this kind of therapy in age-related, I like the quotes in there because it implies we're sort of talking about the same thing, but we don't know what we're talking about.

You always have to turn lemons into lemonade. And I would say, for the people here who represent men's health, I think it's good that you're here because I think you're getting short-thrifted because there is a need here. I just don't think we understand it well, possibly because there's not funding in this area.

I think we are applying what we know from -- even the testosterone trial, that age range is not in the age range of which most of the people are getting the prescription.

So I heard already, I don't know if it's really applicable, even if it shows a positive efficacy to apply. So I think there's a lot more that we need to understand about what's normal in the men population as the men go through their life

cycle. And it's up to those who treat men, who are interested in men's health, to really, really push to get these data out there so we can take the quotes out of this point B. We don't even know if it's a disease. I think it is, but we don't.

I'll just end with my last comment, which would be I think, conceptually, in the day of digital medicine that we live in, it is not too hard to link a prescription for this testosterone with, "Did you get a testosterone level check?" Now, we can debate what type, free, total, et cetera, but I'm always doing these authorizations.

I'm like, this is a lot of my time. And something as conceptually simple as having a level board with a prescription doesn't seem out of hand. So I'll that to that. Thank you.

DR. JOHNSON: Thank you. Dr. Curtis?

DR. CURTIS: Kate Curtis. So I think Dr. Chai stole my last original point. But I in general agree with everything that's been said. Clearly, the indication needs to be clarified so

that it clearly reflects the intent of the label that Dr. Hirsch described to us earlier. And there clearly need to be large, well-controlled studies looking at safety and efficacy for this age-related hypogonadism.

But that was the thought. In addition to the safety and efficacy studies, I think we need some studies about what is it, how do we diagnose it, and what are the hard clinical outcomes that are associated. What are we trying to fix? And once we know that, is testosterone the best way to fix it? As Dr. Adler said, for the example of bone mass, there may be other drugs that may be more appropriate than testosterone.

So I think there needs to be a whole host of studies around this, not just safety and efficacy, and including all the age groups as well.

DR. JOHNSON: Thank you. Dr. Howards?

DR. HOWARDS: I agree with the comment that has been made that we will be better able to answer these questions after Dr. Snyder's NIH study is available, which will be hopefully not too long

from now.

I agree with treating the classical group. I think everybody agrees with that. But I do have one thought that's maybe slightly different. And that is, I think other men who aren't in the classical category who have a very low testosterone and have symptoms that are bothersome, to focus on Dr. Alexander's point, should be treated.

How low is really low? It's a lot lower than 300, but I don't know exactly what it is. But from my clinical experience, if a man comes in with a testosterone of 100 and he's symptomatic, he will benefit from treatment. I don't think there's any doubt about it. He's no different from the classic. He has the same problem.

I have little confidence in the effect of education and labeling on outcomes. However, I do think we need to change the labeling. And I don't want to get into the specifics of how it should be changed. And the reason I have so little confidence in these, I can give you one specific example.

Twenty-five percent of urologists treat men with infertility with testosterone, and even many endocrinologists treat men with infertility with testosterone. So labeling and education have not been effective. And I certainly concur that we need a large randomized clinical trial.

DR. JOHNSON: Thank you. Dr. Erstad?

DR. ERSTAD: Brian Erstad. And again, I agree with many of the previous speakers. I think the current labeling that uses wordings such as conditions such as for primary and idiopathic for secondary hypogonadism, that is the barn door. And so I think we do need to change the labeling.

I think the approval paradigm needs to be changed to include clinical endpoints, not just a surrogate marker, testosterone concentration. I think strong consideration should be given to using age-related testosterone concentrations with, of course, appropriate collection procedures to define a deficiency. And again, I agree that more studies will need to be done, but I'll talk about that later under some of the following questions.

My final comment, I guess, would be, I think the potential for inappropriate prescribing has not only been mentioned by a number of speakers, but I think it's indirectly demonstrated by the fact that current guidelines do not recommend screening general populations, and I think that says a lot right there in terms of the potential for abuse.

DR. JOHNSON: Dr. Phillips?

DR. PHILLIPS: I really agree with a lot of the current speakers, particularly Dr. Burman, Dr. Garnick, and Dr. Shehab, so I don't want to say a whole lot more at this point because I think it's been said and said again. But I think, until we have some better selection criteria, embedding the Endocrine Society Guidelines and really using those -- because I think there's a lot greater potential for managed care, and organized care systems, and professional organizations to provide oversight that will help move things in the right direction, in a safer direction until we have more information to guide our decision making.

DR. JOHNSON: Thank you. Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Regarding the first question, I think there is broad agreement about the classic hypogonadism group. Regarding the second question, I think it's actually perfectly summarized in Dr. Hirsch's slide number 11 of what is needed to address age-related hypogonadism. And these are two steps. One is to actually show that age-related hypogonadism exists and is actually a pathophysiological issue and not just a sign of normal aging, and then secondly, a requirement for randomized trials that show efficacy and safety data, as for any new indication.

The problem I see, though, is that, as far as I know, nobody is actively seeking that indication, at least as far as I am aware of. So I don't think it's in the authority of the FDA to require asking sponsors for an efficacy trial if they don't seek that indication. I would obviously fully support such a trial. It's clearly needed, but I am not sure whether this committee or the FDA has the authority to request it.

Regarding the safety trial, which FDA has the authority to request, I will hold those comments for question 4.

DR. JOHNSON: Yes. And Dr. Tyler?

DR. TYLER: Linda Tyler. Thank you. I am a director of pharmacy in an academic medical center. As such, I don't have the opportunity to read in this area very much. So first of all, thank you for the opportunity. It's been extremely interesting to dive into the data. Pretty much everyone of the panel has mentioned an area that needs research. So imagine my surprise at how little we know about this topic.

So in answer to the first question, by our current approach, what data do we generate about specific populations? And the answer is, we don't. The research up until this point in time has really been around new dosage forms, and there has been some exciting work from a pharmaceutical standpoint in terms of new dosage forms, but it does not inform who are the patients that we really need to generate it from.

In fact, this highlights a huge gap. We assumed efficacy or the efficacy was not well established. But even if it had been many years ago, our standards have changed, but the labeling has not kept up with this.

So part of the question is, how do you go back and collect the data that you really want, and many of you addressed that. But it's pretty clear in my mind, when I look at the labeling at this point in time, that the labeling actually needs to be narrowed slightly. We do not have the evidence for age-related indications, and that's probably a stretch of what the original intention is in the current labeling.

It's clear that well-collected, well-analyzed, more than one level of testosterone needs to be included to make the diagnosis, perhaps some clinical symptoms. And I also don't see a lot around monitoring and how you monitor patients on an ongoing basis.

To Dr. Nguyen's point -- and I appreciated her comments earlier and several comments -- does

the labeling really make a difference. We do want the labeling to reflect the contemporary evidence as we know it. And where it really has an impact is in the day-to-day lives of our patients because it's what the payers will pay for.

So I know that may not be totally logical, but it is the reality that we face every day. Our payers care what the labeling looks like, and that's what they're going to pay for. And we probably see that in the data of the median use being three months. That's kind of when patients caught up that the payer was not going to pay for it, and the mean use was six months.

There's so much about the scenario of the data at this point in time, to Dr. Lincoff's comments, it's like many of the things that we learned in the Women's Health Initiative. So I look forward to what happens next, but it's clear we need more data for many of the indications.

DR. JOHNSON: I would like to thank the committee for your comments. I am going to do a very brief summary of what we talked about, and

then we are going to take a very short break. When we come back, we will talk about discussion point number 2, which is cardiovascular safety signal. We will begin with Dr. Tyler. I'm going to go around the other way.

If you brought up topics related to cardiovascular issues with the discussion on number 1, I will be sure to transfer those in so you don't necessarily have to repeat them again.

So allow me a brief consensus is that, indeed, the group agrees that the current information is appropriate for the population with primary hypogonadism, that there is a clear need for this population. However, when we look at part B and the age-related hypogonadism, that is less clear; that indeed further studies are required, and that we really need to understand both the efficacy and also the risk of using this medication for this population. And that in order to provide safety to our patients, even though we are waiting with baited breath for the T study, that we may want to look at the labeling, at least

in the interim, to caution patients of what we do not know about the efficacy of this medication and the potential risks.

Thank you very much. We'll take a 10-minute break, and we will start again at quarter of and move through cardiovascular issues.

(Whereupon, a recess was taken.)

DR. JOHNSON: Let us go ahead and get going with question 1, and again, we're going to go around the room, and the advisory committee is going to be asked to give their comments on these issues. We will then follow this directly with voting on two questions. And those will require votes, and we will come to those after this area for discussion.

Again, this time, we will go around the room in the opposite order, with Dr. Tyler starting following my reading of the discussion issue.

So now we are going to discuss, the totality of the data indicates a cardiovascular safety signal associated with the use of testosterone therapy, including your discussion, the strength of

the signal, whether you believe the signal is restricted to a certain subgroup of the population using testosterone, e.g., older men, or rather, it applies to all users, and then whether the current evidence concerning the association of major adverse cardiovascular events and testosterone replacement therapy warrants inclusion in the labeling. Dr. Tyler?

DR. TYLER: Thank you. Linda Tyler. To the first question, the strength of the signal, I particularly appreciated Dr. Falconer's comments earlier this morning. Looking at, in particular, two slides that she had, one was slide 27, which was the reanalysis of Dr. Xu's study.

When you looked at major adverse cardiovascular events in the recalculation, it was in 1 percent in both areas and so there was very little difference. There was an absolute risk reduction of 1.5 percent in all events, 6.7 percent versus 5.2 percent in placebo. So to me, it's not a terribly strong signal around the cardiovascular disease.

When you look at the five observational studies which were summarized on slide 18, she's got them beautifully mapped out, but what she also talked about which really resonated with me is the multitude of problems in looking at observational data and the multitude of problems in looking at all five of these studies together.

There's no question there's all kinds of biases around this in terms of, patients were not classified consistently across the five studies. We don't know their underlying disease, and that was pretty well not talked about in any of the studies. The classification of cardiovascular events was inconsistent at best and not adjudicated in many cases.

Somebody brought up earlier today the timing of events, that actually in many of these studies that were mapped out in this observational table, the events were after three months, yet the greatest risk period may be in the first three months. So that particular point has not been clarified.

How levels were monitored and at what levels patients were at is not well delineated. There are small sample sizes here. The actual dosage forms that were used are not clearly or clearly described in many of the studies.

To kind of get to the question of, is there a particular age group at risk, obviously older patients are at greater risk for cardiovascular disease, but are they at additional risk because of the testosterone products, because of the testosterone, or because of their underlying baseline risk?

That's not clear in these observational trials. Many of them did not distinguish between the age or were in a selected age population. By the time you start getting into -- because these were relatively small studies, even with the ages, you now are in subset analysis with multiple problems with subset analysis.

So I think an answer to the strength of the signal, it's extremely muddy. We do not have clear understanding about what age group might be at

risk.

To the last question, does current evidence concerning the major adverse effects in testosterone replacement warrant inclusion of the labeling? Clearly, there are studies that show that there is an association with cardiovascular events. It would be my opinion that, if there was some way to word that there may have been an association but the causation is unclear, it would be important to flag that out.

Some of that is already flagged out in the reporting of the events that have occurred in terms of myocardial infarction and stroke being included in the package labeling.

DR. JOHNSON: Thank you. Dr. Gerhard?

DR. GERHARD: So I believe also that the evidence regarding cardiovascular safety is obviously very insufficient. We need more data. At this point, I don't think there's evidence for a clear causal association, but I believe we do have a signal of a reasonable strength. There are problems with all the studies we see, but certainly

enough reason for concern, I believe.

I also don't believe that we have a lot of information regarding the heterogeneity of this potential safety signal with regards to age. Obviously, the population where it's really of concern is this large off-label population that uses it presumably for age-related hypogonadism.

Given this large group of off-label use and the pretty much lack of credible data or strong data on the efficacy or effectiveness in that population, I believe it is important to include some language regarding the cardiovascular safety concerns in the label, obviously not to the degree maybe of a black box or so. I think we don't really have that level of evidence, but to make sure that there are serious concerns that, at this point, have not been adequately addressed.

DR. JOHNSON: Thank you. Dr. Phillips?

DR. PHILLIPS: I'm on this end of the table and I already don't have a lot to say. I agree there's important limitations of the observational data that we have so far, and there is a

cardiovascular signal that is concerning, but certainly not confirmed. And because there's a potential mechanism for it and there's a lot of questionable use, it is important for the public to know that we are uncertain, but there are potential safety concerns, and have that information to tailor patient decision-making.

So again, I think there's a difference between an association and causation. And it's important to have something in the labeling saying we don't have an answer, but there are some potential safety risks that are being further investigated.

DR. JOHNSON: Thank you. Dr. Erstad?

DR. ERSTAD: Brian Erstad. I'll take these questions in the order they are given. I think the overall signal is weak, but it's present in selected populations. I think it's important to note that, obviously, the appropriate studies, the ones we'd like to see, haven't really been done.

For biological plausibility, there is conflicting data on overall cardiovascular safety,

but there's data to support biologic plausibility in selected populations. Future studies should include elderly men with or at high risk for cardiovascular disease, in particularly, those who are taking testosterone at high doses or concentrations.

I don't think there is enough evidence to state that a signal, if present, is restricted to a subset of the population yet, but selected subsets, again, those same ones I mentioned, patients with excessive long-term replacement, elderly, patients at high risk for cardiovascular disease are more of a concern.

Finally, I think until appropriate studies are performed, the labeling should be worded that a potential risk of major cardiovascular events cannot be excluded at this time, particularly in patients who are at current high risk for cardiovascular disease.

DR. JOHNSON: Thank you. Dr. Howards?

DR. HOWARDS: Stuart Howards. I think there's a consensus that the strength of the signal

is inconclusive. But that means it could be real because it is inconclusive. And I think, as far as that goes, I'd like to repeat my favorite quote of all time from Yogi Berra, "Predictions are difficult, especially if they're about the future."

As far as a subset of population, it depends. Once we have information, hopefully we will, whether it's a cumulative long-term effect or immediate or short-term effect. If it's the former, then all subsets, all ages would need to be involved. If it's the latter, certainly you wouldn't have to worry about somebody giving the drug to go through puberty.

As far as labeling, I think it is important to have something in the labeling, but I think it's equally important that it not be frightening, since we don't know at this time, so that it would clearly state that we do not know that there might be a risk, rather than that there is a risk or just even that there might be a risk without saying we do not know.

DR. JOHNSON: Dr. Curtis?

DR. CURTIS: Kate Curtis. So, yes. I agree that the strength of signals is obviously inconclusive, as we've talked about. But I think it's not so helpful to say it's inconclusive and we need more studies. Given all the limitations that we've talked about and, really, the heterogeneity of the studies that have been conducted, and design, and methods, inclusion/exclusion criteria, it would be very helpful if some group could come together and come up with some consensus statement about what is the best way to study this, so that moving forward, we don't get another batch of studies that we can pick apart the same way that we did these.

Again, the data are insufficient to say if there is an effect, whether it's restricted to one subset of the population. However, I think it is more important to think about this. We have certainly talked about a population for which the benefits are not clear, either. And in that group, the risk-benefit ratio is going to be different. So if there is a risk, that's the group that it may

be more important to.

Finally, I agree there should be some very carefully worded statement added to the label. Clearly, this is a big issue. It's been a big issue in the media. It's a big issue with providers and with patients. And people will be looking to this, so it seems at this point, in a mission to say nothing, but it would need to be a carefully worded statement that essentially summarizes the evidence in a very succinct, easy-to-understand way and shows the uncertainty.

Taking a leap here, I didn't know this until someone mentioned it earlier. There is a statement right now in the label about venous thromboembolism. And it says VTE, including DVT and PE, have been reported in patients using testosterone products. And I don't know what the level or the comfort with that evidence is, but if it's a similar amount, that could provide a sort of framework for us to think about a statement here, but that evidence may be more confirmed than this evidence. Thank you.

DR. JOHNSON: Dr. Chai?

DR. CHAI: I agree with my predecessors, and I will just put into the record my thoughts on A and the strength of the signal. I believe it is not strong. I don't know what other words I can use to say. Inconclusive was another word that was used twice.

Whether I believe the signals are restricted to a certain subset, I can't say because I don't think the signal is strong enough for me to be able to say which subset. And again, in terms of the labeling, cautious labeling in terms of that there's some suggestion to a possible cardiovascular side effect would be something that's, I think, totally reasonable. Thank you.

DR. JOHNSON: Thank you. And I agree with what all of my colleagues have said. On part B, I'd just say that my concern -- and this was somewhat mentioned already -- is that those with preexisting heart disease in one of the studies appeared to be the group at highest risk. So I really think that we need to give special concerns,

special caution to that group when they consider this medication.

Now, to Dr. Herring?

DR. HERRING: Thank you. I agree with my colleagues here. I do think it's dangerous to attempt to determine the strength of any potential signal based on studies that are either severely underpowered in the case of the randomized trials aren't able to determine causality in the case of the larger observational studies, other than to rule out humongous relative risks or their inverses.

I am a little ambivalent about the labeling. I worry that any type of label we'd be comfortable putting on the drug might be dismissed by the reader.

DR. JOHNSON: Thank you. Dr. Adler?

DR. ADLER: Robert Adler. I agree with much of what has been said. I think there's reasonable evidence that men with low testosterone are probably at increased cardiovascular risk, and we see this in the profound hypogonadism of androgen

deprivation therapy.

The question is whether the ways we try to change that by giving testosterone will make things better or worse, but the signal we have so far is inadequate as far as a risk with testosterone. It really is analogous in many ways to the situation with the postmenopausal woman or to the woman with early menopause.

The thromboembolic phenomena I think are probably real. And it would be a good thing if we had easy and inexpensive ways to identify those patients, male and female, who are at higher risk before they given any kind of sex steroid because I think this is a problem that we should be able to do a better job with.

So I think that I agreed with the fact that it's not going to be easy to change the label to reflect the concern we have with a possible cardiovascular signal. And I also agree with the concern that we may not be able to change the behavior of prescribing clinicians.

DR. JOHNSON: Thank you. Dr. Alexander?

DR. ALEXANDER: Rich Alexander. I agree the signal is, I think, inadequate is the best word for it. There's too much unknowingness in all of them. They are overlapping. They are contradictory. I think it would potentially needlessly alarm the 2 million men getting the 15 tons of this material annually.

If you're going to change the label, you could put it into cautions and warnings, saying, "Caution is advised in men with a preexisting heart condition." And I wouldn't say anything more than that until there are better data. I just think it can needlessly alarm and scare a significant population.

DR. JOHNSON: Thank you. Dr. Lincoff?

DR. LINCOFF: I also agree with some of the previous speakers, in particular Dr. Herring pointing out it's a weak signal because it couldn't be anything but a weak signal with the number of events that we have. But it's a signal. There's biological plausibility. And I vigorously disagree with the approach of being overly conservative with

the label.

I think that even the DVT caution I think is -- to say that something is observed with this drug, I mean, everything is observed with everything. So I think that it needs to make clear that there is a potential. There's a signal that needs to be evaluated. It's being evaluated. But until then, we can't rule out an excess risk.

I'd also take an extreme, which I realize is just almost a straw man, but there have been box warnings for data that's not much stronger than this. And I would think omeprazole and clopidogrel would be an example.

I think we need to inject some reality into what has been an uncontrolled use of a drug until there's data that's sufficient to rule out real cardiovascular risk.

In terms of who that is, I don't think we can find anything specific. I think it's the general principle that those at a higher risk will have a higher absolute risk from a potentially hazardous drug. Because the problem is the

patients who have the high cardiovascular risk often are the ones that are the diabetics and obese, who have the low T. So these coexist in many of the same patients. So I think the general principle here is, there are many criteria by which we know we can rate cardiovascular risk, and that that that's going to mark the patients at higher absolute risk. But I don't think that's all that useful because I think it's also going to identify the population that you want to use the drug if this indication is useful.

DR. JOHNSON: Thank you. Dr. Burman?

DR. BURMAN: I agree the strength of the cardiovascular signal is weak with the possible exception of venous thromboembolic disease. The studies are obviously conflicting regarding the correlation of testosterone therapy with CV risk. The studies are mainly retrospective and did not always have pre-designated independently adjudicated CV outcomes.

The studies encompass the heterogeneous population and use different doses in preparation

of exogenous testosterone. In short, it is difficult to reach a solid conclusion regarding the association of testosterone therapy and CV events. And this would only be a correlation and causation is even more difficult to prove.

With regard to the population, I agree with what you had said regarding the potential risk in men with a previously known cardiovascular disease. And I agree that some cautionary note should be included in the package insert. It would be prudent to mention the cardiovascular risk is an area that has been examined, but there are no conclusive results yet.

DR. JOHNSON: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: Glenn Braunstein. The strength of the signal is very weak for all the reasons that have been elaborated upon. Secondly, for B, where the signal should be restricted to or is restricted to a subset of population, I don't believe so. I think patients with hypogonadism do have an increased cardiovascular risk that's associated with hypogonadism, irrespective of

whether they are being treated or not treated.

I note that, in the Finkle study, which has been oft quoted here. There was no risk, no increased risk in those patients over the age of 65 who had cardiovascular disease. So I don't think there's a subset that's been defined yet. And I don't think there should be any change in regards to the labeling at this time until we have more knowledge.

DR. JOHNSON: Thank you. Dr. Dmochowski? I say it different every time.

DR. DMOCHOWSKI: Roger Dmochowski. Strength of signal, weak to inconclusive. I don't think there is a subset. I think the analogy to the female experience is very, very germane here. And I think probably, if there is a risk, it's across all comers who are exposed to this.

Lastly, I do think there should be a sentence in the label that says -- again, gets to the concept of the potential, but it has not been clearly delineated or defined.

DR. JOHNSON: Thank you very much.

Dr. Shehab?

DR. SHEHAB: Nadine Shehab. I believe the totality of the data does indicate that a signal for cardiovascular adverse events exists, albeit weak. Although the studies that demonstrate correlation between testosterone exposure and cardiovascular outcomes are lacking in consistency and may differ in absolute risk and relative risk, there is biological plausibility and temporality.

In addressing some of the muddiness in these epidemiological studies, I would just like to bring out a point that I don't know has been brought up before, but I think Dr. Adler alluded to it. The studies that have demonstrated some benefit on cardiovascular outcomes with testosterone are mostly related to endogenous testosterone levels and not to exogenous testosterone administration.

So I would just emphasize that that needs to be delineated when we are talking about epidemiological studies that have demonstrated or that have evaluated their relationship to cardiovascular outcomes.

I have also heard causality mentioned a few times. And I would just like to say that I would not expect any observational epidemiologic study to demonstrate causality, and I don't think we need to wait for an observational study to demonstrate that before we consider putting something in label. And if it is possible to put something in the label that the cardiovascular adverse events are being explored, I think that would be a good thing, given that this is a line of products that essentially has not demonstrated clinical benefit as of yet.

DR. JOHNSON: Thank you. Dr. Domanski?

DR. DOMANSKI: Yes. So I think a couple things. First of all, I think when the agency and the government labels something, they ought to say what they know and not go beyond that. And also, I think we keep using the term, "There's a weak signal." Putting on my engineering hat, I use that term all the time, so I am guilty as well, but we don't really know whether it's dangerous or not. It's not that there's a weak signal that just needs a finer instrument to ferret it out. We just don't

know the answer. There may be a problem. There may not be.

I think that what the labeling should reflect is what we know and perhaps what we don't know. Right now we know that there is no proof that in this older age group, there's any efficacy at all. And I think labeling can reflect that, number one. Number two is that we cannot exclude a cardiovascular risk with the data that are available, but we certainly haven't proven it. And I think it goes beyond the data to suggest that we have. And I certainly think things like black-box warnings are totally inappropriate.

DR. JOHNSON: Thank you. Dr. Teerlink?

DR. TEERLINK: So I come to this from the perspective also informed earlier. I think it may have been Dr. Herring who brought this up in terms of the numbers of patients, keeping in mind that, if we really are doing a population-based cutoff for this T value, it's 1.3 million patients. Just make it based on the number. So I'm concerned that we may be exposing a lot of patients who don't even

have a disease entity to a drug that we don't know about the safety issues.

Then also, I was impressed by the FDA's comments about all the flaws of observational studies. I actually believe that, which is why you have to have a randomized controlled trial and you can't use observational studies to really look at the safety signal.

I do think there is a sufficient signal for concern, and I actually refer to the sponsor slide CO-56, where people have been talking about the heterogeneity as a flaw, as a weakness. But actually, if you look at this, you have all of these studies that do all sorts of different approaches to a meta-analysis. They are doing all this in all these different kinds of patients, yet every point estimate is against the testosterone replacement therapy.

So I think there actually is a signal. It is weak because it's coming from observational data. But I think there's enough signal to support that there is a signal for concern. So I think

that, yes, there is a signal for concern. I agree that their population is usually going to be colinear in terms of risk factors, so there's really not enough data to discern which one is which.

To be clear, in terms of my previous answer to question number one, I think that we should change the labeling such to exclude the age-related low T to start with. If we're not going to do that, then we need to be stronger in terms of the safety signal. And that's where I might be tempted to disagree with my friend and colleague here and agree with Dr. Lincoff in terms of saying I'd even consider a black-box warning.

DR. JOHNSON: Thank you. Dr. Garnick?

DR. GARNICK: Marc Garnick, Boston. I think there's a definite signal. My confusion is not my -- not confusion, but my questions relate to the fact that we really have not discussed any issues relating to differential pharmacokinetics. I think we have been applying the pharmacokinetics of the absorption, whether it be parenteral or topical to

the primary and secondary hypogonadal population in just assuming that the age-related older patient with an age-related testosterone deficiency is absorbing the agents in the same way.

I think there's a real opportunity here to have a registry for patients that have cardiovascular events to actually look at what the testosterone levels are. I think labeling is definitely indicated. I would not go as far right now as a black box, but if I am a potential patient that has some queries about testosterone replacement and I am engaging in such a discussion with my physician, I would certainly want to know about the VTE issues. I would certainly want to know about the yet-unresolved cardiovascular issues.

If for no other reason, that would be a very, very potential important prompt for that patient to suggest, Well, maybe we should continue to measure my testosterone levels to make sure that they are not superphysiologic and also have some sort of efficacy measure, so if the agent is not

working in the first two to three months, then the patient should go off of the therapy.

So I think labeling definitely needs to be promoted up to either the precautions of the warning section and also state that these agents, from a cardiovascular perspective, are undergoing additional safety evaluations. But I would urge collection of information that looks at differential pharmacokinetic parameters in different patient populations, including those of different comorbidities.

For example, the absorption of testosterone topically or parenterally may be completely different than a patient with a body mass index of 32 compared to someone that's 25. So we need to go back and look at the information that correlates T levels or other levels of hormonal manifestations with those patients that exhibit the cardiovascular signal.

In terms of 2d, as I mentioned, the cardiovascular issues need to be associated with T replacement. They need to be inserted in the

product insert. As I mentioned again, patients who are on these medicines chronically need to be aware, however low, that there is a risk, and centers can probably minimize if an efficacy signal is not established, and therefore taking them off of the agent.

DR. JOHNSON: Thank you. Dr. Thomas?

DR. THOMAS: Abraham Thomas. I'll just be quick. If the signal was strong, we wouldn't be having this meeting.

(Laughter.)

DR. THOMAS: It's the truth. The groups may be affected by just the fact that there's different rates of events in these groups, so I think it's hard to say that it's restricted to a single population based on these small studies, even when grouped into a meta-analysis.

Then finally, I do think there probably needs to be some information in the labeling just so that there's an expression that there is some concern, though we're not sure if it's there or not, and further studies have to be done because

this should make patients and providers think twice about the fact of whether they should take this medication or prescribe it also, what type of evaluation should be done. It's pretty clear that the evaluation that's recommended for diagnosis before treatment is not being followed most of the time or at least a fair proportion of the time.

DR. JOHNSON: Thank you. Dr. Boineau?

DR. BOINEAU: So I agree with the other panelists that the signal is poor. I agree with Dr. Herring that that's related to the quality of the data that we've collected. They are either poor observational studies or they are very small, randomized clinical trials or one-arm trials.

That said, I am concerned that it is going to take a long time if a clinical trial is done to collect safety measures, and that there may be a large number of patients that are exposed to a drug that may be hazardous. And if we do not put something into the label to indicate that we are concerned, particularly when the only improvement is a lab value -- we don't know if it is going to

improve your symptoms or signs, that that needs to be taken into consideration by the patient and the physician when they are discussing starting a drug that may not have a benefit and may have a significant risk.

DR. JOHNSON: Thank you. Dr. Gordon?

DR. GORDON: Yes. I concur that there's a very weak signal, if any signal at all. I think that the evidence that we have is obviously contradictory and, unfortunately, it's from questionable studies. And more importantly, it's from studies of populations not the primary user of this product, as it seems.

So I think that until we have the appropriate evidence to really make a full evaluation, I don't know that we have sufficient basis to make any major changes to the label. If you had to add a small warning cautioning about this, that seems reasonable, but I definitely don't think there's any evidence to support putting a black-box warning on it at this stage.

DR. JOHNSON: Thank you very much for these

thoughtful comments. I'm going to give you a general consensus. I hear from the majority of members of the advisory committee that their interpretation is that the signal is weak, but that there is potential biologic plausibility with the cardiovascular risk for this medication. Age-related risk is unclear because of the quality of the studies, but countered against that is that the efficacy is unclear, and it has not yet been studied.

So that balances out that if we were going to use it for those who have significant cardiovascular risk, we also do not know if it will be effective at treating their low testosterone levels and their overall symptoms.

Finally, in terms of labeling, there was certainly not a complete consensus, but I would say that, generally, the advisory committee feels that a cautionary note is indicated. How strongly cautionary that should be varies with members of the committee from simply a statement to a black box, but I do think that the consensus is that

awareness of potential cardiovascular risk is important for the FDA to include. Any thoughts?

(No response.)

DR. JOHNSON: Well, thank you very much. And now let us vote. So we have two voting points. And with the first one, you have seen this indication many times already today. I will not read it to you again. However, I'm going to give you just a moment to go through it and remind yourself of the primary and potentially secondary indications for testosterone replacement therapy.

Then the question that the FDA wishes us to answer is, should the FDA revise the current indication for testosterone therapies. And so that's a yes or no. And then please provide rationale for your vote. If you vote for a change in the indication, describe the specific changes that you would recommend for this indication.

So now, with the help of my colleague, Ms. Bhatt -- yes, I'm sorry? Of course.

DR. GERHARD: Tobias Gerhard, just a question to FDA to clarify what is meant by, "Would

you revise the current indication?" If a committee member feels, for example, that -- as I think suggested by many of the indications -- should be tightened up to make clear that the classic hypogonadism group is the intended group, would that be considered a revision or not?

DR. JOFFE: Yes. That would be considered a revision.

DR. GERHARD: All right.

DR. JOFFE: Basically, you would vote no if you would want us to leave things exactly as is. Any changes should precipitate a yes vote.

DR. JOHNSON: For voting questions, we will be using an electronic voting system for this meeting. Once we begin to vote, the buttons will begin flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds with your vote.

If you are unsure of your vote or if you wish to change it, press the corresponding button until the vote closes. After everyone has completed their vote, the vote will lock in. The

vote will then be displayed on the screen. The DFO will read the vote for the record.

Next, we will go around the rom. Please state your name and your vote for the record. And you may make a statement on the indication for the vote that you chose. And we will continue in the same manner for the two voting questions. And just to warn you, Dr. Gordon, you're going to be the first one again.

I'm sorry. Dr. Gordon, you do not vote, so never mind.

DR. GORDON: Unless you changed the rules --

DR. JOHNSON: Dr. Boineau will be the first to vote or the first to give statement after the vote. Are we ready? You may vote.

(Vote taken.)

MS. BHATT: The voting result, yes, 20, no, 1, abstain, 0, no voting, 0.

DR. JOHNSON: Very good. Robin, if you'd like to, begin

DR. BOINEAU: I'll make this quick. I believe that we should change the labeling so it

reflects the classic syndrome and not allow it to be expanded upon that.

DR. JOHNSON: Thank you.

DR. THOMAS: Abraham Thomas. Besides the things I mentioned concerning safety, I think what I would probably include in the labeling the specific mention of the testing that's required, rather than just saying low testosterone levels, so people know you should measure in the morning at least once, preferably twice, following the Endocrine Society recommendations.

DR. JOHNSON: Thank you. Go ahead, Dr. Garnick.

DR. GARNICK: Yes. I voted yes because I think the current label has not done the job in terms of precluding the largest population of patients who were receiving the agent, which is age-related testosterone levels.

Also, I think the label should indicate that, in addition to the primary and secondary hypogonadal states that are in the label, I think any other component that the product would be

indicated for needs to include some symptoms associated with low testosterone.

So the label as it currently is, is basically a label for testosterone replacement in patients that have a low laboratory value for any of the norm primary and secondary indications. If there is going to be a label, it has got to include symptoms that could potentially be ameliorated by testosterone replacement therapy.

I completely agree with Dr. Thomas that somewhere in the label, the necessity for baseline monitoring, efficacy monitoring, and continued testosterone monitoring needs to be placed in there.

DR. JOHNSON: Thank you. Dr. Teerlink?

DR. TEERLINK: I voted yes for all the reasons that you've heard me say so far.

DR. JOHNSON: Thank you, sir. And Dr. Domanski?

DR. DOMANSKI: Yes. I voted yes because I think that the indications that the agency gives should be limited to the primary group. And that

should be clear.

DR. JOHNSON: Thank you

DR. SHEHAB: Nadine Shehab. I voted yes. I'd like to see the label reflect the following, the efficacy and safety of testosterone on conditions of low testosterone, other than primary or secondary hypogonadism, have not been established, and the correlation of testosterone to clinical outcomes in conditions such as age-related hypogonadism has also not been demonstrated.

DR. JOHNSON: Thank you. Roger?

DR. DMOCHOWSKI: Roger Dmochowski. I voted yes and, again, it has to do with the tightening of the language.

DR. JOHNSON: Thank you.

DR. BRAUNSTEIN: Glenn Braunstein. I voted because I do think that the classical group has to be separated from the age-related hypogonadal group. I am not against the age-related hypogonadal group continuing to get therapy until we get the data, but it needs to follow certain guidelines. And there needs to be a discussion

about the limits of the knowledge that we have at the present time.

DR. JOHNSON: Dr. Burman?

DR. BURMAN: Ken Burman. I voted yes. I agree that we should emphasize the classic abnormalities of hypogonadism, that we should probably put in there that testosterone should be measured in the morning and maybe the specific assays, mention the effects of comorbidities. We should have baseline and monitoring studies for signs and symptoms as well as testosterone levels. And we should have noted a comparison to an age-related normal range.

DR. JOHNSON: Thank you. Dr. Lincoff?

DR. LINCOFF: Michael Lincoff. I voted yes. And I'll just confine my comments to the indication, since that's what the question is, not all the other warnings that we had discussed. But I think it should be very clear that it's just for the primary or secondary fare for these designated reasons, and remove the idiopathic, and remove the indication for any of the age-related. That

doesn't mean people can't use it off label, but it shouldn't have the support of a label that says that that's an indication until and unless there's data that supports that.

DR. JOHNSON: Thank you. Dr. Alexander?

DR. ALEXANDER: Richard Alexander. I find myself in the enviable position of having voted no for exactly the reason that a drug is indicated, when it's proven to be safe and effective, neither of which is the case yet for this indication in my opinion.

DR. JOHNSON: Thank you. Dr. Adler?

DR. ADLER: Robert Adler. I voted yes. And my reasoning is really exactly that of Dr. Burman, that we should separate out the organic causes of hypogonadism from any age related, and that measurements, symptoms, and following the patients should be a part of the labeling.

DR. HERRING: Amy Herring. I also voted yes for the reasons stated by my colleagues.

DR. JOHNSON: Julia Johnson. I voted yes. And I would say I have heard it from others, but

specifically remove the indication for idiopathic gonadatropin or luteinizing hormone-releasing deficiency. I think that is too generic, and that's where our age-related issue comes forward.

DR. CHAI: Toby Chai. I voted yes, and I don't have any additional comments to add.

DR. CURTIS: Kate Curtis. I voted yes, and I don't have anything to add.

DR. JOHNSON: Thank you. Dr. Howards?

DR. HOWARDS: Stuart Howards. I voted yes, and I would add that I feel -- which nobody seems to agree with -- that in addition to the classical patients, patients with very low testosterones, documented properly, such as, say, 100, should be treated.

DR. JOHNSON: Thank you. Dr. Erstad?

DR. ERSTAD: Brian Erstad. I voted yes, and I gave the reasoning for and some of the wording. Previously, the wording, I didn't like. That probably needs to be changed. And also, I think the labeling should basically include wording that the benefits and risks of testosterone therapy for

age-related declines in testosterone concentrations have not been established.

DR. JOHNSON: Thank you. Dr. Phillips?

DR. PHILLIPS: Marjorie Shaw Phillips. I voted yes also. I think the current labeling is vague and has been subject to misinterpretation. I'd like to see the diagnostic criteria specified by the Endocrine Society put into the labeling. In addition to the wording about idiopathic -- the statement that these men usually have low serum testosterone concentrations, even though that is applying to primary hypogonadism, I think is used by someone that briefly looks at the labeling as an excuse for taking someone who has symptoms but lacks a low testosterone for an opportunity to try it.

DR. JOHNSON: Thank you. Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. I voted yes. I believe the label should be tightened up as suggested by many on the committee, and I also believe that the label should have an additional statement that actively states that the age-related

hypogonadism is not a currently-approved indication, given that, that is the largest group currently using the drug.

DR. JOHNSON: Thank you. Finally, Dr. Tyler?

DR. TYLER: I voted yes as well for many of the reasons that everyone has stated. The indications need to be narrower.

DR. JOHNSON: Now, we're to our second vote. The question from the FDA is, should the FDA require sponsors of testosterone products to conduct a study, e.g., observational or controlled clinical trial, to further assess a potential cardiovascular risk with the use of testosterone replacement therapy?

Your choices are, no, a study is not required or, yes, it is, but only for current indications of testosterone therapy. When explaining your vote, indicate what indications should prompt the need for cardiovascular study or, yes, and regardless of the indication for testosterone therapy, a cardiovascular study should

be done.

Just a side note, provide rationale for your vote. Again, if you vote yes with either option B or C, indicate the type of study that would be required, observational or controlled clinical trial. And include a discussion of the study population that should be enrolled as well as an acceptable degree of risk that would need to be excluded. Yes?

DR. DOMANSKI: Could I just have a point of clarification? With respect to this, I assume that we're not talking about -- we're not talking about feeding at the public trough for this. This would be an industry-sponsored study that you're talking about. You'd be requiring it. Is that the bottom line?

DR. JOFFE: Yes, that's correct.

DR. DOMANSKI: That's a key point. So assuming that, presumably it also means that if they were seeking an indication other than the current one, it would require a trial. Is that also correct?

DR. JOFFE: Let me clarify option B just to make sure everyone understands what we're asking. So option A is, no, you don't need it. We don't think any further clinical study is needed to cardiovascular risk. Option B is saying yes, but only for certain indications.

So what we're trying to get pit here I supposed we limited testosterone to patients who had classical hypogonadism and only those patients. Would we need the companies to go do the cardiovascular safety study for their products? Or if you think, actually, the indication can include age-related hypogonadism or sponsors should go and do studies for age-related hypogonadism, is it their population we would want to get cardiovascular risk assessed?

So we are trying to get a distinction on which part of the indication prompts the need for cardiovascular --

DR. DOMANSKI: So if we vote yes, if we say yes to any of this, what we're saying is if we're an indication for a current indication, we're in

effect telling them a trial that works for a safety endpoint.

DR. JOFFE: No, not necessarily. If you think they need to do a cardiovascular safety study no matter what, whether it's the current indication, whether you change an indication, or there's a new indication, then you'd vote C.

But if you think there's only certain settings where you'd need to assess cardiovascular safety, only certain indications, then you'd vote for B.

DR. DOMANSKI: Thank you.

DR. JOFFE: Is that clear?

DR. DOMANSKI: Yes. It is.

DR. CHAI: Can I ask another clarification question? This is Toby Chai. Are we assuming the indication -- we assume that just got changed or are we assuming it's the indication that's currently the way it's written right now?

Do you understand what I'm saying? Because we just took a vote about indications. Are we going to go now vote as if we went 20 to 1 and it's

got changed to whatever we think is the new indication?

Are we going to vote based on the way it's currently written in the record?

DR. JOFFE: Right. I wouldn't make an assumption about what the indication is, what it's going to be changed to. If you think that there is some indications that need cardiovascular risk and some don't, regardless of how it ends up being labeled for indications, then you'd vote B.

If you think they're going to need cardiovascular safety for every indication for testosterone, then you'd vote C. So I would take out the question of how we're going to finally decide on labeling fro these products when you vote on this question. Is that clear?

DR. JOHNSON: Dr. Howards?

DR. HOWARDS: So does this mean that if we vote for B or C, that there will be no testosterone available? Because there have been no cardiovascular proper studies done?

DR. JOFFE: No. That doesn't impact whether

testosterone comes off the market, for example, or not. And we explicitly didn't say postmarketing study. There's different options here. One option could be, yes, a company could get some indication and then, after they get approved or that indication, they can do a cardiovascular study. Another option might be that they would do the cardiovascular study as part of a development program they're doing for a specific indication.

We didn't want to get boxed in to whether things should be pre-approval or post-approval. We're just trying to get a sense of whether at this point going forward. We should do cardiovascular studies, and it won't affect the availability of the current testosterones.

DR. HOWARDS: Does that mean that a new provider, a new industry provider, will have to go through that type of study, whereas all the previous ones did not?

DR. NGUYEN: I think, again, if you read option B word per word, it basically says for certain indications. So if you believe a sponsor

who is seeking an indication of age-related hypogonadism and that is the indication where you are most concerned about the signal, then this requirement would apply. Whether or not we ask that requirement pre-approval or post-approval, certainly is something that will be safe for future discussion.

DR. HOWARDS: I'm still concerned and confused. And maybe it's me. But it seems to me that this would be very unfair to the next company that comes up for approval because they have different rules that the other companies did not have to follow.

DR. JOFFE: Right. So let me clarify. We have to treat companies fairly and all on the same playing field. So we wouldn't set an unreasonable burden for a new company, say, that's bringing out another testosterone topical product that, in all other respects, is similar to all the other testosterone products. That really wouldn't be fair.

So that's not something we would do. And I

don't think you should take that into account when you think about how you're going to be voting on this question.

DR. HOWARDS: Thank you. I now understand.

DR. JOHNSON: Dr. Gerhard and then Dr. Domanski?

DR. GERHARD: I'm sorry. I have another clarification question, still not quite clear to me. Assuming no company is seeking an extension to age-related hypogonadism, I think that should be studied, even though the indication that the company holds is for the classic indications. Is that a B or is that a C?

DR. JOFFE: I think you touched on this issue before. I'm not sure FDA really has the authority to force a company to go study a new indication. We have a lot of authorities for safety and serious safety concerns.

So suppose, I'm just saying, we narrow the indication, and none of the companies wanted to go study age-related hypogonadism, and they accepted this narrow indication, we couldn't go and force

companies to do studies in age-related hypogonadism. They would have to have an interest in doing that, and then they would approach us. And we'd be happy to work with them to develop such an indication, but we wouldn't have regulatory authority to require that of a company.

DR. GERHARD: Even for safety aspects? If there is the majority -- if a million patients take it off label, you wouldn't have the authority to ask for safety studies?

DR. JOFFE: Well, safety studies, you can always ask for, but what we're trying to do here, our hope here today, is to really try and narrow use to patients where science more clearly shows that there is benefit for such use. So I know what the current use is like, but we're hoping that we can make a shift and change in that, so that, really, we get these products used by patients where we think there's benefit there that clearly outweighs risk.

DR. GERHARD: I fully agree with your intent, and I think that labeling will hopefully

make some dent. But I doubt that you'll be completely successful with a labeling change lowering the inappropriate use completely. So I think generating additional evidence in that population is key. And since there is so much off-label use, regardless of the indication that's held, I would think safety studies are important. And that then is C, I guess.

DR. JOFFE: Yes. I think we would have to take that back internally. And see, I don't think you'd really need to take that so much into account when you answer this question. I would take this question -- we try to be as simple and clear with this question as possible. We're just saying think through testosterone and the possible indications where the companies have them now or they don't have them now, and just think through whether you think we need to get cardiovascular safety regardless of what the indication is. If that's what you feel, then you should vote C.

However, if you think that there is indications for which it's not really reasonable,

appropriate, feasible, whatever reason, to get cardiovascular safety, then you should vote for B. And then when you vote for B, you'll explain in your vote which indications you think need the cardiovascular safety and which ones don't.

DR. JOHNSON: Dr. Domanski?

DR. DOMANSKI: I think the explanation is right, but it's going to be lost when this goes out over the airwaves because that's really what's there. I think B is not properly stated. I think. And I could be wrong, of course. I think it has to say yes, but only for new indications, because, I mean, it's currently indicated for the primaries. But it's not indicated for age-related.

So if you, say, get rid of the word "certain" and put "new," then it forces the people who come in with a new indication to do it, but not somebody who comes in with an indication for primary. Well, I don't know. I mean, if you vote this, then you end up with that. I may be wrong. Maybe that's not the way to word it, but I don't think you've got it right there.

DR. JOFFE: But some people might feel that, even for some of the current indications, that cardiovascular safety should be --

DR. DOMANSKI: So what you've said is you're not going to force -- we have a number of companies that have this indication, and they haven't done a trial. So now, I come in with a comparable pill and you're going to tell me go do a trial, or I'm going to give a monopoly to the people who currently have it.

DR. JOFFE: No. What I'm saying is we'd hold all companies to the same standard. So for example, say we decided that this needs to be looked at in the postmarketing setting. We're going to look at it in a postmarketing setting with a brand new product, and we'd go back to the old ones, and we'd say you also need to look at it in postmarketing setting.

DR. DOMANSKI: So you can take somebody who's already got an indication and say, wait a minute. If you want to keep marketing this, you've got to go back and do some more work?

DR. JOFFE: Yes. We have regulatory authority from 2007 to actually -- and it's nice -- require companies to do studies, if we think there's a serious cardiovascular risk. And we have a lot of input into the design of a trial. We actually have to sign off on the trial design. We also come up with timelines, and if those studies are late, there could be civil penalties. So we have a lot of regulatory teeth in getting these studies.

DR. DOMANSKI: So in effect, if they don't go back and do it, you can take these drugs off the market for primary hypogonadism.

DR. JOFFE: I wouldn't say take it off the market.

DR. DOMANSKI: Well, that's what you're in fact doing.

DR. JOFFE: I would say civil penalties is what the law provides us with. If we require postmarketing safety studies with all products and companies don't do it, they are late in doing it, there's a potential for civil penalties.

DR. DOMANSKI: Suppose they don't have the money to do it? I mean, it's a funny situation. I won't perseverate, but I think you've got a problem with that kind of thing.

DR. JOHNSON: Yes. And I'll tell you, we promised we would be done by 5:00. We only have about 10 more minutes, but a quick question from Dr. Garnick?

DR. GARNICK: I have a very, very simple question. Are we voting initially for question 4, yes and no, and then going to A, B, or C? I don't know. Are we voting for 4A, 4B, or 4C? And if that's the case, which buttons do we press?

(Laughter.)

DR. JOFFE: That's a very good question.

DR. GARNICK: The problem with doing that is, if you're voting no, then that comes up at C. Correct? Or the voting would be A. Got it.

DR. JOFFE: Right. So you should just look at the letters at the very bottom of each button, and it's not a yes/no vote. It's going to be an A, B, or C vote.

DR. JOHNSON: So this is an A, B, or C vote, not a yes/no vote. Thank you. That was a very good question.

Dr. Adler, question?

DR. ADLER: Just a comment, and that is that we can -- just to remember that age-related hypogonadism and obesity-related hypogonadism could fit under the current indication of idiopathic gonadatropin deficiency. So that would not necessarily be a new indication, and that is a present indication because those patients do indeed have idiopathic gonadatropin deficiency.

DR. CHAI: I'm sorry. But we just voted to change the indication. Don't you see what I'm saying here? That's my first question.

DR. TEERLINK: But they may not want to.

DR. ADLER: I agree with you, but we didn't vote that specific change. We voted to change it.

DR. JOHNSON: Dr. Braunstein?

DR. BRAUNSTEIN: If we take idiopathic out, that excludes common syndrome and other congenital problems, so it's actually inappropriate to take

idiopathic out. I think, yes, the labeling needs to be changed, but we need to clarify exactly what the groups are, classical versus non-classical.

DR. JOHNSON: If I am correct, Dr. Joffe, if we put B, then it's because there is something in the preexisting indication that we think needs to be addressed; is that correct? Not everything in that current, but something in that needs to be addressed? Am I correct?

DR. JOFFE: If you vote for B, you think that there's at last something in the indication that you think you need cardiovascular safety data for and then --

DR. JOHNSON: Not a new indication, but the current indication, certain aspects of it need to be examined.

DR. JOFFE: I wouldn't get too hung up on current indication or new indication. I know folks are going back there again. I would just think about the possible indications for testosterone, regardless of what we end up with in the label, and think through whether you would want cardiovascular

safety data to support all of those indications, or whether you would only want cardiovascular data to support some, or one, or some of those indications.

DR. JOHNSON: I'm not sure we'll be terribly helpful to you, but we are about to vote.

(Laughter.)

DR. JOFFE: Good luck.

DR. JOHNSON: Thank you. So if people would kindly vote A, B, or C.

(Pause.)

DR. JOHNSON: Vote A for, no, a study should not be required; B for, yes, a certain indication; C, yes, regardless of indication.

(Vote taken.)

MS. BHATT: The voting results, A is 1, B is 16, C is 4, no voting is zero.

DR. JOHNSON: So colleagues, now what we will do is go fairly rapidly around the room starting with Dr. Tyler. I would say that if you want to specify this certain area, do so succinctly. Thank you very much. Dr. Tyler?

DR. TYLER: Linda Tyler. I believe that the

classical hypogonadism, we would say that the benefit justifies the risk and I am not as concerned about doing the cardiovascular study in that group. That also is a group that is a very small group in light of everyone who is using the drug right now.

The greater concern, however, is in the age-related diagnoses. There, the risk may not outweigh the potential benefits and the benefits have not been well-delineated.

DR. JOHNSON: Thank you. Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Dr. Tyler, I assume you voted B?

DR. TYLER: I voted B.

DR. GERHARD: I voted C, although I completely agree with you, but I wanted to make a stronger point. And I want to make the point very clearly that I think, even if a sponsor has a product that only holds an indication for the classic hypogonadism, but their product is practically used off-label in large numbers for age-related hypogonadism, they need to provide

safety studies in that population.

I agree that for the classic indications, the benefit-risk is probably clear, and the numbers don't support cardiovascular safety studies. But every sponsor, regardless of the indication that their product holds should be responsible for those safety studies in age-related hypogonadism.

DR. JOHNSON: Thank you. Dr. Phillips?

DR. PHILLIPS: Marjorie Shaw Phillips. I voted B, and I waiver between B and C for some of the reasons that Dr. Gerhard mentioned. And I think my main concern also is in those where the benefit is questionable and we really don't know the risks of the idiopathic or the age-related hypogonadism.

I think to do that, you have to do a prospective randomized trial with defined endpoints and measures, objective measures, and validated instruments, and testosterone measurements as well as H&H.

DR. JOHNSON: Thank you. Dr. Erstad?

DR. ERSTAD: Brian Erstad. I voted B. And

it's because I think that age-related hypogonadism is the largest group where the benefit-risk assessment is the most difficult.

DR. JOHNSON: Thank you. Dr. Howards?

DR. HOWARDS: Stuart Howards. I voted B, but I agree very strongly with what Dr. Gerhard said.

DR. JOHNSON: Yes. And Dr. Curtis?

DR. CURTIS: Kate Curtis. I also voted B, but I also agree with what Dr. Gerhard said. I was reading it as indication. I guess, whether it's a current or future indication, I think that, given the current use, age-related hypogonadism should be studied.

I also just wanted to quickly say that we did see in the Xu meta-analysis, but not in all of the meta-analyses, that there were some different findings by the industry funded versus the non-industry-funded findings. It's unclear why that is, but I think that needs to be sorted out a little bit if another industry-funded study will be done.

DR. JOHNSON: Thank you. Dr. Chai?

DR. CHAI: Toby Chai. I voted B also, and I think it's intent versus reality. Reality is the drugs utilized for a population that it was not originally intended to be used, in my understanding of how the language is. And we just voted on it. So I think that if we want to look at reality, we got to do these safety studies.

Whether you call it age-related or low T, whatever you call it -- and to design a study specifically, now whether it should be randomized or observational, I think going prospectively, looking at those cardiovascular risks and other risks is indicated.

DR. JOHNSON: Julia Johnson. I voted B for the reasons already outlined by my colleagues.

Dr. Herring?

DR. HERRING: Amy Herring. I voted B. Rationale was mostly that of Dr. Phillips. I feel strongly it should be a randomized controlled trial and, also I'll comment on the acceptable risk because the population at risk is so large, I think

that that should be relatively low.

DR. ADLER: Robert Adler. I voted B mainly for the reasons that Dr. Tyler gave.

DR. ALEXANDER: Richard Alexander. I voted for B. The poor lads, for 30 years, have had their lives changed by testosterone repletions. This has never been an issue. Now, when we are using it in a different way, the issue is raised. And I think that's where the question should be asked. It would be randomized prospective double-masked trial to once and for all finally answer the question.

DR. LINCOFF: Mike Lincoff. I voted B. I think that patients who have the established organic hypogonadism couldn't really be randomized to placebo. And I don't think there's much question of the safety risk, the risk-benefit. I absolutely believe it needs to be a randomized clinical trial, but no observational study would be sufficient.

I think the trial should be large enough to rule out a risk similar to that of the diabetes or obesity trials, which means it has the upper

95 percent confidence limit of between 1.8 and 2.0, and that would establish the size.

DR. JOHNSON: Dr. Burman?

DR. BURMAN: Ken Burman. I voted C, but could have voted B as well. The cardiovascular studies we heard about today included mainly low testosterone with age-related changes, but it wasn't clear that they did not include other patients, such as with authentic hypogonadism.

It's difficult to predict what future indications should be, and certainly I am less concerned with treatment of classical hypogonadism with testosterone and cardiovascular effects than I am with the age-related changes. And I wanted to be conservative and prudent in voting C, in case there are future indications that we can't predict.

DR. BRAUNSTEIN: Glenn Braunstein. I voted B. If the testosterone trials currently underway show effectiveness in the age-related hypogonadal group, then I would like to see an industry-sponsored, along with NIH-sponsored, double-blind placebo-controlled WHI-type study that

looks at safety and additional efficacy.

DR. JOHNSON: Yes?

DR. DMOCHOWSKI: Roger Dmochowski. I voted B. My only comments were, I do think that trial should be a controlled trial, but it should really try to represent what's going to happen in the general population, so a much more naturalistic setting, if you will, with potentially relaxing on inclusion and exclusion criteria to really capture what the experience is going to be when and if it would be approved for that indication.

DR. SHEHAB: Nadine Shehab. I concur with colleagues that those with etiology other than classic hypogonadism are most important and practical to study based on numbers exposed. But based on Dr. Joffe's answer that he gave, that the current label currently includes those etiologies, I voted C to ensure that the cardiovascular studies are conducted by the sponsors who currently hold labels for these drugs.

DR. DOMANSKI: So I voted B as well, with the idea that people who want a new indication, not

the primary one, not the primary hypogonadism, but a new indication should have to show safety and efficacy.

DR. TEERLINK: John Teerlink. I voted B. And contrary to my perhaps perceived-contentious questioning earlier, I'd like to thank the sponsor for really coming here with an open approach to this meeting. And it's greatly appreciated. I wanted to vote C because I think this is a really important scientific question and I really would love to have an answer. But unfortunately, I think it probably would not be approached, so that's why B for the patient population that we've been discussing.

I also think that the FDC and FDA need to talk. And you guys need to talk about these disease awareness ads that are making therapeutic claims or alluding in these ways to therapeutic claims. There needs to be a way to stop that because that's, I think, one of the things that got this whole thing going.

So in terms of the specifics of the trial, I

think there is enough of a signal here to kind of move it to the 1.8 upper 95 percent confidence interval, consistent with the diabetes and other recommendations.

It should be the study population that the industry wants to have enrolled, well, actually wants to have get the drug. So these are patients who should have evidence of coronary disease, risk factors for all of these things, and of an age range in which they are actually going to give the drug.

DR. GARNICK: Marc Garnick. I would have voted A had it only been the primary and secondary indication, but I voted C because the continued off-label use is going to mandate the use of cardiovascular monitoring.

I too want to commend the sponsors on their relatively objective evaluation, but I think the sponsors are in a very, very good position to help their sales force to help physicians understand the necessity for getting baseline testosterone and continued testosterone evaluations in the

population of physicians that they are detailing, , so the physicians can become much more aware of the appropriate utility of these agents.

DR. THOMAS: Abraham Thomas. I voted A because I don't actually think this is a trial that should be done by the sponsors. I think this is a trial that should be done by the NIH and FDA, just like the Woman's Health Initiative. And the sponsors can help pay for it. The size of these trials usually for cardiovascular safety are quite large. They are about 8 to 9 million prescriptions. If you look at the estimates of sample size, a rough calculation probably would be the cost for trial between 60 and $120 million. That's between $8 and $15 per prescription.

So I think it could be done financially by the sponsors who are supplying the product, but there are a lot of unanswered questions that would be best answered by an NIH/FDA trial, including which type of delivery system is actually better, because we don't know if there are safety differences in injections versus transdermal. And

there are much differences, greater differences in level throughout the course of treatment.

DR. BOINEAU: So I voted B. I think Dr. Gerhard stated quite clearly the issues for the problem. And I think the level of evidence is so low for efficacy at this point that I think that the level of benefit has to exceed baseline if we're looking at risk.

DR. JOHNSON: Thank you. I'm going to do a very brief synopsis. On our first vote on labeling, there was a consensus that labeling should be changed, that information should be tightened and indications only for reasons that are related to low testosterone, with clear indications for testing to diagnose low testosterone, and that age-related is not a clear indication.

Then for voting on 4, the consensus was that, yes, but with certain indications, although honestly, B and C really interchanged each other in that the need is for the study for a randomized controlled trial and that, indeed, it is critical to look at cardiovascular risk with this

medication.

DR. JOFFE: Can I ask one follow-up question? Not everybody answered the type of study that should be done, so I was just wondering if anyone on the panel thinks that an epidemiological study could address the signal? And those who do, please provide some rationale.

DR. JOHNSON: Yes, Dr. Thomas?

DR. THOMAS: This is Abraham Thomas. I forgot to say it, but I think, definitely, it has to be a randomized clinical trial, placebo-controlled. I know, if you're using injections and transdermal, it might be hard to completely placebo-control that.

DR. JOHNSON: Dr. Gerhard?

DR. GERHARD: Thank you so much for this question. I was worried that I wouldn't get to say this. And I assume I am in the minority on the panel. I strongly advocate to not limit the cardiovascular safety studies to clinical trials. I think a large well-designed clinical trial is important, but it shouldn't be the only work done,

I think. Well-designed observational studies using large databases where our data sources are getting better, there have been lots of developments in the methodology for these types of studies, I think they're an important compliment to the large clinical trial.

DR. JOHNSON: Yes?

DR. DOMANSKI: I tell you, in terms of sponsorship, I just can't let this one go. I really think there should be industry sponsored. I think there's an opportunity cost for NIH and, frankly, I think they've got more important science to spend that kind of money on a budget-limited environment.

DR. JOHNSON: Thank you. And before we adjourn, any last comments from the FDA?

DR. JOFFE: Yes. I'd like to thank all the panel members for this very useful discussion and all the recommendations. We're going to carefully take those back internally and think about them. And we'll let you know what our final decision is. I'd also like to thank some behind-the-scenes

folks.

Before doing that, I want to thank Julia Johnson, who always does a great job as chairperson. Thank you. And behind the scenes, I'd like to thank Kalyani Bhatt, Jeannie Roule, and Christine Nguyen. The three of them handled a lot of the logistics, which made this all possible. I look forward to seeing everyone tomorrow.

Adjournment

DR. JOHNSON: So we will now adjourn, although I am going to ask the advisory committee to stay for just one moment. Panel members, please do remember to take all your personal belongings with you because we are cleaning up the room at the end of the day. All materials left on the table will be disposed of. Please remember to drop off your nametags at the table on your way out so they can be used tomorrow and thank you very much.

(Whereupon, at 5:04 p.m., the meeting was adjourned.)