FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Tuesday, January 9, 2018

7:59 a.m. to 4:24 p.m.

College Park Marriott Hotel and Conference Center

General Vessey Ballroom

3501 University Boulevard East

Hyattsville, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning, everyone. We have a very full agenda, so I'm going to ask that everyone take their seats so that we can get started.

My name is Vivian Lewis, and I'm the chair of the committee. I would like to remind everyone to please silence their cell phones, smart phones, and other devices if you haven't already done so. I would also like to identify the press contact for FDA, Andrea Fischer. Andrea's in the back waving her hand there, and that would allow us to direct any questions to her if there are any from the press.

I would now like to ask all of the members, consultants, and the FDA panel to go around the table and identify themselves by name and institution for the record. Let's start on this side with Dr. Joffe.

DR. JOFFE: Good morning, everyone. I'm Hylton Joffe. I'm the director of FDA's Division of Bone, Reproductive, and Urologic Products in CDER.

DR. DUNNMON: Good morning. I'm Preston Dunnmon. I'm a cardiologist in the Division of Cardiovascular and Renal Products at FDA.

DR. WIEDERHORN: Good morning. I'm Roger Wiederhorn, a urologist in the Division of Bone, Reproductive, and Urologic Products. I'm a medical reviewer.

DR. LINCOFF: Good morning. My name is Michael Lincoff. I'm an interventional cardiologist at the Cleveland Clinic, a former member of the Cardiac Renal Drug Advisory Committee.

DR. WILSON: Good morning. Peter Wilson. I'm a preventive cardiologist and endocrinologist and an epidemiologist from Emory.

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

endocrinologist.

DR. GASS: Margery Gass, gynecologist, executive director emeritus of the North American Menopause Society and current board of trustees for the International Menopause Society.

DR. DRAKE: Matthew Drake. I'm an adult endocrinologist at the Mayo Clinic in Rochester, Minnesota.

DR. SHAW: Hello. Pamela Shaw. I am biostatistics faculty at University of Pennsylvania.

MS. BHATT: Good morning. My name is Kalyani Bhatt. I'm the designated federal officer for the Bone, Reproductive, and Urologic Drugs Advisory Committee.

DR. LEWIS: I'm Vivian Lewis. I'm a reproductive endocrinologist at the University of Rochester.

DR. BAUER: Good morning. Doug Bauer. I'm a general internist and clinical epidemiologist from University of California San Francisco.

MS. SORSCHER: My name is Sarah Sorscher.

I'm with Center for Science in the Public Interest, and I'm the consumer representative.

DR. BISHOPRIC: I'm George Bishopric. I'm here as a patient representative. I'm also a pathologist at the University of Miami.

DR. BRANNIGAN: Bob Brannigan. I'm a urologist at Northwestern University Feinberg School of Medicine in Chicago.

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

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist at Rutgers University.

DR. KIRKALI: Good morning. I'm Ziya Kirkali. I'm a urologist at NIDDK NIH.

DR. HOWARDS: I'm Stuart Howards. I'm a urologist at the University of Virginia and Wake Forest Medical School.

DR. MAGER: Don Mager, professor of pharmaceutical sciences at the University of Buffalo.

DR. REJ: Good morning, everybody. I'm Bob

Rej with the Wadsworth Center of the New York State Department of Health and the School of Public Health, the State University of New York at Albany, and I'm a clinical chemist.

DR. NAHUM: Good morning. My name is Gerard Nahum. I'm with Bayer Pharmaceuticals. I'm vice president of the clinical development there.

MS. BHATT: Before we start the meeting, we have one consultant on the line.

Dr. Dmochowski, are you on the phone?

(No response.)

DR. LEWIS: And we have two other panelists who we assume will be joining us a little later, Dr. Yu and Dr. Edwards.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some are quite strongly held, of course. Our goal for today is that the meeting will be fair and open and a good forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into

the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place only in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing meeting topics during breaks or lunch. Thank you.

Now I'll ask Kalyani Bhatt to read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's meeting of the Bone, Reproductive, and Urologic Drugs 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 committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflict interests when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee

is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of new drug application NDA 206089, oral testosterone undecanoate capsules, submitted by Clarus Therapeutics for the proposed indication of testosterone replacement in males for conditions associated with a deficiency or absence of endogeneous testosterone: primary hypogonadism, congenital or acquired, and hypogonadotropic

hypogonadism, congenital or acquired. This is a particular matters meeting during which specific matters related to Clarus Therapeutics' NDA 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 accordance with 18 USC Section 208(b)(3) to Dr. A. Michael Lincoff. Dr. Lincoff's waiver addresses two of his employer's current research contracts with a competing firm for which they receive between $700,000 and $750,000 total in funding for one and between $7,000,000 and $7,500,000 total in funding for the other. Dr. Lincoff does not receive any personal remuneration or salary support from these studies. The waiver also allows Dr. Lincoff to participate fully in today's deliberations.

FDA's reason for issuing waivers is described in the waiver document, which is posted on FDA's website. Copies of the waiver may also be obtained by submitting a written request to the

agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests 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 product at issue.

With respect to FDA's invited industry representative, we'd like to disclose that Dr. Gerard Nahum is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Nahum's role at this meeting is to represent industry in general and not any particular company. Dr. Nahum is employed by Bayer Healthcare.

We would like to remind members and temporary voting members that if the discussion involves any of the 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 firm at issue. And just a correction, it's Gerard Nahum. Thank you.

DR. LEWIS: Thank you. Let's now proceed with the FDA opening remarks from Dr. Joffe.

FDA Opening Remarks - Hylton Joffe

DR. JOFFE: Good morning, everybody. Welcome to today's advisory committee meeting. I'm pleased we were able to start despite some delayed flights and cancelled flights. It's always a little nerve-wracking scheduling these during the winter in D.C., but it seems like everything's going okay so far.

What I'd like to do in the next 15 minutes is give a highlight of some of the key issues you'll be hearing about and discussing over the course of the day for this marketing application for oral testosterone undecanoate capsules. The proposed trade name is Jatenzo, and I'll refer to the product as Jatenzo during my presentation.

Testosterone itself has poor oral bioavailability because of the first-pass effect through the liver. Jatenzo contains a prodrug, testosterone undecanoate, and is formulated to be lipophilic so it can bypass the liver by being absorbed through intestinal lymphatics, making Jatenzo orally bioavailable. Once the testosterone undecanoate is absorbed, it's converted by circulating esterases to testosterone.

The applicant is seeking the standard indication for its testosterone replacement therapy like we've granted for other testosterone products. And if approved, this product has the potential to significantly change the landscape with testosterone therapies because the oral route may be easier to use than some of the more cumbersome routes with commonly used currently approved products such as injections and topical gels.

This is Jatenzo's second advisory committee meeting and second review cycle. Some of the issues identified during the first review cycle are shown on this slide. In the first review cycle, we

noted that absorption of the product depended on how much fat was included in the meal that was eaten around the time the product was taken, and that raised concerns that there may be erratic testosterone concentrations from day to day as patients would change their food intake from day to day.

Another issue was non-robust efficacy when accounting for missing data. There was also a signal with increased blood pressures on cuff measurements in prior phase 3 trials, and also a signal for adrenal insufficiency in dogs.

The applicant's resubmission includes a new phase 3 trial and other studies, and some of the key features of the phase 3 trial are shown on this slide. First, it was randomized and active controlled. The comparator was Axiron, another testosterone replacement therapy. The applicant revised the Jatenzo starting dose and titration regimen to improve on the robustness of the efficacy results.

In this trial, the applicant titrated their

product based on testosterone Cavg, which is a time average testosterone concentration calculated from the pharmacokinetic profile where you measure testosterone concentrations over 24 hours and then calculate the Cavg. The trial was to include ambulatory blood pressure monitoring at our request given the signal we'd seen in the earlier trials, and it also included an ACTH stimulation substudy to assess for adrenal insufficiency in humans.

Areas of focus for today, first the FDA agrees that the phase 3 trial meets its primary efficacy endpoint. The applicant also appears to have adequately addressed the food effect concerns by conducting a new food effect study and also by additional analyses of food data from their new phase 3 trial. Where we're going to be spending much of our time is on these issues shown here.

First, we're concerned about the potential for Jatenzo to increase cardiovascular risk in the population who will use this product if approved, based on what we've seen with regard to Jatenzo's effects on cardiovascular risk factors. Another

issue is whether a certain type of collection tube known as sodium fluoride EDTA tubes are critical for safe and effective use, and I'll get into that in a few minutes.

Next, the issue will be whether the titration scheme, which is proposed for marketing, which differs from the titration scheme used in the trial, is adequate to assure safe and effective use of the product. We'll also look at potential adrenal effects and the subjects who are outliers for peak testosterone concentrations, and then also the effects of Jatenzo on the testosterone metabolite DHT, or dihydrotestosterone, which itself is a potential androgen.

So this slide in a very high level gives an overview of the blood pressure and heart rate effects. You'll be hearing more about this in detail from Dr. Dunnmon in a little while. As you can see, Axiron has essentially no meaningful effects on blood pressure or heart rate, whereas Jatenzo appears to have some clinically significant effects.

For example, if you look at the overall data on average systolic blood pressure reading -- and these data are from ambulatory blood pressure monitoring -- you can see that the mean increase of Jatenzo was 5 millimeters of mercury compared to essentially no change with Axiron, so the treatment difference is about 5 with an upper bound of the same confidence interval of about 8.

If you look at those who have a history of hypertension, these results are magnified, so the treatment difference becomes 7 with an upper bound of a treatment difference of about 12. As you can see, Jatenzo also increases heart rate at about 2 beats per minute with no change with Axiron, so the treatment is about 2 with an upper bound of the 95 percent confidence interval of 4.5.

It's important to note that these changes occurred despite more Jatenzo treated subjects having escalation of their antihypertensive therapy compared to Axiron treated subjects.

When you look at lipids, it's well known that testosterone can reduce HDL cholesterol. But

if you look here, for example, at the shift from normal HDL at baseline to below normal at the end of this new trial, you can see that about twice as many Jatenzo treated subjects shifted to below normal, 29 percent, compared to the 15 percent of subjects on Axiron.

On the bottom of the slide, it shows the shifts from normal to above normal on the other lipid parameters, and you can see that there is numerically slightly more subjects that meet this criteria with Jatenzo than Axiron.

Putting this all together, we're concerned that these cardiovascular effects will increase the risk for adverse cardiovascular events with Jatenzo in men who will use this product with real-world use. This concern applies not only to the small population of men with classic hypogonadism, meaning those who have intrinsic damage to their hypothalamus pituitary adrenal glands, but also to the much larger middle-aged and older population who are receiving testosterone therapy for uses that are not FDA approved.

The applicant is proposing to have healthcare providers monitor blood pressures with cuff in the clinic, but it's not clear that that will adequately mitigate this risk because if a subject has an increase of 4 or 5 or 6 millimeters of mercury, that may not necessarily be discernible to the healthcare provider and may not necessarily lead to intensification or initiation of antihypertensive therapy, so over time, those subjects could be at risk of further cardiovascular events.

Turning to the tube issue, in the new phase 3 trial, the applicant measured plasma testosterone in a tube type known as sodium fluoride EDTA tubes, and this is different to how testosterone is usually measured in these trials and in clinical practice, usually as serum testosterone in serum tubes.

The applicant states that sodium fluoride EDTA tubes are needed with Jatenzo to prevent the conversion of testosterone undecanoate to testosterone in the test tube after you've drawn

the blood and before the blood's analyzed; and that's because sodium fluoride EDTA tubes include an esterase inhibitor that can block that conversion. The applicant states that sodium fluoride EDTA tubes, rather than the standard serum tubes, should be used in clinical practice when monitoring patients with Jatenzo.

We'll be presenting some of the data that the applicant's produced for this, and I'm sure the applicant will be sharing their data as well. And in those data, we do see changes or differences between sodium fluoride tube measurements and serum measurements, but it's unclear whether that's all due to stabilization of testosterone undecanoate or whether there may be other factors that are explaining those differences or contributing to those differences such as differences in assays used, differences in specimen matrices, and differences in storage conditions such as at room temperature or on ice.

With regard to the titration regimen, as I mentioned, in the phase 3 trial, Jatenzo was

titrated based on the Cavg pharmacokinetic parameter, which is not practical for real-world use, so the applicant is proposing dose titration based on plasma testosterone drawn in the sodium fluoride EDTA tubes 3 to 5 hours after the morning dose. And our question for the committee will be whether this titration regimen proposed for clinical practice reasonably reflects what titration decisions were made in the trial so that we can generalize the trial results to real-world practice.

With regard to adrenal effects, we saw some signals in the dogs, which could potentially indicate a signal for adrenal insufficiency. So we asked the applicant to include ACTH stimulation testing in a subset of subjects in the new phase 3 trial. Twenty-four Jatenzo treated subjects and 8 Axiron treated subjects underwent this testing.

All these subjects had normal ACTH stimulation at baseline, and at the end of the study, there were 5 Jatenzo subjects with an abnormal result compared to none with Axiron, and

this is using the standard criteria of at least meeting an 18-microgram per deciliter cutoff for serum cortisol.

With regard to the testosterone Cmax outliers, when we look at testosterone therapies, we have standard secondary endpoints to assess for unacceptably high testosterone exposures. On this slide, the first three rows show our standard Cmax criteria. The middle column shows the FDA targets that we apply to those criteria, and as you can see, Jatenzo met the first two criteria.

The third line, Cmax greater than 2500 nanograms per deciliter, the FDA target is that no subjects meet that threshold. And as you'll see, 2 percent or 3 Jatenzo treated subjects did so, and the applicant has attributed those cases to spurious results from Axiron contamination. I'm sure you'll be hearing about that later on as well.

Our last row shows a modified Cmax criteria using a cutoff of 2,268, and this is chosen to approximate the 2500 cutoff because the 2500 cutoff

is based on serum testosterone measurements. These testosterone measurements were done in plasma, which tend to run lower, so a correction factor was applied. And that analysis picks up one additional subject, which met the threshold and had no obvious explanation for why that happened.

DHT or dihydrotestosterone, ideally when you take testosterone replacement therapy, it should restore testosterone and its metabolites to the normal range for young, healthy men.

For DHT, as shown in this table, you can see that the majority of subjects, both with Jatenzo and Axiron, had maximal DHT above the upper limit of normal, and a significant number had a maximal DHT above twice the upper limit of normal with about 34 percent with Jatenzo and 17 percent with Axiron.

When you look at Cavg, which again is this time average concentration applied to DHT, about half of the subjects were above the upper limit of normal with comparable results between treatment groups.

I'd like to end by just walking everybody through the discussion and voting questions. There are three discussion questions and one voting question. The first discussion question has several subparts. The first discussion question reads as follows. Discuss whether the safety of Jatenzo has been adequately characterized. If additional safety data are needed, discuss the types of data that are needed and whether these data should be obtained pre-approval or whether they can be obtained post-approval.

With regard to this question, we'd like you to specifically cover the following. First, the effects of Jatenzo on cardiovascular risk factors, including blood pressure and lipids. Of course, testosterone also can increase hematocrit, which can increase viscosity of blood, which may also contribute to cardiovascular events.

We want you to take all of this into account and discuss the potential for which Jatenzo could increase the risk of adverse cardiovascular outcomes in the population that will likely use the

drug if approved.

We would also like you to discuss the supraphysiologic DHT concentrations in some subjects; the subjects who had maximal testosterone concentrations that exceeded those prespecified FDA targets; and then the adrenal related findings.

For question 2, we'd like you to discuss whether the titration regimen proposed for marketing will appropriately identify patients who require titration or discontinuation of Jatenzo.

Question 3 is to discuss whether the sodium fluoride EDTA tubes are critical for the safe and effective use of Jatenzo. If you conclude that these tubes are not critical, discuss how the standard serum tubes will ensure safe and effective use given that the phase 3 trial used the sodium fluoride EDTA tubes.

The voting question is whether the overall benefit-risk profile of Jatenzo is acceptable to support approval as a testosterone replacement therapy, and we'd like the rationale for your vote.

Thank you for your attention, and I'll turn

this back to the chair.

DR. LEWIS: Thank you. Dr. Joffe.

Before proceeding with additional FDA presentations, we've been joined by one other panel member.

Dr. Yu, could you please introduce yourself and your institution for the record?

DR. YU: My name is Chongwoo Yu. I'm the clinical pharmacology reviewer in the Office of Clinical Pharmacology at FDA.

DR. LEWIS: And Dr. Marathe?

DR. MARATHE: Hello. This is Dhananjay Marathe. I'm a pharmacometric reviewer within the Office of Clinical Pharmacology at FDA.

DR. LEWIS: Dr. Howards introduced himself. Dr. Dmochowski I'm told is on the phone. Can we hear from you this time?

DR. DMOCHOWSKI: Very barely, yes, I can hear, but the sound quality is really poor.

DR. LEWIS: Thank you.

Let's go forward with the FDA presentations. I'm sorry. We're now ready for the sponsor

presentations.

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

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any financial relationships. If you choose not to address this issue at the beginning of your presentation, it will not preclude you from speaking.

Let's proceed with Clarus Therapeutics.

Presentation - Robert Dudley

DR. DUDLEY: Madam Chairman, members of the committee, members of the Food and Drug Administration, good morning. My name is Bob Dudley. I'm an actual scientist by training, a pharmacologist and toxicologist, but I also serve as president and CEO of Clarus Therapeutics. Our presentation will demonstrate that Jatenzo's therapeutic profile is largely consistent with that of currently approved testosterone replacement therapies or TRT products.

As Dr. Joffe noted, the proposed indication for Jatenzo, like all approved testosterone replacement therapies, will be for the replacement of testosterone in symptomatic hypogonadal men with a deficiency or absence of endogenous testosterone. The active ingredient in Jatenzo is testosterone undecanoate or TU.

TU is a fatty acid ester of testosterone that serves as prodrug of testosterone, and the chemical structure is pictured here, and it highlights the ester linkage of the fatty acid to

the testosterone as shown in the blue circle. TU has a long history of use as an oral treatment for male hypogonadism in over 80 countries around the world in all of the major pharmaceutical countries but has never been approved in the United States. A unique aspect of Jatenzo is that TU is absorbed into the circulation via the intestinal lymphatic pathway.

As shown on this simplified figure, oral drugs are typically absorbed into the portal circulation, which flows into the liver. Currently available oral alkylated androgens like methyltestosterone are absorbed by this route, but they have a long history of hepatotoxicity. In contrast, absorptive cells in the small intestine process TU as a fat, which is then absorbed into the lymphatic circulation, thus bypassing the liver.

TU takes one of two pathways. The primary pathway for TU absorption into the systemic circulation is via that lymphatic system. Once absorbed, TU in the blood is acted upon by

non-specific esterases to then liberate testosterone or as noted here, T.

Secondarily, TU may be metabolized to testosterone within intestinal cells, but the metabolic capacity of those cells is very large, and the testosterone there is largely metabolized. Thus, only a small amount of testosterone actually sees its way into the portal circulation. And here again, the liver is a mighty force when it comes to metabolizing testosterone, and it is largely if not completely metabolized there.

Finally, TU is pharmacologically inactive even though it may circulate at relatively high levels after oral administration, However, as noted earlier by Dr. Joffe, the presence of circulating TU can lead to a problem, and that problem is the inaccurate measurement of testosterone unless blood is collected properly, a lesson we learned I would say late into our 12-year development program.

The importance of proper blood collection for TU is summarized here. Non-specific esterases

in blood can convert TU to testosterone after the blood has been collected. This was initially demonstrated in a study by Sylvain LaChance, who is actually here today on our responder panel, and later confirmed by Clarus.

In our initial phase 3 studies, we underestimated the potential magnitude of this issue. However, to ensure the accurate measurement of testosterone in our new phase 3 study, we employed a more appropriate blood collection method to ensure accurate testosterone measurements. Proper blood collection in a PK trial of oral TU is critical to avoid overestimation of testosterone, which could result in wrong-dose titration decisions and inaccurate efficacy measures.

Fortunately, the solution is really quite straightforward. Blood should be collected in the presence of an esterase inhibitor, in this case sodium fluoride, to prevent conversion of TU to testosterone in blood in the collection tube. Clarus used sodium fluoride tubes to collect blood in study 15012. And so that everyone knows, these

tubes are available commercially for clinical use.

Finally, this blood collection method required that we establish a new eugonadal testosterone range on which to determine efficacy, one that accounts for the difference in the results between the two kind of collection tubes, and therefore the two matrices that are slightly different.

The impact of blood collection methodology is depicted in this graph. These are data from study 15012. Clarus compared the testosterone values as measured by LC/MS/MS from hypogonadal men who received oral TU and whose blood was collected in standard tubes, depicted here by the dark orange line, and then a match sample collected in sodium fluoride EDTA tubes, the gray line. And each of those tubes were handled as would typically be the case. Of course, the purpose of sodium fluoride was to inhibit the conversion of TU to T.

When blood is collected in the standard tubes yielding serum, testosterone values are markedly higher, but as you would expect, the peak

effect reaching its maximum when circulating levels of TU are high. These data show that the overestimation of circulating testosterone levels due to post-collection conversion of TU to TU was on average about 15 percent.

Clarus conducted a variety of new studies to support resubmission of our NDA. Clarus filed the original NDA for oral TU in 2014. Then again, as Dr. Joffe noted, we participated in an advisory committee, across the hall actually, in September of that year. After this meeting, the FDA issued a complete response letter.

Guidance provided by members of the advisory committee and ensuing discussions with the FDA helped us identify a clear path to address the unresolved concerns. Principally, this path involved conduct of a new phase 3 trial to confirm efficacy based on circulating testosterone response. We also conducted a new food trial to more fully characterize potential food effects on Jatenzo. And in addition to these studies, Clarus conducted other ancillary clinical studies as well

as additional preclinical studies to support its resubmission.

Not surprisingly, Clarus learned important lessons from our new studies of Jatenzo. First, as I mentioned earlier, proper blood collection is critical, and I won't belabor that point on this slide. Next, we identified an improved dose titration algorithm using a start low dosing approach. This resulted in the revised titration boundaries and substantially improved efficacy compared to our previous phase 3 trial.

Third, we know with greater confidence that food has a clinically insignificant effect on testosterone response after oral TU. Fourth, we determined that oral TU has no clinically meaningful effect on adrenal function. And finally, we observed that oral TU may increase systolic blood pressure in some men.

During the conduct of study 15012, we had a central laboratory change that the FDA asked me to share with the committee and that there was an associated protocol amendment. During this

open-label trial, the CRO's medical monitor saw an unexpected number of Axiron patients being uptitrated. Upon further investigation, an internal investigation by the central lab found that its testosterone measurements on which Clarus used to determine dose titration were not accurate.

Because there was no way to ascertain how long this central lab would take to identify the cause of the problem and fix it, Clarus decided to identify a new laboratory that already had in place a validated assay for testosterone in sodium fluoride EDTA plasma. All patients who were affected by the lab change was at various points in the study as depicted in the yellow area. Subsequently, they were held at their testosterone dose before the change and until the new lab had a completed re-assay of properly frozen visit 2 PK samples and then the correct testosterone concentration or average testosterone concentration calculated. This change is represented in the purple area.

Once a new average testosterone level was

calculated, patients were assigned to the proper Jatenzo or Axiron doses at visit 3b depicted in green, whereupon they proceeded to the end of the study as per the original protocol. So after initiation of the protocol amendment, every subject had two opportunities for dose adjustment based on correct testosterone values proper to the PK efficacy visit, which is visit 7. Finally, the lab change did not negatively impact subject retention or primary efficacy as Dr. Swerdloff will address shortly.

During today's presentation, we will explore three main themes. Our clinical data support the conclusion is an effective method to restore testosterone levels to normal in hypogonadal men. Moreover, we have identified a dose titration algorithm that can be used to achieve efficacy for individual patients. This scheme also allows for healthcare professionals to determine when a patient should be discontinued from Jatenzo.

The PK results used by the FDA as the primary means of assessing efficacy for

testosterone replacement products meet the requirements for approval and are consistent with past precedent for testosterone replacement therapy products.

Next, Jatenzo's general safety profile is consistent with the profiles of approved testosterone replacement products. We did, however, observe a greater increase in systolic blood pressure compared to Axiron, and Drs. Danoff, White, and Kaminetsky will discuss how to deal with this blood pressure increase in clinical practice.

Jatenzo also lowered HDL cholesterol more than Axiron, but this may not reflect a change in HDL functionality as will also be discussed. We've also confirmed in our new food effects study that dietary fat will not have clinically significant effects on a patient's testosterone response to Jatenzo. The changes we made to bolster the overall Jatenzo development program and its results, combined with what we had previously discovered, give us confidence that we can offer the FDA and this committee strong support for

Jatenzo's approval as a new treatment option for symptomatic hypogonadal men.

With this background then, I would like to present the agenda for the rest of today's meeting, and now I would like to ask Dr. Amory to come forward.

Presentation - John Amory

DR. AMORY: Good morning. My name is John Amory. I'm a clinician and clinical researcher at the University of Washington with a longstanding interest in andrology. I've participated as an investigator in several of the studies presented here today. I have no personal financial interest in the outcome of this meeting, although I am being compensated for my participation here today.

I have been asked to speak about the presentation, diagnosis, and treatment of hypogonadism. Hypogonadism is manifested in multiple ways in many different tissues. It's typified by a low concentration of testosterone as well as symptoms and signs that are consistent with the syndrome.

What you're looking at now is a schematic of a male with normal testosterone on the left contrasted with a male with hypogonadism on the right. In the middle, you can see the various organ systems that are affected.

Primarily, hypogonadism manifests as a decrease in sexual drive or libido. Secondary sexual characteristics that are maintained by testosterone starting at puberty are also affected such as body hair. A low concentration of testosterone also causes a profound decrease in muscle strength and function and has negative influences on body fat distribution and increases the risk for obesity. A low concentration of testosterone decreases bone mineral density and also leads to anemia through a decrease in the production of red blood cells.

Several of these manifestations are illustrated in this photograph from the New England Journal of Medicine, which depicts a pair of identical twins, one of whom had a slow-growing pituitary tumor for several years before it was

diagnosed. As you can see, compared to the eugonadal twin on the left, the hypogonadal twin on the right has several features consistent with the syndrome of hypogonadism. You'll note that he has gynecomastia, an increase in abdominal obesity, and a loss of sexual hair. Importantly, you'll note that he's several inches shorter than his identical twin. This is due to osteoporosis from his hypogonadism and spinal compression fractures.

So how does one diagnose hypogonadism in a man without an identical twin? The diagnosis of hypogonadism requires two features. The first is by chemical evidence of testosterone deficiency. This is usually defined as a low total testosterone measured twice on two separate days, separated by at least a week, of less than 300 nanograms per deciliter.

In addition to biochemical evidence of hypogonadism, an individual has to have either signs or symptoms of hypogonadism to qualify for the diagnosis. The signs are decreased bone mineral density, anemia, or reduced muscle mass and

strength. Symptoms consistent with a diagnosis of hypogonadism also include reduced libido and diminished sexual function.

Frequently indeed, it is sexual function that brings men into the office. However, upon questioning, they will also describe additional symptoms such as hot flushes or sweats, a generalized decrease in energy, poor concentration, or a depressed mood. In reality, these patients are suffering from a syndrome with some or all of these symptoms that negatively affect functioning throughout the day.

What types of patients are appropriate for treatment with testosterone? Here are the American Urological Association and Endocrine Society criteria and positions for treatment with testosterone. The AUA importantly does not recommend treatment with testosterone in men with normal testosterone concentrations, as there is no demonstrable benefit of testosterone therapy in such men.

The goal of therapy is to achieve a

testosterone concentration in the mid-normal range and regular monitoring is recommended. The monitoring includes a symptomatic response to treatment, biochemical improvement in testosterone levels, and an assessment of side effects. These guidelines are followed very closely by the prescribers of testosterone replacement therapy. These include primary care providers, internal medicine physicians, endocrinologists, and urologists, primarily.

So what are the benefits of testosterone replacement therapy? As I mentioned, it can affect libido and sexual function in a positive way. Testosterone therapy can increase bone mineral density, muscle mass, and strength, decrease obesity, and improve anemia.

Much of the best data that speaks to this come from the recently completed NIH-funded T trial, which was published in the New England Journal of Medicine in 2016. This study was a well conducted prospective, randomized, placebo-controlled trial of testosterone therapy in

older hypogonadal men. The investigators randomized 788 older men with a mean age of 71 and symptomatic hypogonadism to either testosterone or placebo, and then followed them prospectively for 12 months.

In this graph, the effects of testosterone treatment on sexual function in the men in the study compared with placebo is depicted. As you can see, there's a statistically and clinically significant 30 percent improvement in sexual functions in the men who were randomly assigned to testosterone compared to those who were assigned to placebo. This effect was sustained through the duration of treatment. These results from this large trial are similar to those we see in smaller trials of younger men with low testosterone and low libido.

Another important issue for older hypogonadal men is bone density, which if reduced can predispose to hip and spine fractures. On this graph, you can see the effect of testosterone on bone density in the men in the study. Testosterone

treatment in pink leads to a greater increase in bone mineral density of both the hip and the spine compared to placebo.

What about the side effects seen in this study? This trial did a very nice job of independently adjudicating side effects and outcomes, and this table depicts those. Reassuringly, there were no really concerning differences in prostate, blood, or cardiovascular events between the two groups.

In the far right column are the 394 men who were assigned to testosterone compared to the 394 men assigned to placebo in the second column. Starting from the top of the table, you can see there was a greater increase in PSA in a subset of men who were assigned to testosterone, but there was no increase in either prostate cancer diagnosis or worsening of lower urinary tract symptom scores as determined by the International Prostate Symptom Score.

Moving down the table, you can see about 2 percent of the men who were assigned to

testosterone developed erythrocytosis with a hemoglobin greater than 17.5. This is something that's seen rarely, about 2 percent of the time, with most formulations of testosterone. The next area of the table shows the risk of cardiovascular events in the third area. You can see there was no difference between the two groups, either in terms of myocardial infarction, stroke, or the composite endpoint, including death.

This study was not designed and is underpowered to look at cardiovascular endpoints. Obviously, that will require more patients and more time, nevertheless, the absence of any safety signal I think is notable.

Despite the positive benefit-risk ratio seen in this trial, there are some limitations and risks with testosterone replacement therapies as a class and with individual delivery methods. Let's begin with the most popular options.

Topical transdermal products can be difficult for some men to use. The gels are challenging to apply correctly and can be messy.

More importantly, if a patient has a wife or girlfriend, and that wife is of child-bearing age or he has children, there are risks of transferring the topical testosterone to these individuals. In children, this transference has been reported to initiate precocious puberty.

Testosterone patches can avoid the problem of transference, but they cause frequent skin irritation in about half of men who are using them and are not popular. The only other real option for this chronic condition is injectable testosterone, which comes with its own set of potential limitations such as injection site pain, potential pulmonary oil microemboli, and in extremely rare cases, anaphylaxis.

Some patients are not able or willing to deal with these limitations over a long period. As a result, some patients switch from one delivery method to another. They switch for a variety of reasons: the lack of efficacy, inconvenience, or side effects related to the delivery system. Some patients even discontinue treatment altogether

because of these limitations.

In addition to these product-specific side effects, there are well known adverse class effects of testosterone due to its physiologic activity, and these include the increased PSA; an increased hematocrit as you saw in the data from the T trial; lipid changes; and a very slight increase in the risk of venous thromboembolism. Testosterone is well known to suppress spermatogenesis and can lead to azoospermia, and occasionally we'll see a patient who develops edema. Although not listed here, blood pressure increases have recently become more commonly associated with testosterone as a class.

What are the monitoring requirements for a patient who's receiving testosterone replacement therapy? First, we check the patient to make sure that the sexual function or other aspects of hypogonadism that has brought him into treatment is improving on therapy. We also monitor testosterone concentrations regularly to make sure we've achieved the testosterone concentration in the

therapeutic range. We always monitor patients for side effects as well as for blood pressure changes, and men receiving testosterone need to be screened for prostate cancer.

Lastly, it's always important to check the hematocrit yearly at least to catch those 2 percent of men who are going to develop erythrocytosis. If a man does have erythrocytosis, you can adjust the dose down or manage it with therapeutic phlebotomy or discontinuation as appropriate. We take all of these factors into account before deciding whether or not to continue therapy long term.

To summarize, treatment of men with testosterone deficiency and signs or symptoms consistent with hypogonadism is very appropriate. The side effects of testosterone therapy are well known to clinicians and manageable with monitoring. And I will say as a clinician who treats a lot of men with hypogonadism, I invariably get the question, "When are we going to have a testosterone pill?" Many of my patients are unhappy with their current treatment options.

Imagine, if you will, a 20-year-old patient with newly diagnosed Klinefelter's syndrome of whom there are over 300,000 in this country, or a young man who has lost his testes to cancer or trauma. Such a man is looking at thousands of injections of intramuscular testosterone or tens of thousands of applications of a testosterone gel during this lifetime. A safer oral option would offer these patients and doctors a formulation of testosterone that would provide safe administration and titration to achieve optimal results.

In today's talks, you will hear about Jatenzo, an oral testosterone designed to meet the need I've described. My colleague Dr. Swerdloff will now present the Jatenzo program and its efficacy results.

Presentation - Ronald Swerdloff

DR. SWERDLOFF: Good morning. I'm Ronald Swerdloff. I'm professor of medicine at the David Geffen School of Medicine at UCLA and chief of endocrinology at the Harbor-UCLA Medical Center. I've been participating in the area of andrology

for some time, and I'm a past president of the American Society of Andrology. I've also participated in the development of the guidelines for many organizations. I participated in the testosterone trial, the T trial, that Dr. Amory described, and I'm the overall principal investigator for the studies that are under consideration today.

Clarus designed the 15012 study to accomplish four mail goals, which are identified by the FDA and by the previous advisory committee. They are, to test a titration scheme refined from those in earlier studies and one that would improve efficacy from the earlier trials; two, to study a starting dose lower than in previous studies, thus reducing the risk of treating patients with unnecessarily high starting doses; third, to ensure that the participants followed their usual diets in the PK sampling days in the food setting and throughout the other studies; and lastly, to enhance patient retention.

Study 15012 was a primary efficacy study.

The patients were randomized 3 to 1 to either Jatenzo or Axiron in an open-label design. The study randomized 166 patients to Jatenzo and 55 to Axiron, and these were symptomatic, hypogonadal men with testosterone levels below 300 nanograms per deciliter on two separate occasions. Of note, 92 percent of the patients completed the study.

The study design, as shown previously by Dr. Dudley and is seen here, provided two opportunities for dose titration after the laboratory change, and those two titration points are seen in the red circles on the cartoon. Patients could be titrated to visit 3b and again at 5b prior to the final PK assessment, and the final PK assessment was done at visit 7, again shown by the encircled area.

The primary efficacy endpoint for testosterone replacement product is based solely on the PK data. This is the FDA standard, the analysis method, for approval of all testosterone replacement therapy. As a result of the titration protocol, most of the patients' doses were titrated

upward rather than downward.

All patients started at 237 milligrams BID depicted in purple at the far left. At the first titration, one-third of the subjects remained at the starting dose as shown in the next purple bar in the middle panel, and two-thirds increased to 316 milligrams, the yellow bar, again in the middle panel.

Only 4 subjects had reduction at the first titration. On the right in the last panel are the doses after the second titration. Seventy-two percent are at the two highest doses, while most of the other patients are at the starting dose with only 3 patients at lower doses. All of this suggests that 237 milligrams is an appropriate starting dose because very few patients require dose reductions. Thus, I think we can say that the titration was effective as it brought all the patients into the same range.

These are the concentration profiles from visit 7. The three lines depict the patient groups whose final doses were 237 milligrams BID in

purple, 316 milligrams in yellow, and 396 milligrams in red. All three profiles are closely aligned and fall within the middle portion of the eugonadal range, thus showing again that the titration scheme worked. However, at visit 2, prior to dose titration, the patients who ended up at the higher doses had lower concentration, so this reflects the uptitration that was done between the two titration times.

According to this target set by the FDA, the primary efficacy outcome is the proportion of men who have an average testosterone concentration in the eugonadal range. This proportion should be greater than 75 percent. The proportion needs to have a lower bound of the 95 percent confidence interval greater than 65 percent.

The results of the primary outcome were very positive; 87.3 percent of the patients were in the eugonadal range. That compares to the requirement of greater than 75 percent. These prospectively defined sensitivity analyses described in the briefing book demonstrated comparable efficacy and

reflects the robustness of the efficacy results. 81.3 percent was the lower bound of the 95 percent confidence interval, greater than the FDA target.

Let's look at the results of the secondary Cmax targets. There were three secondary targets that deal with the maximum testosterone concentration as defined by the FDA. Greater than 85 percent should have peak circulating testosterone less than 1500 nanograms per deciliter. Less than 5 percent should have peak circulating testosterone between 1800 and 2500 nanograms per deciliter. And finally, no patient should have a peak circulating testosterone greater than 2500.

Jatenzo met two of the three secondary efficacy targets. 90.7 percent of the patients had a Cmax less or equal to 1500 nanograms per deciliter, easily meeting the criteria. Two percent of the patients had peak circulating concentration between 1800 and 2500 nanograms per deciliter, again meeting the criteria. Three subjects did not meet the final target, having peak

testosterone values greater than 2500.

Clarus investigated these three one-time excursions and determined that they were most likely due to sample contamination. The FDA has accepted this determination in their briefing document.

To assess the potential food effect with Jatenzo, Clarus conducted a second food study. Study 16015 was designed to assess the effect of dietary fat on testosterone exposure. In this study, 18 men consumed each of the 5-meal options shown on this slide. The central blue bar is the 30-gram fat reference meal, and all the other bars are compared to the reference meal. Each bar then represents the ratio of the testosterone exposure with the indicated meal versus the testosterone exposure after the 30-gram fat reference meal.

The diet represented by the gray bar on the far left is the fasting state, while the one on the far right is the highest fat high-calorie meal. Importantly, this and the 45-gram fat meal do not increase exposure, which was the primary concern.

As you can see, the last two were very similar to the blue bar, the reference meal.

The first green bar representing the meal with 15 grams of fat -- that's the second bar -- shows a 25 percent decrease in exposure, but this is manageable through dose titration. The fasting bar on the far left shows that testosterone exposure is reduced by approximately 40 percent in comparison to the reference meal. Because of this, Clarus proposed that Jatenzo, as with many other medications, be taken with food.

I will now present the efficacy overview. Clarus achieved the goal set to address previous efficacy concerns. 15012 had a lower starting dose, a real-world diet, and a revised dose algorithm. These led to the successful efficacy results. 87.3 percent of the patients attained a testosterone concentration in the eugonadal range. Two of the three Cmax targets were met.

The food effect demonstrated that even a high-fat, high-calorie diet did not result in an excessive testosterone exposure. Taken together,

these results demonstrate that Jatenzo is an effective approach to restore circulating testosterone levels to normal in symptomatic hypogonadal men. Thank you very much.

Presentation - Theodore Danoff

DR. DANOFF: Thank you and good morning. This presentation will focus on the general safety results of 15012, however, the Jatenzo safety data set is comprised of three phase 3 studies. Studies 09007 and 15012 had active comparators. Median duration of treatment with Jatenzo was 364 and 141 days, respectively. Study 12011 was a single-arm study with median duration of treatment of 113 days. Study 15012 used the final dose titration algorithm proposed for label.

All three phase 3 studies had similar demographic characteristics, which included a range of patients typical for the treatment population. The men studied were mildly obese, and the comorbidities of pre-diabetes, diabetes, and hypertension were common.

The treatment-emergent adverse events in

15012 are summarized here. The occurrence of an TEAE was higher with Jatenzo than with Axiron. There were 2 patients with serious AEs on Jatenzo. One was a patient with a periumbilical abscess. The other was a patient with A Crohn's disease flare resulting in a small bowel obstruction that I will mention later. Neither was attributed to study drug, and both patients completed the study.

Discontinuations due to AEs were low, and there were no deaths on study. Looking at details of these TEAEs, there are some expected findings related to the dosage forms. GIAEs were seen only in the Jatenzo group and are likely due to the formulation and route of administration. These AEs are generally mild, and no patient had to discontinue treatment due to these GIAEs.

Conversely, topical testosterone replacements can cause skin irritation. We can also look at the TEAEs associated with the physiologic activity of testosterone. TRT class labeling instructs that healthcare providers monitor for changes in hematocrit, lipids, and PSA.

These lab abnormalities were seen with Jatenzo.

The TEAE of hypertension listed here document changes to antihypertensive medications. We told the investigators that they could record these adjustments as AEs. None of these AEs led to discontinuation from study. Dr. White will discuss blood pressure changes on Jatenzo in greater detail.

The pooled safety database of all phase 3 studies allow us to further characterize treatment-emergent events on Jatenzo. The incidence of TEAEs on Jatenzo is essentially identical to that seen to the active comparators. There were 471 patients treated with Jatenzo and 215 patients were treated with either AndroGel or Axiron, two FDA-approved transdermal testosterone preparations. Dr. White will review MACE events in his presentation.

Hypogonadism can cause mild anemia, and testosterone treatment is known to cause increases in hematocrit. Looking at the mean change from baseline, the average absolute hematocrit increase was 2.6 percent in the Jatenzo group and 2 percent

in the Axiron group. The majority of the patients remained in the normal range for the lab, which goes up to 41 percent.

We also identified outliers whose hematocrit went above 54 percent. Eight Jatenzo patients had a hematocrit above 54 percent. There were no clinical events associated with these increases. No patient had to discontinue due to the elevated hematocrits. Monitoring hematocrit is part of testosterone class labeling and will be included in the Jatenzo label. If the elevation is persistent, TRT class labeling describes general management approaches.

Another aspect of evaluating TRT is examining the active metabolite of testosterone, DHT. Testosterone treatment of hypogonadal men causes DHT plasma levels to rise. The final DHT levels are essentially identical in the two treatment groups.

We also examined the frequency of values above the upper limit of normal. For the average DHT concentration, the frequency of values above

the upper limit of normal was similar between the Jatenzo and Axiron treated groups. Almost all of the patients in the study had a Cmax greater than the upper limit of normal.

The Jatenzo group had a higher frequency at 2 times the upper limit of normal with 34 percent versus 17 percent. The difference decreased at greater than 3 times the upper limit of normal, 7 percent versus 4 percent, and no patients had a Cmax greater than 5 times the upper limit of normal. The literature suggests that these increases have no clinical significance.

We also followed up on an observation in our dog toxicology studies that showed reductions in adrenal gland weight. To do so, we conducted cosyntropin stimulation testing in a substudy of 15012. We examined peak post-stimulation cortisol levels for both Jatenzo and Axiron patients. We utilized the usual threshold of 18 micrograms per deciliter for any reduced response as well a threshold of 15 micrograms per deciliter, which is a published cutoff threshold to rule out primary

adrenal insufficiency.

All 8 Axiron patients had peak cortisol levels above 18. When we looked at Jatenzo patients, we found one significant outlier. This outlier is the patient with the SAE due to the small bowel obstruction from Crohn's disease that needed treatment with high-dose steroids. These exogenous steroids can suppress adrenal function. There were 4 other Jatenzo patients who did not have peak cortisol levels above the prespecified limit of 18, but all were above the 15-microgram per deciliter threshold to rule out primary adrenal insufficiency.

In summary, the adverse event profile of Jatenzo is similar to transdermal T formulations, except for GI events, which were mild, tolerable, and probably related to the formulation. Data suggests that changes, although small, in hematocrit can be monitored and managed as they are with other TRTs. There is no evidence of clinically significant adrenal function suppression.

Now, Dr. White will conclude the safety evaluation with a review of the CV safety results.

Presentation - William White

DR. WHITE: Good morning. I'm Dr. William White. I'm actually a professor of medicine in the Calhoun Cardiology Center at the University of Connecticut. I'm also a hypertension specialist and work in the field of cardiovascular drug safety. I've had a long-standing interest in non-cardiac drugs that cause an excursion of blood pressure in the upper direction. I'm here actually as a consultant to Clarus today to present an overview of the cardiovascular safety findings in their development program.

As you've heard, there were two prior studies, 09007 and 02011, that showed small increases from baseline in blood pressure on Jatenzo. To better evaluate these blood pressure changes with FDA input, integrated blood pressure assessments were incorporated into the 15012 protocol. That included clinical blood pressures that were assessed at key time points to define the

magnitude and time course of changes as well as ambulatory blood pressure monitoring at baseline at the end of study to define the pharmacodynamic relationship between blood pressure and the twice-daily dosing regimen of Jatenzo versus the once-daily dosing of Axiron.

You've seen this diagram before. I just wanted to reiterate that blood pressures were obtained in the clinical setting, that is clinical measurements at baseline, again at visit 2, and at visit 4b when there was post-titration at the end of the study. Ambulatory blood pressure monitoring occurred in everybody in this trial at baseline and then again at visit 6, which was one day before the end of the study, visit 7.

The clinician blood pressure measurements were standardized in this study according to the American Heart Association guidelines using all seated measurements, back supported, feet on the floor, arm supported at the heart level, and with at least a few minutes of rest. They were measured in triplicate using a digital oscillometric device

attended in the non-dominant arm with attention to proper cuff side, and the cuff blood pressures measured in triplicate were average.

Seen here are the baseline values of 127 in the Jatenzo group versus 124 in the Axiron group. And remember, there's a 3 to 1 randomization scheme, so there was a 3 millimeter difference at baseline. The least-square mean differences between the treatment groups was about 2.7 millimeters of mercury, higher on Jatenzo than on Axiron.

This is the time course of the changes from baseline in the clinic systolic blood pressure by visit in all treated patients. You'll note that blood pressures were relatively stable in both treatment groups until after visit 4b. And at visit 7, both treatment groups rose a little bit and higher on Jatenzo relative to Axiron.

Now, there was concern brought up about the fact that this curve does not plateau at this time point in the 140-day study, so I went back and looked at study 09007. It's more complex. Let me

just orient you to the X-axis. Each one of these days of the study represents a full dosing period or two dosing periods. Day 30 and day 65 is 12 hours of observations for the 12-hour dose, and day 90 is the 24-hour period of observation in housed patients in a BID dosing regimen. This is against AndroGel, not Axiron, at 1 percent, and the Jatenzo formulation was somewhat higher in concentration than it was in the 15012 study.

What I want to point out is that in both situations for both drugs, there was a small increase in blood pressure by the end of the dosing period. But at day 90, you'll see where there was a second dose and blood pressures actually fell in concert with the circadian rhythm of blood pressure at night when people are probably resting or sleeping, and then went up a little bit in the morning. But importantly, there was no cumulative effect over time of either drug causing a significant increase in blood pressure after 30 or 90 days.

It was also noted that there was a somewhat

discrepant finding if you were treated medically for hypertension at baseline or not. About 50 percent of the patients in the 15012 trial had a history of hypertension and were on antihypertensive drugs. And similar to the pattern seen in all patients, the blood pressures began to rise between visit 4b and visit 7, about 4 millimeters systolic in the treated hypertensives and only about 1 millimeter of mercury in those patients lacking a history of hypertension.

Now, I'm going to show three different patterns of outliers for the clinical measurements taken in the 15012 study to put this in somewhat a clinical perspective. We have a hard time understanding what a 4-millimeter increase means in an individual patient because that's a population change. This first figure is a distribution of changes from baseline in clinical systolic blood pressure at visit 7. The lower blood pressures are to your left and the higher to the right. The blue is Axiron patients and the orange is Jatenzo.

You'll note that about 20 percent of the

patients who are randomized to Axiron had at least a 10-millimeter increase in blood pressure, and about 30 percent, Jatenzo patients, had a proportional increase of 10 millimeters or higher, which I believe is a clinically detectable blood pressure in an individual patient. And the changes were not really driven by lower values that would not be detectable such as 0 to 5 millimeters of mercury.

Another way of analyzing this is according to a change like that and a result in blood pressure that you might consider hypertensive, and I'm going to talk a minute about the changes in the guidelines. But in this particular table, the top group are people who went up by 10 millimeters or more, and their result in blood pressure at visit 7 was either 140, 150, or 160.

You'll note that the only category in which there was a significant or clinically important difference in the proportions were those patients who went up by 10, and that resulted in 140 but less than 150. That was 15.4 percent of the

Jatenzo patients versus 9 percent of the Axiron patients. For all the other categories, 150, 160, or those who went up by 20 or more and resulted in 140, 150, or 160, the proportions were pretty much the same for Jatenzo and Axiron.

Finally, a couple of months ago, the American College of Cardiology and the American Heart Association published a new classification scheme for hypertension based on clinical measurements in which stage 1 hypertension is now called those individuals with 130 to 139 systolic or 80 to 89 diastolic, and stage 2 is now defined as those patients who are greater than 140 over 90. Patients who were greater than 140 over 90 would be initiated on an antihypertensive drug. Patients in the stage 1 category would be initiated on an antihypertensive drug only if they have an ACC-AHA calculated risk score of 10 percent or higher.

In looking at the patients who started out lower and upshifted into a higher category, in the shaded groups, the proportion of patients were in fact 31 percent of Jatenzo individuals and

32 percent of Axiron, so quite comparable. Within the 15012 study, every one had an ambulatory blood pressure study, but only about 80 percent were evaluable. This is fairly typical for device error, patient non-compliance, and so forth, but it was balanced between the two treatment groups.

I'm going to focus a little bit about ambulatory blood pressure monitoring in the next few slides. I've been working with this methodology for nearly four decades. This particular methodology uses a small recorder that can obtain automatically blood pressures at various intervals over the day and night. In this particular study, they were set at 30 minutes.

In order to meet quality control criteria, it was required that there was at least 23 hours of recording time with no more than 2 hours of missing data and no more than 80 percent of device-accepted values missing as well. The analyses of ambulatory blood pressure historically or typically are 24-hour mean daytime, nighttime, and hourly mean changes from baseline.

The 24-hour systolic blood pressures were fairly similar at baseline in Jatenzo and Axiron patients at 127.5 versus 127 millimeters of mercury. The least-square mean changes between the two treatment groups was 4.8 millimeters of mercury, which was statistically significant.

In looking at the profile of the hourly changes from baseline on Jatenzo, which is orange and which the dose was given twice, and in Axiron in blue, which the dose was given once in the morning, you'll note that there's a variation in the difference over time that ranges from about 7 or 8 millimeters of mercury during the first few hours of the dosing period to as low as about half a millimeter or millimeter in the middle of the night.

It's clear that Jatenzo increased blood pressure to a greater extent than the Axiron topical product in this particular study. With the data at hand, an assessment for why did this happen was evaluated using the variance associated with the correlations between a variety of parameters.

You see the R-squared values for clinical changes and the 24-hour blood pressure changes left and right for hematocrit as a marker of volume and viscosity. For potassium as a potential marker, for mineralocorticoid excess, changes in heart rate as an adrenergic parameter, and of course concentrations of testosterone average or maximal, there was in fact very little found for any of these parameters as it related to changes in blood pressure, either clinic or ambulatory.

The heart rates in the clinic started at about 70 beats per minute in each treatment group and rose by just 2 beats per minute in each treatment group to 72 by the end of the study. The ambulatory changes from baseline in the heart rate derived from the ambulatory blood pressure recording are shown in this figure and demonstrate that Jatenzo patients rose by about 2 beats per minute over time, and the Axiron patients in fact had no change in heart rate.

Just to pause for a second and talk about blood pressure and heart rate, my findings are as

follows. At baseline, patients randomized to Jatenzo had higher systolic blood pressures in the clinic, and a greater number of them had a medical history of hypertension. The changes in clinic blood pressure were in fact greater in treated hypertensives, which is a finding that I've seen with almost every class of drug that raises blood pressure, whether it's for arthritis therapies, depression, and so forth. And it's a group of patients who we actually would be scrutinizing more carefully as well in practice.

The various outlier proportions of clinical relevance were similar for Jatenzo and Axiron, and importantly no patient in this program developed severe hypertension or required urgent management of their hypertension. With the data at hand, an evaluation for mechanism failed to find scientific rationale for any of these blood pressure changes on one testosterone formulation versus another. And the heart rate changes, which were in the 1- to 2-beat per minute range on Jatenzo, I do not believe would be characterized as clinically

significant.

Shifting to lipids, lipids were obtained in study 15012 as well as in study 09007 in the fasting state at various intervals in the trial. First for 15012, the mean LDL cholesterol values were fairly similar at baseline, and by the end of the trial, Jatenzo patients rose by 3.5 milligrams per deciliter and Axiron patients fells by 4 milligrams per deciliter.

In the 09007 study, which had balanced patient randomization about 150 per treatment arm and the comparison was now made to AndroGel 1 percent, again fairly balanced at baseline but no change in LDL cholesterol over the course of this study for one year.

Going back to study 15012, the mean HDL cholesterols were a little higher in the Jatenzo group at baseline, and by the end of the study in Jatenzo treated patients fell by about 7 milligrams per deciliter versus 2 milligrams per deciliter in the Axiron patients. In the 09007 study, there were fairly similar findings to 15012, and by the

end of the year, the drop in Jatenzo patients was 11 milligrams per deciliter versus about 7 in patients treated with AndroGel.

Now, the clinical relevance of a fallen HDL is unclear given that numerous studies in recent years have called into question the role of HDLc by itself in forecasting cardiovascular events. HDL particle concentration has been recently demonstrated to be more strongly predictive of cardiovascular events, so we quantified that in a substudy of 09007, and in this particular figure, the HDL cholesterol changes are shown in solid blue bars for both Jatenzo and AndroGel and in the multi-colored stack bars the HDL particle concentrations.

So despite the lower HDL concentrations seen in the blue bars in both treatment groups, Jatenzo and AndroGel had increases in HDL particle numbers, which is a metric that is inversely associated with cardiovascular events.

There were very few cardiovascular events in these phase 3 studies. This is a pooling of

Jatenzo patients, 471 individuals, and transdermal testosterone of 215, about 1 percent in each of the groups. Most of these included non-fatal events, MI, coronary revascularization for unstable angina, and non-fatal stroke. There were no deaths in the program.

There was one patient in 15012 -- by the way, I reviewed all of the narratives and clinical material for all of these events, and one patient did have multiple coronary events and had a small MI about 2 weeks after he stopped the trial, was treated with a single-vessel angioplasty, and recovered. But that person was outside of the study window, so it's not part of the numbers here in the table.

In summary of the overall cardiovascular safety, there are moderate increases in systolic blood pressure on Jatenzo. I haven't shown the data, but there are lesser changes in diastolic blood pressure, about 2 millimeters of mercury. There are small heart rate increases seen on ambulatory recording only, but I don't believe

these to be of clinical relevance. There are changes in hematocrit that was observed as shown by Dr. Danoff, which is a known testosterone class effect.

The changes in the lipoproteins observed, including LDL changes that were small and is consistent between studies and the HDL particles involved in cholesterol efflux despite HDL reductions, are of interest, but they I don't believe are a problem with management. The cardiovascular events were very infrequent, they're balanced, and I don't think there's any way to look at causality there.

So as a clinician who sees a lot of patients and who's done a lot of clinical investigation in this field, I'd like to address these issues because I think they are relevant. In my mind, blood pressure is a measurement that can be assessed by anybody: primary care physicians, nurse practitioners, subspecialists, and referred to the appropriate person for management.

Clinical measurements can detect clinically

important blood pressure increases, keeping in mind that when you see in a population an upward shift of 4 millimeters of mercury, that's not a value that you will be able to determine in an individual patient. You will be looking for people who are higher than that. In fact, the reason that that shift occurred was because of a slight imbalance in the proportion of people who went up by 10 or 15 millimeters of mercury. Those people would be recognizable in clinical practice.

I should point out that the changes in the 24-hour monitoring was clearly supported of or comparable to what was also seen in both of the studies in which clinical measurements were made. So I would think that if blood pressure increases do occur on this drug, you have a couple of options just as you would for somebody who's on an NSAID working for arthritis or an SNRI working for depression. You would initiate, or uptit [ph], or add in any hypertensive drug if it was efficacious, and if it was clinically indicated, you would stop the drug. Those are your two basic options.

The increases in hematocrit, which is a known effect of testosterone replacement therapy, can be monitored and managed effectively, and I'll leave that to the others to discuss. The monitoring of lipids are indicated in patients in this group because, after all, they're a higher risk population in general of hypogonadism, so we manage the HDLs as would be typical in clinical practice. The HDL changes seen are interesting, but they need to be viewed in light of the evolving understanding of HDL particle data.

So I take all of this stuff into summary, and I think that there are issues that are all managed and can all be managed in clinical practice. Thanks very much.

Dr. Danoff?

Presentation - Theodore Danoff

DR. DANOFF: Thank you, Dr. White.

Let me summarize our overall safety conclusions and describe our proposed Jatenzo risk mitigation plan, one that addresses both testosterone replacement therapy class risk and

those that we have identified with Jatenzo.

As we have described during today's presentation, the general safety profile of Jatenzo is similar to other TRTs with some differences. First, our oral formulation may cause minor GI symptoms. In addition, although we did observe changes in HDL cholesterol, Jatenzo did not cause reductions in HDL particle concentrations. Therefore, the changes in HDL cholesterol may not have a negative impact on cardiovascular risk.

The hematocrit changes we saw were expected for a TRT. Increases greater than 54 percent were infrequent, easily detectable, and are manageable like they are for all patients taking TRTs. We did see higher blood pressure elevations in the Jatenzo arm of 15012, but they were of a magnitude that did not cause an acute risk. We suggest that this risk can be managed in clinical practice.

As you've heard, it's important that BP be regularly monitored, especially in patients with a history of hypertension. If clinically significant increases are observed after initiating therapy,

the healthcare provider and patient need to decide whether to manage the blood pressure increase or stop Jatenzo.

We plan to disseminate this information through a variety of approaches. We've included warnings about the increase in blood pressure in our proposed medication guide, which will be available to every patient when the drug is dispensed, as well as on our website.

We will also send out a Dear Doctor letter when the drug is approved and after it has been on the market for about six months. We will send the letter both to current prescribers to TRTs and likely prescribers. This information will also be presented at national meetings. Our representatives will reinforce the message when they interact with the healthcare providers.

Clarus is also committed to post-approval activities, which will enhance the understanding of Jatenzo's safety and use profiles and thereby allow its continued safe use. The four proposed post-approval activities are shown here. I will

describe each of them on the next several slides.

After launch, if MACE events like MI, stroke, or death are reported to the company, enhanced data capture and follow-up will be initiated. The same emphasis on data capture and follow-up will also be applied to events which may be related to adrenal insufficiency. The specific data capture forms for MACE events and adrenal insufficiency will be developed, which will be used to prompt those reporting the event to provide all relevant information. Clarus will follow up on these reports in order to get as complete a record as possible, which will help in the evaluation of these events.

We also propose more direct methods to evaluate the risk of MACE events and adrenal function. To complement the CV outcome trial that has been designed in collaboration between the FDA and TRT NDA holders, we propose conducting an observational cohort study looking at MACE events in the real-world setting. In the study, we would assess the relative instance of MACE events in

patients receiving Jatenzo compared to those receiving other TRTs. The rates would be compared adjusting for potential confounding using appropriate epidemiologic methodologies such as propensity scores.

The events identified in databases would include non-fatal MI, stroke, and in-hospital CV deaths. Similar methodology is currently being used to evaluate CV risks for other drugs, including mirabegron, a drug approved in 2012 for overactive bladder, which showed a blood pressure and heart rate signal during its clinical development.

Because of concerns about the impact of Jatenzo on cortisol production, we will conduct a new dedicated cosyntropin stimulation study. This study will be a randomized two-arm study of hypogonadal men treated with Jatenzo or Axiron. Adrenal reserve for cortisol production will be evaluated using the cosyntropin stimulation test. The proportion of patients with a peak post-stimulation cortisol level greater than 18 at

6 months will be the primary endpoint, but we will also measure other relevant analytes.

Lastly, we propose a drug utilization study. As the FDA notes in its briefing book, Jatenzo will be easier to use than current commonly prescribed testosterone replacement therapies, so it could change the landscape of testosterone therapy. In order to evaluate whether this change impacts the patient demographics, we propose a drug utilization study which will evaluate the age and other demographic characteristics of the patients prescribed Jatenzo as well as other TRTs.

The data will come from drug utilization databases which capture prescriptions from various sources. If the analysis indicates that there are important differences in the age distribution of those who are receiving Jatenzo scripts compared to other TRTs, we will direct our safe-use educational campaign to educate healthcare providers to appropriate prescribing. The risk mitigation plan Clarus is proposing, including the postmarketing commitments, will expand our understanding of

Jatenzo and help ensure that the drug continues to be used safely.

Dr. Kaminetsky will now discuss patient management with Jatenzo.

Presentation - Jed Kaminetsky

DR. KAMINETSKY: Good morning. My name is Jed Kaminetsky. I'm a consultant for Clarus, and I was an investigator in the phase 3 program. I'm a practicing urologist with a focus on men's health. Over the course of my career, I've treated thousands of men dealing with the signs and symptoms of hypogonadism.

There's a lot of talk about testosterone replacement therapy being a lifestyle medication, and I take exception to that. If you have low testosterone and you have symptoms, you deserve -- if you have low testosterone as defined by the Endocrine Society guidelines and is symptomatic, you have a real medical condition that merits treatment much like other hormonal deficiencies, hypothyroidism for example.

As you heard from Dr. Amory, the men we see

are often deeply dissatisfied with their lives, a dissatisfaction that affects both their personal and professional lives. They're often suffering from a diminished libido and have unsatisfactory sex lives. They frequently experience diminished energy, lack of enthusiasm, and focus. These are the signs and symptoms of hypogonadism.

There are well established guidelines for diagnosing and initiating testosterone replacement therapy in these men. The first step is to order testosterone levels to confirm the initial diagnosis. We also take a complete medical history looking for the contraindications to testosterone replacement therapy as seen on this slide. We do a physical exam that includes measuring blood pressure and digital rectal exam. If the blood pressure is not well controlled, it's important to ensure that it's managed before initiating testosterone replacement therapy. Only then could we discuss the testosterone replacement options available.

As you saw earlier, although all the

commonly prescribed therapies have the potential to provide the benefits of TRT, they also have risks associated with their routes of administration. We don't want to minimize these risks and limitations. Gels are difficult to use. Injections may be intolerable for some men. Both have black box warnings, gels for potential transference and injections for potential microemboli.

As a result, what I frequently see is patients switching from one delivery option to the other. Some patients actually discontinue treatment altogether often due to inconvenience or side effects related to the delivery system. Dissatisfaction can also be due to lack of efficacy as a result of subtherapeutic testosterone levels. In fact, in a study looking at gel usage, less than 20 percent of patients remained on therapy at one year.

Today we've been discussing a new option to these therapies, Jatenzo, a titratable oral testosterone capsule. Jatenzo lacks many of the limitations of the currently approved therapies.

When we start a patient on testosterone, we start by monitoring with a follow-up visit at approximately one month after initiating therapy. At this visit, we check for symptom relief. We check testosterone levels. Based on that, we consider possible dose titration. At this visit, we'd also evaluate for potential side effects including blood pressure.

If there's a clinically significant elevation of blood pressure, physicians would manage it the same way they would manage any patient with elevated blood pressure no matter what the etiology. They would either initiate blood pressure medication, or if the patient is currently taking one, consider increasing the dose. If the perceived risk is too high, then the decision would be to discontinue Jatenzo or consider another form of therapy.

This decision would have to be made with the consideration that some level of elevated blood pressure might be a feature of any testosterone formulation. All patients who continue with

testosterone replacement therapy are then monitored at subsequent visits. If the symptoms are not improved despite acceptable T levels, they should consider stopping therapy. If the T level is subtherapeutic and symptoms remain, we would then consider increasing the dose. We'd also check to see if the patient is having known testosterone replacement therapy side effects.

In the case of Jatenzo, we would also want to evaluate for GI issues, and of course we continue to follow the blood pressure. In addition, at this time, we obtain lab values like hematocrit, lipids, and PSA. In the case of an elevated hematocrit, depending on the magnitude, options will include a drug holiday, decreasing the dose, or a therapeutic phlebotomy. In the case of abnormal lipids, we might also consider statins and dietary changes. In the case of an elevated PSA, patients should be referred to a urologist for further evaluation. Over the long-term, we like to see these patients at six-month intervals.

A testosterone is a highly controlled

regulated substance. This helps ensure that monitoring continues and appropriate patients are treated. In my right hand here I have this little device. In my state, New York, in order to write a prescription, which must be sent electronically, I need to get a specific unique numeric code for each prescription. This helps ensure that only men who are followed appropriately receive treatment. This is very similar to the control and regulation over something like opioids.

Jatenzo might not be the perfect solution for all patients, but it's a major step forward. All TRT products have class effects such as potential increases in hematocrit, PSA, as well as changes in lipids. Jatenzo results showed a small increase in blood pressure over its testosterone gel comparator, which is why Clarus has recommended regular blood pressure monitoring. Patients taking Jatenzo might also have GI adverse events due to its oral delivery system, so it's not appropriate for patients with abnormal GI anatomy or function.

Meal time BID dosing may be problematic for

some patients, however, dietary fat has minimal impact on T exposure. Clarus plans on preparing an educational program that will emphasize proper patient selection due to the importance of monitoring these patients and the nature of Jatenzo's potential limitations.

Clarus is also planning to do studies to further characterize Jatenzo. As one of those physicians who treat men with low testosterone, I'm confident that I will be able to manage the limitations associated with Jatenzo. I'm also confident that Jatenzo offers meaningful benefits to these men. It has the advantage of being an oral treatment with ability to customize the dose. Results show that this dosing is effective in bringing most patients into the eugonadal range.

It also offers the benefit of testosterone replacement therapy as a class, including improved bone mineral density, improved muscle mass and function, as well as improved libido and sexual function. Because it avoids the severe risks and limitations of most of the commonly used

testosterone replacement therapies, gels and injections, it should improve adherence necessary for any chronic therapy.

This balance of limitations and benefits suggests that Jatenzo might well be an option that patients have been asking for, a testosterone replacement therapy that's efficacious, that allows men to stay on therapy and allows them to resume their normal lives. Thank you, and Dr. Dudley will conclude.

Presentation - Robert Dudley

DR. DUDLEY: Thank you so much for your attention. In addition to those of us who have spoken this morning, we have a series of experts that are available to take questions today. Please note they've all been compensated for their time, and they are listed here. With that, I thank you so much for your attention.

Clarifying Questions to Industry

DR. LEWIS: Thank you. Before we proceed with clarifying questions, we do have one other panel member who's joined us.

Dr. Edwards, could you please state your name and affiliation for the record?

DR. EDWARDS: Beatrice Edwards. I'm coming from Temple, Texas from the Central Texas Veterans Health System. I was at MD Anderson for five years.

DR. LEWIS: Thank you.

At this time, we'd like to take clarifying questions for Clarus Therapeutics. Before you ask a question, please remember to state your name for the record before you speak, identifying which presenter your question is for or if it's a general question for all presenters. We will have time for discussion, so if it's more of a comment than a question, please remember there's time for discussion later.

I'm going to start with Dr. Howards. If you just raise your hand a little bit, Kalyani will take your name down so that we can try to get to everyone, so Dr. Howards and then Dr. Lincoff.

DR. HOWARDS: Stuart Howards. This is a general question for the entire panel as they deem

appropriate. I have no concerns that Dr. Kaminetsky will properly monitor and select his patients. However, as came up in 2014 in Dr. Snyder's excellent review, it turns out that 80 percent of current prescriptions for testosterone are given by non-urologists and non-endocrinologists.

In other words, they're given by family practitioners and generalists and who knows who else. And there's no doubt that many patients who are not appropriate are treated. There's great overuse of testosterone treatment. And in addition, there's relatively poor follow-up. For instance, there's a lack of testing of PSAs and hematocrits, and many of the patients, indeed, never had a testosterone before they were treated, no testosterone measured.

So my question is what are the sponsor's thoughts on the issues of appropriate treatment in determining whether or not the prescribers are really complying with the management? Particularly, I'm concerned that once this drug is

available, which will be very attractive to patients and a clear advantage for patients, the system for titration will not be followed by many practitioners. That's sort of a generic question for everybody.

DR. DUDLEY: Okay. I think there were three parts if I remember them correctly. We'll start with the first, which I think is a corporate responsibility question. I have been in the development of testosterone products for essentially my whole career, and I will be the first to say that I am opposed to inappropriate use, totally.

I think some of the evolution of T clinics, for example, are not in the best interest of public health, but I think that those type operations, if you will, and the inappropriateness of some physicians to use these products in men who are not hypogonadal should not overly influence decisions or the availability of products that might actually help a large swath of the individuals that use these products that are looking for reasonable

alternatives.

With respect to a generalist comment or generalist physician, Dr. Amory is a general internist in Washington, so I'd ask him to speak to that, and then Dr. Danoff to speak more closely about the drug utilization program, which we're serious about, which is identifying people who are prescribing mills, if you will, in which we would look at very carefully. So if those two individuals would come up, please.

DR. AMORY: Thank you. Let me begin by saying I think there is a problem with the overdiagnosis and overtreatment of inappropriate men. I think we all see that, and I often see patients who have come to me from other clinics where they've been inappropriately diagnosed and inappropriately treated.

That being said, as an educator, one of our jobs is to go out in the community and teach people who are appropriate to treat and what are the benefits. Obviously, if you're treating a man who doesn't have a true diagnosis of hypogonadism,

you're exposing them to harm without giving them any benefit, and that is inappropriate.

With respect to the general physicians and general internists who are prescribing testosterone, in my experience there's a subset of people in general internal medicine, or internal medicine, who feel comfortable with this. Also, many of those patients have been seen and diagnosed by an endocrinologist or urologist, and then are being referred back to their primary care provider for long-term therapy. So the distribution of providers who are prescribing testosterone I think is appropriate.

DR. LEWIS: Dr. Lincoff? Oh, I'm sorry.

DR. DANOFF: So just briefly, as Dr. Dudley said, we are seriously committed to making sure the appropriate men are treated and that their treatment is appropriately monitored. We'll do this in part through education, so the healthcare providers and other prescribers are well aware of why you need to monitor levels, why you need to monitor symptoms, and why you need to monitor blood

pressure.

We'll do this through various outreach programs, including documentation we send to them at national meetings and through our company representatives. But we'll also monitor using -- I described the drug utilization study, so we'll be able to see if there are changes in prescribing patterns. Similarly, database searches can look through prescribing database like IMS to see if there are prescribers who are prescribing an unusually large number of prescriptions. Again, our representatives can reach out to these providers and assure that they are monitoring the patients appropriately.

DR. LEWIS: Dr. Lincoff?

DR. HOWARDS: Thank you.

DR. DUDLEY: You're welcome.

DR. LINCOFF: I will defer my comments regarding what I consider grave concerns regarding the implications of the blood pressure elevations without hyperbole, but I will ask a question, three parts in priority so if time limits, we don't have

to go through all of them, regarding the blood pressure.

First and most importantly, I challenge your assertion that this is something that is easily monitored and managed for several reasons. First of all, the clinic-based blood pressure measurement changes were substantially less than those by the APBM, 2.6 versus 4.8.

Secondly, despite the fact that nearly twice as many patients in your agent's group, 5.9 versus 2.2 percent, had changes in their blood pressure medications, there was still this marked difference in blood pressures.

Third, it's well known that just in general practice, blood pressure is often not well managed and that a majority of patients are not at optimal levels, even when they're being followed for this, and that the time periods between adjustments in blood pressure medications in clinical practice are quite broad

Echoing Dr. Howards' point, many of these practitioners are not going to be expert

necessarily in blood pressure management. So I'd like you to expand on how you think that short of giving every patient ambulatory blood pressure monitoring, how you anticipate that there will be a reasonable way to monitor and interdict in those patients who have an elevated blood pressure response. And that's the first and most important part of my question.

DR. DUDLEY: Okay. Thank you very much. Dr. White is a hypertension person and will answer that way better than I would.

DR. WHITE: Thank you, Dr. Lincoff. First, I'd like to make some clarifying comments with some data. Can we bring up the U-697, please? Slide 1 up. Please have the slide up on the screen. Something's blocking it? Bear with me.

I do want to point out that there's a little bit better concordance between the clinic and the ambulatory blood pressure in those patients who actually had ambulatory monitoring. Remember, 20 percent did not have an ambulatory blood pressure recording. Sorry you can't see this, but

we definitely need to see the next slides I'm about to call up.

The clinic blood pressure excursions, in the ABPM population, Jatenzo was actually closer to 3.5 millimeters of mercury versus the ABPM. So it was somewhat higher, and part of that was because there were more people in the ABPM population who were actually probably hypertensive actually than people who did not actually where the monitor and have an evaluable study. So unfortunately, those are the data, and I'm sorry you can't see this.

Are we not going to be able to see any of those slides I'm calling up?

(No response.)

DR. WHITE: Can we bring up U-763? You cannot? Oh, I'm sorry.

DR. DUDLEY: They're working on it.

MS. BHATT: We're working on it.

DR. WHITE: Okay, because these are impossible to describe -- okay, thank you.

Now, with regard to the hypertension drug starts, to avoid any confusion, recall that the

investigators at the sites were asked not to change any hypertensive regimens during this study, and for the most part, they did not. There were 12 patients who had a new or changed dose of an antihypertensive med, and 10 of them were evaluable. Two actually had the drug changed at the very end of the study.

If we could put up slide 3 for a moment, these are individuals in whom antihypertensive drugs were initiated where you see the blue line, the blue vertical line, and for whom had some modification of their blood pressure. But note, what struck me about this was, number one, the blue lines do not line up with the actual visits, so the drugs were actually not initiated by the investigators but rather an outside physician in virtually every instance; and they were started in people who really didn't have hypertension. As you can see, there were about 130, 135, et cetera.

So the fact that the people who got treated really didn't need to get treated is why the drugs didn't have much of an effect on the overall blood

pressure findings. And there were only 10 people in whom there were drugs initiated, and in those 10, it was at various times during the course of the study, very late in some instances, and even at the end of the study.

So I don't think we can utilize the information regarding the blood pressure drugs and the fact that they were perhaps not efficacious, keeping in mind it was obviously a study and not a clinical practice in which the drugs were asked to be withheld for confounding reasons.

I understand your lack of faith in the general physicians, but I hope that people can rise above that concern. We all have been in practice a long time, and we've gone out and seen practice habits of various physicians. I personally think that with this drug, probably 80 percent of patients who got treated with it will not have a blood pressure that needs to have any intervention whatsoever, and 20 percent will have a blood pressure increase, which may require some change. They may have to have a non-pharmacological therapy

introduced if their blood pressures are in the stage 1 range, the new stage 1 range, or a drug initiated if they're in stage 2, or stop it.

I'm going to give you an example. If I have a patient with depression, and they go on an SNRI that they find to be very efficacious for their depression, and their blood pressure goes up by 10 or 15 points, I'm probably not going to ask them to stop their SNRI. I'm probably going to ask them to do something about that from an intervention standpoint.

On the other hand, I have somebody who's taking 2400 milligrams of ibuprofen and their blood pressure goes up by 10 or 20 points, I'm going to switch them to a different NSAID because there are options for that. So I think that that's the way I would manage this in practice, but I think it's up to the sponsor and the physicians like Dr. Amory, who talk about hypogonadism on a regular basis, to educate the public to be on the lookout for blood pressure increases.

DR. LEWIS: Thank you. I'd like to try to

get to everyone's question, so Dr. Braunstein, then Dr. Bauer. Let's try to be as direct as possible.

DR. BRAUNSTEIN: Glenn Braunstein. If we could go to CC-11 from your presentation.

DR. DUDLEY: CC-11? Yes, sir.

DR. BRAUNSTEIN: I have a question concerning plasma versus serum. There is obviously a conflict in the literature as to whether one needs to use plasma for TU measurements or T from TU measurements versus serum. You show on this slide that the serum levels are about 15 percent higher. We know that just adding sodium fluoride to the testosterone assay also depresses testosterone measurements by about 15 percent.

My question is have you taken patients who have received TU, taken blood, and over time looked at the effect of just time on testosterone generation in the test tube; not adding TU to blood and then watching what happens over time, but taking patients who have taken TU to see if there really is a change over time?

DR. DUDLEY: I'm very actually familiar with

the earlier studies that you described suggesting that TU doesn't convert. I funded those studies, so yes, I believe this is real. I believe that Dr. LaChance should be --

Did you look at those type of studies? If you would come forth; Sylvain LaChance who has most recently published -- and actually you identified a small flaw. Actually, when he's coming up, if I could have slide 1, please.

This really sets out the history, and I think it's instructive. Initially, the study by Dr. Wang, who I've worked with for many years, demonstrated that TU didn't look like it converted, although TE did, and it was suppressed by sodium chloride. We went forward on the basis of those studies until the paper by LaChance et al. was published, presented at an endocrine meeting, and I looked at it and said, "That can't be true," and in fact, we were skeptical. But when we went back and really looked at it, they were right.

In blood -- not plasma, not serum, in blood -- when there are blood cells present, you

get that conversion. So when that was identified, then we switched tubes. But let me ask Sylvain LaChance, who did really the seminal work, to answer your question.

DR. BRAUNSTEIN: Yes, I understand the conversion when you add TU to a test tube. I'm asking if you take a patient who's taken TU and then take blood, and hold the blood for 30 minutes in one sample, hold another sample for 60 minutes, hold another sample for 90 minutes, and then measure the testosterone, do you actually see a significant increase in testosterone in the blood?

DR. DUDLEY: I believe we have a slide that addresses that.

DR. LaCHANCE: Hello. My name is Sylvain LaChance. I'm the associate director at InVentiv Health. I was deeply involved in the investigation of how to collect the samples correctly for T measurement. Can you put slide number 2, please?

This is the in vitro test. We compared the TU concentration, evaluated different TU concentrations in blood and evaluated the different

ratio between TU and T. We compared the time of incubation between 30 and 60 minutes. We can see an increase between the time zero that didn't have any TU. This was done with the same donors, the same samples, but the TU concentration was increased over time.

DR. BRAUNSTEIN: But you're adding TU to the test tube.

DR. LaCHANCE: Yes.

DR. BRAUNSTEIN: I'm asking have you taken a patient who's taken TU, taken their blood and taken one sample of blood and aliquoted it 30 minutes, 60 minutes, 90 minutes before spinning it and separating the serum, and then measuring testosterone in the serum?

DR. LaCHANCE: No. The answer is no, we haven't tested using inker [ph] sample or real samples.

DR. LEWIS: Thank you. Dr. Bauer?

DR. BAUER: I'll try to be quick about this. I think this is for Dr. Amory. My question has to do with the generalizability of the results from

who the drug is likely to be used in. For example, it looks like 60 percent are prescribed by PCPs. I think that's probably going to be much higher with a easily usable oral preparation.

The question is, what's the age group of that distribution? I noticed the data that you showed really was limited to individuals up to age 65, and I think the T trials, the mean age was actually considerably higher than that. It was a 70 as I recall.

DR. DUDLEY: The T trial, if I recall, went to 75. Yes? I think Dr. Amory might be able to provide some discussion here. Slide 1 up.

This shows prescribers, but it doesn't talk about age of patients. If you'll look at the course of any testosterone trial that I've been involved with, and there have been many, the average age of those men is always right about 50 to 54.

Dr. Amory?

DR. AMORY: In response to your question, there are really two populations. There's the

classic hypogonadism population, including the men with idiopathic hypogonadotropic hypogonadism, or Klinefelter's, or some sort of testicular injury, or cancer. Those probably account from 15 to 25 percent, really, of the people who are prescribed testosterone.

The mean age of people receiving testosterone prescriptions is probably in the 45 to 55 range. In the T trial that you mentioned, the mean age was 71. That was asking a very specific question about what's the risk and benefit in an older patient population. I wouldn't say that's that common in clinical practice. Most of the patients are middle-aged men who are noticing a decrease in sexual function, and then there's that subset of patients who are early in terms of their hypogonadism and require long-term therapy.

DR. LEWIS: Thank you. Ms. Sorscher, and then Dr. Wilson.

MS. SORSCHER: I have a related question. I understand that the FDA said that you're seeking approval for classic or primary hypogonadism

similar to what other testosterone products are already approved for. That requires testicular failure, either congenital or injury or illness. I'm looking at slide CC-20, and I'm looking at slide CC-34, and neither one of them specified testicular failure. Of course, then there's the reference to the T trial, which is not classical hypogonadism; it's age related.

So the question for Dr. Swerdloff would be, were the patients who enrolled in the primary efficacy study, did they have classic or primary hypogonadism? Then just for the company in general, when you talk about who's appropriate for treatment with this drug, are you thinking about slide CC-20, where you don't specify that they have testicular failure, or are you going to be more specific in your materials to doctors than you were at this meeting when you do the marketing?

DR. DUDLEY: Dr. Swerdloff, and then Dr. Danoff, please.

DR. SWERDLOFF: Thank you for the question. In this study, I don't believe the individuals were

required to have anatomical defects since this was primarily not a study that was evaluating this particular aspect. With regard to the position of Clarus, I think they've made it very clear that they intend to promote this drug with adherence to the FDA guidance, which has been put forth and which was enunciated by yourself.

Now, what happens in clinical practice of course is not necessarily the same as what the FDA guidelines are, and the Endocrine Society guidelines may not be exactly the same as either one may be. The Endocrine Society guidelines have just been updated and submitted for comment to the membership of the organization. A large number of comments came back. The new guidelines will be published in probably March or April. But the results basically emphasize the importance of selecting individuals who are appropriate for treatment and do point out the FDA position on who's an appropriate candidate.

The T trial itself, as you know, was a study that was done in the older age group. It was

supported by the National Institute of Aging, and its primary goal was to try to determine if testosterone replacement in men who had low testosterone levels and symptoms would improve their functionality and would make them more independent and capable of functioning in regular outpatient society. It did have a lot of positive results. It had some results which were not hoped for.

DR. DANOFF: Obviously, this was a PK trial, which is the traditional way for approval of the past towards a classical indication. Our entry criteria only required that they have too low testosterone, which is traditional. But we also made sure that everyone had a symptom, and we were able to -- all the patients had symptoms consistent with hypogonadism. About two-thirds of the patients identified either primary or secondary hypogonadism.

As a company, we will have to educate physicians, and re-educate physicians, as to the appropriate indications and the appropriate

populations to be done. Again, this will start with the information that is on our proposed label, and we'll continue with presentations at meetings and various publications.

DR. LEWIS: Thank you. Dr. Wilson, and then Dr. Rej.

DR. WILSON: Peter Wilson. My question's about blood pressure. Do you have data to show us concerning the concentration of testosterone and the blood pressure levels during the course of these studies? You have lots of blood pressure measurements and you have lots of testosterone levels, and I would think there's a scatter plot or an extremes [ph] plot.

DR. DUDLEY: Dr. White.

DR. WHITE: Could I have slide 1 up? Thank you. This figure actually show the average testosterone concentrations at visit 7 and the changes from baseline and blood pressure showing no distinct relationship.

Can we have slide 2 up? This is the maximal changes seen and the relationship with 24-hour

blood pressure, also no real relationship seen.

Does that answer your question?

DR. WILSON: That helps. So that's part of it. What about very high testosterone levels in the fraction with uncontrolled blood pressure? It would be similar, probably the same database.

DR. WHITE: I don't remember that analysis, personally.

DR. DANOFF: I'm not sure we have it on a slide, but we have looked to see if the people who had the highest blood pressures had the highest Cmaxes or Cavgs, and there was no apparent relationship there.

DR. LEWIS: Thank you. Dr. Rej, and then Dr. Gerhard.

DR. REJ: Robert Rej. I have a question regarding the testosterone measurements, and it's in three parts, and I'll put them all out at once. I just want to have a reassurance that all the measurements that were used in the studies were from the second laboratory using a validated LC tandem mass spec method for measuring testosterone.

The second part of the question is that numerous external quality assurance and proficiency testing programs have shown a large laboratory to laboratory difference among labs and methods for measuring testosterone. And the Centers for Disease Control and Prevention have established a program for the accurate assay of hormones. And my question is, was the method validated or compared to the CDC method for measuring testosterone?

The last part is that since testosterone monitoring would be an important part of monitoring therapy should the drug be approved and only a small minority of laboratories use LC mass spec for measuring testosterone, what is the cross-reactivity of the parent drug, the TU, with the common immunoassays for testosterone?

DR. DUDLEY: I'm able to answer the first two questions, and I'd like Dr. Nichols, as director of the core laboratory at Vanderbilt, to address the third. In response to the first, yes, we've used a validated LC-MS system. The correlation between the original lab, which is a

CDC gold start lab if you will, and the lab we used is essentially identical. I believe that will address that question, maybe the first two.

Dr. Nichols?

DR. NICHOLS: Sure. When I saw the data for the story -- I'm Jim Nichols, and I'm a professor of pathology, microbiology, and immunology at Vanderbilt, and I'm a medical director of clinical chemistry at that lab. My biggest concern was, as you were mentioning, most labs are using immunoassays. I have not seen data about the cross-reactivity of TU with the immunoassays.

I was basically asking the question what's the matrix effect of sodium fluoride EDTA with these assays because this is a very unusual tube. It's not commonly found in most laboratories and clinics, so this is going to become a new tube that asking the major vendors -- if you could bring up slide 2 -- or actually slide 2.

The major vendors are Roche, Abbott, Siemens, Beckman Coulter, and Ortho. These immunoassays are the common ones that are going to

be testing or analyzing clinical specimens coming from patients that may be on this drug, and my concern was the sodium fluoride EDTA.

A study has been done study 16014, using Roche, and there were 94 patients. These are normal patients who are not on the drug, who were tested with serum versus sodium fluoride. If you can bring up slide 3, there were minimal differences between the sodium fluoride EDTA and the standard serum assay and that Roche immunoassay.

We use Abbott in our institution, the Abbott ARCHITECT, so we drew 3 volunteers just as a small pilot to see if we had a big problem with a matrix effect with sodium fluoride EDTA tubes, and we use lithium heparin as our hospital as the standard draw tube. If you can bring up slide 1. And all three of these were well within the variability of that assay. But to answer your original question, I don't know that it has been looked at, what the cross-reactivity, of TU as the parent drug, is with these immunoassays.

DR. LEWIS: Thank you. Dr. Gerhard, and then Dr. Dmochowski on the phone.

DR. GERHARD: Toby Gerhard, and my question is for Dr. Danoff, I believe, regarding the proposed utilization study; two questions. The first is, the way I see this is that you're basically looking for the effect of the introduction of this new oral product, that it would change or look different than the use for the existing products. But my understanding is that even with the existing products, there is a very large proportion of off-label use already, so I don't think it would need to be different for it to be problematic.

The second question is once you have implemented these studies and you identify problems with prescribing, where the use might be off label or in other ways problematic, the response to that to me is unclear. You're talking about targeting high prescribers and increasing education.

There is large literature that shows that provider education on safety concerns couldn't be

less effective if you tried. So I don't know whether you have new approaches to this or whether it's basically just something you're proposing to do to cover the basis because I'm not aware that any interventions that don't change reimbursement or really make structural changes have ever been shown to be effective.

DR. DANOFF: What we will be able to do with the drug utilization study is see if the population is changing; for instance, if more elderly men or hopefully more younger men start using it who might be the Klinefelter's patients who are not being able to be compliant with their testosterone.

As to what happens, there are limitations to what you can do, but we feel that education -- part of the work is education; part of it is -- and this is not exactly a safety concern. This is a prescribing off the label. But obviously, many of these men will be getting benefits without any adverse events. They aren't necessarily having a safety issue.

As we saw in the testosterone trial, these

men were getting benefits. But there is a limit, and we think that through education, education through direct mailings, education at meetings, education provided by our company representatives like a medical science liaison, should help to improve the situation.

DR. DUDLEY: May I make just one additional comment for those of you that may not be familiar with actually how prescriptions are filled and covered by insurance? The insurance industry has actually gone quite a ways from several years ago when they either didn't look or generally cover testosterone prescriptions.

That's changed quite dramatically. Most testosterone prescriptions now, as I think the practicing physicians would tell you, go through step edits, so there are more checks than there used to be, and that definitely has had an impact, as it should, on I think the inappropriate use of testosterone products.

DR. GERHARD: Do you have any data on those effects? I have not seen those.

DR. DUDLEY: Well, as I said, we haven't done a study. If you look at -- I can tell you from -- and I realize you'll consider this anecdotal, but it's truthful. When we have done our own market research -- and I've been on the phone with several listening medical directors for the insurance agencies, and they are very much in tune to overuse. And I think if you look at the available insurance data -- and I'm not sure what those databases are -- that there is no doubt that there has been a significant seachange in how they view these products.

DR. LEWIS: Thank you. Dr. Dmochowski on the phone, and then we'll be taking a short break.

DR. DMOCHOWSKI: Thank you very much. Pertinent to the chair's instruction, I'll hold my comments about the hypertension signal until we have the philosophic discussion. Let me ask five explicit and very directed questions related, in a general fashion, to the safety and efficacy data that was presented.

First, of the three patients who achieved

very high serum levels, a one-word explanation was given. I'm sorry. The early part of the conference had very bad tonal quality. It sounded like either the explanation was dehydration or depolation [ph]. Could you just reiterate that for me?

Number 2, of the seven pages who are down-titrated either to a very low dose or very, very low dose regimens of drug administration, is there anything unique about that population? Did they tend to have less BMI? Was there something about that population metabolically that indicated a very, very low need for --

Number 3, regarding the patients with GI side events, any signal in that population for those that are more prone to GI side events related to this particular formulation.

Number 4, explicitly, what were the criteria for hematocrit-based discontinuation? I believe I heard that 57 was encountered on several circumstances that did not reach threshold. That would reach my personal threshold in prescribing,

so I'm just curious about what was adjudicated in the protocol.

Then finally, in the substudy related to the cosyntropin administration, we have one patient who had very low levels simultaneous with a pulse steroid administration for a comorbidity as a primary treatment. Is there any data or any information in your general data regarding patients who have co-administration of systemic steroids and any aberrations of T levels related to same? I'm talking about either inhaled pulmonary or use of steroids for other indications. Thank you.

DR. DUDLEY: Thank you. Dr. Danoff, please?

DR. DANOFF: Let me try to do them quickly. The three gentlemen who we identified with Cmaxes greater than 2500, the word was I think "contamination," which is what we felt happened, that there was transference from people in the clinic at the same time who were receiving Axiron onto either the tubing or the body of the people who were taking Jatenzo, and that got into the tube.

The second question is the three who down-titrated, they did not have unusually small BMIs nor were we able to identify any other factors that were unique to them.

The people who had GI adverse events, these adverse events typically were very mild, and no patient stopped treatment due to these GI adverse events, and we weren't able to identify any particular characteristic of the patient that would predispose them to it, but it was relatively uncommon and very mild.

The criteria we used for the hematocrit was not 57 but 54, and essentially the people who had the high 54 were at the final visit, so they were ending their study. In previous trials, we also used a 54 cutoff, and during the course of the trial, there were a couple people who had to either hold on testosterone or more commonly had therapeutic phlebotomy, which effectively lowered their hematocrits.

Your last question was --

DR. DMOCHOWSKI: Related to the substudy and

the steroid administration.

DR. DANOFF: Yes. And what I heard from your question was does steroid administration affect testosterone levels. I'm unaware of data to that, but Dr. Swerdloff can speak to that.

DR. SWERDLOFF: The answer to the question is yes, steroid levels in a pharmacologic range do suppress testosterone levels, and they appear to suppress it at two levels, at both the hypothalamic pituitary and probably at a testicular level also.

There's another point, however, to your question about the one individual who is the largest outlier on the cosyntropin skin test. For those of you who remember the slide, there was about three individuals who were in the 17 range that were considered to be non-responders. The individual at the bottom is the --

DR. DUDLEY: Slide up, please.

DR. SWERDLOFF: -- thank you. The individual at the bottom, as you can see, the outlier, we were puzzled about this particular individual. You remember he was the one with

Crohn's disease that had received steroid medication during his episode of bowel obstruction. When we measured the CBG level, this individual had very low CBG levels, and when we corrected his pre-cortisol using the formulas for CBG, he actually normalized, and he went into the normal range. So it was a CBG problem.

We looked at the CBGs in the individuals who were below the line there, and one of the other individuals, correcting for, as best you can using the Cooley formula that was published in the JBC, also normalized. So there were a couple of CBG issues that may have played a role in these gray area values.

This additional slide just shows -- could you put it up, please, slide 2? This shows the data when replotted by calculated three-quarters, all levels. So there was a positive effect, and the black dot there represents the individual who seemed to be the outrider. So as best we can tell, there may have been a couple of issues that influenced that one outrider value, I think the

biggest of which was the lowest CBG in the entire population.

DR. LEWIS: Thank you. We'll now take a 10-minute break. Let me remind the panel members not to discuss the issue at hand during the break. We will reconvene at 10:40.

(Whereupon, at 10:28 a.m., a recess was taken.)

DR. LEWIS: We will now proceed with the FDA presentations.

FDA Presentation - Preston Dunnmon

DR. DUNNMON: Professor Lewis, distinguished panel members and guests, ladies and gentlemen, my name is Preston Dunnmon. I'm the cardiologist from the Division of Cardiovascular and Renal Products who consultatively reviewed the ABPM ambulatory blood pressure monitoring data for the reviewing division from study CLAR 15012.

My goal this morning is to show you why we think that drug-induced blood pressure elevations are in important, to show you in a review the regulatory history of the blood pressure effect of

Jatenzo, and then to show you the results that cardiorenal felt were important for the review division to consider during the NDA evaluation process.

To begin, it has been known for quite some time that blood pressure elevations are related in an exponential manner to the occurrence rates of cardiovascular events. In 2002, Lancet published this large meta-analysis of 61 prospective observational studies of blood pressure and cardiovascular mortality.

In 1 million adults with no previous vascular disease recorded at baseline, during 12.7 million person-years at risk, there were approximately 12,000 deaths from stroke, 34,000 deaths from ischemic heart disease, and 10,000 deaths from other vascular causes in subjects between the ages of 40 and 89 years.

The meta-analysis related mortality during each decade of age at death to the estimated usual blood pressure at the start of that decade. On this slide, you can see that for subjects between

the ages of 40 and 69, each 20 millimeter of mercury increase of usual systolic blood pressure or an increase in 10 millimeters of usual diastolic blood pressure is associated with a 2-fold increase in death due to ischemic heart disease.

I'll point out, when I show these at times, people will say, "Wait a minute. These are straight lines. Why is this not -- you're telling me this is an exponential relationship." Note that the Y-axis here is not linear, it's going up as an exponential functional, so that's why these look like straight lines instead of curves going upward.

A similar finding can be seen here with stroke mortality, as far as the relationship that's been demonstrated with stroke mortality and blood pressure, showing that for subjects between the ages of 40 and 69 years, each increase of 20 millimeters of mercury of usual systolic blood pressure or 10 millimeters of usual diastolic blood pressure is associated with a greater than 2-fold increase in death due to stroke.

It is on this background of understanding of

the relationship between blood pressures and CB deaths that concern arose when cuff blood pressure elevations in prior phase 3 trials with Jatenzo showed what appeared to be exposure-related systolic and diastolic blood pressure elevations in routine safety follow-up of Jatenzo-treated subjects.

To more accurately assess this finding, study CLAR 15012 was designed to confirm that a lower starting dose of Jatenzo with subsequent dose titrations based on circulating testosterone concentrations would limit super-target testosterone exposures and assess the blood pressure effect of oral Jatenzo administration compared to topical Axiron therapy by ambulatory blood pressure monitoring.

For those of you who don't see a lot of these ABPM results, ABPM is the most comprehensive method for assessing systolic blood pressure, diastolic blood pressure, and heart rate in the clinic. It involves a 24-hour acquisition of these parameters with pressure and pulse data collected

multiple times per hour over the 24-hour period. These multiple readings each hour are then averaged to produce hourly averages of systolic blood pressure, diastolic blood pressure, and heart rate over the 24-hour monitoring period.

What you see on this slide are the relevant design and analysis details of CLAR 15012 that were prospectively agreed to between FDA and the sponsor. Specifically, this was a 4-month, randomized, open-label, active comparator trial comparing oral Jatenzo with topical Axiron.

The dose of Jatenzo was titrated based on plasma testosterone Cavg. Sample size and power calculations for the ABPM evaluation were based on the daytime systolic blood pressures, assuming that a trial with 35 subjects treated with topical Axiron and 105 subjects treated with oral Jatenzo, all of whom had baseline and follow-up on treatment ABPMs at visit 6, would have 85 percent power to rule out a baseline corrected 5-millimeter systolic blood pressure increase in oral Jatenzo-treated subjects relative to topical Axiron controls with

95 percent confidence.

The FDA agreed in principle to this prespecified analysis but pointed out that elevations of systolic blood pressure less than 5 millimeters of mercury can be clinically relevant over time and that the magnitude of the elevation of the systolic blood pressure would have to be assessed in the context of the clinical benefit provided by Jatenzo therapy.

These assumptions led to the enrollment of 222 hypogonadal men who were randomized 3 to 1 to oral Jatenzo or to topical Axiron. This was a large ABPM study that successfully met its enrollment targets with 135 on Jatenzo and 45 on Axiron having interpretable ABPM data at baseline and on treatment at visit 6.

This slide shows you the raw data for hourly average systolic blood pressure from these ABPMs. Please focus on the left, which is the hourly average systolic blood pressure data from the 135 Jatenzo-treated subjects with baseline and on-treatment ABPMs, with the black line showing the

screening average systolic blood pressures over the 24-hour monitoring period, and the red line showing the visit 6 on-treatment average hourly systolic blood pressures for Jatenzo-treated subjects over the 24-hour monitoring period.

The separation of these curves over the entire monitoring envelope is clearly demonstrated. In contrast, if you look over to the right, the screening versus visit 6 on-treatment curves of hourly averaged systolic blood pressure, over the 24-hour monitoring period for the 45 Axiron-treated subjects with baseline and follow-up ABPMs, were not different.

Cumulative function distribution analyses were also performed to further assess the demonstrated effect of Jatenzo on systolic blood pressure. On the left as before, the Jatenzo hourly average systolic blood pressures were demonstrated at baseline in black and on-treatment visit 6 in red. The separation of these curves is apparent for the entire envelope of systolic blood pressures recorded as opposed to being an outlier

effect at the upper range of recorded blood pressures. On the right, you can see that the cumulative function distribution curves of hourly systolic blood pressure for baseline versus week 6 on treatment for the Axiron group were not different.

Daytime in this study was defined as the period between 7 am and 11 pm. Nighttime was defined as the period between 11 pm and 7 am. This slide demonstrates the control-corrected analysis of systolic blood pressure for these separate time periods in the entire 24-hour period in blue. These blue bars showed the point estimate and 95 percent confidence intervals of the treatment effects of Jatenzo relative to Axiron with respect to change from baseline in systolic blood pressure for the three periods: daytime, nighttime, and 24 hours.

This can be thought of as a double-delta analysis of control-corrected change from baseline. The green bars below the blue bars show the change from baseline systolic blood pressure for the

Jatenzo group and the Axiron group individually, which are the single delta components of the double-delta analysis.

What is shown is that relative to Axiron, the increases and mean hourly systolic blood pressure in all three time periods is driven by increases in systolic blood pressure in the Jatenzo treatment arm. The Axiron subjects did not experience changes in systolic blood pressure on therapy compared to their own baselines.

For the daytime result, the point estimate for the control-corrected increase in hourly mean systolic blood pressure is 5.2 millimeters of mercury for the Jatenzo-treated subjects relative to Axiron-treated subjects with the upper bound of the 95 percent confidence interval of the difference being 8.2 millimeters of mercury.

Note that for all time periods, the upper bound of the 95th percent confidence interval for the difference in the change from baseline in systolic blood pressure between the oral Jatenzo and topical Axiron treatment arms exceeded

4.9 millimeters of mercury, which was the threshold defined by the sponsor for defining a clinically significant difference in systolic blood pressure elevation between the groups.

Here, you see the same single-delta and double-delta analyses for diastolic blood pressure for the three time periods with similar results. The increases in diastolic blood pressure in the Jatenzo-treated group compared to the Axiron group in the double-delta analyses of active control-corrected change from baseline was driven by the diastolic blood pressure increases in the Jatenzo arm.

For the daytime result, the point estimate for the control-corrected increase in hourly mean diastolic blood pressure is 1.9 millimeters of mercury for the Jatenzo-treated subjects relative to Axiron-treated subjects with the upper bound of the 95th percent confidence interval of the difference being 4.1 millimeters of mercury.

Similar single-delta and double-delta data -- similar results were seen here for heart

rate on this slide, again demonstrating that the double-delta active control increase in heart rate for Jatenzo- versus Axiron-treated subjects was driven by the heart rate elevation in the Jatenzo-treated subjects in all three treatment periods.

For the daytime result, the point estimate for the control-corrected increase in hourly mean heart rate is 2.1 beats per minute for the Jatenzo-treated subjects relative to Axiron-treated subjects with an upper bound of the 95th confidence interval of the difference being 4.6 beats per minute.

Similar single-delta and double-delta analyses for daytime systolic blood pressure effects are shown on this slide for high-risk subgroups of subjects with a history of hypertension or a history of diabetes. Note that the point estimate for the active control-corrected change from baseline for the Jatenzo-treated subjects relative to Axiron-treated subjects with a history of hypertension is 7 millimeters of mercury with the upper bound of the 95th percent confidence

interval being 11.6 millimeters of mercury. The results were driven by increases in the Jatenzo arm.

Of note, the results for the point estimate of the control-corrected treatment effect for those with a history of diabetes was similar to the overall ABPM population at about 5 millimeters of mercury. However, in those with a history of diabetes, the point estimate for the active control-corrected change from baseline for Jatenzo-treated subjects relative to Axiron-treated subjects on nighttime systolic blood pressure, which I haven't shown here, was higher at 9.1 millimeters of mercury with the upper bound of the 95th percent confidence interval being 16.3 millimeters of mercury, part of this difference being driven by a lack of dip of blood pressure in the evening.

In conclusion, it was DCRP's opinion that the blood pressure upward shifts seen with oral Jatenzo are clinically significant and that their consequences may be amplified over time by the

upward shifts in heart rate that have been seen. Based on the Lancet data, these changes if sustained with chronic therapy can be reasonably expected to progressively increase the risk of cardiovascular events in successive decades of life.

I'd like to leave you with two examples here, and I've taken these from average inputs from the data set from 15012, where I had the data. But things like smoking status was not recorded in the database, so I decided to just give you two individual examples.

Reflecting the baseline demographics of the men enrolled in CLAR 15012 as assessed by the online ACC-AHA 2013 cardiovascular risk assessment tool, if you take a 52-year-old African American male, diabetic smoker with a background total cholesterol and LDL and HDL changes that occurred in the trial with Jatenzo therapy, a 5 millimeter of mercury rise in systolic blood pressure increases the absolute 10-year risk of MI, stroke, and death due to cardiovascular disease from 30 to

33 percent. Obviously, the relative increase is higher.

For a 65-year-old subject with those same background demographics and cholesterol changes, a 5-millimeter rise in systolic blood pressure increases 10-year risk for MI, stroke, and death due to cardiovascular disease, an absolute 4 percentage points from 46 to 50 percent with a relative risk increase that would be higher. Thank you for your attention.

FDA Presentation - Roger Wiederhorn

DR. WIEDERHORN: Good morning. My name is Roger Wiederhorn. I'm a medical officer in the Division of Bone, Reproductive, and Urologic Products at the Food and Drug Administration. I'd like to reiterate our appreciation to the members of the advisory committee for volunteering their time and participating in the meeting today.

My talk will focus on several additional clinical effects of oral TU, testosterone undecanoate, that were noted in clinical trial CLAR 15012. I will primarily focus on the effects

of TU on serum lipid profile; hemoglobin and hematocrit; comparative TNT metabolite exposures between oral and TU and topical Axiron; DHT, dihydrotestosterone and estradiol outliers; and areas where there appear to be differences between oral TU and topical Axiron. My talk will also encompass the effects on adrenal function, including cosyntropin testing.

Both oral TU and topical Axiron decreased cholesterol by approximately 10 milligrams per dL. Oral TU decreased high density lipoprotein by 6.8 milligrams per dL, whereas topical Axiron HDL was essentially unchanged. Lower density like for cholesterol was increased by oral TU by 3.2 milligrams per dL, but topical Axiron decreased LDL by 2.9 milligrams per dL. Both drugs increased triglycerides, but the increase in triglycerides was approximately 4-fold larger for oral TU compared to topical Axiron.

Shift analyses provide additional information about drug effects. For high density lipoprotein, shifts from normal to below normal at

the end of the study occurred in 28.9 percent of oral TU subjects versus 14.8 percent of topical Axiron subjects. I believe this was already presented. Shifts to above the normal range at the end of the study occurred for cholesterol in 7.8 percent of TU subjects versus 3.7 percent of topical Axiron subjects.

With respect to LDL, 11.4 percent of oral TU subjects and 9.3 percent of topical Axiron subjects shifted from normal range at baseline to above normal range by study-end. For triglycerides, 13.3 percent of oral TU subjects and 9.3 percent of Axiron subjects shifted from normal range to above the normal range by the end of the study.

Overall, hematocrit and hemoglobin average changes were not remarkable. Oral TU patients increased their hematocrit by 3 percent at the end of the study versus an increase of 2 percent for topical Axiron patients. Hemoglobin increased by 0.7 grams per dL for oral TU patients and by 0.5 grams per dL for topical Axiron patients at the end of the study.

While the difference between groups in mean changes in hematocrit and hemoglobin were not remarkable, in an evaluation of maximum post-baseline hematocrit values, 4.8 percent of all oral TU subjects had at least one baseline hematocrit above the normal range defined as 54 percent, while 3 subjects had more than one post-baseline hematocrit above the normal range. None of the topical Axiron subjects experienced a post-baseline hematocrit above the normal range.

Using a cutoff value of 50.4 percent for normal hematocrit range, which was used in some of the oral TU prior studies, oral TU 20 percent or 33 of 166 oral TU subjects, and 13 percent or 7 of 55 topical Axiron subjects, had an end-of-study hematocrit above the normal range.

With the mean differences between oral TU and topical Axiron for TC average or T metabolites, mean TC average was 403 nanograms per dL for oral TU and it was 380 nanograms per dL for topical Axiron. Mean dihydrotestosterone to T ratios were comparable at 0.18 and 0.19. TU and DHTU

concentrations were not measured in this protocol. Mean dihydrotestosterone Cavg was comparable at 73 nanograms per dL for oral TU and 74 nanograms per dL for topical Axiron. Mean estradiol Cavg was comparable at 32 nanograms per dL for oral TU and 33 nanograms per dL for topical Axiron.

Outlier analysis may add additional information about T metabolites. Let's first look at Cmax and DHT Cavg for dihydrotestosterone. Approximately 34 percent of oral TU subjects had a dihydrotestosterone Cmax of greater than 2 times the upper limit of normal and 6.6 percent had a dihydrotestosterone Cmax of greater than 3 times the upper limit of normal compared to Axiron, where 16.7 percent had a Cmax greater than 2 times the upper limit of normal and 4.2 percent had a Cmax of greater than 3 times the upper limit of normal. The results for DHT Cavg between TU and Axiron were comparable.

This slide shows a 24-hour average of DHT concentrations after BID dosing with oral TU and illustrates excursions of average DHT to above the

upper limit of normal defined as 65 nanograms per dL, which occurs approximately 4 to 6 hours after each dose. The red line is for visit 2, the blue line is for visit 4, and the black line is for visit 7. The dash lines represent the Cavg for the respective visits.

Turning to estradiol, 84.9 percent of oral TU patients versus 78.7 percent of topical Axiron patients had an estradiol Cmax of greater than 1 time the upper limit of normal; 3.4 percent of oral TU patients versus 6.4 percent of topical Axiron patients had an estradiol Cmax of greater than 3 times the upper limit of normal; and 2.1 percent of Axiron subjects had an estradiol Cmax of 5 times the upper limit of normal.

In this slide, oral TU results are shown in red and topical Axiron in blue for the 24-hour PK period. Topical Axiron has estradiol levels above the upper limit of normal for almost all the time points for the 24-hour PK period.

In a previous NDA submission, Clarus performed a 90-day dog study. Multiples of

exposure were 2 times and 5 times by area under the curve. If in 90 days of treatment there was a dose-dependent increase in severity of adrenal gland atrophy in the zona fasiculata that correlated with 30 to 35 percent reduction in adrenal weights in all TU-treated eugonadal dogs.

The atrophy was partially reversed following a 4-week recovery period. Cortisol levels were near the lower quantification limit. Based upon the uncertainty of these nonclinical study results, a human cosyntropin stimulation test was requested.

In the cosyntropin study, 24 oral TU subjects and 8 topical Axiron subjects entered the study. The oral TU subjects had received between 105 to 107 days of study medication and received their last dose of study medication the night before the cosyntropin stimulation test.

Five of 24 oral TU subjects had an abnormal cosyntropin stimulation test response defined as a serum cortisol of 18 micrograms or less at 30 or 60 minutes after a 250-microgram dose of cosyntropin. The individual subject results are

shown in table 2 in this slide. Of note, patient 102-023 highlighted in blue, this subject received prednisone 60 milligrams a day for 2 weeks 2 months prior to this cosyntropin stimulation test. And this was the patient that was previously discussed by the sponsor in their presentation. This may or may not have had a significant effect upon test results.

How do we interpret these results? Well, abnormal results occurred only in the oral TU group. Cosyntropin is associated with supraphysiologic adrenal stimulation, and ACTH may have informed abnormal results, but ACTH was not presented with the cosyntropin data nor was CBG presented with the cosyntropin study data.

There were low basal cortisol levels in some subjects at baseline raising a question about assay performance. The sample size was small. Subject selection was nor randomized but was voluntary. There was variability in the time of conducting the test, 6:25 am to 3:45 pm., and baseline cortisol is best measured between 6 am and 8 am. The study

duration was not sufficient to rule out adrenal insufficiency with long-term treatment, and the sponsor has proposed a repeat study as you heard this morning.

We feel that a longer duration, more robust cosyntropin stimulation test will be more informative. Thank you.

Presentation - Dhananjay Marathe

DR. MARATHE: Good morning, everybody. My name is Dhananjay Marathe. I'm a senior reviewer in the Division of Pharmacometrics within the Office of Clinical Pharmacology at CDER FDA. I will be presenting considerations for the dose titration algorithms.

The titration algorithm proposed in the label is different from that utilized in the phase 3 study CLAR 15012. This study had titrations based on Cavg measurements that were derived from 0 to 24 hours sampling post-dose, and it utilized Cavg thresholds of 350 and 800 nanogram per deciliter for up and down titrations.

There were 2 titration visits, visit 2 and

visit 4b, before the final study endpoint day. In the label, the applicant's proposed titrations are based on a single PK sample. Let's call it Cx, in the 3 to 5 hour post-morning dose window with the same thresholds of testosterone concentrations, that is 350 and 800 for up and down titrations.

A concordance analysis was proposed by the applicant to justify that the outcome of both titration algorithms would be similar. It consists of two terms. A numeric concordance is when the subjects will have same up or down titration using the two algorithms; that is Cavg or Cx based algorithm. Effective concordance is when subjects may have different titrations using Cx compared to the Cavg based algorithm, but the study outcome, that is the percentage of subjects in the eugonadal range of 252 to 907, will not be altered. The total concordance is the sum of numeric and effective concordance. I will illustrate these concepts in more detail in the next few schematics.

First, let's look at the numeric concordance. Here I have shown the Cavg on the

horizontal axis and Cx on the vertical axis. The upper left rectangle represents the subjects who have Cavg less than 350 as well as Cx less than 350. These subjects will have uptitration as per the criteria for both algorithms, that is Cavg or Cx based algorithm, so these subjects fit the characteristic of numeric concordance.

The middle rectangle represent subjects with Cavg between 350 to 800 as well as Cx between 350 to 800. These subjects won't have any titration for both the Cx and Cavg algorithms. Again, they fit the characteristic of numeric concordance.

The lower right rectangle represents the subjects who have Cavg greater than 800 and Cx greater than 800. These subjects will have down titrations as per the criteria for both the algorithms. So again, these subjects also fit the characteristic of numeric concordance.

Now, let's look at the effective concordance. Here in the same schematic, I have represented the eugonadal range of Cavg of 252 to 907 by a green color. The subjects in the

rectangle denoted as cell 1 has Cavg less than 350 but Cx between 350 to 800, so the Cavg algorithm stipulates uptitration. On the other hand, Cx algorithm stipulates no titration for these subjects.

Now, there exists a subset of cell 1 where subjects have Cavg between 252 to 350 and one such possible subject is shown by a blue star in the schematic. For this subset, even though there would be no titration for the Cx algorithm for the label, they are already within the green eugonadal zone, so this subset of cell 1 would fit the characteristic of effective concordance.

There are two other rectangles denoted as cell 2 and cell 3, which contain subjects with potential effective concordance. Subjects in both cell 2 and cell 3 have Cavg between 350 to 800, so both would have no titration for the Cavg algorithm, but the cell 2 has Cx less than 350 and cell 3 has Cx greater than 800. So cell 2 subjects will have uptitration and cell 3 subjects will have down titration as per the Cx algorithm proposed in

the label.

The applicant provides the following considerations for effective concordance in these two cells, cell 2 and cell 3. Firstly, the testosterone exposure is approximately dose proportional. Second, the change in Cavg with the largest dose increment by 33 percent or dose decrement by 25 percent in each titration step still allows movement within the eugonadal Cavg range with the Cx algorithm.

Let's apply these considerations to cell 2. A subset of cell 2 with Cavg between 350 and 682 would still have Cavg within the green eugonadal range even after uptitration that is stipulated by Cx algorithm.

For illustration purpose, here I am showing an animation of the anticipated shift in Cavg and Cx with such a dose uptitration for a borderline subject in this subset, which is shown by a blue star and who still remains in the green zone after uptitration. Thus, this subset of cell 2 with Cavg less than/equal to 682 would fit the characteristic

of effective concordance.

Let's apply these considerations to cell 3. The subjects in whole cell 3 would still have Cavg within the green eugonadal range even after down titration that is stipulated by Cx algorithm.

For illustration purpose, here I am showing an animation of the anticipated shift in Cavg and Cx with a dose down titration for a borderline subject in this cell, who would still remain in the green zone after the down titration. Thus, the subjects in entire cell 3 would fit the characteristic of effective concordance.

Based on these considerations, the applicant proposed to bridge between the Cavg based titration algorithm used in the study and the single sample, that is Cx based algorithm for labeling purposes. As I stated earlier, they have proposed a single sample in the 3 to 5-hour post-morning dose window with the same thresholds of 350 and 800 for titrations.

The justification for the proposal is as follows. There was strongest correlation between

Cx and Cavg at 4 hours for the observed data. High total concordance was observed with the analysis method that was described earlier for C4hour and Cavg algorithm in the range of 88 to 93 percent for visit 2 and visit 4b based on the observed data in study CLAR 15012.

Further, a simulation-based exercise was carried out using a population PK model to justify that a 3 to 5-hour sampling window would be suitable in lieu of sampling at a fixed 4-hour time point from a practical perspective. The simulation analysis had certain limitations. For example, the observed data at titration visits in the phase 3 study was not really reproduced, so we decided to mainly rely on the analysis with observed data for our conclusions.

This figure shows the concentration time for 5-hour plasma testosterone at different visits. Let's focus on the red profile observed at titration visit 2 when all subjects are taking a dose of 237 mg BID. The red dotted line shows the Cavg derived from 0 to 24 hour sampling on that

visit. A comparison of concentration at different time points, for example, 2, 4, 6, 9, 12-hour post-morning dose, what the Cavg suggests is that C6 hour is a close representation of Cavg for the whole profile.

Overall, based on the observed data, Cx at 6 hours most closely mimics Cavg on a population as well as on an individual level. Further, there was a relatively strong correlation between Cx and Cavg at 4 hours and 6 hours, while there was relatively weaker correlation at other time points such as 0, 2, 9 or 12-hour post-morning dose.

The table here summarizes the numeric effective and total concordance between Cx and Cavg based algorithms for representing single time point sampling at 2, 4, and 6 hours for the observed data at different titration visits 2 and 4b. As seen in the table, the numeric and total concordance values were 64 and 88 percent for C4hour and 79 and 98 percent for C6hour for visit 2. Thus overall, the numeric and total concordance for both 4-hour and 6-hour sampling seemed reasonable.

The median Tmax for this oral administration product is around 2 hours, so a window of 3 to 5 hours is likely to have some samples that mimic Cmax rather than the Cavg for the same subject depending on the sampling time across different visits for the same dose, and this may unduly influence titrations towards a lower dose.

On the other hand, a shallower PK profile over a 4 to 6-hour time window means that it could likely yield less extreme values and it would not be as sensitive to the sampling time for the same individual across different visits. Thus in conclusion, we believe that a 4- to 6-hour post-morning dose window for sampling for titration decisions seems more appropriate with the titration thresholds of 350 and 800 for the labeling purpose.

With that, I would like to hand it over to our next speaker from FDA, Dr. Yu. Thank you.

FDA Presentation - Chongwoo Yu

DR. YU: Good morning, everybody. My name is Chongwoo Yu. I'm a senior clinical pharmacology reviewer working at the Office of Clinical

Pharmacology at the FDA. I'm also the primary clinical pharmacology reviewer for the oral testosterone undecanoate new drug application submitted by Clarus Therapeutics. I have also served as the member of the FDA's Bioanalytical Method Validation Guidance working group.

In drug development, bioanalysis has a significant implication as we need to have confidence that we can rely on the concentrations, in this case, testosterone, and also the PK parameters used for the efficacy and safety assessment, especially for this NDA.

First, I will provide some background information on the potential of the TU to T ex vivo conversion and its impact. This will be followed by a summary of the applicant's bioanalytical approach used during drug development and the applicant's proposal for dose titration in clinical practice. Then sample collection handling preparation methods will be discussed along with a summary of the applicant's data.

As a part of bioanalytical method

validation, the stability of the analyte of interest should be demonstrated, in this case, from the blood drawn into the test tube through the separation of plasma or serum from the red blood cells and other blood components. There are literature reports raising a concern that there might be a TU to T ex vivo conversion that can lead to artificial higher testosterone concentration than the actual value, which can affect the efficacy assessment as testosterone concentration is the primary efficacy endpoint for testosterone replacement therapy.

The applicant has employed liquid chromatography-tandem mass spectrometry methods from two different labs during their clinical drug development. Because of the concern of the potential TU to T conversion, the applicant has taken an approach of measuring testosterone concentrations in plasma collected in sodium fluoride EDTA tubes instead of serum collected in plain tubes to prevent the potential TU to T ex vivo conversion.

In addition, the applicant proposes to conduct dose titration based on the testosterone concentration from plasma in sodium fluoride EDTA tubes in the clinic. Two things to note, in general, clinical laboratories measure testosterone concentrations from serum in plain tubes. It should be noted that the primary efficacy analysis in dose titration in the pivotal phase 3 efficacy and safety trial, mainly the CLAR 15012 study, was conducted based on the testosterone concentration measured from plasma in sodium fluoride EDTA tubes.

To focus on the main topic for discussion today, here are two questions that we should be thinking about during this presentation. First, did the applicant's approach of measuring testosterone concentrations from plasma in sodium fluoride EDTA tubes adequately support their clinical data in this NDA? In other words, can we rely on the applicant's clinical data submitted? The other question is whether measuring testosterone concentrations from plasma in sodium fluoride EDTA tubes is critical for dose titration

of this oral TU therapy.

To put everybody on the same page, I would like to briefly explain the difference between serum and plasma sample preparation. For serum, blood is collected in tubes with no anticoagulants added and is required to sit for at least 30 minutes for clotting before proceeding with further preparation. However, for plasma, blood is collected in tubes with an anticoagulant to prevent clotting.

For this NDA, it should be noted that the applicant used sodium fluoride EDTA tubes when measuring testosterone concentrations in plasma where sodium fluoride served as an esterase inhibitor and EDTA served as an anticoagulant. The applicant is concluding that their approach is useful in preventing the potential TU to T ex vivo conversion based on their data obtained during drug development.

Now I will be presenting a summary of data from three different studies that the applicant submitted in support of their bioanalytical

approach and clinical development. In the first study, the applicant has conducted a study comparing the effect of different types of test tubes and matrices on testosterone concentration measurements.

In this study, the applicant conducted both in vitro and in vivo assessments. For the in vitro assessment, different known concentrations of TU were added to plain tubes and subsequently serum was prepared. It should be noted that the same in vitro assessment in plasma, prepared from blood collected in sodium fluoride EDTA tubes, was not conducted in this assessment.

In this assessment, the applicant has observed an increase of serum testosterone concentrations as the concentration of spiked testosterone undecanoate increased. TU to DHT conversion was not observed, and therefore will not be discussed further in this presentation.

For in vivo assessment, a single oral dose of 316-milligram was administered in 8 hypogonadal men. This study compared the PK profile of

testosterone from serum in plain tubes, serum in sodium fluoride tubes, plasma in sodium fluoride oxalate tubes, and plasma in sodium fluoride EDTA tubes.

It should be noted that while serum in plain tubes were left in room temperature for 30 minutes, the other three types of samples were left on ice for 30 minutes prior to further sample preparation, and therefore no direct comparison between serum and plain tube versus plasma in sodium fluoride EDTA tubes under the same temperature was conducted.

As the applicant has used plasma in sodium fluoride EDTA tubes in the pivotal phase 3 trial and is proposing to use this approach for clinical practice, we will focus on the comparison of serum in plain tubes with plasma in sodium fluoride EDTA tubes for the rest of this presentation.

As shown in the figure on the slide, higher testosterone concentrations were observed from serum in plain tube compared to plasma in sodium fluoride EDTA tubes and therefore higher PK

parameters as a result. There was a higher difference between the two types of samples around the Tmax where testosterone concentrations were higher than other time points.

It should be noted that this study had a small sample size of 8 subjects and a high intrasubject variability in testosterone concentration was observed. Also, it should be noted that bioanalysis was conducted at a different laboratory using a different LC-MS/MS method compared to what was used in the phase 3 pivotal study. The applicant believes that factors such as temperature times esterase inhibitor, namely sodium fluoride concentration, and genetic and environmental factors can potentially affect the non-specific esterase activity.

The second study was a clinical study that the applicant conducted to establish the eugonadal testosterone normal concentration range based on their sample collection and preparation approach. This study was conducted in 97 healthy males and there was no oral testosterone undecanoate

administered in this study.

Testosterone concentration from serum in plain tubes were compared with those from plasma in sodium fluoride EDTA tubes that were obtained from same subjects. It should be noted that bioanalysis for serum and plain tubes and plasma in sodium fluoride EDTA tubes were conducted at different labs using different LC-MS/MS methods.

The eugonadal testosterone concentration range for serum in plain tubes, which is the red panel on the figure, was 304 to 1030 nanogram per deciliter, which is comparable to the widely accepted serum eugonadal testosterone concentration range. In this study, the eugonadal testosterone concentration range for plasma in sodium fluoride EDTA tubes was 252 to 907 nanogram per deciliter, and this range was used for the primary efficacy analysis in the phase 3 trial.

In general, testosterone concentrations obtained from serum in plain tubes were higher than those observed from plasma in sodium fluoride EDTA tubes with a mean difference of 14.2 percent. The

potential cause of the observed difference of testosterone concentrations may be either an additive effect, namely sodium fluoride EDTA, or the different sample handling preparation of different matrices at different labs.

Now I will discuss the third study, which was the pivotal phase 3 efficacy and safety trial conducted in a much larger population of 166 subjects compared to the first study that I presented. The applicant has generated serum over plasma concentration ratios from testosterone concentration measured from serum in plain tubes with those measured from plasma in sodium fluoride EDTA tubes from each subject.

In the figure, the X-axis shows the median plasma testosterone concentrations observed and the Y-axis shows the geometric serum over plasma ratio of samples within the decile. This plot is constructed based on 1533 ratios from the oral TU treatment and 484 ratios from the Axiron treatment arm. It should be noted that the plasma and serum testosterone concentrations were measured at

different labs using different LC-MS/MS methods.

As shown in the figure, the mean serum over plasma ratio from subjects treated with Axiron, which does not contain TU, was 1.17 indicating that on average, the serum testosterone concentrations were 17 percent higher compared to the plasma concentrations when subjects were not treated with TU.

For the TU containing Jatenzo-treated patients, the mean serum over plasma ratio was 1.30 indicating on average serum testosterone concentrations were 30 percent higher compared to plasma concentrations. Considering that the Axiron group was not treated with TU, it appears that the 17 percent difference between serum and plasma testosterone concentrations potentially came from the non-TU related factors such as additives, in this case sodium fluoride and/or EDTA or different in matrices; in this case plasma versus serum or different sample handling and bioanalytical methods used from different labs.

It is unknown why an additional 13 percent

difference between serum and plasma testosterone concentrations was observed from the same subjects in the TU-containing Jatenzo treatment arm. The applicant believes that one potential contributing factor may be the TU to T ex vivo conversion.

As the applicant highlighted in their AC meeting backgrounder, this figure shows us how the difference in individual concentration translates into PK parameters. The green line in the figure is to help you, showing when the testosterone PK parameters obtained from serum and plasma are the same. The blue bars in the figure are for the non-TU-treated Axiron group, while the orange bars represent the TU-treated Jatenzo group.

As you can see, the black line on the figure shows that the mean difference of Cavg and Cmax obtained from the non-TU-treated Axiron group was 16 percent. The figure also shows that there was a mean of 15 percent and 25 percent additional difference in Cavg and Cmax, respectively, observed from the TU related Jatenzo group. While the cause of this additional difference is unknown, the

applicant believes that a potential source of this difference might be due to the TU to T ex vivo conversion as only the Jatenzo group was treated with TU.

With this, now I would like to summarize my presentation. The applicant concludes that there was a concentration-dependent TU to T ex vivo conversion based on their in vitro assessment. Temperature and time may be contributing factors based on literature for TU to T ex vivo conversion, however, the applicant has not independently investigated these factors.

It should be noted that bioanalysis for serum in plain tubes and plasma in sodium fluoride EDTA tubes was conducted at different laboratories using different LC-MS/MS methods. In general, higher testosterone concentrations were observed from serum in plain tubes compared to those from plasma in sodium fluoride EDTA tubes following oral TU administration.

While the cause is unknown, it appears that the following can be potential contributing factors

to this observed difference. First, a mean of 14 to 17 percent higher testosterone concentration was observed from serum in plain tubes compared to plasma in sodium fluoride EDTA tubes from same subjects not treated with TU, and this can be due to the contribution of additives, in this case sodium fluoride and or EDTA.

Second, a mean of an additional 13 percent higher testosterone concentration, 25 percent higher Cmax, and 15 percent Cavg values from serum compared to plasma in TU-treated subjects, after subtracting the mean of 14 to 17 percent difference observed in subjects not treated with TU, indicates that this may be due to the TU to T ex vivo conversion.

Last but not least, different sample handling and preparation procedures can also be a contributing factor to this observed difference. We would greatly appreciate your input on this important question of whether it is critical to measure testosterone concentrations from plasma using sodium fluoride EDTA tubes for the safe and

effective use of the applicant's oral TU therapy. With that, I would like to thank you very much for your attention. Thank you.

Clarifying Questions to the FDA

DR. LEWIS: Thank you. Are there any clarifying questions for the FDA? And remember, we'll have opportunity for comments later. Dr. Adler, and then Dr. Lincoff.

DR. ADLER: I have a question for Dr. Wiederhorn. I am trying to put this together. I see outcomes of decreased adrenals, increased blood pressure, changes in serum lipids. Is it due to a metabolite? Is it due to changes in steroid-binding globulins? Is it the pharmacokinetics of the testosterone? Is there any way to get a mechanism behind the outcomes that have been measured in the various studies?

DR. WIEDERHORN: I'm not aware of any all encompassing mechanism, and some of this is contradictory because you would say if the drug raises blood pressure, well, how could someone be hypoadrenal?

I think the only thing that we saw -- and I think my team leader Mark Hirsch pointed this out -- was that in looking at DHT concentrations, if you look at the up and down that goes twice a day, it's never really in the normal range that much. It averages out to the normal range, but it's high and low. And that's just pure conjecture. That's the only thing I can see. I'm not aware of anything else.

DR. LEWIS: Thank you. Dr. Lincoff, and then Dr. Braunstein?

DR. LINCOFF: Thank you. My question is for Dr. Dunnmon. You had mentioned in your slide 11 there was a difference in patients with diabetes versus those without in terms of the nighttime dip. The nighttime dip on this ambulatory blood pressure has been clearly associated with -- or failure to have the nighttime dip has been clearly associated with adverse outcome.

Do you have any more data regarding -- and patients with diabetes are often more likely to have a lack of that dip, so this may be

particularly important. Do you have more data regarding how many patients with diabetes in each group failed to have that dip as compared to those without and the treatment effect, et cetera?

DR. DUNNMON: Dr. Lincoff, I can give you an overall summary of that. Could you please bring up the ABPM backup slide, number 7? We focused on the daytime results because that's where our major focus and most of the data came from.

This is I think Dr. Wiederhorn's slide 7, not the ABPM slides. So this would be ABPM backups, slide 7.

To be talking just for a moment while they're bringing up my slides, the data was internally consistent. When you look at nighttime blood pressure results in the diabetic subgroup between systolic pressures, diastolic blood pressure, and heart rate, there's no placebo here, so what you can't know is what the placebo would have been acting like. But there was a bit of a suggestion here that what may be occurring -- yes, slide number 7, please.

The thought that crossed our minds when we saw this is that there's potentially a nighttime dip occurring in the Axiron-treated arm that is being erased in the oral treatment arm.

Can we get my backup slides up? There we go. What you see here is the ABPM subpopulation of those with a history of diabetes. That's everybody with a history, whether they're type 1 or type 2.

So what you see here is daytime systolic blood pressure, nighttime systolic blood pressure, and 24-hour. I really ignore those 24-hour results because they're being driven overwhelmingly by the daytime two-thirds of the period, and you think, well, you're normally going to get a dip in people at night. But when you look at this and you think those aren't many people, there are 33 ABPMs there in the oral Jatenzo group versus 13 ABPMs in the topical Axiron group, but that's still a lot of ABPMs.

Keep in mind you're getting hourly average pressure data and 2 readings per hour over 24 hours in 13 people. So what I don't have here to put

this in context is the placebo. I would suspect that the placebos could very well behave the same way you're seeing the topical Axiron's behaving, although it might be more pronounced as far as the dip.

But what's feeding into that difference of 9.1 with that upper confidence interval of 16.3 on the nighttime pressures, not only do you have a greater than 5-millimeter rise in your Jatenzo group, which is commensurate with what they did during the daytime, but then what you're also getting in that double-delta analysis is the drop going on at nighttime in the Axiron arm.

DR. LEWIS: Thank you.

DR. DUNNMON: That 9.1 is essentially -- or that blue bar is essentially the top green bar, which is the oral Jatenzo minus the lower green bar, so it gives you that 9.1 result. And that would be compatible with a nighttime dip going on in that group.

Could you go to the next slide here since we're on the subject? Go to the next slide,

slide 8 please. You can see here for the diastolic blood pressures, the trend of the result is incredibly concordant. You get a drop in the topical Axiron nighttime diastolic blood pressure ABPMs, so that's feeding into that difference of 6 with an upper bound of the confidence interval the difference of 11.3

Go to the next slide, please, slide 9. This is the heart rate data, where you see kind of the same thing here with the bump in the heart rate that you've seen in the daytime hours in the nighttime heart rate subtracted difference there. And you're seeing the Jatenzo group behaving commensurately with what they did in the daytime hours with the pulse going up about 2 beats per minute, but what you're seeing in the Axiron group is a fall at night on 13 ABPMs.

DR. LEWIS: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. I'd like to ask the FDA about additional safety information. The sponsor has indicated that the oral TU has been available in 80 countries for a number of years, so

there's a substantial amount of safety information that's probably available from that experience, as well as TU injections have been available in the U.S. now for a while, so I'm sure the FDA has substantial information on the safety of that.

Could you provide the overall safety data from the outside sources?

DR. HIRSCH: Hi. I'm Mark Hirsch, medical team leader in urology. I could answer about the injectable. At least for the injectable, we actually have a very small population of patients who have taken that probably as a result of the REMS that is involved with that product. So we don't have that much.

In regard to outside of the United States, data for the oral TU formulations, I really can't comment on that. I don't know if there's anyone from OSE, Office of Surveillance and Epidemiology, who's willing to comment on that or available. But for injectable, we don't have that much from the currently approved to address these issues.

DR. LEWIS: Anyone? No? Thank you. Dr.

Gerhard, and then Dr. Brannigan. And could people please be careful to speak into the microphone? It's hard to hear sometimes if you don't.

DR. GERHARD: Toby Gerhard. A general question for FDA, while these findings were very specific or the studies presented were very specific to the studies that were done, I didn't see any information, or as we've seen in the questions to the sponsor, regarding utilization patterns, questions regarding how much of the use of testosterone treatment is actually off label versus on label.

Just looking briefly in the literature, there are estimates going to, in the VA population, off-label use exceeding 90 percent, 4-fold increase in utilization between 2000 and 2010, and I think will really affect the discussion later on. Is there any data?

I believe at the last meeting, there were some utilization data presented. The sponsor also commented on recent changes in how insurance might reimburse testosterone and that that would

alleviate some of the issues with off-label prescribing. But without seeing any data on this, it's really difficult to put that into context.

DR. JOFFE: This is Hylton Joffe. We did look at drug utilization data back in 2014 -- you're correct -- when we brought the issue of age-related hypogonadism to the committee, and I think there are probably quite a few folks on this committee that overlap with that committee. We haven't looked very closely at it since then. We certainly could pull up some of those data to give you a sense, but those are from a few years ago.

Since then, we've made some public statements about the appropriate use of testosterone. We've published about it, and those low T ads that we used to see on TV have disappeared to my knowledge. So there may be some subsequent changes since then, but I would say overall, you're correct, the predominant use, the majority of use, is in men who do not have what we call classic hypogonadism. There are men who have age-related hypogonadism and obesity-related

hypogonadism who have low testosterone levels and symptoms because they're on opiates, for example, but I don't have specific numbers for you today.

DR. LEWIS: Thank you.

DR. GERHARD: Just a quick follow up. For all of those off-label indications, there is no demonstrated efficacy of the treatment, correct?

DR. JOFFE: For these off-label uses, no one has submitted to FDA an application asking us to review and determine whether there's efficacy to support a labeled claim in our labels. This gets to the issue of practice of medicine, which FDA does not generally regulate. We try to make it pretty clear that the appropriate use for testosterone are in these men who have classic hypogonadism because we know pretty clearly if you're a Klinefelter's patient or you've had your testes removed, your testosterone levels are low and they shouldn't be, and when you increase testosterone, you're really returning that to the normal range.

These other cases of hypogonadism are a

little more squiggly or swirly. For example, in age-related hypogonadism, testosterone levels can go down with age. Then the question is, is this just the normal process; is it related to comorbidities or the medications, and how do we know that increasing testosterone in that population substantially leads to benefit?

Now, you've heard about some published data, which has not been submitted to FDA for review for an indication. Just looking at that published data, there are some issues that jump out in terms of whether, for example, the patient-reported outcomes would be up to speed for regulatory decision-making. Some of the changes in those publications were very, very small and we'd question some of that clinical significance.

DR. LEWIS: Thank you. Dr. Brannigan, and then Dr. Mager.

DR. BRANNIGAN: A question for Dr. Dunnmon. Just for background, you touched on the adrenal effects with data from the 90-day dog study. I just wondered if you could give us a little bit

more specific information about that. There was a comment about dose-dependent atrophy of the adrenal gland with 4 weeks recovery. Atrophy diminished to mild. Can you clarify or quantify that a bit more, please?

DR. JOFFE: Yes. We can have a pharmacology-toxicology expert speak to that.

DR. SUMMAN: Hi. I'm Mukesh Summan. I'm pharmacology and toxicology supervisor for the Division of Bone, Reproductive, and Urology Products. Can you be more specific in what information you're looking for?

DR. BRANNIGAN: The extent of atrophy, so it's dose dependent, but was it in the mild to moderate range, moderate to severe, and how did you quantify mild, moderate, and presumably severe as was presented in the slide?

DR. SUMMAN: The study data are presented by the applicant, and it would be the applicant's pathologist that makes the determination of the severity of the pathology findings. We found that the severity changes were described, as by

Dr. Wiederhorn, as mild. So the change was from minimum to moderate -- minimum, mild, and moderate -- and they then changed. There was only a slightly lower change in the short recovery period where there was one individual animal with a moderate finding. So we concluded that the change was therefore partially reversible.

DR. BRANNIGAN: Thank you. Can I ask one other question of Dr. Yu? Just from a practical standpoint, the special tubes for the blood draw, how readily available are they to labs? And do you have information about the cost of these tubes compared to the standard tube?

DR. YU: It is my understanding that for routine bioanalysis, the tubes are available. I think we have to distinguish between the bioanalysis for drug development versus bioanalysis for clinical implementation. My presentation and the scope of my review is solely focused on the drug development part.

Did you have another question?

DR. BRANNIGAN: I guess we can bring this up

during the discussion later today. Thank you.

DR. JOFFE: This is Hylton Joffe. I'd like to just introduce our colleague from the Center for Devices and Radiological Health who could speak to your question.

DR. LIAS: My name is Courtney Lias. I'm the director of the Division of Chemistry and Toxicology Devices at FDA, and we regulate both testosterone assays and blood collection tubes. Sodium fluoride EDTA tubes are available. They're not significantly different in price. They may be less available than serum tubes, so smaller labs may not have them necessarily in stock, and many labs may not have validated testosterone assays for use with that type of tube at this time. So we're not aware of assays currently available for use with that type of tube.

DR. LEWIS: Thank you. Dr. Mager, and then Dr. Wilson. And I'll ask people to please try to ask just one question because we want to get to everybody.

DR. MAGER: My question is for Dr. Marathe

regarding the effective concordance. You mentioned that it seems reasonable, but I'm still questioning that. In the examples you showed, for example, the patients that would have been in those additional cells where there was movement after you decreased the dose or increased the dose, you noticed that it pushed them very close to the edges in both cases. And in those cases also, we have no consideration for interoccasion or interindividual variability in those concentrations.

I'm a little surprised with the focus on pharmacokinetics that not more modeling and simulation was done in support of those types of decisions about time points, et cetera. It certainly seems that the 6 hour is a better choice than the 4, but I'm very concerned about the lack of modeling and simulation to support those decisions.

You've shown that you can push that very close to the edge. There's variability that hasn't been considered under that, and there's really no identification of sources of variability in this

application. I'm wondering about body weight, albumin concentrations, age, a number of the factors that would explain the interindividual and interoccasion variability.

So number one, how comfortable are you when you're pushing it up to those edges like that? It sounds to me from what you've said that the sponsor's model may in fact not be valid in that the simulations don't match the observed data, so we can't necessarily rely on that. But there's no indication of covariate relationships or any other information to help understand the ramifications of some of the decisions that are made.

I don't know if the FDA conducted any additional analyses to help support the decisions.

DR. MARATHE: So yes, it is true that there was quite a bit of interoccasion variability. The sponsor did include body weight as a covariate on clearance as well as volume, but even after incorporating that, there was around 25 percent interoccasion variability in clearance and around more than 40 percent interoccasion variability on

volume of distribution.

Even after accounting for interoccasion variability, there was around 43 percent residual proportional variability. That means for an average concentration of 600, the error will be around 250. So yes, there was quite a bit of error, and that's why we could not utilize that model. And the sponsor also evaluated other covariates, but none of them were significant. And that's why we relied more on the observed data rather than any kind of modeling and simulation.

DR. LEWIS: Thank you. Dr. Wilson, and then Dr. Rej.

DR. WILSON: Yes. Peter Wilson. My question is a follow-up related to slide number 10 by Dr. Yu, and it has the eugonadal T range establishment. I'm speaking as an endocrinologist who writes prescriptions for testosterone. There's a very wide therapeutic range, and I understand how product development led to tightness and accuracy. But as you can see in this slide, the therapeutic range is very wide, if we can pull that up. If you

have the handout, you'll see what I'm talking about. For instance, it goes from 300 to 1,000, or with the other units, almost 300 to 900.

So my question is how tight, if you were to just use one or the other assays? Again, it would be a scatter plot with a line through it. Could you use either assay for care, and would it lead to any misassignment for care? This is the question that the endocrinologists and the urologists and the primary care physicians -- is the patient in the therapeutic range?

DR. YU: I would appreciate if you can pull up backup slide number 6. And while that's being pulled up, backup slide number 6 is basically how this study was conducted regarding the establishment of reference range, which is a generally widely accepted approach of using a 2 standard deviation range.

I'm not sure if the slide is coming up. No. Next slide. Yes. I just wanted to first touch upon how this was generated, and it is my understanding it's a widely accepted clinical

approach in terms of establishing reference range.

Coming back to the bioanalytical question in terms of can we use either of these ranges, actually part of your question was part of the question that I had for the sponsor, which I'll leave for later discussion. But in general, as long as the bioanalytical method is validated per the agency's bioanalytical method validation guidance, then it is, in general, expected that you would not have a significant difference regarding the outcome of numbers. It would be comparable. Obviously, you would not have an identical number, but the use of internal standard and calibration curves will address some of the concerning factors.

In other words, I would actually leave a part of this discussion for later this afternoon because that's part of my question to the applicant.

DR. LEWIS: Thank you. Dr. Rej?

DR. REJ: Robert Rej. This question is for Dr. Yu. There are any number of studies that have compared serum versus plasma for any number of

metabolites, and in general, serum tends to be higher for lipids, for amino acids, and so on. And the reasons for this are thought to be that maybe there is some water redistribution due to the anticoagulant.

Do you think that the lower values in the sponsor's study exceed those that you would normally expect? And you stress that the results came from different laboratories, and maybe you could comment on the model of using different laboratories to compare those.

DR. YU: I will start from the last question regarding different laboratories. I have looked carefully at the methods, and their validation process is for drug development per the agency's bioanalytical method validation guidance, which regulates bioanalysis for drug development purposes.

In review of the applicant's bioanalytical method validation and performance, it appears to be, as of today, our current thought that it is compliant. And I also did look into a little bit

more detail in terms of their analytical methodology. For example, even if you run the same model of mass spectrometer in the same lab, unless you do a direct correlation analysis, there would be some difference but not significant, so a comparable result would be expected.

I did look into the methodology generated from both laboratories. It appears that they have used the same platform of mass spectrometers, which is a triple quadrupole actually manufactured from the same manufacturer as well. So I think this would be more towards not the detection part, but it would be more towards a matrix additive and all the other factors regarding sample collection handling preparation as I've highlighted in my presentations.

I do have some similar questions that you've raised to me for the applicant for our discussion this afternoon, but my understanding is right now, this time is for clarification to the agency, so I would leave that part out for further discussion later today.

DR. JOFFE: This is Hylton Joffe. I would just like to add that internally, we're still not clear whether the differences we're seeing with the sodium fluoride and serum tubes fully are explained by the stabilization of TU or whether these other factors may be contributing or playing a major role. So we have differences of opinion within FDA on that.

I do want to give our colleagues again from CDRH an opportunity to comment if they would like.

DR. LIAS: Courtney Lias, CDRH, FDA. As you saw on the reference range study, you can tell there is a difference between the two laboratory assays. So in men who were not taking the drug, there was a different testosterone measurement using the two assays. But there isn't data available to us yet to tell why there is that difference, whether it's the assay itself, sample handling, or preparation, or a matrix effect between serum and this plasma. And there's also not a lot of information yet on whether the different ways individual samples are handled in

these studies would make a difference.

DR. REJ: I have a follow-up question for Courtney. It's my understanding that no FDA cleared device for testosterone uses fluoride EDTA as a sample; is that correct?

DR. LIAS: That's true. Certainly a manufacturer could come in and validate sodium fluoride as a matrix and get clearance or approval.

DR. LEWIS: Dr. Bauer. That will be our last question of the morning, and then we'll have some opportunity a bit later if you haven't gotten your question in, so please make sure we get your name.

DR. BAUER: Thank you. Doug Bauer. I guess this is a question for Dr. Dunnmon or maybe just for FDA in general. We spent a lot of time this morning talking about biomarkers and risk factors for disease, particularly cardiovascular disease, but we've heard on several occasions that there are plans to actually do a clinical endpoint trial with cardiovascular endpoints.

I am really quite uncertain to how the panel

is supposed to incorporate the knowledge of that information into our discussions about this application and what ramifications that trial might have for the other testosterone replacement treatments assuming that it's a class effect.

DR. DUNNMON: With respect to your last sentence first, because I think that's the easier one to tackle, the data from 15012 would suggest this is not a class effect. I haven't looked at the PK variance across the exposures of these two things, but I know the urologists have, and from what I understand, there's not an exposure explanation of this.

As far as extrapolating epidemiologic data that I showed you in the beginning -- not this program necessarily -- uniquely any program where you've got drug induced elevations of blood pressure, which we see many of them, what we do know is that when you lower blood pressure by a certain amount, that the risk that you end up having for a lifetime -- and we know this from looking at this internally at DCRP over many

years -- your risk for cardiovascular events with that one item being changed in that whole risk calculator goes back to about what it was if you had never had hypertension.

If you lower it 10 millimeters of mercury, your risk ends up being what that 10 millimeter of mercury decrease number is. Say if you go from 150 to 140 and you treat your 150 with drugs, your risk goes down.

Well, we have not required obviously every developer to test this in the other direction, but there's absolutely nothing biological to indicate that if you do the reverse and you give something that boosts your blood pressure 10 millimeters of mercury, that it's not going to do the same analogous thing as any hypertensive lowering it, and therefore lowering your risk. So we're pretty confident in applying those large data sets from Lancet in risk-free people and that kind of behavior.

I think that what you're seeing here is that the background population without risk, you can

generally assume it's going to behave the way that I showed you in those curves. What you can also see from analyzing 15012 is exactly what you would expect, that in the higher risk groups of people, for instance those with hypertension to start with, your point estimate for the treatment effect as far as the control subtracted difference of 7 millimeters instead of 5, just tells you in all those curves I showed you, that if you take people who are more vulnerable to start with, because they have a disease affecting their vasomotor control, they are going to have an exaggerated effect. And that's exactly what we would expect, and I think you see that in multiple arenas. So I hope that answers a bit of what you're getting at.

DR. JOFFE: This is Hylton Joffe. I'll just add to that. For those of you who were on our panel back a few years ago, you may remember that we discussed cardiovascular safety of testosterone therapies and showed some conflicting data based on epidemiological studies and meta-analysis of clinical trials. And basically after that advisory

committee, our conclusion was that there was conflicting data based on those studies, and we couldn't rule out that there was an adverse cardiovascular effect.

So we've as a class asked testosterone replacement therapies to more definitively assess cardiovascular safety, and that's an ongoing cardiovascular outcome trial. There's a consortium of testosterone replacement therapy sponsors who are working on that now. We've never, in any of the approved products, got ambulatory blood pressure monitoring.

What we do note though is that we have Axiron in this comparator where we don't see anything. What prompted us to do this in the first place were some changes on cuff blood pressures, and I'm not aware of seeing those kinds of changes with other products. Maybe others can speak to this also. So those are some of the considerations.

I saw the company had on one of their slides saying that there's blood pressure effects with

other testosterone therapies. My sense is that that's postmarketing reports of hypertension in patients who have used that, and we've added that into labels or perhaps hypertension adverse event reporting, but I'm not aware of seeing this degree of blood pressure difference, even on cuff pressures, with other testosterone therapies. If the company has data that supports that, I recommend that they show that after lunch in the follow-up questions.

DR. DUNNMON: One thing I'd like to add to the comment Dr. Joffe made, when you look at 15012, you see a trend that you see across other things -- at least that I've looked at -- where clearly the ascertainment ability of the ABPM is superior to random blood pressures. There are a litany of methodological limitations to previous studies that have used random blood pressure or even tried to time them but didn't do the acquisition really carefully.

So I tend to give this study a lot of weight because this is a large ABPM study, and I've seen

looking across different studies in this arena that there's a large difference in what's being reported that may just be the variability of the ascertainment technique, the ascertainment ability of the techniques.

DR. JOFFE: And one more thing to clarify about that cardiovascular outcomes trial is the product being studied is a topical testosterone, so any data that comes from that, it's not clear how applicable it would be to this product. So if this product got approved, one question then is, well, would it need a postmarketing trial like that? But then the question is, can you do such a trial when you've already seen these kind of changes preapproval? And I'm going to leave that for the committee to discuss during their deliberations.

DR. LEWIS: Thank you. We will now break for lunch. We're going to shorten the lunch break because we do have a lot to discuss, and we also need to have the open public hearing to allow people to speak. Let me remind panel members not to discuss the meeting topic during lunch amongst

yourselves or with any member of the audience. We will reconvene at 1 pm, please. Thank you. Oh, and please remember to take your personal belongings with you.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

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

(1:12 p.m.)

Open Public Hearing

DR. LEWIS: Welcome back.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known, its direct competitors.

For example, the financial information may include sponsor's payment of your travel, lodging, or other expenses in connection with your attendance here. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address the

issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insight and comments can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Could we please have speaker number 1 come up to the podium and introduce themselves? Please state your name and the organization you are representing for the record.

MR. DALLAGRANA: Hi. My name is Jason DallaGrana. I have hotel and travel here to come speak with you today. I'm not representing any

organization, just myself. I was diagnosed with Klinefelter's syndrome in July, so I've got about five months under my belt. I'm starting to take testosterone treatment as of July, so that's about five treatments of injections. I'm deathly afraid of needles, but yet I have to do this the rest of my life, so it's difficult.

I've attempted other products. The gel I cannot use. My skin does not -- it's allergic to its carriers. So it would basically be nice to have another option out there, and from what I understand, there really isn't. Basically, that's all I really have to say, and thank you for your time.

DR. LEWIS: Thank you. Could we please hear from speaker number 2?

(No response.)

DR. LEWIS: Could we hear from speaker number 3, please?

MR. SCHWARZ: Good afternoon. My name is Stefan Schwarz. I have no financial disclosures to share, and I have Klinefelter's syndrome.

Klinefelter's syndrome is the genetic condition that occurs in 1 and 500 males. There is no cure for the condition, and testosterone therapy is our best and most effective option. Testosterone therapy is a necessity for those living with Klinefelter's syndrome because it replaces what we are unable to produce naturally. It greatly assists those who are born with this condition to live with its effects.

I was diagnosed with Klinefelter's syndrome in 1996 at the age of 26. Shortly after my diagnosis, I developed and published a website to assist with support and education for those with the condition. The website still exists today and can be found at klinefelterssyndrome, all one word, .org.

I immediately began on testosterone therapy after my diagnosis occurred initially using a patch called Androderm, which was not a viable option for me. I then switched to testosterone injections, which I administered myself. I have been self-injecting testosterone by intramuscular

injection every 11 days for the past 22 years. That works out to around 700 injections over that period of time. This number of injections has built up extensive scar tissue.

Jatenzo offers patients who have Klinefelter's syndrome or just low testosterone another choice for replenishing the testosterone we are unable to make naturally. It has been many years since there was a viable testosterone method that could be taken orally. Striant, which was FDA approved in 2003, was one such method of placing a tablet under the tongue or in the cheek, and it dissolved over a period of hours. Though still available today, it is not widely used as many men do not like this treatment.

There used to be an oral testosterone replacement choice, but it came with many consequences, including the ability to work with standard dosages. The dosage was required to be large and therefore caused liver toxicity with many patients. At least in the United States there was no longer an option to use an oral testosterone

replacement method.

As I mentioned earlier, I've been injecting every 11 days. It took time to determine the exact frequency for which I should receive my injection. Those who have this condition are unique with a unique set of symptoms and to different degrees. We are square pegs for round holes and sometimes need to adjust the frequency for our injections.

Those of us who have been on testosterone therapy for many years know what we need to combat the symptoms of low testosterone. This is our hormone replacement therapy. We are not taking this therapy to bulk up or for any other reason other than the necessity to have a normalized testosterone level.

My current form of testosterone therapy, testosterone cypionate, significantly improves my quality of life, helps to increase my low libido levels, greatly improves fatigue, increases focus and concentration, and helps to keep my bone density at a normal level. I'm a different person, much better able to handle my life since my

diagnosis and since starting on testosterone therapy back in 1996.

The only negative about my current form of testosterone therapy are the peaks and valleys one has to deal with during the injection cycle. In the beginning, just after the injection, you experience a high, almost a euphoric feeling. During the 11-day cycle, the testosterone in your body decreases, and around the 11th day, I feel the need and my testosterone level has decreased, and sometimes lower than the normal range.

Jatenzo however would be a daily oral medication and would eliminate the peaks and valleys and keep my testosterone level at an even keel throughout. Some forms of testosterone therapy also have risks of passing the testosterone to women and children, but Jatenzo being an oral method eliminates that issue.

There have been many choices that have come on the market over the past 10 to 15 years. Those of us with low testosterone need choices, and this gives us another viable option. There might be a

few risks or side effects, but those risks occur with any method of testosterone therapy. The positives far outweigh the negatives, and frankly we need testosterone replacement therapy. It is our lifeline since we are unable to produce it naturally.

I hope you will give serious consideration to approving Jatenzo for use by those needing testosterone replacement here in the United States. Thank you so much for your time and for allowing me to present my views on this extremely important subject.

DR. LEWIS: Thank you. Could we please hear from speaker 4?

MS. COVER: My name is Virginia Cover. I'm an AXYS board member. AXYS is a nonprofit advocacy information organization that represents individuals who have extra X and Y chromosomes. The largest group of our constituents are those with Klinefelter's syndrome. Clarus paid my airfare and hotel to attend and speaker here, otherwise I have no relationship with them.

I'm the mother of a 30-year-old man who was diagnosed prenatally with Klinefelter's syndrome. Klinefelter's syndrome, which is the presence of one or more extra X chromosomes in a male is characterized by testicular failure and hypogonadism. The majority of older teens and adults will need lifelong supplemental testosterone. But for two-thirds of the males with Klinefelter's syndrome, the genetic condition goes beyond being only an endocrine disorder. It can result in learning disabilities and in social skills deficits. Between 10 and 25 percent of males with Klinefelter's also meet the criteria for high functioning autism, and many more will score high in the domains tested for autism even though they don't meet the full criteria.

I'm also a social worker. I hold an MSW from the University of Michigan. My practice focus became children and young adults with developmental disabilities when it became apparent to me that our son was going to be one of the children with 47 XXY who was affected by both learning and developmental

disabilities.

At Stony Brook University, where I spent the majority of my career, I saw a number of children and young adults with Klinefelter's syndrome who also had developmental and learning disabilities. A number of them had sensory processing disorders that went with the developmental disabilities. And for those who were beyond the age of puberty and had been prescribed supplemental testosterone, nearly all of them seemed to have difficulty complying with the treatment. Once my own son was prescribed testosterone, it became apparent why it was so difficult.

Testosterone is not optional for many with 47 XXY. Teens may not progress normally through puberty without supplemental testosterone. By the late teens, testosterone is necessary to allow them to build muscle and achieve adequate bone density as well as prevent early osteopenia and osteoporosis.

Adequate levels of testosterone are necessary to prevent fatigue and mood disorders.

This is particularly true for a man with autism spectrum disorders who are also prone to depression. But the means of delivering testosterone has included injections, patches, gels, implanted pellets, and some uncommon methods like buccal lozenges.

They all have disadvantages. Injections are unpleasant and cause roller coaster levels of testosterone that many say result in mood swings. Implanted pellets function better, but they can result in considerable pain and bruising every three months when they're inserted. Gels are goopy and smelly. Men with the sensory issues of autism generally dislike the slimy feel.

Patches have similar tactile unpleasantments [ph]. Few of the men that I saw were able to comply reliably with their testosterone treatment. Most told me that if only testosterone were available as a capsule or a pill they could take it easily every day.

When our son was 13, we began trying various methods of testosterone administration. We went

through gels, patches, and pellets. At one point, he developed an abscess after pellet insertion and refused to continue using that method. He eventually developed skin irritation from any gel or patch that he tried that was commercially available.

Finally, his endocrinologist has prescribed a compounded testosterone cream that's been satisfactory. We live on Long Island, and there in fact are several very good reliable compounding pharmacies that are available to us, but his insurance does not cover it of course, so I pay for it out of pocket.

An oral testosterone product is absolutely essential for the population of men with Klinefelter's syndrome. They need to use testosterone throughout their lives and should not have to struggle along with only the current methods of administration that are available.

I know that this hearing has focused largely on physical risks, but I can say that in the Klinefelter community, there is a very strong

ability of families and the individuals who are affected to consider the cost and the benefits of any particular administration and make an educated decision along with their healthcare provider. So I think that it should be an option that is available to this particular group because they use it throughout their lives. Thank you.

DR. LEWIS: Thank you. Could we hear from speaker 5, please?

MR. GLISSMAN: Good afternoon. My name is Gary Glissman. Our family lives in Omaha, Nebraska. I'm the father of a 33-year-old son with Klinefelter's syndrome who is dependent on daily testosterone replacement therapy. I'm also the chairperson for the board of directors of AXYS, the national association for X and Y chromosome variations. I'm a registered nurse with more than 40 years of experience in health care, and I'm currently the chief operating officer for the Urological Cancer Center in Omaha, Nebraska. I have no financial relationship with Clarus other than their minor support to attend this meeting.

My purpose today is to explain how critically important testosterone therapy is for individuals with Klinefelter's and that many individuals struggle with maintaining adequate blood levels of this hormone when having to rely on injections or daily gel application. An acceptable oral medication option is not currently approved for use, and an oral option could make a significant difference in the quality of life for thousands of people that have issues with testosterone depletion, including my son.

It is important I think for you to understand that Klinefelter's syndrome is a very common genetic condition estimated at 1 out of 500 male births, which means that there are more than 500,000 individuals in the United States or the equivalent of more than half the population of Washington, D.C. There are more than 6 million individuals worldwide.

Almost all of these Klinefelter individuals are unable to naturally produce sufficient amounts of testosterone. They are dependent on external

supplements similar to diabetics that require external insulin. While it may not be immediately life threatening for Klinefelter males to not maintain adequate testosterone levels, insufficiency does have a very negative impact on their mental and physical well being, and in some cases it can be considered life threatening on a long-term basis.

Besides the risk for developing serious physical illnesses, my son would truly have died years ago from either suicide or some other extreme consequences of mental health difficulties related to insufficient testosterone, and I can't emphasize that enough. For 20 years, we've been trying to deal with this child, and it's been extremely challenging trying to get him on a maintenance testosterone system.

Many individuals today do not start or stay on testosterone therapy because of the issues with the current forms of replacement therapy, even though they know they should use it to maintain their health. Testosterone has to be kept at

effective blood levels, and currently the only way to achieve that is through the other options you heard talked about earlier.

Time-release injections require months and months of trial and error to determine the right amount. Injections can be painful and produce a roller coaster effect as you've heard that many individual simply do not tolerate well. All of these problems just cause some people to give up.

It is impossible to know the exact percentage of Klinefelter individuals that have these difficulties with current therapies, but it could be as high as 40 percent or more. Certainly it means that thousands and thousands of men are putting their health at risk and living in emotional distress simply because of difficulties with taking this drug.

Almost all of these individuals would potentially benefit from having an oral testosterone option. We are asked about this option repeatedly by individuals and families that are involved with Klinefelter treatment, and we

have to constantly explain that an acceptable oral alternative is simply not available in the U.S. Technology has changed that, and a testosterone pill is now possible. Although the pill you've heard discussed today requires monitoring and may not solve all the problems with treatment compliance, it provides significant improvement over the kind of gyrations patients and physicians currently have to endure.

Speaking from our own family's experience and as a representative for the hundreds of thousands of Klinefelter men in the United States, I respectfully urge the committee to approve the oral testosterone medication being proposed today. This approval could mean the difference between a chance of living a long, positive, successful life or a shorter, more challenging and painful existence. Thank you for your time.

DR. LEWIS: Thank you. Speaker 6, please?

MS. KELLY: My name is Sheryl Kelly, and I live in Ohio. I will receive travel and expense reimbursement for this meeting. I do not represent

any organization, although I do provide voluntary assistance to AXYS.

My oldest son William, now 31, was diagnosed at age 23 with 47 XXY Klinefelter's syndrome by Air Force doctors when he tried to join the Reserves. Despite our seeking help for Will's childhood developmental difficulties and taking him to numerous doctors from a young age, no one ever suggested a simple blood test for genetic abnormality.

Will's diagnosis started an odyssey of education and searching for the best medical care. While not a doctor, I'm a lawyer, and I have pretty good research skills, and I also have with me copies of peer-reviewed medical articles that support my statements.

As you know, this condition is not inherited, and it results when a male is born with an extra X or Y chromosome occurring as a result of a random error in disjunction of sperm or a division. It is not curable. There are variations of the condition involving multiple copies of the X

and Y chromosome.

You can tell this has taken a toll on us. A 47 X male produces insufficient testosterone throughout his life. Ultimately, almost all organ systems are associated with an increase risk of morbidity and mortality. Despite the fact that 47 XXY and its variants affect an estimated 1 in 500 males, a frequency. Similar to Down's syndrome, it is extraordinarily underdiagnosed primarily because, unlike Down's, there is substantial variation of clinical presentation.

Men with XY variations have serious and complex comorbidities with an average 11 and a half years shorter life span than normal males. They are at substantially increased risk for breast cancer, type 2 diabetes, and we know sufficient testosterone reduces insulin resistance, other immune system related disorders such as lupus, ataxia, gynecomastia, certain germ cell tumors, osteoporosis, and a range of learning autism spectrum and other neuropsychological impairments.

Testosterone is critical to neurocognitive

development and function with recent imaging studies confirming structural brain differences in XY individuals. It is important to remember that there currently are no clinically accepted treatment protocols for this genetic condition beyond administration of testosterone. Effective testosterone treatment of all consensus is frustratingly lacking in the medical community as to what is effective -- does have a positive effect on decreasing certain comorbidities and improving quality of life.

An overwhelming issue with the XY population -- and this is recognized by the FDA in its description of shortcomings with current forms of approved treatment -- is consistent compliance with dosing regimens decreasing or eliminating effectiveness. Topical forms such as AndroGel and Arimidex require the person to stay dry and not have physical contact with any other person, especially women or females, for 4 to 6 hours after application because of the serious health risks that are posed to such persons that come into

contact with the testosterone.

Many, including my son, have serious adverse skin reactions to the gels, creams, and patches with blistering and abscesses. Injections are frequent and painful and do not provide consistent levels. A form of quarterly injection is available, Aveed, but per FDA approval requires the doctor to complete certification. Doctors, including my son's endocrinologist at the Cleveland Clinic, refuse to administer Aveed. No doctor we have spoken with, including my son's, recommend the pellets.

It is important to remember that what doctors consider a normal testosterone level in a normal male is generally lower than what an XY male needs. For XY males, testosterone therapy is not a matter of sexual function. It is a matter of ameliorating serious health problems and achieving a meaningful quality of life to a person. Each XY individual I know wants to be a productive, self-sufficient, contributing member of society, but many have tremendous difficulty due to the

associated health issues.

My son has been unable to find an effective form of treatment. Consequently, he has been off the testosterone for almost a year and is unable to work or have a really meaningful life. He has osteoporosis and extreme fatigue. We have no famous poster boy that puts an acceptable face on this condition to increase general societal acceptance and to generate research money, although some in the scientific community have postulated that George Washington, the father of our country, was 47 XXY.

We know any medication has its drawbacks. I would note -- and for the cardiologists that are on the panel -- we do have and use a blood pressure monitor at our home thanks to my husband's high blood pressure, and my son's blood pressure is consistently low.

I ask that you do not penalize these individuals because of possible misuse or because of potential shortcomings in the medical community with its administration of Jatenzo that you have

expressed today. Jatenzo will, I truly believe, increase adherence to treatment and importantly provide consistent levels, mitigating the numerous associated health risks. It will mean a world of difference to the lives of these individuals that words cannot sufficiently convey.

Thank you, Dr. Dudley, for meeting with us at AXYS, and the other medical professionals, at our conference last summer. And to the FDA, I thank you for the opportunity to address you today in support of the application by Clarus for approval of Jatenzo.

DR. LEWIS: Thank you. Could we hear from the next speaker, please?

MR. BREGANTE: Hello. My name is Ryan Bregante. I'm from San Diego, California. Clarus paid for my travel. I don't support anybody else, just myself. I'm from San Diego. I was born with something called Klinefelter's syndrome, also known as 47 XXY. Unlike most men in this room, my body does not make testosterone.

Ever since I started puberty at the age of

13, I have been using injection testosterone. Now that I'm older, I wouldn't want the next generations of kids with low testosterone to go through this cumbersome process. What 13-year-old enjoys shots weekly, let alone adults? So every 7 days in order for me to live a more normal life, I stab myself with a big needle that causes physical pain, scar tissue, and a roller coaster of emotions.

I've tried many forms of testosterone, including the gels and patches. I live a super active and adventurous life where these processes become messy and are a burden. As technology moves forward, so does innovation. But I feel that the forms of testosterone we have available today are like experiencing dial-up internet and AOL.com all over again.

America can be the forefront of leading this innovation, and the rest of the world will follow. In the generations to come, this step forward will allow people to push the boundaries further just like we are doing here today. I look at this new

concept like diabetics who got upgraded to the insulin pump. It became life-changing for type 1's all over the world to just live a more normal life.

In closing, I truly believe that this idea not only will change my life but hundreds of thousands, if not millions, all over the world. Thank you.

DR. LEWIS: Thank you. Could we hear from speaker 7? 8? Sorry.

MR. LANE: Hi. My name is Randy Lane. I'm from Seattle, Washington, and I was part of the trial, and they supplied me the travel time out here. I was a healthy individual growing up and everything, very sports-minded, did a lot of sports, skiing and everything. But in 2011, I got diagnosed as having low T, and I started the testosterone injections. That doctor put me on one injection a month. It started off, "Hey, this is great," and very quickly started to taper off, and I got more and more tired and wasn't doing much for me. As I moved, it became more difficult to get the drugs and get the injections and everything,

and I ended up stopping and said, "I'm really not feeling it."

I found another men's clinic to go to for the testosterone treatments, and they were one that liked to really push everything to the highest level; so yeah, okay, now I feel like a race horse. But it took over my mood swings, became very dramatic, easily angered and stuff like that, and it affected my work and how things were going. It also created a lot of acne and stuff, and it became very painful. My skin, my torso was just covered with it, and I was very miserable.

As time went on, the injection sites started getting more and more bruised, more pain every time I was doing the injection, and it became much more difficult to give those injections. I also work as a consultant and stuff and travel a lot, so 20, 30-plus round trips a year, many weeks at a time, makes it very difficult to take that drug with you, have the needles and everything to go on those travels. It became very difficult to supply that.

I sought out another doctor because I didn't

feel what was going on was right. He asked to re-equalize and get a new baseline and try to figure out what else was going on. We tapered the drug down for a while trying to get control of the acne and stuff, and then finally ceased the injections for a number of months. That effect was like turning me into a zombie. My numbers had plummeted. I was absolutely exhausted all the time, getting up, doing anything, being motivated for work, a real struggle, absolutely fatigued and very unresponsive to things.

So that affected my work again in a very negative way. They called and said how about this drug trial, and I went into that, an oral form. All the blood draws, all the other activities happened that needed to happen, watch all the blood pressure, that was all a piece of cake in comparison to what I had gone through with the injections and what had happened up to this point.

Very balanced, very even. My temperament is great. There are no problems with that. I don't have big swings in the testosterone. I feel

energized and active, and everybody noticed around me. Work became much easier to go and do. It was very easy to travel with it. And it was just so much better of a world with that drug available. When the trial ended, I had to find other stuff again. I'm back to being pretty fatigued, and it takes a lot more work and stuff to get up every day and go forward.

The availability of this drug in an oral form rather than feeling like a pin cushion -- if you think about it, I'm only 49. How many more years of getting stabbed if I go back to the injection and how much do I have to deal with on the acne and other things that affect if this doesn't become available? So I encourage you to consider putting this out there and having all the protocols. Those of us that need it will go through it to get it. Thank you.

DR. LEWIS: Thank you. Speaker 9, please?

MR. MAFFEI: Hello, everyone. My name is Kelsey Maffei. I'm from Silverton, Oregon. Clarus has covered the expenses for airfare and lodging

for me to be here today. I'm a 37-year-old adult male living with Klinefelter's syndrome. I was diagnosed at the age of 27. I didn't start testosterone replacement until about two years ago.

I'm not here today to endorse Clarus Therapeutics or the products that they offer. Rather, I am here today to endorse an idea, the idea that an effective testosterone replacement in the form of a pill would be a welcomed alternative for many who rely upon testosterone replacement therapy to lead a productive life.

I'm here today to discuss TRT, how it affects my life, and the reasons why a pill alternative would impact my life. Through sharing my story, I hope to shed some light on the challenges faced by people with Klinefelter's syndrome in an effort to positively influence a perception of an alternative therapy that would make it easier for me to participate in the world in which I live. While the effects of Klinefelter's range across a wide spectrum, which has been highlighted already, the main effects that

I experience are infertility and low testosterone. The former cannot be treated, but the latter has successfully been mitigated through TRT.

Like I said, I began TRT in February of 2016 as a result of the cumulative negative effects associated with low testosterone. Some of the effects are depression, lack of energy, low libido, weight gain, low confidence, and difficult making decisions in a timely fashion. After several blood tests that confirmed a low level of testosterone, which is less than 100, my doctor prescribed me to start TRT with weekly intramuscular injections in my thighs. February 19th of 2016, I had a nurse at the hospital instruct me on how to do that process, and to this day that's the process that I replicate every 7 days at home.

I like many people am not fond of needles, but in an effort to avoid the detrimental effects I experience with low testosterone, the outcome justifies the means. For me, the means includes the weekly anxiety and sometimes cumbersome nature of the process.

Depending on where I am on the day that I inject, which is typically on Saturdays, whether that's at home, traveling for work or pleasure, or just out camping in the woods with my family, there are lots of factors that I have to take into account to ensure that I am successful in following that process. First and foremost, I need to make sure that I have a sterile environment to inject the medicine and that that environment is comfortable. If I'm in an environment where I'm tense, it results in my thighs basically being tense or locked up, and it results in pain for sometimes the next couple of days where that injection site was at intramuscularly.

I need to make sure I have enough medicine in the vial to maintain the consistent weekly dose. If I need to get that from the pharmacy prior to, I need to make sure I have enough money to obtain that. I also need to make sure I have enough supplies, so I need to have alcohol swabs; syringes; two different needles, one for the draw and one for the injection; and then also a place to

properly dispose of that. I've got two children. My daughter's 5 and my son is 8, both through artificial insemination donor sperm. But I need to make sure that they have a safe environment in which they can be around that stuff so that I can maintain the proper levels to be productive for them.

While there are currently several alternatives to weekly injections such as gels and other things mentioned today, there's not currently an approved TRT alternative with the ease of the pill form. Such an alternative would remove many of the barriers and hurdles that I experience on a weekly basis with TRT.

In my opinion, the TRT industry is predicated on the assumption that aging men are attempting to gain back the glory days they once had, the days in which they had a lot of energy and they had increased libido; they had more muscle mass and can do things that maybe they can't do when they're older. In my case, TRT is not a means to simply supplement my life or to boost energy

levels to that I experienced when I was younger. Instead, TRT for me is a means to ensure that I'm able to fully participate in life as a contributing member of society, as a positive role model for my children, and as a competent man in pursuit of my goals.

It is for the reasons I mentioned today that I endorse the idea of an effective TRT replacement in the form of a pill. When determining if a pill form of testosterone is a viable option, please consider people like myself who live with Klinefelter's and who rely upon TRT to maintain a comfortable and productive life. Thank you.

DR. LEWIS: Thank you. Speaker 10, please?

MR. DAVIS: Good afternoon. My name is David Davis. I am from Dallas, Texas. I live with 47 XXY as well, also known as Klinefelter's syndrome. It's interesting that no one else in my family has the condition and none of their children have this condition as well. I was diagnosed at age 18. When I saw my endocrinologist for the first time, he was a little bit scary, but he gave

me the hope of a better future than I had already with T therapy.

I recall having hand tremors as a child, increased heart beat when I got really nervous, and depression, but that was before my T therapy. I began taking testosterone injections at age 18 to improve my quality of life. These injections are very painful for me. As it turned out, I was allergic to the old [ph] compound that is included in the testosterone.

It seemed that the medical provider should never decided what level of testosterone I needed. I had ups and downs all the time, increased/decreased, regardless of what levels of testosterone they gave me. After several years of injection therapy, I moved to a variety of patches. Again, I was allergic to the adhesive. As the T levels increased, I did start having side effects of severe acne. It was really horrible. However, the benefits far outweighed the acne I was having as painful as it was.

Later in life through insurance changes, I

had the opportunity to try therapies, patches, gels, and compounded medications, some of which insurance covered; some didn't. While some of these therapies may cause adverse side effects, others were tolerable, but in most cases, I had a very difficult time maintaining my testosterone levels.

I'm now 54 years of age, and my therapy is testosterone gel from a pump apparatus applied to my thighs every morning. It's a messy gel. It takes about 5 minutes to dry. I monitor my overall health. My internist works with other professionals. Basically they report back to him, and he takes care of all of my needs. We do blood pressure and blood testing every 4 months on a regular basis. If I have other medical needs, he draws blood at other times as well.

During interim times, I keep in touch with my internist via the website. I'm really big on the internet. Other conditions that have been diagnosed is I have aged, but it seems more familial versus testosterone involved. I do have

diabetes type 2. I have diverticulitis, slightly elevated blood pressure, depression, and anxiety, however, checking with my family, that's very familial. So I don't think it's directly related to testosterone therapy because my family has the same problems.

All of these medications are currently controlled very well right now by other prescriptions. I adhere to my prescribed medications very closely as they're easy to take. My adherence to taking T therapy, however, on the other hand, depends on how busy I am in the morning. If I'm really late to work or busy, I don't put the T therapy on because it takes 5 minutes to dry at least or get it all over my clothes, so it's worthless. When I don't take my T therapy, I feel more body aches, I have a lot more depression, and increased anxiety. I actually develop kidney stones, and I have reduced concentration and memory as well.

I ask that you consider a new form of testosterone therapy for persons like me who have

never had the ability to build testosterone on their own. My feeling is every action we do in life requires a risk. As you've heard, it is typical for me to devote time and attention to my health and my therapy. A pill form for this therapy would be easy for me to remember to take every morning as I take my other pills or prescriptions and vitamins.

I believe that adherence would significantly increase over the populous, thus improving the overall health of people with my condition. Again, no messy gels, no prolonged drying times, painful shots, or allergies to the medications. Most importantly, the pill is highly unlikely that the testosterone can be transmitted to someone else like the medication I take today. Professionally, I'm sure that the pharmacy benefit managers and pharmacists will find this a positive because they would not have to handle the product. This improves safety for their employees, handling risks, and time.

I would like to leave you with this thought.

The easier the prescription is for me to take, the more likely I am to adhere to what is prescribed. There's always a risk, but the benefits could improve my quality of life. Thank you.

DR. LEWIS: Thank you. Speaker 11, please?

(No response.)

DR. LEWIS: Is speaker 11 here? No. Okay. Oh, I'm sorry. Speaker 11 is here.

DR. SHAPIRO: I'm here.

DR. LEWIS: Apologies.

DR. SHAPIRO: No problem.

Thank you for the opportunity to speak today. I'm Dr. Daniel Shapiro. I'm a physician and a senior fellow at the National Center for Health Research. Our center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policymakers, and those are the perspectives that I bring with me today. We do not accept funding from industry, and therefore I have no conflicts of interest.

Prescriptions for testosterone replacement

have been on the rise. In 2013, it was estimated that over 2 million men in the U.S. were on a testosterone drug commonly receiving this from their primary care visit. As men age, we know that testosterone levels decline, and doctors figure what's the harm? And as you know, for many of those men, the risks have far outweighed the benefits.

That is not the indication that we are here to discuss today, and for men who have hypogonadism, replacing testosterone, as we've heard, could provide a chance of living a normal life. However, this first of a kind testosterone drug could also be misused, which could harm millions. Jatenzo met its narrowly defined efficacy endpoints, however, the trial did not demonstrate efficacy of relevant patient-related outcomes, and the results do raise concern of potential harm. We have the following concerns.

Number one, the measures of drug efficacy were based solely on pharmacokinetics such that the intended drug did replace the missing or deficient

testosterone, and while this is important, it is not a patient-centered outcome. Outcomes of interest to patients could include physiologic parameters such as muscle strength, bone density, psychological parameters, behavior and mood, and global parameters like overall health and well-being. Other measures may include activities of daily living, social impairment, emotional distress, self-satisfaction, and resilience, which we've heard from the patients themselves.

These types of dimensions are the patient-centered outcomes, and although some of them did improve on the drug, there were no significant differences between that drug and the active comparator. Therefore, the important issue is how well this drug compares to the other treatments and how the risks stack up.

Number two, we have concerns about the cardiovascular safety of Jatenzo. They seem to be more significant than the others in the class. The data indicate that blood pressure parameters exceed clinically dangerous thresholds. In addition,

hypertensive patients had even more significant climbs in their blood pressure. Furthermore, these trends suggest that over time, blood pressure measurements may continue to rise without any apparent plateau.

It must be noted that these subjects have been grouped according to outdated clinical guidelines. We note that the new guidelines define stage 1 hypertension as systolic 130 to 139 and stage 2 140 and up. With these lower thresholds in mind, these trends in the data are more clinically significant and concerning.

Although the sponsor contends these effects were not correlated to the drug or the testosterone level, there is a clear cardiovascular safety signal that we cannot ignore. These safety concerns may be further compounded in the population that is likely to misuse this drug off label.

Number three, we have concerns about the adrenal effects of the drug. We agree with the endocrinology consultant that the data are

insufficient at this time. We urge the FDA to require the sponsor to assess the effects on adrenal function in a well-powered study with standard methodology. Adrenal insufficiency can have life-altering and life-threatening consequences. Therefore, before the drug is approved, we need to establish safe use.

Last, we need additional information on drug-drug interactions. The sponsor did promise separate analysis of subjects taking lipid-lowering drugs like statin-fibrates, niacin, Omega 3-oils, et cetera, however, those analyses were not provided. Given this drug's pharmacology, the lipid-lowering drugs could affect its efficacy. Such information would be useful for patients and prescribers and should be included on the label.

In conclusion, testosterone replacement therapy can help patients with hypogonadism to live a normal life. A new oral drug might be beneficial, but this drug does raise concerns of potential harm. On a chemical level, the drug works, but we don't know whether it meaningfully

helps patients in the long run, at least not from a data perspective, though thank you for the perspective of all the patients and families today. Long-term studies with patient-centered outcomes may provide us more certainty.

In addition, the data do not provide reasonable assurance that the drug is safe. We need additional data on drug interaction data as well as safety data before this drug is approved. Furthermore, if we consider potential misuse as part of the risk-benefit evaluation, then the potential for harm may surely exceed the drug's benefits. Therefore, at this time, we cannot recommend approval.

Thank you so much for the opportunity to share our perspective, and thank you to all the speakers today.

Clarifying Questions to the Industry or FDA

DR. LEWIS: Thank you. Thank you to all of our speakers.

The open public hearing portion of this meeting has now concluded, and we will no longer

take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We have a few minutes for additional clarifying questions. Let me stress that these should be questions because we do have quite a few discussion items to go through, and I know that many people have discussion items to be addressed. So let's start with Dr. Howards, and then Ms. Sorscher.

DR. HOWARDS: Stuart Howards. I had a question, which I'll get to in a minute, that relates precisely to the last question asked before lunch. And that is that, clearly, the two Lancet slides are very concerning. My question, not knowing anything about the cardiovascular literature for the FDA, are there other studies that don't agree? Because, as we all know, there are often studies that say something's dangerous and another study that says it's not dangerous. So I have no comprehension of the other literature

on this topic, and I'd like a brief summary of where it is. Thank you.

DR. DUNNMON: The number of small trials that look at blood pressure effects of drugs are legion. They're generally fairly small, but what makes the Lancet data so powerful is that was a meta-analysis of 61 trials of patients who did not have vascular disease at baseline, who then were followed with 12.7 million person-years of follow-up. The number of events that were provided by that analysis were in my experience unparalleled.

Dr. Lincoff, I love your comment on this, but to have a study where you had 12,000 strokes from death, 34,000 from MI, and 10,000 from other vascular causes I think is unparalleled. And so the power of this data comes from the fact that it is not one study; it is 61 well designed trials that got combined into very large numbers looking at a very hard endpoint, death. And that's what came out of it. So I think that that one's probably the most powerful literature baseline we have to work with.

DR. HOWARDS: Thank you. That's very helpful.

DR. LEWIS: Ms. Sorscher?

MS. SORSCHER: I have two questions. One was I just wanted to confirm with Dr. Yu. The normal reference range that's being used as a target for these studies, that's based on testing done with the serum samples with the 30 minutes at room temperature. Is that right?

DR. YU: Yes, that is my understanding of the general practice.

MS. SORSCHER: Then I don't know who at FDA can answer this, but for the first phase 3 trial, the one that did not have robust findings, what was the titration scheme in that trial?

DR. JOFFE: This is Hylton Joffe. It's probably best for the applicant to address that. Basically, the very first trial, patients were overtreated and testosterone concentrations were too high, which led to a change in the titration regimen, which is the second trial, which then we felt efficacy was more marginal and not robust in

accounting for missing data. But if you have any specific questions about the earlier trials, I'll recommend --

MS. SORSCHER: And just to clarify, by first trial, I mean the trial that was considered at the initial advisory committee meeting.

DR. DUDLEY: Sorry. Could you repeat that?

MS. SORSCHER: FDA mentioned in its presentation that the regulatory history of this drug was that it was considered at an initial advisory committee meeting and that there was some issue with the sensitivity -- I'm sorry, with the robustness of the results of that trial. The efficacy wasn't shown when they eliminated certain factors. I was just curious about what was the titration scheme in that trial and how it may have impacted the efficacy results.

DR. DUDLEY: Certainly. Slide 1 up, please. These show the different titration patterns across the studies. The real message here is that we've learned, as we've gone along, to better and better titrate with tighter and tighter boundaries. The

study in question that was asked related to the middle study, 12011. There the starting dose was substantially higher than in 15012. That was the reason for our start-low approach, if you will, the recommendation by the earlier committee.

Then the sampling time was 3 to 5 hours, which was predetermined and validated in that study, but the titration range you see was a little bit wider, 250 to 700. So we've now narrowed that range to 350 to 800, and the efficacy has improved from 75.0, which fell below that on sensitivity analyses, to now 87.3. And all of the sensitivity analyses to 90 percent are down to about 85 percent.

MS. SORSCHER: And there was just one uptitration in that trial?

DR. DUDLEY: No. All of the trials that were designed from the very beginning have 2-dose titration categories. That kind of mirrors clinical practice over the years that I've been working on these.

MS. SORSCHER: But the request now is for

just one titration in the label?

DR. DUDLEY: No, ma'am. Still the opportunity is for 2-dose titrations. I would turn to the clinicians. It could be more than that if they needed to. We just studied two to demonstrate that in two cycles, and in this case 87.3 percent of the men were moved into the normal range.

DR. LEWIS: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. Braunstein. To the sponsor, I'd like you to discuss the titration scheme insofar as it appears that many of your patients were overtreated on the basis of the titration scheme. For instance, if you look at LH levels, the LH levels in the TU group, at baseline, about 0.7 percent were below the limits of detection, but by the end of the study, 41 percent were below the limits of detection. Similarly, for FSH at baseline, none of the patients were below the limits of detection, but at the end of the study, 32 percent were below the limits of detection. So that suggests that you're overtreating a substantial number of patients.

Also, since the patients with primary hypogonadism and patients with secondary hypogonadism are two different populations in many respects, I'd like to see the data broken out by primary hypogonadism specifically.

DR. DUDLEY: Dr. Danoff, would you like to respond to that, please?

DR. DANOFF: We have not broken out the LH levels based on primary hypogonadism. What we could work on -- well, there's not much time left, but we could try to do that analysis for you. Given the shortness of time, I'll do my best to get you an analysis looking at the LH levels and numbers below the limits in the primary and secondary hypogonadism populations. The endpoint we were titrating to obviously was the testosterone Cavg, which is the target that the FDA asked us to work towards.

DR. BRAUNSTEIN: Yes, I understand the Cavg, but the problem is that the Cavg that you achieved for many patients appeared to be over what their hypothalamic pituitary gonadal axis required. So

we know that testosterone levels, the range is really quite wide in the normal population. Some patients will be perfectly normal towards the lower end of normal, and some patients require a higher level of testosterone and have the same LH-FSH levels in responsiveness of the tissues.

So the fact that about a third of your patients had undetectable levels of LH and FSH really suggests that many of the patients were overtreated by your titration scheme.

DR. LEWIS: Thank you. Dr. Nahum?

DR. NAHUM: Thank you. Gerry Nahum. I have two questions, and they're actually quite basic. We've spoken a lot today about the different methodologies for the analysis of testosterone levels, but one thing -- and if it was here, I missed it. We haven't really discussed the bound versus free testosterone. And it used to be in the good old days, we talked a lot about free testosterone, but I haven't heard any discussion about that or SHBG binding and what fraction is bound and what should be normal in terms of free

levels versus total levels, for instance. So I'd like to know what the current thinking about that is and whether that should be considered.

The second question that I have is specifically about those potential subjects who would have low testosterone levels but not have Klinefelter's syndrome and what the effect on sperm counts, motility, morphology would be, and overall fertility in those people treated with this compound, and whether there's any data that's been collected about that specifically.

DR. LEWIS: The sponsor?

DR. DUDLEY: Would you like us to take a stab at that?

DR. LEWIS: Go ahead.

DR. DUDLEY: I'm going to go in reverse order. Relative to the effects of testosterone on spermatogenesis, we have Dr. Amory here who is a pretty big name in male contraception, so he'll be able to answer that.

DR. AMORY: So the effect of exogenous testosterone on spermatogenesis has been well known

and well studied. In fact, many of us have been working to try and develop a male contraceptive on that basis. If you look at men who are just given injections of testosterone for periods of time, 67 percent of them will develop azoospermia. Sperm analysis was not part of this study, but I would anticipate that the number would be similar to that.

DR. DUDLEY: Dr. Danoff, SHBG and free T.

DR. DANOFF: We did measure SHBG in this trial and calculated free T. The SHBG was lower in the Jatenzo group than the Axiron group, which is -- let me show you slide -- that's not the SHBG. Let me just show you the calculated free T, which we calculated from the SHBG. This is slide 1.

This is calculated free T levels calculated based on albumin levels, SHBG and total T. What you can see is that our free T levels were somewhat higher than the free T levels in the Axiron group but well within the middle of the normal range. But to remind you, the Cavgs are the same in the two groups. The difference represents a little bit

lower SHBG in the Jatenzo-treated patients.

DR. LEWIS: Dr. Wilson, and then Dr. Edwards.

DR. WILSON: Thank you. As part of practicing, we screen patients, at least ask questions, and sometimes more extensive testing for obstructive sleep apnea for patients who may have received testosterone. And the question is whether the sponsor or FDA has any additional information related to this and other products for patients with obstructive sleep apnea?

I guess specifically my question is related to this because of the high testosterone at night because of the BID dosing, whether you've done any ancillary studies. Patients perhaps with obstructive sleep apnea may have worsening of symptoms in the middle of the night.

DR. DANOFF: In this trial, we excluded men who had significant sleep apnea or uncontrolled sleep apnea, so we don't really have the data to address this, but this warning appears on all the testosterone replacement product in the standard

labeling.

DR. DUDLEY: Just one comment. The peak is quite transient. It peaks about 3 to 5 hours, and then it drops pretty precipitously. So for most people, by the time they're sleep, it's relatively low.

DR. WILSON: So as a follow up, you used something like the Pittsburgh questionnaire to exclude users? Is that you did?

DR. DUDLEY: No. I don't believe that we used that questionnaire. No, that's not right.

DR. WILSON: You just asked the patient whether they had OSHA or not, yes/no type of question?

DR. DANOFF: It was one of the exclusion criteria that the investigators asked about. But I should mention that during the trial, there were no adverse events or serious adverse events related to sleep apnea, and I don't believe any adverse events related to it.

DR. WILSON: You can see where I'm going a little bit. I think with the safety studies that

are planned in the future, it would be helpful to know more than just whether it's in the medical record, a physician asking yes/no, a little more because this is a concern for those of us writing this prescription for patients. A simple asking the patient yes/no may not be enough.

DR. DUDLEY: Absolutely.

DR. DANOFF: Very well taken.

DR. LEWIS: Thank you. A couple more questions, and I'll remind the panel, please, we will have time for comments later. Dr. Edwards?

DR. EDWARDS: Yes. I had a comment on the Lancet article. I'm looking at it on line, and it's just the abstract, so I can't look at the whole article right now. It was done in Canada, so the majority, 90 percent plus of these patients are Caucasian. They have no ethnic minorities. Ten thousand men were treated with testosterone, 20,000 controls, and what they found over five years of follow-up was a higher mortality in the group that was in the lowest tertile of testosterone. The group that was in the higher

tertile of testosterone had a lowered mortality with a hazard ratio of 06.67. So what we're not observing there is a dose-response effect, if this is really related to a drug in terms of mortality. We're seeing the inverse.

So that's one comment on that paper. But then I went to the testosterone trial because that's a prospective study and it's randomized, and unfortunately in the JAMA 2017, they are finding that with specialized coronary imaging, those on testosterone have more build-up of coronary plaques.

DR. LEWIS: Thank you. I think we've pretty much done all -- Dr. Drake, and then we'll be taking a break.

DR. DRAKE: Matthew Drake. I had a question related to the ACTH stimulation test specifically. It looks like at baseline that no subjects in either the Jatenzo group or the Axiron group basically failed to stimulate with the ACTH stimulation. My question was, has the company broken this out to individual data points to see

if, in general, there's a trend? Because we know that the Axiron group only had 8 subjects. It looks like it would find before [indiscernible], find afterwards.

The question is whether there are several patients that were stimulated before treatment with Jatenzo, moved down into the perhaps insufficient range. Is there a general baseline to endpoint with a trendline that we could basically see individual points over the course of this 4-month study or so?

DR. DANOFF: Do we have the trendline for the maximum at baseline? What I can show you -- the trendline analysis I have, I can up slide -- first what I'd like to do is remind you that it is known that testosterone suppresses cortisol production, and this was published -- slide 3, that you just took down. Can you put slide 3 up for me?

This is a publication that came out a couple years ago, in 2005, where they did not an ACTH test but a CRH skin test in normal men made hypogonadal

through treatment of leuprolide, some of them replaced with testosterone. And what you can see is that the men who were given testosterone, which is represented in the triangles, which is the lower line, they have less production. So it's recognized that testosterone has some effect on the adrenal gland.

We've looked at baseline as well as -- we did stimulation tests at baseline, and I don't have a spaghetti plot, but I have some summarized data. If you can put up slide 3, which summarizes the numbers without the spaghetti plot, if you just turn your attention to the mean, the maximum cortisol levels at this one in visit 8, which is the second block down, not the pre-injections, in the Jatenzo group, it goes from 23.3 to 21.6 versus 25.2 to 23.5. So the amount of reduction of the maximum production is similar, not statistically different. And I'm sorry I don't have the spaghetti plot.

DR. LEWIS: Thank you. Dr. Shaw?

DR. SHAW: Thank you. I had a question for

Dr. White. This is going back to the morning, and it was a follow-up. Dr. Lincoff asked my question, but I think I still need further clarification. This relates to slide 67 and slide 69. This is about the differences in the presented data for the clinic blood pressure and then the ABPM blood pressure.

You had I think some explanations in the sense that there are different patients in the clinic blood pressures, that it was more complete and only about 80 percent were in the ABPM study. What I wanted to point out, just to jog everyone's memory, is that for all treated patients, the difference in blood pressure at visit 7 was about 2 or a little less for Jatenzo in the clinic blood pressure, but it was 5 or a little bit over 5 when you looked at the ABPM. But then in the graph on slide 69, the differences between the two types of measurements seems worse for those who have hypertension in that the graph you see here is not even quite 4 points for those with treated hypertension. And then we had earlier data

presented where the difference was 7.

So it's a difference in words, so maybe I'm not comparing the same people here. It was 7 for those with a history of hypertension, the difference. That's quite a lot, and the upper end of the interval was almost 12, which can't be fully explained by the fact that it was a smaller group of patients I think.

So my basic question to you is, we'd love any more insights you have in terms of how these differences arise, if they seem more extreme, if you compared it patient by patient with both measurements, and is this concerning in terms of monitoring hypertension in the clinic? So basically, a little help or insight that you may have in interpreting this data and what it means for monitoring patients for hypertension in the clinic.

DR. WHITE: I will try to answer this concisely. The population who had ambulatory monitoring -- show slide 2, please -- had a little bit higher blood pressure difference in the clinic

compared to all patients. It was about 3 and a half millimeters of mercury up and it was about 5 millimeters for ambulatory because the 20 percent of patients who did not have an ambulatory monitor had a lesser effect. So that's number one, so they're not that different as you might think.

Secondly is that in practice, to this day, physicians use clinical measurements to make management decisions in hypertension. The epidemiologic studies that you saw and the clinical trialist collaboration study you saw were all clinical measurements. So in comparing ambulatory to clinic, that's a little different let's say because we don't have any outcome study for ambulatory blood pressure the way we do for clinic, and I've been doing research on ambulatory monitoring for 35 solid years. It's just one of those things that isn't out there yet.

That said, we use it in clinical research because it's a very good way of looking at the pharmacodynamic effects of any kind of drug that's potentially vasoactive, and it does get rid of some

of the observer bias and gets more information. But you've got to be sort of careful about these subgroup analyses, those on blood pressure meds, those not on blood pressure meds.

For example, in the Axiron group, which is on slide 600 -- can we put up BU-600? I just want to show this for a minute. Slide up for slide 1. Now that looks pretty funny, I'm sure, to everybody, that in Axiron, people who had treated hypertension went up 4 millimeters of mercury. People who did not have hypertension didn't change. It's the exact opposite effect of what happened in the Jatenzo treatment arm, but the baseline blood pressures in people with treated hypertension was several millimeters lower than people who didn't have hypertension.

So part of this is progression to the mean, and it's the case for both of those treatment groups when you start subdividing. You don't have the same baseline blood pressures any more. So for the people who went up, their blood pressures were lower at baseline, and for the people who went

down, their blood pressures were higher at baseline.

Some of this is confounded by baseline blood pressure measures in saying it cannot be controlled for. You have miniscule sample sizes in the no-treatment hypertension group and treated hypertension group in this particular period. You've got 20 people. That is not enough to be definitive for this subgroup who did or did not have hypertension.

So I do want to caution about that throughout this program, that when you take the data in its totality, I think it's probably pretty robust. When you start splitting it up by subgroups, those who had this, those who had that, you lose a lot of power.

DR. LEWIS: Thank you. I think Dr. Rej might have one last question.

DR. REJ: This is Robert Rej. I have a question about the drug itself and it would be three related components. I may have missed it, but what are the typical circulating concentrations

of TU? The second part is what's known about the bonding of the drug to sex hormone binding globulin? And the third part is what are the relative molecular ratios of TU to T in treated patients?

DR. DUDLEY: I think I might have Dr. Dalton come forward from the University of Michigan, one of the world experts on androgen receptor binding who can answer those questions. As he's coming up, we did not measure TU and DHTU in this study. We did measure TU and DHTU in a subfraction of men in the 09007 trial.

Do we have 09007 DHTU levels? I'm sorry. We do. I'll have Dr. Dalton present that.

DR. DALTON: Hi. I'm Jim Dalton. I'm a professor of pharmaceutical sciences, dean of the College of Pharmacy at the University of Michigan. Could I have slide 1 quickly? This is the data from the 09007 study, and you'll notice in the right two most columns -- we'll look at the second column from the right, which is mole or AUC, which gives you a feel for the exposure to a T, DHT, TU,

and DHTU as you go from the top to the bottom of that slide. And these are corrected for changes in the binding affinity, for example, of those different analytes to the androgen receptor as well.

You can see the TU and DHTU only supply about 1 to 2 percent of the overall pharmacologic activity of the primary analyte testosterone and DHT. Although the circulating exposure to TU and DHTU is very much higher, they contribute very little to the pharmacologic effect.

DR. LEWIS: Thank you.

DR. DUDLEY: Did you have a follow-up? I'm sorry.

DR. REJ: Yes. My concern is going to be related to the question from the FDA, number 3, regarding the measurement procedures. I still didn't see the actual concentrations of TU unless I missed it.

DR. DUDLEY: No. We'll get those. That slide came up, and then it went away, like quickly. We'll need the 09007 TU and DHTU. Slide 1 up,

please. These are the TU and DHTU levels observed in a subpopulation of about 26 men in 09007, the TU concentration on the right and the DHTU concentration on the left. The concentrations are high. These are roughly -- peak TU is about 22,000 nanograms per deciliter, and peak DHTU is about half that. They are degraded very rapidly.

That reminds me of the other part of your question that I quickly forgot. Because these compounds don't have an affinity for the androgen receptor, they won't have an affinity for SHBG either because that's basically the same circulated androgen receptor.

DR. LEWIS: Thank you.

Dr. Yu, I think you have one last point of information for us about the blood pressure. No? Is it something else?

DR. YU: Yes, it's something else. It is actually a follow-up question regarding the same aspect, but I think it's a trend of a three-part question that I have.

The first question that I do have is a

clarification question for the sponsor. We noted that there was a relatively low endogenous testosterone concentration in the first study, namely the in vitro spiking that you've actually tested out. Can you clarify? The mean was 26 nanogram per deciliter, which seems really low to us.

DR. DUDLEY: Yes.

DR. DANOFF: The study was done at a single site where they had a number of men that had -- I think it was Klinefelter's. It was Dr. Swerdloff's site, where we did the 15013 study. And these were a number of men who had known very low levels, which was what we were aiming for to help us understand the study. Those low numbers are actually correct.

DR. YU: So those are from hypogonadal men.

DR. DUDLEY: Yes.

DR. YU: Okay. The second part of my question is regarding all this discussion throughout the presentations today, you've heard that different methods from different labs from

different sample collection and preparation procedures were used. And we're also trying to see if we can hash out the potential cause of this. But in light of trying to address this question, I'm aware that, for example, from your phase 3 study, for especially visit 7, I know there's a difference of opinion in terms of what assay and what labs were good or bad.

I am aware that you do have plasma in sodium fluoride EDTA tubes versus serum in plain tubes collected and analyzed at different laboratories from the same subjects. Have you ever did any correlation analysis for that to address if there's any factor or correction factor we can come up with to address the question? Have you done any correlation analysis with those sets of data?

DR. DANOFF: We haven't done a formal correlation analysis, although while we were trying to figure out the problem we were having with the initial lab, which caused the switch, when we got the first lab running their assay again properly, we got the same results.

I would like to disabuse the idea that it might be an cross-lab issue because -- if we can bring up the LaChance paper. The LaChance paper, what the division showed and what we showed was the PK curves from our visit 7 from the red top serum as well as the sodium fluoride EDTA tube -- if you can bring up slide 1, this is the data from the LaChance paper, where they ran the same -- they ran this study in their clinic. The clinic is near their lab. They ran both the serum and the sodium fluoride EDTA plasma.

What you can see at the peak is there's a large difference, the exact same finding that we showed. We didn't do this very careful cross-correlation that you're suggesting because our data exactly mimicked the LaChance data. And just to remind you, our plasma assay was run in the LaChance lab. So that's why we don't think it's a cross-lab issue because when the same lab -- and I should tell you the LaChance paper also it's an oral TU that is not our oral TU. It's in development by a different company.

DR. YU: Thank you for the clarification. That is well understood, however, I think correlation analysis might further help addressing this issue.

My last question -- because I think where this is heading towards is how do we utilize this drug if this is to move forward and get approved. So my question to you is given that you have used a special method using plasma in sodium fluoride EDTA tubes for dose titration in your phase 3 and seeing this difference, what are your thoughts or positions and rationale if we are to hypothetically use the plain serum in plain tubes using the dose-titration algorithm that was used in your phase 3 moving forward?

What are your thoughts and rationale on that question?

DR. DUDLEY: We'll show you that information in a minute, but I wanted to make sure that I alerted people to the fact that we're already working with laboratories about using the sodium fluoride EDTA. So by the time this drug were to be

approved, if the division so chooses, there will be some assays available, LC-MS and probably a couple platforms also. So that work's underway, and now in answer to your question.

DR. DANOFF: So we have looked at what would happen if an error or by choice a red top tube was used for dose titration. And what we find, not from necessarily the data but from the nature of the change, is that it won't cause men to go to an unsafe high level. If anything, it will drive down the dose-titration levels.

What I've done is I have a little cartoon here that I can show you of the idea of what would happen. If you could bring up slide 1. So the eugonadal range is shown, that we work on, is shown on the right, 252 to 907. Our titration boundaries that we're using, 350 to 800, sit within that titration range.

Let's look at scenario A. If the concentration is drawn in a sodium fluoride EDTA tube, in this scenario, we have a value just within the titration range. A person would not be

titrated because they're within the range. The red top tube, the serum, would give a higher value, as was just depicted, and it would indicate a down titration.

So for people who are near the top of the range, it will tend to down-titrate them. Of course, because the dose increments are relatively small, it will probably keep them still within the eugonadal range, but it's not driving them to the higher dose.

Let's look in the middle of the range. It doesn't make any difference. At the low end of the range, scenario C, if somebody's true value is below the titration range, as measured in sodium fluoride EDTA, the red top might put them within the eugonadal range, which would suggest no-dose titration.

In that scenario C, instead of being titrated up, which would be beneficial to them, there is no titration done.

So in the scenarios where you get discordant results, it pushes your titration down. At the

high level, it keeps you probably within the eugonadal range. At the lower end, it might not bring you into the benefit, but in no situation does it cause an unsafe situation.

DR. YU: So in other words, am I hearing from the applicant that you believe that using plasma and serum from plain tube would not make a big difference regarding dose-titration outcomes?

DR. DANOFF: We did our trial -- obviously, with the plasma in sodium fluoride EDTA tubes, we are aiming for accuracy. I think that if the wrong tubes are used, it won't cause an unsafe condition. So that would be my view. We are advocating what we put our proposed label, is that sodium fluoride EDTA tubes be used.

DR. YU: Thank you.

DR. LEWIS: Thank you. We'll now take a 10-minute break. I'll ask everyone to come back promptly and remember not to speak to each other during the break about the matters at hand.

(Whereupon, at 2:37 p.m., a recess was taken.)

Questions to the Committee and Discussion

DR. LEWIS: Thank you, everyone. I'll ask people to please take their seats so that we can move to the discussion and voting questions. We will now proceed with the questions to the committee and panel. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will move on now to the questions. We have four. Three of the questions are for just discussion. The fourth is a vote. The first question at hand has four parts, and we'll take each one individually. The first question is whether the safety of Jatenzo has been adequately characterized.

If additional safety data are needed, discuss the types of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval; specifically -- we'll start with

part A -- the effects of Jatenzo on cardiovascular risk factors, including blood pressure and lipids, together with the effects on hematocrit, and the potential for Jatenzo to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug if it is approved.

So this is the time to give our comments, and I will be calling on people in turn. Dr. Lincoff?

DR. LINCOFF: I think it's important to put together the prognostic information with these blood pressure changes. The off-quoted Lancet study from 2005 with the one point some million patient-years came to the bottom-line, boiled-down conclusion, that a 2-millimeter systolic blood pressure change would be -- in this case a reduction because these were antihypertensive trials -- expected to produce a 7 percent reduction in ischemic heart disease mortality -- so I'm not talking about a grouped composite endpoint -- and a 10 percent reduction stroke mortality. That's 2 millimeters.

Now, it's true that that's an office blood pressure, so it is a reasonable question to say is a more sensitive technique such as ABPM going to detect changes that are less relevant prognostically. And I take issue with the assertion that that's never been tested. There have been some studies. The largest that I know of, and there may be others, was a Danish study published in Hypertension 2005, with 1700 patients who did not have known vascular disease followed for about 10 years, who over that 10 years about 10 percent died, so 170 some deaths.

The blood pressure changes by ambulatory blood pressure were more predictive than the office-based measurements. And every 10-millimeter change was associated with a risk ratio of 1.5. So it's log linear, so what a 5-millimeter change that we're seeing here might have predicted you could try to extrapolate. But it was log linear throughout the range. There was no too low and no small change.

So there is prognostic information.

Obviously, this is a much more difficult technique to do than just measuring a blood pressure, so there will not be millions of patients with ABPM and clinical outcome, but there are data to show that ABPM does have prognostic significance. It's not just an over-sensitive means of measuring blood pressure.

Now having been said then, this is a very large -- this is to me at least a startling high blood pressure difference for a pharmacologic reaction. Sibutramine, which was removed as a weight-loss drug, had a 1- to 3-millimeter increase in systolic blood pressure and the observation of increased cardiovascular outcome. Causation of course can't be proven.

Torcetrapib, which was a CTP inhibitor, which was tested in a large-scale trial, was associated with a 1.5 risk ratio increase in mortality. The trial was stopped early. The change in blood pressure was 4.6 millimeters. And grant it, that was office space; that wasn't ABPM. But the point is that these are ranges of blood

pressures that are important, and it's not enough to just say, well, that this is all just the people who -- it's driven only by the people who had large changes.

All of these measurements, when you take a mean change and you look at what the potential is, it's the same. There are always some people who are going to have large changes and some people who are going to have small changes. And I'm not convinced that in practice, even careful practice, even practice with good physicians, that small changes in blood pressure that may be predictive over a long term of outcome are going to be effectively managed by antihypertensive therapy.

Now, this is only going to be applied to patients, the 350,000 I estimated from what we heard, who had Klinefelter's or true absence of testosterone. Those are relatively lower-risk patients. They're younger. I think that would be a risk-benefit that nobody would really argue with. But if the, quote, of "2 million" prescriptions, individual people is true, then that's 82 percent

of people who are not in that group, and many of those are patients who are exactly in the group that we're worried about cardiovascular risk. So I think that this, to me, is the overriding issue.

The other issue is with pulse. Pulse is a weak correlate, and I don't think it's an established surrogate. HDL we've got trial after trial now that it failed to show that HDL is even predictive at all. These changes in LDL are very small and it is measurable and treatable. I think at least from my view as a cardiologist, the issue here that we need to focus on for cardiovascular safety is blood pressure effects.

DR. LEWIS: Thank you. Dr. Wilson?

DR. WILSON: I've even looked up this morning exactly the number that came out of the torcetrapib, and it's 5. That was the other big one out there in terms of a signal for adverse blood pressure effects for an agent that we didn't know that until the medication was used, so I share the same concern.

A 5-millimeter difference for systolic blood

pressure in the clinic is something most clinicians -- and I agree with Dr. White. We address this on a daily basis, and we can treat it. But on a population basis, this is a very large effect and of great concern, I think especially to put in frames, so to speak, Dr. Lincoff's comments, for those who are at moderate to higher cardiovascular risk; so younger individuals, those without much cardiovascular risk. And it's hard to pick.

You could use a risk equation or you could take for instance -- age under 40, for instance, is very little in the way of heart attack or stroke before age 40, borderline for our diabetic patients. It's not so much of an issue. For instance, I thought it was especially enlightening to hear the story from several patients and families with Klinefelter's. Those people, from puberty to age 40, they are not at high cardiovascular risk, so it may be a very different concern.

Secondarily, the lipids, as soon as a boy

goes through puberty and testosterone effects take purchase, HDL cholesterol goes down. So that is entirely expected, and it's a natural phenomenon for somebody who is low on testosterone who gets replaced. Secondarily, our older patients who are obese and often have low HDL, it's a slightly different issue if their HDL goes even further lower.

So I'm not so concerned about the HDL effects, but I really do come back to the blood pressure effects, especially for those at risk for cardiovascular events.

DR. LEWIS: Thank you. Dr. Adler?

DR. ADLER: Robert Adler. I wanted to just mention the hemoglobin and hematocrit effect. For those who have classic hypogonadism often have mild anemia, so the rise in hemoglobin and hematocrit is fine as long as the patients are monitored properly. So I don't see that as a major stumbling block.

But I agree with what has been said by Dr. Lincoff and Dr. Wilson, that the concern goes

beyond the patients with classic hypogonadism. And a lot of the patients that I see today who have various vague complaints and often have low testosterone levels are obese, diabetic, older men, and they are already at high cardiovascular risk. So anything that's going to raise that cardiovascular risk is likely to be multiplied in that setting.

So I think we're really talking about two different populations. Again, we've done this before, those who have organic hypogonadism and those who have the changes in testosterone that we see with aging but magnified by very often concomitant obesity and type 2 diabetes.

DR. LEWIS: Thank you. Dr. Gerhard?

DR. GERHARD: Toby Gerhard. I'm echoing my previous speakers here. I think there are really two completely different questions in front of us. So the first is the sponsor's product versus available topical or injectable testosterone treatments in patients that clearly need the treatment. So that's the on-label indication.

For this, where there was an active comparison of the new treatment to the available treatments, there are some concerns regarding the increases in blood pressure obviously with the uncertainty that comes when making extrapolations from surrogates. But obviously there is a significant benefit of the therapy overall and clearly a need for therapy, and also as demonstrated by the public comments, a need for an oral dosage form.

For some patients, an increase in cardiovascular risk may actually be an acceptable tradeoff in comparison to the benefits from an oral dosage form, particularly again for younger patients where the baseline risk is comparatively low. In addition to that, in this population, on label, well designed and conducted observational post-approval studies should be able to quantify these risks in various age and risk groups.

However, the second question -- and again, although the comment was made that FDA isn't in a business of regulating the practice of medicine, I

think that question cannot be ignored, and that's the oral testosterone versus not taking testosterone in patients with low T, so the off-label use. And there the comparator is non-use, so any potential harms are probably larger.

Really of importance is that the majority today, as far as we know, although the data isn't very good, of testosterone use in the U.S., maybe even a large majority, takes place in this group. And this is despite the difficulties with the administration of these products, injectable or topical as described in the public comments.

For this population, the benefit is not clearly established and the safety concerns are potentially dramatic. So there are a few observational studies clearly with limitations that have estimated increases, 1.5 to 2-fold increase in the cardiovascular event risk, even higher risks, relative risks in the older age group. And if those estimates were true and applied to a population of potentially millions of elderly men,

this would translate into thousands, probably tens of thousands of cardiovascular events and deaths.

So I think one question really is have you or would you consider going to FDA really aggressively limiting off-label use? Obviously, this is done for other products. Clozapine is regulated, Accutane. I've probably attended more than a dozen opioid advisory committee meetings here where none of the concerns relate to on-label use. They're all about abuse of these products.

So wouldn't you be able to think about creative ways to really limit aggressively the use of these drugs to the population where there was a clear need? Because I think before the use in this low T population is allowed to become routine, there has to be traditional phase 3 trials, not trials that are based on pharmacokinetic -- finding replacement levels for these replacement therapies. Now I'm done.

DR. JOFFE: This is Hylton Joffe. I'll take a stab at that. In general, FDA shies away from regulating off-label use. It's not something we

like to do. There are things, for example, like REMS with ETASU, which are elements to assure safe use, which are additional elements that can involve things like healthcare provider training that they have to certify that they take, and pharmacy training to make sure that a healthcare provider who's certified is the one who's writing the prescription.

So there are those kind of additional elements that could be done, but that then is a burden on the healthcare field, so you have to then weigh the cost and benefits and whether it makes sense to do that.

For example, Aveed is one of our other testosterone products. That actually has an ETASU REMS, and in that case, there are these pulmonary oil microembolism, so we really wanted healthcare providers to know that they need to observe patients in the clinic after getting the injection to make sure patients don't have these potentially life-threatening pulmonary complications.

So the question with something like that is

what is exactly the healthcare provider mitigating and is there a way to cut down on the risk? With POME, it involves watching patients in the clinic or however long they get watched before they get sent home. For something like this, what are we telling healthcare providers to do; to only prescribe it if you have classical or to do something with blood pressure? So you'd have to think through what are really mitigable if you were to go down that route.

Out of all the FDA drugs approved, I think there's probably how many ETASUs? I think around 20 or -- 30 maybe; in the 20's. So it's not something we commonly do, but we do do it when we feel we need to have something -- where we feel the drug is important for patients and we can have the benefits outweigh the risks when we implement that.

DR. GERHARD: I think in this situation, if there is an appreciable risk increase in elderly men taking this drug, then you're talking about this. This is an unusual situation, and certainly the absolute risks here are of a much greater

magnitude than the risks from, let's say, agranulocytosis in patients taking clozapine.

DR. LEWIS: Thank you. Dr. Lincoff, and then Dr. Nahum?

DR. LINCOFF: I would just expand on that. Again, there are groups, Klinefelter's and others, with primary gonadal failure, that the benefit clearly is unequivocal and the risks are relatively small. I mean, qsymia for example, because of the risk for birth defects, was through certified pharmacies. It was a burden, but the people who take care of these smaller populations of patients are, I believe at least, accustomed to dealing with maybe a bigger burden in terms of prescribing.

But I agree with Dr. Gerhard that if this is to be expanded to a population with just low T, then we need outcome trials. And the existing outcome trial that's going to be conducted is not this compound. So I think that it's important to have availability for a group of patients that really have a difficult problem with existing administration of the existing forms, but there

should be limits in terms of what can be applied, in the absence of outcome data, to other populations of patients.

DR. LEWIS: Thank you. Dr. Nahum?

DR. NAHUM: Thank you. I guess I have one big take-away here, is that it's clear that there is some increased population-based risks that we need to consider here that are cardiovascular in origin and also adrenal in origin, but both of those are really predicated on an idea that's bigger than treating any individual patient. And they depend on two things as far as I can see, which is the size of the population that's actually going to use the product, and that's including all off-label indications, as well as the duration of use.

So some of the things that we're considering here really would not even be I think items of discussions if this were a short-term therapy. But of course the idea here, I think, for the target population of use is that it's going to be a long-term, potentially lifelong therapy, where the

risks are going to become cumulative over time, and that this then becomes something that we need to consider on a population level.

So I guess the way I'm thinking about this really is there are specific small populations of people who have an unmet medical need who are at low risk for the downstream cardiovascular complications that could arise, or adrenal complications, idiopathic Addison's, et cetera. It might be a reasonable tradeoff in any particular patient's case, but at the wider population level, we start to think, well, gee, these kinds of cumulative risks are going to get larger and larger, and they're going to be having an adverse effect on patients who potentially shouldn't even be using it to start with.

I guess my way of looking at this is if you're looking at it at an individual patient level that there could be some very strong rationale for wanting to use a drug like this, but that at a population level, assuming that it's used off label for a myriad of purposes that it shouldn't be, that

it's an unreasonable risk.

So how to balance that and whether labeling can get to that, or whether a program -- and I'm not proposing anything like this, but there are programs that FDA has, for instance, like iPledge, for some kinds of drugs where it's very, very restrictive in terms of who can get it, for how long, what reason, what kind of tests they need to have before they get their next prescription, et cetera.

If perhaps we were willing to put that level of scrutiny behind the prescriptions and usage of the drug, then on any individual basis, it might be just fine. But this is my current thinking about it, and I just thought I'd throw it out there.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: Thank you. I think our role really should be to decide or discuss whether a drug is efficacious and safe. Clearly, there's a long history of using testosterone in patients with classic hypogonadism such as Klinefelter's syndrome, where the drug has been shown to be very

efficacious, so I don't think there's any question about that.

As far as safety is concerned, it appears to be also very safe in patients with classical hypogonadism. The real issue comes in the patients with age-related low testosterone, where the drug for testosterone is generally used off label.

I assume that many of the patients in this trial fell into that since there is a substantial number of patients who are overweight and obese. And it's in that group where there's increased cardiovascular risk factors independent of testosterone, and adding testosterone to that group, a testosterone product that may have additional cardiovascular risk signals such as this one, is where it may be dangerous.

I think we should say that it is safe for individuals -- or appears to be safe and efficacious for individuals who have primary hypogonadism, the classical type, but it should not be indicated for secondary -- not secondary, but age-related hypogonadism. I know we say that all

the time, but the FDA has that in their brochures, but to make it very clear that this is -- and until safety is shown from a cardiovascular standpoint, that it really should be restricted to patients with primary hypogonadism.

DR. LEWIS: Dr. Gass?

DR. GASS: I would just like to call to mind that there are some interesting parallels here with menopausal hormone therapy for women. And if you care to look at the label on estrogen therapy for women just for the simple purpose of hot flashes, you'll find a lot of serious side effects and a lot of precautions on when and where to use it.

So I think in looking at the bigger picture here, maybe there is something that can be done with the label to call attention to potential risks that have not been determined, even in the face of the fact that estrogen has demonstrated some risks and yet is still on the market, some similar risks.

DR. LEWIS: Dr. Dmochowski, we haven't heard from you. Are you still on the phone? Do you have anything to contribute to this question 1A?

DR. DMOCHOWSKI: I'm happy to. I think [inaudible - interference]. I agree with what has been said. Clearly, I'm a urologist, so I don't have the same level of expertise regarding the hypertension concerns. I think the concerns are significant. It does sound as if -- Dr. Braunstein's discussion, shared by Dr. Lincoff, related to dichotomization of this population in terms of risk is very valid, and perhaps that should dictate where we go with a REMS if that's what the FDA would like post hoc, if indeed the decision is made to approve this. I think there's a signal for hypertension here that is concerning for myself as a practicing urologist. Let me put it like that. I think that's all I've got to say.

DR. LEWIS: Thank you. Dr. Wilson, did you have another comment?

(Dr. Wilson gestures no.)

DR. JOFFE: Hylton Joffe. I'll ask one quick question. I heard something about maybe doing a trial in this broader population. Because

this question also asks about pre- or post-approval, do folks think it would be even ethical doing a cardiovascular outcomes trial in this broader population given what we're seeing based on the cardiovascular risk factors?

DR. LEWIS: Dr. Braunstein, and then Dr. Wilson?

DR. BRAUNSTEIN: I believe it is ethical to do it, especially because there's a concern about off-label use. We need to answer the question. We know from a number of different trials that unless you do a true, what should be a placebo-controlled trial -- but in this case, I'd accept a comparator-controlled trial, a comparator that doesn't have the same cardiovascular risk factors, specifically to see if this drug is worse than what's on the market. But I'd rather see a long-term placebo-controlled trial looking at cardiovascular risks over time. We know that, for instance, the WHI trial is an example of a trial that was carried out in a large population, and although I think the initial data analysis was

somewhat flawed, it finally got sorted out.

Similarly, there are a number of examples of therapies that were accepted as being absolutely efficacious, that when really tested turned out not to be efficacious; for instance, the Vineberg procedure for cardiovascular disease as a classic example.

So I do think that a long-term trial is warranted in the population at greatest risk for cardiovascular disease, which is going to be the obese, diabetic, hypertensive population who may have a low testosterone on a couple tests.

DR. LEWIS: Thank you. Dr. Edwards, and then Dr. Wilson.

DR. EDWARDS: If we're concerned about the older adult population, we do have some results coming back on testosterone effect in older adults over the age of 65. We know that testosterone does not improve memory. We know that it does accelerate plaque buildup. And with these effects on hypertension, cardiovascular becomes a big issue.

Testosterone is recommended in older adults for frailty, which is sarcopenia and malnutrition, a combination of those two, and frailty's associated with mortality. The beneficial effects of testosterone therapy do increase lean muscle mass. So there is an increase that occurs in these patients in prospective studies, but the effect does not last. If you discontinue testosterone, within 6 months you've lost all the benefit. And of course in older adults, we have to think about prostatic hypertrophy and urinary symptoms.

So we have to keep thinking about the benefits that it may bring but with some of the risks attached to it. And we do expect cardiovascular issues in about 50 percent of our seniors, if not a little bit higher than that.

DR. JOFFE: But just to clarify my question, if you do a cardiovascular outcomes trial, you're going to have to enrich it with patients at higher cardiovascular risk to ensure you have enough events. You're seeing these changes on blood pressure, for example, how do we feel about doing

an outcome trial with those results?

DR. LEWIS: Dr. Lincoff?

DR. LINCOFF: Yes, I think that's the key issue because these kind of trials are safety trials, so unless you're offering a benefit, it's hard to say; I want to randomize you to something that might make you worse. So the null hypothesis is that -- but I think the purported benefit is that this is a therapy that's easier to take, and in that regard would expose more people to the potential benefits of the testosterone therapy.

So I think if it's positioned in a real-world format -- now I'm not saying not randomized because I believe randomization is the only way to do this, but in a real world in that you're not trying to artificially enforce study drug compliance, but you're allowing patients to either receive the standard of administration approaches, topical, whatever, versus this oral.

So you're making the advantages available in terms of potential compliance versus a larger scale assessment of what the cardiovascular risks might

be in terms of excess events. I think from that standpoint it may be beneficial because what you're offering people is the potential of benefit from the standpoint of improved efficacy because of improved ability to comply.

Now whether or not testosterone does anything I think has been the topic of the T trials. It is the topic of another cardiovascular outcome trial looking at safety for topical formulation. And I don't think you necessarily have to answer that. I think the issue is compared to the other available forms.

Other studies will assess the issue of whether or not testosterone should be used at all in this population. But I think that until and unless we reach a point where we no longer think testosterone should be used in this population, it is reasonable to look at different forms of administration and to say you have benefits, you may have risks, let's assess that relative balance.

So I do think you could randomize patients, at least at the current state of equipoise. That

may change over time, but that's often the case.

DR. LEWIS: Dr. Wilson?

DR. WILSON: To build on that, there's potentially another trial that could be targeted towards patients with Klinefelter's as they enter the age at which their risk for cardiovascular disease goes up. For instance, let's say this medication was made available to Klinefelter's patients, and they could be randomized at a clinic basis, not at a provider basis, to usual care versus a multiple risk factor intervention type of care with very much going after blood pressure control, lipid control, and other risk factors, to see if it really makes a difference and to see whether that risk factor control is achievable, which would provide this medication to all patients with Klinefelter's potentially, but then would actually address especially the cardiovascular risk because they're going to be potentially at very high risk after years, and they're entering their 50's, 60's, and 70's.

DR. LEWIS: Dr. Drake?

DR. DRAKE: So we've heard strong support for dichotomizing the group that's been studied here into those, for instance, with primary gonadal failure, Klinefelter's, versus those who've had age associated or obesity associated hypogonadism. I would just caution this group to be a little bit careful because to my understanding and my review of what we've seen so far, I've not seen that data broken out carefully.

So while it may be that that Klinefelter's is absolutely the right or primary gonadal failure, or hypogonadism, or whatever it is that causes primary gonadal dysfunction or failure, we really have to see that data delineated. As of right now, it seems lumped. So rather than saying that it is the right population, I would say it may be, but I think that has to be looked at much more explicitly.

DR. LEWIS: Dr. Gerhard?

DR. GERHARD: I would just caution to try to do this in a postmarketing setting whether randomized or not. I think from all that we have

seen in terms of utilization history, this will be, if available as an oral dosage form unregulated or just with safety warnings in the label, an extremely widely used drug, with or without aggressive marketing. And by the time you have the safety results from your trial, you'll just have very, very large numbers of people that might have already been affected.

So I think the risk in that population, given that we don't know whether there is a benefit in that population, is just something that I'd be very careful about.

DR. LEWIS: Dr. Bauer?

DR. BAUER: I just want to follow up on that because I'm really concerned about the diffusion of a medication like this and use by a generalist who feels like they're doing net benefit, but in fact aren't specialists in this area and therefore aren't really aware of the proper way to monitor or perhaps even the proper endpoints to be looking at.

In my own practice, when men come to me that have low testosterone, one of the easy things for

me to do when I explain to them maybe they'll have to give injections or use creams or patches, then it's a moot point. When they find out that I could write a prescription for them that they can take orally, I think those conversations become much, much more difficult. And I have great, great doubts, although well intended, that the sponsor's efforts to try to train physicians, particularly busy primary care physicians, that this is likely going to make a meaningful impact on the ability of getting this to the right patient population.

DR. ADLER: Can I follow up --

DR. LEWIS: Yes, Dr. Adler?

DR. ADLER: -- Robert Adler, follow up on what Dr. Bauer just said? And that is while I understand the problems of the patients with Klinefelter's syndrome and the like, and the difficulties in using any of the current preparations of testosterone, that doesn't seem to make a difference for the huge number of men, older men, who have this low T syndrome. They don't seem to find a barrier to injections, or testosterone

gels, or patches.

So I think your concern, Dr. Bauer, about the widespread use of this convenient form is very well taken. I don't think we have any data that doctors as a group are very teachable, and I therefore think that this would be a very widely used preparation, and it would be a great concern if there really is cardiovascular risk.

DR. BAUER: Can I just add they are not teachable in the absence of well done trials, hopefully randomized with clinical outcomes; then they are teachable. And I think the Women's Health Initiative was a good example of that, then the rates of estrogen use plummeted afterwards.

DR. LEWIS: With that, I'll summarize the first subquestion, effects of Jatenzo on cardiovascular risk factors, including blood pressure, lipids, hematocrit, and potential of the drug to increase the risk of adverse cardiovascular outcomes. The panel was very concerned overall that the group in which the drug is likely to be used will include a large number of people who are

at great risk for adverse cardiovascular outcomes and that the blood pressure changes are very concerning and a lot of concern among the panelists that this will result or can result in a huge great population risk for adverse cardiovascular outcomes that are very serious.

People in general also thought that there was likely to be a difference between the younger primary hypogonadal patients from whom we heard, especially during the open public hearing portion, may differ -- certainly in terms of risk profile, they differ -- and that the impact on their cardiovascular health may not be as great, however, we don't necessarily have those data either.

We talked a little bit about what kinds of data would we like to see, and there wasn't much concordance there except that people weren't really so persuaded that the FDA could do much in terms of postmarketing or labeling. Labeling is another potential option that could make a difference, but I think there wasn't real agreement among panelists about how effective that would be. However, people

were interested in hearing other means of restricting the ability to prescribe the drug greatly that the FDA could exert.

In terms of effects on the lipids, those were not as concerning to the panel members. The clinical significance was not as clear and there was not concern about the elevations in hematocrit overall.

Let's look at the second question, part B -- we have B, C, D -- how concerned are people about the supraphysiologic DHT, dihydrotestosterone, concentrations in some subjects. Any discussion there? Dr. Braunstein?

DR. BRAUNSTEIN: I'm not aware of any adverse issues concerning elevated DHT versus elevated testosterone. Certainly individuals who are getting transdermal testosterone will have high DHT levels. Many of them have above the upper limit of normal as we saw with the Axiron for instance, but the same is true of AndroGel and some of the other transdermal preparations. And in our current state of knowledge, that in and of itself

doesn't seem to have an adverse effect.

DR. LEWIS: Dr. Mager?

DR. MAGER: I just wanted to agree with the previous comments that the data don't appear to justify any safety signal from the increased DHT because it is in both populations. I guess, for me, the scientific question is not -- because again, the Cmax is transient, right? These things are changing. The question is not whether the Cmax itself is the issue, it's whether the pulsatile nature of the administration is an issue.

There are many examples where hormones given in a pulsatile manner versus a slow, sustained manner results in paradoxical outcomes. So it may not be the absolute concentration, but it may be this pulsatile hit of that concentration over time, so both pharmacological agents like nifedipine as well as other hormones, parathyroid hormone and others, where there's a big difference between pulsatile administration versus slow, sustained release. But I agree with the previous comments that we don't have data to really suggest that the

Cmax is necessarily an issue.

DR. LEWIS: I'm sorry. We're talking about the DHT concentration right now.

DR. MAGER: As was I.

DR. LEWIS: Oh, okay. I thought you were moving on to question C. Anybody else?

(No response.)

DR. LEWIS: So people weren't very impressed with the impact of the DHT concentration in some subjects, but that's a good segue -- thank you, Dr. Mager -- into question C.

Subjects with maximal testosterone concentrations, Cmax exceeding the prespecified targets, how well has the safety of Jatenzo been characterized? And if we think there are additional safety data that are needed, could we talk about what those are and whether they can be obtained pre or post? Dr. Lincoff?

DR. LINCOFF: I think from the experience of this trial, I don't think this is a major issue. First of all, this is measurable. And second, I think there's a reasonable argument that this was

contamination, 3 out of the 4 patients, so I wouldn't think that this would be an overwhelming issue. One would have to continue to follow the levels until one reached a safe level, but I think this is a measurable controllable issue.

DR. LEWIS: Dr. Howards?

DR. HOWARDS: I think just to be equitable to the sponsor, certainly with intramuscular T, you get all kinds of high levels in every patient. I think these occasional high levels are irrelevant, are not very critical compared with the already approved intramuscular route.

DR. LEWIS: Dr. Mager?

DR. MAGER: Just on that last part though, I think there was a paper -- and JAMA internal medicine I think has a lot of caveats, but it did suggest that the cardiovascular risk factors were higher with injectable forms of testosterone versus the topical forms. And there are a lot of issues probably with interpretation of that study, but again, it's an open question to me whether or not pulsatile versus sustained release is the way to

go. But just again, to clarify, I don't think that this particular part C is an issue.

DR. LEWIS: Anyone else?

(No response.)

DR. LEWIS: Overall, people did not think that the subjects' maximal Cmax testosterone concentrations exceeding the prespecified targets, that was not seen as a big safety concern.

Let's talk about adrenal related findings, including the ACTH stimulation results, how big of a safety concern is this, and if we need additional safety data, what kind and when. ACTH, Dr. Wilson?

DR. WILSON: My reading of this is we've only seen one or two-year data. I don't think there's anything beyond two years of exposure to medication. For chronic use, as an endocrinologist, I would like to see longer safety data for sure for this. I'm not sure what interval, but one year is just not long enough.

DR. LEWIS: One year or two years you said is not long enough?

DR. WILSON: I'd be curious what my other

colleague endocrinologist would say on this. I would say two years may not be long enough either. I would expect four or five years, then they'd get tested. If the medication gets approved and released, they will certainly be candidates for that testing.

DR. LEWIS: Dr. Braunstein?

DR. BRAUNSTEIN: In regards to the ACTH or the cortisol results from ACTH stimulation tests, I'm not terribly impressed that this is clinically significant. There's a lot of different criteria that are used for inappropriateness of this test such as finding an increase of 7 micrograms per deciliter over baseline, having a doubling over baseline, and having a level over 18, are the three classical criteria. But I think that Dr. Swerdloff explained that the CBG level was down in the one patient who had the very low level that went up from 1.8 to 11, and others had low CBG levels.

This is probably a class effect of testosterone slightly inhibiting adrenal cortisol production, but I don't think it's clinically

relevant. However, there is one caveat, and that is some patients with primary hypogonadism have it on the basis of polyglandular autoimmune deficiency syndrome, and therefore one has to be aware of that, although that usually occurs after the adrenal insufficiency shows up. But adrenal insufficiency in association with primary hypogonadism, type 1 diabetes, and other conditions can go together.

DR. LEWIS: Dr. Drake?

DR. DRAKE: I guess I'm a little bit unclear as to the adrenal findings at cortisol levels that we see. It's been a fairly small study. There were 8 patients in the Axiron group and 24 patients in the other group. And we've talked about the spaghetti plots, and I haven't really seen that data.

I think eventually if this medication were to go to approval, that certainly it should be followed much longer term, one year, two years, something like that. But I would also -- given the potential trend that we see for a decline in

cortisol levels in response to treatment with this medication, for at least a more definitive study, I would actually like it to be done in a way where it's based on levels measured first thing in the morning, not measured at 3:45 in the afternoon, sort of the way we normally do things clinically.

So I guess I would like that to be cleaned up a little bit, but in terms of a longer term follow-up, I would definitely like that to be done at one year, two years, at some point, at least in a small cohort of people were this to actually go, and that could be post-approval. But prior to approval, I would, again, like to make sure that -- and at the same time measuring CBG levels as well as the rest of it.

DR. LEWIS: Thank you. Dr. Dmochowski?

DR. DMOCHOWSKI: Actually, most of my comments [inaudible - interference]. I do think that the post-approval study looking at patients on chronic steroidal supplementation for whatever indication would probably be indicated just to make sure that we're not missing the signal.

DR. LEWIS: Thank you. Anybody else, adrenal?

(No response.)

DR. LEWIS: So with the adrenal findings, the ACTH stimulation test results, most of the panelists did not think that these findings were of great clinical significance, although everyone has commented on the need to have longer term follow-up data, especially as this will be a medicine that will be used chronically and because primary hypogonadism can be associated with people with other kinds of endocrine dysfunction, which may arise over time.

In terms of obtaining further data, this should be done under more standardized acceptable clinical conditions along with measurements of CBG and ACTH. Most of what I heard sounded like people thought this could be done post-approval.

Let's move on to question 2, also a discussion question. Discuss whether the titration regimen proposed for marketing will appropriately identify patients who require titration or

discontinuation of Jatenzo. Dr. Mager?

DR. MAGER: I don't think that the titration algorithm as proposed was particularly well supported, and I think the analysis by the FDA was actually a bit better and that a 6 hour may be better. I'm a bit saddened that here in 2018, this is sort of where we're left with therapeutic drug monitoring, is measuring a single concentration without the use of any sort of modeling and simulation to support it.

I think there's a wealth of data that's available now, and maybe this is going to be done now; I don't know, but you could do population modeling to really help guide that. And it doesn't have to be that sophisticated. You could put these types of models through an app on your phone. These measurements could be placed in, and we have much better techniques to make projections for dose on an individual patient level.

If you do the population analysis first and then take a single feedback measurement or more, you get better and better. We know that Bayesian

feedback adaptation is a really useful way of tailoring dose and to address these. Is it really necessary with the wide window here that we have? Maybe not.

So I have to resort to the language of the FDA and say, yes, that the 6-hour time point is probably reasonable. Is it the best we can do? Absolutely not. I think there are better ways of doing things, but a 6-hour time point certainly showed superiority over the 4-hour time point, which, again, to me was not particularly well supported.

I think that's, again, easily addressed. You could move this out to the 6-hour time point or open up the window to include that region as was suggested here, but the 3- to 5-hour window I felt was not particularly well supported.

DR. LEWIS: Thank you. Anyone else? Dr. Shaw?

DR. SHAW: Hi. Yes, I just wanted to echo that sentiment. I was also impressed by the differences between the 3 to 5 and the 4 to 6. And

I wondered also if this decision relies on which tube you're going to use because the 3-hour time point seemed to be the maximum difference between the plasma and the serum tubes, and that when you got to 6 hours, it seemed that that disappeared. So that could be a consideration I think, and going back as far as 3 hours did not seem well supported to me either.

DR. LEWIS: Dr. Adler?

DR. ADLER: Robert Adler. If we know that the current state of monitoring patients on testosterone is not very good, can we really expect that physicians will order a 6-hour level and that patients will show up at the exact right time and have their blood tested at the 6-hour level? I'm pessimistic about that.

DR. LEWIS: Ms. Sorscher?

MS. SORSCHER: I was just struck by the number of different approaches that were taken to titration with this drug and by the fact that it didn't always yield consistent efficacy results. I would like to see, before the drug is approved,

that it would have instructions for dosing and titration that would reflect the way it's going to be used in clinical practice and that have been shown to be effective, and we don't seem to be quite there yet with the evidence we have.

DR. LEWIS: Dr. Lincoff?

DR. LINCOFF: I think part of the issue here is parity with the other testosterone compounds. I don't think the monitoring of dosing and the dose adjustments are necessarily optimal for any of them. I think they're all subject to the variable of a single-drawn sample, but pragmatically that's how stuff's done in the real world. And although there may be more sophisticated methods that would lend themselves to algorithms on hand-helds, I think for the near future, we're left with trying to find a time point where you can draw it, and if properly done, to have a reasonable prediction.

I thought it was actually pretty elegant that they managed to -- with the help of the FDA using these numeric responders and the treatment responders, however it was, but together. And I

agree with extending to the 4 to 6 hour rather than 3 to 5 but that they were able to find a single time point that predicted a very close relationship to what you would predict on the C using the entire integrated over the 24 hours.

Given those considerations, I think this is as good an approach as any other for this type of therapy, and I think this is reasonable. There may be more refinements in the future, but I think they did a good job. With some adjustments, I would go for the 4- to 6-hour window of finding a reasonable algorithm for dose adjustments.

DR. LEWIS: Thank you. Dr. Braunstein, then Dr. Wilson.

DR. BRAUNSTEIN: I hadn't raised my hand on this. It's really for the next one that I want to talk about.

DR. LEWIS: Dr. Wilson?

DR. WILSON: I think this was mentioned this morning, but the data I believe are already in their database for albumin and sex hormone binding globulin, and either obesity or body mass index,

especially the last, might help with refining the dosing. Some of the patients I've prescribed testosterone weighed 250 to 350 pounds and some of them weigh 150 pounds, and that might certainly help out.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: I agree with the comment that the company's gone through incredible effort to try to get this thing sorted out. And as far as the 6-hour test, it could be made a requirement that you cannot prescribe this drug unless you have a 6-plus or minus 30-minute test.

DR. LEWIS: Thank you. Anybody else? Dr. Mager?

DR. MAGER: I just wanted to clarify that I also thought the 6-hour time point is reasonable, that I think that is the best we can do given what we had. But I do wish that we had more information about the predictors of variability, albumin, and a number of other factors that go into it. But I agree that the 6-hour time point is reasonable. But the question itself is what was proposed, which

was 3 to 5, and I did not think that was well supported.

DR. LEWIS: Thank you. Dr. Rej? Nothing? Sorry. I thought you raised your hand. Anybody else in terms of titration regimen?

(No response.)

DR. LEWIS: The panelists generally felt that the approach to finding this titration regimen was reasonable in terms of the modeling, but that there wasn't a lot of weight, evidentiary weight, in choosing 4 to 6 versus 3 to 5. There are generally some concerns about out ways of monitoring the levels of testosterone in people who are taking other kinds of formulations now, so is it possible that we could also tie whatever is decided to be the best titration regimen to the ability to prescribe the drug to a patient.

I think that sums that one up. Let's talk about question 3. Discuss whether sodium fluoride EDTA tubes are critical for the safe and effective use of Jatenzo. If you agree that sodium fluoride EDTA tubes are not critical, discuss how serum

tubes will ensure safe and effective use given that the phase 3 trial used sodium fluoride EDTA tubes.

Dr. Braunstein, then Dr. Brannigan.

DR. BRAUNSTEIN: I have a couple comments on this. First of all, if one looks in the literature, as was discussed earlier, there's a difference in the literature about whether it makes any difference, with TU, whether one uses plasma or serum in regards to the need for inhibitors to decrease the non-specific esterases ex vivo after the blood is drawn. These are two superb investigative groups who have come to different conclusions on that. That's number one.

Number two, I am very, very sure that when clinicians order a testosterone in patients on this drug, even if they put down, "Please draw in a sodium fluoride EDTA tube," which most of them won't, that it's not going to get drawn in a sodium fluoride EDTA tube; it's going to get drawn in a red top tube like all the other testosterones are done, and it's going to be measured either in an EIA or LC tandem mass spec assay if it's a superb

lab. So I don't think that the monitoring of this is really going to follow what was done in the phase 3 trial.

When I looked at the sponsor's figure CC-11 showing the difference between the plasma and the serum levels of testosterone, they followed each other very nicely, which suggests to me that within the parameters of the study and how the serum was handled, that there was not a lot of ex vivo production of testosterone in this particular study.

I do think the sponsor needs to take individuals who are on TU, and to draw blood, and to aliquot that blood into serum tubes, and to look over time -- 30 minutes clotting, 60 minutes sitting on the clot, 90 minutes sitting on the clot, sort of the standard what happens at room temperature in most labs or physicians' offices -- and then take the serum out and measure the testosterone, and see if there really is practically any ex vivo production of testosterone. And if there is, does it make any difference in the

overall thing, because I really think that the titration decisions should be made on the basis of serum if at all possible.

I don't know if it's all possible based on what we have so far, but I wouldn't go full force in saying that this has to be done by sodium fluoride EDTA just because the phase 3 study was done that way. And the sponsor has some data that supports doing that, but not total data, so I would be against that type of procedure. I'd like to see it go to serum if at all possible.

DR. LEWIS: Thank you. Dr. Brannigan?

DR. BRANNIGAN: I completely agree with Dr. Braunstein. This is one of the aspects of this drug's administration and following patients that will go by the wayside. And it's not only going to be the patients who are going to be confused, but I think the physicians and the laboratory staff frankly will be confused. And I do worry about the availability of these tubes. And I agree with Dr. Braunstein's point earlier this morning and again here now. I think that these additional

studies should clarify if the sodium fluoride EDTA tubes really are necessary or not.

DR. LEWIS: Thank you. Dr. Rej?

DR. REJ: A number of observations. One, fluoride EDTA tubes are readily available, so there's no question about a laboratory obtaining them. I guess it's more a question of phlebotomists like to use as few tubes as possible, and to have yet another tube when you're probably measuring lipids, hematocrit, that raises it to three. And there's also the concern about unnecessary blood draw. I think the real question is, is there more than just a systematic plasma versus serum difference in the measurements, and I'm not certain that there is. The data really weren't very clear on that.

More of a concern, it was mentioned by the sponsor that they're looking at commonly utilized immunoassays for the effect of fluoride and EDTA. I think more of an issue is the cross-reactivity of the parent drug, which is present more than 100-fold higher than testosterone, so even a small

cross-reactivity of the drug could influence the immunoassays. That's an easily doable study and actually should have been presented already.

In terms of safety and effectiveness, if the sponsor's data are correct that there is an advantage of using the fluoride EDTA tubes, it may not be the most effective because it might lead to underdosing but probably no effect on safety because, as the sponsor presented, it would lead to recommending a lower dose rather than a higher dose. So I think it's more effectiveness rather than safety.

DR. LEWIS: Thank you. Anyone else?

(No response.)

DR. LEWIS: So in terms of question 3, discussing the use of the sodium fluoride EDTA tubes, the necessity of that for safe and effective use of Jatenzo, the panelists generally were not persuaded that we had sufficient data to make that determination. The sodium fluoride tubes, while they may be readily available in clinical use, this may be confusing to the physicians ordering the

tests, the labs performing the tests, and the phlebotomists who draw the blood. So it may not adhere to the kinds of conditions that were used in the phase 3 trial.

That said, it's possible that this would not affect the safety of the drug but it could affect its efficacy. So overall, more data is, I think, indicated based on the consensus of the panel.

Let's look at question 4, a vote. Is the overall benefit-risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy and provide a rationale for your vote.

For this one, we will be going around the table to get everyone's rationale. There's a specific way to register your vote. Maybe you could --

MS. SORSCHER: I have a question also about the question. When we're answering this, are we supposed to consider off-label risks and benefits or just the on-label risks and benefits?

DR. JOFFE: This is Hylton Joffe. That's a good question. I would read this question as what

the applicant is proposing. So we heard a lot of detail from the applicant on what they intend is the patient population for this drug, so I would answer this question, benefit-risk, in that larger population.

Now if you feel it should not be approved for that, for example, but it should be approved in men with classic hypogonadism, then I would recommend voting no here, but then explaining your rationale of where you think the approval would be. So in other words, I would vote on this question based on what the applicant is proposing.

Is that clear for folks? Dr. Dudley?

DR. DUDLEY: I just want to make sure that everyone realizes we're not proposing widespread use. We're proposing the use that is in the label for testosterone products, that is in essence, classical hypogonadism. I just don't want there to be confusion that we are seeking broader use of that. It's the same indication for every testosterone product that's currently on the market because it's consistent with the FDA's change in

that label in 2014. Thank you.

DR. JOFFE: And one thing to clarify on that is even though there's an indicated use with benefit-risk in FDA's structured benefit-risk framework, you have to take into context the real-world use of the product. You can't turn a blind eye to that. So that's why I think you should vote on this question in terms of thinking what the real-world context of use would be, and then you can always clarify what your intent was with your vote when you provide the rationale.

DR. LEWIS: If there are no further questions or comments concerning the wording of the question, we'll now begin voting on this question. We're going to use an electronic voting system for this process. Please press the button on your microphone that corresponds to your vote. You'll have 20 seconds to vote. Press the button firmly, please.

After you make your selection, the light may continue to flash. If you're unsure of whether your vote has been cast or you wish to change your

vote, please press the corresponding button again before the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and Ms. Bhatt will read the vote from the screen into the record.

(Voting.)

MS. BHATT: The voting results, 9 is yes; no is 10; abstain, zero; and no voting is zero.

DR. LEWIS: Thank you. Everyone has voted, and the vote is now complete. I'm going to ask that we go around the table and have everyone who voted state their name, their vote, and please provide a rationale as to why you voted the way you did. Let's start with Dr. Lincoff.

DR. LINCOFF: Michael Lincoff. I voted no. Explicitly though, this was for the broad population, the 2 million getting prescriptions. If this could be released in a way that would deeply restrict it to the classic primary hypogonadism such as Klinefelter's, until and unless a cardiovascular outcomes trial showed

safety in a broader population, then I would favor making that available. But for the same population that is currently using testosterone replacement products, I believe the hypertension risk is concern sufficient to not approve it.

DR. LEWIS: Thank you. Dr. Wilson?

DR. WILSON: Peter Wilson. I voted no for similar reasons as Dr. Lincoff with a couple other added concerns. One is perhaps people middle-aged who are starting to reach the age where their cardiovascular risk goes up, a real concern about giving this medication to patients who are hypertensive. But I especially favored the approach for individuals with primary hypogonadism, at the gonadal level that means, and for whom this may be especially special therapy, and also the potential consideration of training or background REMS type of approach for the providers who write those prescriptions.

DR. LEWIS: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: Glenn Braunstein. I voted yes for a number of reasons. Number one, I think

the sponsor asked for this to be used in patients with both primary hypogonadism and secondary hypogonadism with structural defects, which is what the FDA requires. They did not ask for approval of this for the use in individuals with age-related low testosterone, which we do know testosterone is widely prescribed off label for that. But nonetheless, I think handling that problem is a different issue and that we shouldn't not put a drug on the market because of potential inappropriate off-label use.

I do think the patients with Klinefelter's syndrome and other forms of classical hypogonadism really deserve an oral preparation that is efficacious and I would hope would be very safe. I think the safety can be monitored, and I strongly recommend a REMS type of program to look at the safety and prescribing habits of the drug. Certainly for primary hypogonadism, one can require not only low testosterone but elevations of LH and/or FSH prior to starting therapy. There are ways of addressing this.

I do think that a cardiovascular safety study should be carried out. I'd accept a comparator study even though I want to see a long-term cardiovascular safety study, placebo-controlled cardiovascular safety study in testosterone in general. I'd be willing to just look at this versus a comparator that's on the market to see if there's an increased risk because of hypertension and the lowering of HDL and increasing of LDL and triglycerides over and above what is seen with some of the others.

I do think that the sponsor should try to change their titration recommendations based on a serum level if the additional tests that were recommended do show that there's a systematic increase in serum testosterone versus plasma testosterone and not an increase over time while the sample sits in the clot. So I do think there's a little bit more work to be done, but overall, patients deserve an oral therapy, and I think that this can supply it for the population of classical hypogonadal patients.

DR. LEWIS: Thank you. Dr. Edwards?

DR. EDWARDS: I voted yes. I think testosterone is a treatment that is used in older adults. Currently, they are using the patches and the gels, but there's a lot of concerns about complications in terms of transferring it to other people particularly and technical difficulties that they are encountering. Yes, they have a number of comorbidities.

I think the basic issue for me is setting in place a safety protocol that allows them to use it in a safe manner, for instance, REMS, but I would also suggest what is used for teriparatide, prospective registry of users, and with periodic evaluations of cardiovascular complications or hypertension, an education to physicians. I think with those two measures in place, there would be some degree of safety for people with primary hypogonadism and, as we know, many of the low testosterone older adults who will be using this drug.

DR. LEWIS: Thank you. Dr. Gass?

DR. GASS: I voted yes. I think the company has done a good job in trying to improve safety. I like what they've proposed for their postmarketing surveillance, and I'd like to see that reinforced. Perhaps they could work with the group that was here today for Klinefelter's syndrome, to collect data. There are a lot of ways to do that for partners; perhaps labeling, warnings, or potential contraindications, people at high risk for cardiovascular disease or other risk factors that we might view as a concern.

Then to encourage postmarketing surveillance, I was intrigued by the man from New York with how New York is trying to monitor testosterone prescriptions and clearly agree with others who would like to be cautious about making a decision on the potential abuse because we already have drugs like that, like the opioids and other painkillers that we have to deal with. And we're going to have to find some other ways to deal with abusive drugs.

DR. LEWIS: Thank you. Dr. Dmochowski?

(No response.)

DR. LEWIS: Are you still with us, Dr. Dmochowski?

DR. DMOCHOWSKI: Yes. Roger Dmochowski. I voted yes, and I voted yes because I do think the sponsor has really endeavored to answer and respond to many of the queries that were brought up in the first round. I do think, though, my yes is provisoed [ph] based upon significant postmarket oversight not only including REMS but also probably including something like a registry and potentially a formal interaction with reimbursement authorities such that there is some assessment of these patients long term for any potential signal that emerges regarding cardiovascular toxicity. Thank you.

DR. LEWIS: Thank you. Dr. Drake?

DR. DRAKE: Matthew Drake. I voted no. I figured that it may be efficacious or good medication for those with primary gonadal failure. I just don't think we've seen that data to my satisfaction as of yet. Again, I'd like to see

that broken out. I do have significant concerns, not necessarily on the individual patient level, for those with age or obesity-associated low T, but when you start to look at a population level where you have increases in blood pressure, it's going to lead to negative cardiovascular events, cardiovascular outcomes, so I do have concerns about that. I also have concerns about the use of a medication that's been studied really, most intentively, in a 4-month study and to then extrapolate for people using that for 20, 30, 40 years. So those are my reasons for voting no.

DR. LEWIS: Thank you. Dr. Shaw?

DR. SHAW: I voted yes for many of the reasons that were already stated, specifically by Dr. Braunstein, that for the indication that's being asked for I felt was a clearly established benefit-risk profile and that that really dominated the reasons for my decision.

I do think that a long-term randomized trial, in this case would be post-approval, is necessary. There is a population that we're

concerned about for which there is equipoise. Even those with primary hypogonadism will get older and be in that high-risk group for cardiovascular events we should be doing any kind of observational study on that scale with that diverse a patient population. I do not want to be the statistician going through that electronic health record data; that, really, these patients would deserve a long-term randomized study for cardiovascular risk factors. But overall, I think that there is, like I said, a clear benefit-risk ratio for the indication being asked for.

DR. LEWIS: Thank you. I voted no. My reasoning largely falls along the same lines as that articulated by Dr. Braunstein. I think that we need more data particularly in the population that's likely to use it.

Dr. Bauer?

DR. BAUER: Doug Bauer. I also voted no. I voted no because, specifically, the indication is the same as the existing preparations, and we know that there is huge off-label use. I think that's

unacceptable, and I don't think that the sponsor's proposals to try to change that frankly are likely to be very successful.

I'm very sympathetic to the fact that there's a population here that really clearly needs an oral preparation, and I think I certainly would be agreeable to a revised indication that could specifically target that low-risk cardiovascular population. I also agree that a randomized trial should be done. I would argue it ought to be done pre-approval not post-approval. And again, I think clinical endpoints really do sway clinicians' practice habits, and I would favor that.

DR. LEWIS: Ms. Sorscher?

MS. SORSCHER: I voted no. This was a tough one because I found the testimony from patients and their families to be very compelling, particularly the patients who struggle with compliance and younger people who have issues with sensory processing and maybe developmental delays where it's very hard to get that compliance.

It's difficult because there are clearly

individuals for whom the benefits outweigh the risks, but FDA also has to think on a population level, and there are these really serious cardiovascular concerns related to the population who's probably going to be using this drug the most. FDA, as far as I can tell, doesn't have very good tools at this time for controlling that off-label use. It's really in the hands of doctors, and it's also in the hands of the sponsor.

I was struck by the fact that even today in their presentation, in front of the federal regulators, they were unable to stick to the on-label use when they were talking about risks and benefits, to the point where we all I think became a little confused about that. And when they're out there in the real world coaching patients and doctors, I just wonder what they're going to say in terms of promoting this drug.

I want to mention some state programs for controlling testosterone abuse were brought up today, and I just want to encourage FDA to look into those programs and make sure that they apply

to this form in addition to the already approved testosterone because the way the rules may be written, it may exclude this drug.

DR. LEWIS: Thank you. Mr. Bisphoric [ph]?

DR. BISHOPRIC: This one's the right spelling. I don't know where they got one. It's Bishopric. I voted yes, and I voted because of sympathy for the men who spoke about primary hypogonadism. It isn't just physical pain. It isn't just compliance. It's that every TSA agent, every customs official that you go through medications with is put in a position to harass, humiliate, and just even if they're well intended, put you in a really unpleasant position to discuss things that are really very personal, and I think they deserve this.

On the other hand, I'm obviously aware that there are a large number of for-profit clinics that are dispensing similar agents based on information seen on the back of pickup trucks, Facebook, and murals by the side of the road. It's a very difficult decision, but I just am, again,

sympathetic.

DR. LEWIS: Thank you. Dr. Brannigan?

DR. BRANNIGAN: This is really a very difficult decision. The patients here did a wonderful job explaining their plight, and having a large practice taking care of these men, every six months they come back and ask the same question, "When are you going to have an oral therapy available?"

I think the questions raised about potential safety issues were compelling and that is the factor that -- even in the younger men with Klinefelter's syndrome, the younger patient cohort, I don't know if we really know, based on the data that was discussed here today, the true safety outcomes, even in that patient population. So I would say it's with a heavy heart that I did vote no.

DR. LEWIS: Thank you. Dr. Adler?

DR. ADLER: Robert Adler. I voted yes. Although I said earlier that physicians aren't educable, there are exceptions. We were taught,

just a few years ago, that we really needed to treat pain. It was the fifth vital sign. So physicians who've overprescribed opiates, we've learned something that, and we have a real problem with it. But states, to a great extent, have changed things, and the federal government as well, to some extent. I had to take two hours of CME on opiates in order to get my license renewed in the state of Virginia, and the CME was on opiates.

Testosterone is a controlled substance. Prescriptions are only good for six months at a time. This is an opportunity not just for this particular preparation but for all testosterone preparations to get the kind of scrutiny, REMS, registries, and proper oversight in order to make testosterone prescribing improved. We will never get rid of all of the outlier doctors, but we can make a big difference. I think if it's done properly -- after all, this is a controlled substance.

This is an opportunity to do it right. And I think for those patients who have Klinefelter's

syndrome and for others who are going to need long-term testosterone, if we do it right, this is an acceptable preparation.

DR. LEWIS: Thank you. Dr. Gerhard?

DR. GERHARD: Toby Gerhard. I voted no. Based on what we know, all indications are that an oral testosterone product would be extremely widely used off label, and the risks that go along with that in the middle-aged to older population are I don't think acceptable. However, there clearly is a need for an oral product, so FDA I believe should really consider mechanisms that are similar to what is in place, for example clozapine or isotretinoin. You cannot fill a clozapine prescription without getting a blood test and show of white blood cell count. You cannot as a woman fill a prescription for isotretinoin without showing pregnancy tests.

Here it seems in many ways -- and I'm no endocrinologist -- certainly for something like Klinefelter's, it would be very straightforward to demonstrate the indication. I would hope that a similar approach would be possible for all the

approved indications. I feel pretty strongly that it can't just be a warning or a black box, or even provider education because I don't think this will work.

There's some indication that we've bent the prescribing for opiates, but it took tens of thousands of tests and press attention for years and a unique epidemic in this country to make that happen. I don't think this will work equally for testosterone, at least not before there would be a real disaster with current use.

So I think this is one of the situations where there really needs to be strict regulations. Obviously, it doesn't apply to all drugs. I see and fully understand FDA's hesitation to be too hands on in regulating the practice of medicine, but I think this is an exception where the protection of public health requires it and the patient population that really needs the dosage form has a right to this medication. So that's why I voted no here, however, I would support an approval with the appropriate restrictions in

place, but those have to be hard restrictions.

DR. LEWIS: Thank you. Dr. Kirkali?

DR. KIRKALI: Yes. I voted yes because I thought the benefit-risk ratio was in favor of the benefit of the drug for the population that's intended for use and certainly the discussion we had all day about the cardiovascular risks that was mainly based on the increased risk of hypertension in this population and would not be a major issue for the population intended for use here, where again, a younger population.

The widely referenced article on the population-based hypertension, the risk of cardiovascular death, although the meta-analysis is a certain strength because it really relates to a number of articles, it really depends on the quality of those articles as well as the individual patient data. And I certainly think that we should perhaps differentiate patient-level differences than the population-level differences. I also voted yes because I used a TU in a country where it was registered during my practice before I came to

the U.S.

DR. LEWIS: Thank you. Dr. Howards?

DR. HOWARDS: Stuart Howards. I voted no. I am very conflicted as I was in 2014 when this compound was previously reviewed because the sponsor is being held to a much more rigorous standard than any of the previously approved drugs, and this is just unfair.

Nevertheless, I'm very concerned about the cardiovascular risks. And in the real world, millions of patients are going to be treated with this drug, if it's approved, who do not follow the criteria listed by the FDA nor the intentions of the sponsor. So we'd be putting a lot of people at risk in spite of the goals of the FDA and the sponsor.

Also, I'd like to mention that in 2014 in the discussions, there was a consensus -- I think it was unanimous -- that there will never be a long-term evaluation of the risks of testosterone because it would be an incredibly expensive study. Clearly, the NIH does not have the funds to do it

and pharma has no reason to do it.

I would unequivocally, enthusiastically approve approval of this compound if there were requirements that it could only be prescribed by qualified subspecialists who took a course on who to give it to, and how to use it, and how to follow up.

DR. LEWIS: Thank you. Dr. Mager?

DR. MAGER: Don Mager. I voted no. I also thought that this was a very difficult decision to make. I wanted to first mention that I really appreciated the patient representatives and the patient advocates that came to speak today. It's very clear there's an unmet medical need. They need and deserve a solution to their problem, and I think that more work has to be done to do that.

Even though I wasn't part of the previous decision advisory committee, I wanted to congratulate the applicant on doing an excellent job at addressing the issues raised at the previous AC. The different study designs and all of the things that were put in place to address the

previous decision I thought was really excellent. I think in the end, it was the real-world issue of the blood pressure risk that was raised, and that was essentially what we were asked to also think about, and that is the real-world risk of the general population.

I would also support, with proper restrictions to subspecialists and also of course specific patient populations, that this would be a very viable solution for them, but given the real-world risks, I felt that the cardiovascular complications from high blood pressure was still a signal that you can't ignore.

DR. LEWIS: Thank you. Dr. Rej?

DR. REJ: I voted yes for many of the reasons that my colleagues also voted yes, but I'm very sympathetic to those who voted no, that the real world dictates lots of things that we can't predict. But overall, I think the sponsor has shown that the safety and effectiveness for the target population outweighs that risk. I have some caveats about the laboratory issues and what was

done, but I think those could easily be solved by the sponsor and the laboratory community.

DR. LEWIS: Thank you. So I'd like to once more thank the panel for their attention, thank the sponsor for their presentation, and of course the FDA, and of course those who spoke during the open panel portion of the meeting, supplying us with very valuable input. Before we adjourn, are there any last comments from the FDA?

DR. JOFFE: This is Hylton Joffe. I want to add my thanks also. I want to thank the applicant. I thought their presentations were excellent and this has been a very professional meeting. I appreciate all the input everybody brought.

I'd also like to thank our presenters and then some folks behind the scenes, Mark Hirsch who has the flu back there, or is recovering, I should say, from the flu back here, who is the team leader for the product; and Jeannie Roule who's the regulatory project manager, who's done a lot of work behind the scenes.

Lastly of course, our AC staff both at this

desk and Kalyani and Vivian for leading this. And we'll see you all with a different sponsor or applicant tomorrow to talk about a different oral testosterone product. Thank you very much.

Adjournment

DR. LEWIS: Thank you. Panel members, please remember to take all your personal belongings with you. The room will be cleaned at the end of today, and any material left on the table will be disposed of; although you can leave your name badges on the table. We will recycle those and use them again tomorrow. We are now adjourned. Thank you.

(Whereupon, at 4:24 p.m., the meeting was adjourned.)