U.S. FOOD AND DRUG ADMINISTRATION
OFFICE OF THE COMMISSIONER
OFFICE OF PEDIATRIC THERAPEUTICS

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PEDIATRIC ADVISORY COMMITTEE

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MEETING

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MONDAY
APRIL 8, 2019

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The Pediatric Advisory Committee met in the Great Room, Building 31 Conference Center, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 9:00 a.m., Robert Dracker, Chair, presiding.

VOTING MEMBERS PRESENT
ROBERT DRACKER, MD, MHA, MBA, CPI Chair
PREMCHAND ANNE, MD, MBA, MPH, FACC, St. John Providence Children's Hospital
DAVID CALLAHAN, MD, Washington University School of Medicine and Washington University Clinical Associates
MARY CATELETTO, MD, FAAP, Winthrop University Hospital and SUNY Stony Brook
RANDALL FLICK, MD, MPH, Mayo Clinic Children's Center
PETER HAVENS, MD, MS, Children's Hospital of Wisconsin and Medical College of Wisconsin
SARAH HOEHN, MD, MBe, FAAP, University of Chicago
RANDI OSTER, MBA, Help Me Health

WAEL SAYEJ, MD, Connecticut Children's Medical Center and University of Connecticut School of Medicine
CHRISTY TURER, MD, MHS, FAAP, FTOS, UT Southwestern and Children's Medical Center
KELLY WADE, MD, PhD, Children's Hospital of Philadelphia

NON-VOTING MEMBERS PRESENT
BRIDGETTE JONES, MD, MS, Children's Mercy Hospital
RONALD PORTMAN, MD, FAAP, Novartis Pharmaceutical Company

TEMPORARY VOTING MEMBERS PRESENT
DAVID COOKE, MD, Johns Hopkins University School of Medicine
ANGELA DELANEY, MD, NICHD, National Institutes of Health
PEGGY DICAPUA, Patient-Family Representative
RICHARD HOLUBKOV, PhD, University of Utah School of Medicine
JAMES MCGOUGH, MD, Semel Institute for Neuroscience & Human Behavior at UCLA

FDA PARTICIPANTS
MARIEANN BRILL, MBA, RAC, MT(ASCP), Designated Federal Officer, Office of Pediatric Therapeutics (OPT), Office of the Commissioner (OC)
JOHN ALEXANDER, MD, MPH, Deputy Director, Division of Pediatric and Maternal Health, Office of Drug Evaluation IV, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)
OVIDIU GALESCU, MD, MS, Medical Officer, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, OND, CDER
ETHAN HAUSMAN, MD, Medical Officer, Division of Pediatric and Maternal Health, Office of Drug Evaluation IV, OND, CDER
SUSAN MCCUNE, MD, Director, OPT, OC

CHRISTINE P. NGUYEN, MD, Deputy Director for Safety, Division of Bone, Reproductive, and Urologic Products, Office of Drug Evaluation III, OND, CDER
JOHN SHARRETTS, MD, Medical Officer, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, OND, CDER
CORINNE WOODS, RPh, MPH, Drug Utilization Analyst, Division of Epidemiology II, Office of Surveillance and Epidemiology, OND, CDER

ALSO PRESENT
YEE-MING CHAN, MD, PhD, Harvard Medical School and Boston Children's Hospital
ALAN D. ROGOL, MD, PhD, University of Virginia

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

9:02 a.m.

CHAIR DRACKER: Good morning. We will now start the meeting. I just want to mention briefly to please fill out the lunch request and hand it in at the desk so we have meals for you at lunch.

Also, you received materials in the mail which we would like returned at the conclusion of the meeting. So please give those to Marieann or to the desk with the ladies out front. Thank you.

I would like to first remind everyone to please silence your cell phones, smart phones, and any other devices if you've not already done so.

I would also like to identify the FDA press contact, Lyndsay Meyer. If you're present please stand. Lyndsay? All right, she should be here shortly. If she comes we'll let you know who she is so you can ask her questions if you need her.

First of all, thank you all. I was just informed this is my last meeting for now so it's been a pleasure being with all of you. I've been here, I think this is my ninth year, right?

Four years as a consultant and four years as a Member, and this year as Chair. I love this Committee, I love working with all of you so it's been a pleasure being with all of you. Thank you.

For topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a very productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee take care and that the conversations about the topic at hand take place in the open forum of the meeting.

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

Also, the Committee is reminded to please refrain from discussing the meeting topics during the break or lunch.

Thank you.

Now, Marieann Brill will discuss the conflict of interest statement.

MS. BRILL: Good morning.

The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee under the authority of the Best Pharmaceuticals for Children Act, the Pediatric Research Act of 2003, the Food and Drug Administration Amendments Act of 2007, the Food

and Drug Administration Safety and Innovation Act of 2012, and the Federal Advisory Committee Act.

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

The following information under status of the Advisory Committee's compliance with federal ethics and conflict of interests laws covered by but not limited to those found at 18 U.S.C. Section 208 is being provided to participants at this 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 interests laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts

when it is determined that the Agency's need for particular individual services outweighs his or her potential financial conflict of interest, or when the interests of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, Members and temporary voting Members of this Committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

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

Today's agenda involves the discussion of drug development for testosterone replacement therapy in male adolescents for conditions

associated with a deficiency or absence of endogenous testosterone resulting from structural or genetic etiologies such as classic hypogonadism.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the Committee Members and temporary voting Members, no conflict of interest waivers have been issued.

To ensure transparency, we encourage all standing Committee Members and temporary voting Members to disclose any public statements that they have made concerning the topic at issue.

Dr. Bridgette Jones is participating in this meeting as the healthcare representative and that is a non-voting position.

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

Dr. Portman's role at this meeting is to represent in general industry in general and not any particular company. Dr. Portman is employed by Novartis.

In order to provide the expert is required to adequately address the topic covered at today's meeting. Dr. Cooke, Dr. Delaney, Dr. Holubkov, Dr. McGough -- where's Dr. McGough? -- Ms. DiCapua will be participating as temporary voting Members.

Ms. DiCapua is participating as the patient family representative which is a voting position.

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

FDA encourages all other participants to advise the Committee of any financial

relationships that they may have regarding the topic that could be affected by the Committee's discussions.

Thank you.

CHAIR DRACKER: Thank you, Marieann. We'll now proceed with opening remarks from Dr. Susie McCune, Director of the Office of Pediatric Therapeutics.

Sorry about that. See, I was so concerned about not being on the Committee I screwed it up.

I'd like to ask all Members, consultants, FDA panel, and DFO to go around the table and please state their name into the record. Thank you. We can start down there, please.

DR. NGUYEN: Good morning, I'm Christine Nguyen and I am the Deputy Director for Safety in the Division of Bone, Reproductive and Urologic Products.

DR. SHARRETTS: Good morning, I'm John Sharretts. I'm Acting Clinical Team Lead in the Division of Metabolism and Endocrine Products.

DR. GALESCU: Good morning, Ovidiu Galescu, Medical Officer, Division of Metabolism and Endocrinology.

DR. ALEXANDER: John Alexander, Deputy Director of the Division of Pediatric and Maternal Health.

DR. HAUSMAN: Ethan Hausman, Medical Officer, Division of Pediatric and Maternal Health.

DR. MCCUNE: Susie McCune, Director in the Office of Pediatric Therapeutics.

DR. WADE: Kelly Wade, neonatologist for Children's Hospital of Philadelphia and Member of the PAC.

DR. HOEHN: Sarah Hoehn, University of Chicago, Pediatric Critical Care and Pediatric Palliative Care, Pediatric Advisory Committee Member.

MS. DICAPUA: Peggy DiCapua, temporary patient representative.

DR. MCGOUGH: Jim McGough, UCLA, child and adolescent psychiatrist and temporary voting Member.

CHAIR DRACKER: I'm Bob Dracker Syracuse, New York, pediatrics, hematology and transfusion medicine, Chairman of the PAC.

MS. BRILL: Marieann Brill, I'm with DFO for this meeting.

DR. TURER: Christy Turer, I'm at UT Southwestern in Dallas. I am a Member of the PAC and in combined internal medicine and pediatrics.

DR. SAYEJ: Wael Sayej, pediatric gastroenterologist, Connecticut Children's Medical Center in the University of Connecticut School of Medicine.

DR. HOLUBKOV: Rich Holubkov, temporary voting Member of the PAC, professor and senior biostatistician, University of Utah School of Medicine.

DR. COOKE: I'm David Cooke, I'm the Clinical Director of Pediatric Endocrine at Johns Hopkins and I'm also the pediatric endocrinologist on the Johns Hopkins Klinefelter Center.

DR. DELANEY: Angela Delaney, I'm at the NIH, pediatric endocrinologist, temporary

voting Member.

DR. FLICK: Randall Flick, professor of anesthesiology and pediatrics, Mayo Clinic, Member of the PAC.

DR. ANNE: Premchand Anne, pediatric cardiology, St. John Children's Hospital, Detroit, Michigan, Member of the PAC.

MS. OSTER: Randi Oster, the consumer representative for the Pediatric Advisory Committee.

DR. CALLAHAN: David Callahan, child neurologist, Washington University, Member of the PAC.

DR. HAVENS: Peter Havens, pediatric infectious diseases at the Medical College of Wisconsin and Children's Hospital Wisconsin, and a Member of the PAC.

DR. CATALETTO: Mary Cataletto, I'm a pediatric pulmonologist at NYU Winthrop in New York and a Member of the PAC.

DR. PORTMAN: Ron Portman, pediatric nephrologist, a non-voting industry Member of the

PAC.

DR. JONES: Bridgette Jones, pediatric allergy, immunology, and clinical pharmacology at Children's Mercy. I'm the pediatric healthcare organizational representative.

CHAIR DRACKER: Okay, now Susie, it's your turn.

DR. MCCUNE: Okay, thank you. I'm just getting my mouse going here. All right, thank you all, welcome to the Spring 2019 Pediatric Advisory Committee Meeting.

I'm going to give you just a few opening remarks, I'm going to talk to you a little bit about personnel update, a little bit about the web-posted reviews, tell you about a workshop that we've been working on, and then report on the non-compliance letters.

So, as you heard Dr. Dracker say today, he is rotating off of the Pediatric Advisory Committee. We have also Mary Cataletto and Bridget Jones today who are also rotating off, and I have plaques for all of them.

I just want to take a second just to remind everyone, Dr. Dracker is the Clinical Associate Professor in the Departments of Pathology and Pediatrics at SUNY Health Science Center at Syracuse, New York, and has been the Medical Director of Summerwood Pediatrics in Liverpool and Camillus, New York since 1993.

He earlier served as Medical Director for the Transfusion Medicine Service at University Hospital in Syracuse, and founded Infusacare Medical Services.

He received his MD from SUNY Health Science Center in Syracuse, followed by a residency in pediatrics and fellowships in pediatric, hematology, oncology, and blood banking transfusion medicine all at University Hospital.

He also has a master's in health services management from the New School for Social Research, New York, New York, and an MBA from Columbia College. I just want to thank Dr. Dracker for his service over the past, sorry, nine years.

I thought I had myself organized but I don't, sorry. I was organized. anyway, Dr. Dracker, thank you so much, we really appreciate it and we will be in touch. You can't get away from us, you know that.

(Applause.)

DR. MCCUNE: All right, next, Dr. Cataletto is a pediatric pulmonologist professor of clinical pediatrics at Stony Brook University School of Medicine in New York.

She has been the Associate Director of the Pediatric Sleep medicine Pediatrics at NYU Winthrop University Hospital in Mineola since 2012. Since 1996, she has been a consulting pulmonologist to Nassau Community Hospital, Oceanside, New York.

She earned her medical degree from the University of Monterrey School of Medicine in Nuevo Leon, Mexico.

She completed her internship and residency at Brookdale Hospital Medical Center in

Brooklyn, New York, and her fellowship in pulmonary physiology and critical care pediatrics at Albert Einstein College of Medicine in the Bronx.

Dr. Cataletto earned her certificate in medical management from the American College of Physical Executives from Carnegie Mellon University and a master's degree in medical management from the H. John Heinz III School of Public Policy and Management.

She is the Chair of the Pediatric Network Steering Committee, American College of Chest Physicians, and her research interest is sleep disordered breathing in children with congenital and developmental abnormalities.

And it's my pleasure to give this plaque to Dr. Cataletto who has been with us since June 2014.

(Applause.)

DR. MCCUNE: And last but certainly not least, Dr. Bridgette Jones has served on the Pediatric Advisory Committee as the pediatric health organization representative.

She is an Associate Professor of Pediatrics in the Divisions of Allergy, Asthma, Immunology, and Pediatric Clinical Pharmacology, Toxicology, and Therapeutic Innovation at Children's Mercy Hospitals and Clinics in Kansas City, Missouri.

Dr. Jones is also the Associate Program Director of the Pediatric Clinical Pharmacology Fellowship Program, the Director of Minority Recruitment within this program, and the inaugural Chair at the Children's Mercy Faculty and Trainee, Diversity, Equity, and Inclusion Committee.

Dr. Jones earned her doctor of medicine degree from the University of Arkansas College of Medicine and did her internship and residency at the Arkansas Children's Hospital and a fellowship in allergy and immunology at the Children's Mercy Hospitals and Clinics in Kansas City.

Dr. Jones has authored many articles on pediatric pulmonology and her research has centered around pediatric asthma. It is my pleasure to present Dr. Jones with a plaque for

her service since 2015 for the PAC.

(Applause.)

DR. MCCUNE: I also wanted to mention for those of you that know Dr. Judy Cope, who was with the Office of Pediatric Therapeutics for ten years and helped to manage many of the PAC safety activities, Judy has taken a position in CBER working with the Sentinel Initiative.

So we will continue to collaborate with her on pediatric safety initiatives but not through the Office of Pediatric Therapeutics.

And I wanted to thank Judy for her ten years of work in the Office of Pediatric Therapeutics. We already had a going-away party for Judy and she had her plaque at that time.

All right, so I just wanted to remind everyone, one of the mandates that we have for this Advisory Committee is to look at the pediatric safety reviews following labeling 18 months following a new pediatric label.

And for many years at the start of the PAC activities, all of those reports were presented

to the PAC.

Over the past few years, we've been doing a number of safety evaluations and when there have not been any new safety signals identified, we have posted that information to the web so that you can review that information, you can review the reviews, the public can review that and can submit any comments to the docket.

So while it may look like we're not continuing to do the safety reviews in the public forum today, I want everyone to be aware that we have 16 web-posted reviews for CDER, 3 for CBER, and 3 for CDRH.

And just so that these are in the record, Aczone Gel, AirDuo RespiClick, Avelox, Caldolor injection, Cubicin injection, Dexilant, Eucrisa Ointment, Liletta, Lyrica, Narcan, Ofirmev, Selzentry, Spiriva Respimat, Symbicort, Tarceva, and Velcade are all of the web-posted CDER safety reviews with no newly identified safety signals.

Adynovate, Ixinity, and Epicel are the

three CBER products and Flourish Pediatric Esophageal Atresia Device, Liposorber, and Medtronic Activa Dystonia Therapy are the three CDRH devices.

All of these have been reviewed, a lot of work by the Office of Surveillance and Epidemiology, the Division of Pediatric and Maternal Health, and the Office of Pediatric Therapeutics.

And no new safety signals for those products were identified.

I want to let everyone know that we have been working with the Institute for Advanced Clinical Trials for Children and the Duke Clinical Research Institute to host the Youth Tobacco Cessation Science and Treatment Strategies Workshop.

It will be actually in this room on the White Oak Campus on May 15th, 2019. I've included the registration site here. Registration is free but we would love you to register. I look forward to that interesting discussion.

And then I am mandated to remind you of the non-compliance letters, they are posted online and I have the link here. For CBER there are two, this is unchanged from the last time I presented to you. For CDER there is 31.

There is one additional new non-compliance letter since I last presented.

The websites list the sponsor, the product, a copy of the non-compliance letter, the sponsor's response if it's available, and the status of the prior requirement. For example, if it's released, replaced, or fulfilled.

And with that, I will come to the end of my presentation and will hit escape so that I do it right. And I want to thank you and I look forward to an interesting discussion today.

CHAIR DRACKER: Thank you, Susan. Both the Food and Drug Administration and the public believe in a transparent process for informing, gathering, and decision-making.

To ensure such transparency at the Advisory Committee Meeting, the FDA believes it's

important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants to advise the Committee of any financial relationship that they may have with the firms at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

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

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

We will now proceed with the presentations from the FDA.

DR. NGUYEN: Thank you very much. Good morning, I'm Christine Nguyen and I am with the Division of Bone, Reproductive, and Urologic

Products in CDER.

Our Division regulates the drug development approval and post-marketing surveillance for testosterone replacement products.

Today I'll cover four main topics, the first is I'll summarize the current class indication for these products, I'll outline the current drug development paradigm for these drugs, I'll approve the TRT products that are used in pediatrics.

And lastly, I'll cover at a high level pediatric drug regulations.

So, hypogonadism, it's defined as a clinical syndrome that results from the failure of the testes to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic-pituitary-testicular axis.

When there's inadequate or absent production by the testes, it's known as primary

hypogonadism and when the pathology is at the hypothalamic or pituitary level, it is known as secondary hypogonadism. Both of these types of hypogonadism may be congenital or acquired.

This slide summarizes the current class indication for this drug class so drug name is an androgen indicated as replacement therapy in adult males for conditions associated with a difficult or absence of endogenous testosterone.

So the approved indication covers both primary and secondary hypogonadism. We've highlighted the specific conditions in blue font to point out the fact that these drugs are approved for specific conditions and as you can tell, these conditions are usually either genetic or structural.

In short, they're permanent causes of hypogonadism. And the indication is really predicated on the drug development paradigm which is actually quite simple.

The basic premise is that testosterone products are to be used as replacement therapy in

men with specific hypogonadal conditions.

And we require that sponsors demonstrate only that a T product reliably and safely increases serum T concentrations into the normal range.

So the primary efficacy measure is a pharmacokinetic assessment of serum testosterone. We do not require a demonstration of benefit by any clinical efficacy measure.

And the rationale for this is because testosterone replacement therapy in men with these specific hypogonadal conditions is a long-accepted efficacious therapy.

This slide contains the elements of a typical Phase 3 trial to support approval of a TRT product. The design usually is an open-label, single-arm study design that contains several periods.

These studies usually last anywhere between 6 to 12 months, and that includes an extended safety extension to evaluate the safety of the product.

These trials tend to enroll anywhere in the 100s, up to 200, subjects and the enrolled participants are adult hypogonadal males and having an average morning serum testosterone concentrations below the normal range.

I should point out that most of these subjects do not have a known etiology for the hypogonadism but, again, the intent of the trial is really just to show that when you give these men the investigational product, it can increase their serum testosterone concentrations into the normal range and, therefore, again, the efficacy end points or serum testosterone concentrations.

There are currently two products that are approved for use in children. This is testosterone enanthate, or TE intramuscular injection, and implantable testosterone pellets.

And this is predicated on the premise that if either primary or secondary hypogonadism occurs prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual

characteristics.

Both products are also approved to stimulate puberty in carefully selected males which clear evidence of delayed puberty.

The FDA-approved labeling for these products recommends an X-ray of the hand and wrist to determine bone age be obtained every six months to assess the treatment effect on the epiphyseal centers.

It should be noted both of these drugs were approved a long time ago in the '40s and '50s prior to the 1962 Kefauver-Harris Drug Control Act.

What this enacted was it required that for a drug to be approved, it not only needed to be safe but it needed to be efficacious.

And for drugs that were approved prior to 1962, FDA undertook the Drug Efficacy Study Implementation evaluation to determine whether or not those drugs should remain on the market.

So both these products underwent a DESI evaluation and remain approved on the market.

So this is important because these drugs were approved a long time ago so it's really unclear if there was clinical trial evidence supporting the approval of these drugs for pediatric patients, actually as well as adult patients, at the time of the original FDA approval.

And although approved, the evidence of these drugs' efficacy and safety is unlikely to align with our current standards for approval in pediatric patients.

All the other TRT products state that the safety and efficacy in males less than 18 years old have not been established and the labels warn that improper use of testosterone in adolescence has been associated with acceleration of bone age and premature closure of epiphyses.

So I'll go ahead and turn the discussion over to pediatric drug development and regulations. So in the U.S., the pediatric age range includes birth to 16 years of age inclusive.

Pediatric product development is held to the same evidentiary standard as adult product

development so for a drug to be a proven shoe-in, it has to demonstrate substantial evidence of effectiveness as well as acceptable safety.

So there are really two main pediatric legislations. The first one is the Pediatric Research Equity Act, or PREA. So under PREA, pediatric studies are required for the indication that's being developed in adults, and this is an important distinction.

When a product contains any of the following, a new indication, dosage form, dosing regimen, route of administration, or active ingredient, we do make certain exceptions, such as when a condition does not exist in children, such as prostate cancer.

The second legislation is the Best Pharmaceuticals for Children Act, or BPCA. Under this act, FDA can issue a written request requesting a company to voluntarily conduct pediatric studies for all approved and unapproved indications for which the active moiety may have health benefit in children.

And this can be issued for on or off patent products and patent exclusivity may be attached.

This slide compares the two pediatric during legislations. On the left-hand side is PREA, right-hand side is BPCA. The font that has been bolded shows the differences between these two legislations.

Under PREA, as I mentioned, the studies are required but they're only required for the indications under review that are being developed in adults.

So, for example, if Drug A is being evaluated for the treatment of anemia in adults, then the required studies in children would evaluate the treatment of anemia.

In contrast, BPCA studies are voluntary and they can evaluate the approved indications as well as unapproved indications. So, under BPCA the same Drug A could be studied for the treatment of hypertension in children, although it is approved for the treatment of anemia in adults.

PREA does not apply to certain orphan indications whereas BPCA, one may request studies for orphan indications.

And lastly, under both legislations, findings from pediatric studies must be labeled. For substantial evidence of effectiveness generally, this threshold is established through two, at least two, adequate and well-controlled clinical trials.

For some pediatric conditions, FDA has established an alternative framework to establish efficacy when the disease manifestation and the expected response to treatment in affected children and adults are expected to be similar.

And we call that extrapolation of efficacy.

The underlying premise for whether one can extrapolate effectiveness is, as I mentioned, there are data to support that this disease manifestation and the treatment response are similar between children and adults with the condition of interest.

So things we look for would be if we were to set up the trials in the two populations, would they have similar end points? Is the mode of drug or biologic action expected to be the same between the two populations?

And whether or not we've had previous experience of drugs in the same therapeutic class.

So, if we determine that the disease manifestations and the treatment responses are similar, what data would we need to support approval?

And this slide kind of summarizes the range of data that we would need. The main thing I want to point out is that there's an inverse relationship between the level of confidence in the similarity of disease and treatment response and the level of evidence required from pediatric studies.

This is self-evident I think.

So, on the right-hand side you see the range of different types of evidence that we would need. Up on top is the more traditional paradigm

where we would need one or more adequate well-controlled study, power on a clinically meaningful end point.

And it goes all the way down to the last option, which is where all we may need is pharmacokinetic as well as safety data to support pediatric approval.

And under that circumstance, certainly we would have high-level confidence that the disease manifestations and treatment response are very similar between children and adults.

So, overall, approximately 60 percent of pediatric programs require at least 1 adequate and well-controlled efficacy trial.

Certainly, we cannot extrapolate efficacy when it has not been demonstrated in adults or another pediatric population for the same indication, in which case, then, we would require adequate and well-controlled trials in pediatric children.

For dosing, we do not extrapolate from adults when we need to obtain pharmacokinetic data

to support dose selection in children. And one common strategy we use is we try to target exposures at doses found to be effective in adults.

These studies are performed in pediatric children with condition of interest, so not healthy children volunteers. And modeling and simulation may be used for dose selection and to improve study design.

Similarly, safety is not extrapolated from adults. These data are needed to evaluate the safety of all proposed doses to be used in pediatric patients. The data should be obtained from the pediatric patient population expected to use the drug.

And importantly, clinical studies would need to be large enough and of long enough duration to detect common and potentially infrequent but not necessarily rare adverse events.

One may rely on existing data such as published literature as supportive evidence of safety. So, thank you very much for your

attention.

CHAIR DRACKER: Dr. Galescu?

DR. GALESCU: Good morning, my name is Ovidiu Galescu. I'm a pediatric endocrinologist in the Division of Metabolic and Endocrine Products.

Today I will go over some of the causes of pediatric male hypogonadism and try to lay the foundation of why the question of a current unmet therapeutic need has arisen. The hypothalamic-pituitary-gonadal axis controls sexual maturation and function.

The pulsatile gonadotropin-releasing hormone signal from the hypothalamus triggers the anterior pituitary's release of LH and FSH which act on the gonads.

Testosterone then is secreted in the Leydig cells of the testes under the influence of LH and provides feedback to basically the entire axis. Other hormones such as inhibin are also involved in the fine-tuning of this system, but that's not the focus of today's presentation.

Of particular interest to us are testosterone's systemic effects. These are generally categorized as androgenic or virilizing and anabolic, though these descriptions are somewhat arbitrary as there is a great deal of maturity overlap between them.

Anabolic effects include muscle mass and strength accrual, bone growth and maturation, red blood cell production, and regulation of platelet aggregation.

Androgenic effects include maturation of sex organs and prostate, initiation and maintenance of erectile function, sexual drive and fertility, enlargement of larynx leading to voice changes and the formation of the Adam's apple, and progression and maintenance of secondary sexual characteristics such as facial and axillary hair.

Testosterone also modulates mood, behavior, cognition and memory, which is hard to categorize. All these things are important because we usually look for and monitor in cases

of testosterone dysfunction and during treatment with testosterone product in pediatric population.

Whenever there is disruption in the HPG axis, the gonadal function can be impacted, resulting in hypogonadism, which can be primary when there is a testicular dysfunction, or secondary due to an upstream defect of the APG axis, resulting in an inadequate LH and FSH signaling to the gonads.

Both these conditions can be either congenital or acquired and the two most common congenital causes of primary hypogonadism are, of course, Klinefelter and cryptorchidism. I'll discuss both conditions in more detail shortly.

There are other conditions under the congenital umbrella that are much rarer. A historic condition is the prenatal exposure to diethylstilbestrol, a drug given to pregnant women to prevent miscarriage between 1940 and 1971.

And male infants exposed to DES in utero had a high rate of testicular abnormalities. This

drug was obviously discontinued after reports of adverse events started coming in.

The acquired forms of primary hypogonadism are due to various diseases directly damaging the testes, with varied examples from mumps to cancer. Chemotherapy and radiation therapy are not an important cause of gonadal dysfunction.

The congenital forms of secondary hypogonadism are primarily represented by Kallmann Syndrome, the hypogonadotropic hypogonadism form, and idiopathic hypogonadotropic hypogonadism.

In the acquired branch of secondary hypogonadism, we have any disease that damages the pituitary gland or affects the HPG axis such as intercranial tumors, hemochromatosis, sarcoidosis, histiocytosis X.

Although there are many conditions that fit under this umbrella, the compounded incidents and prevalence is likely much smaller than that of hypogonadotropic pituitary dysfunction due to traumatic brain injury from motor vehicle

accidents, sports injuries, general accidents.

The last group in this category is pediatric and teenage drug and alcohol abuse.

These are the conditions that I will try to focus on today and I'm going to start with the poster child of hypogonadism, Klinefelter Syndrome, which refers to a group of chromosomal disorders in which the normal male karyotype has at least one extra X chromosome.

It is the most common human sex chromosome disorder with a prevalence of 1 in 500 males. In 2008, it was estimated that approximately 250,000 men in the United States have Klinefelter Syndrome.

The condition is, however, significantly underdiagnosed, especially in pediatrics with only approximately 10 percent of diagnoses being established below 18 years of age.

Cryptorchidism is a condition in which one or both testes do not descend into the scrotum and it is very common, affecting approximately

three percent of full-term neonates and the percentage being much higher in premature infants up to 33 percent.

The prevalence will decrease to 0.8 and 1.5 percent at one year of age.

However, apart from the risk of infertility associated with this condition, studies report a one percent risk of Leydig cell depletion resulting in testosterone deficiency for every month the testes remain undescended.

Several conditions may cause structural damage to the testes such as trauma, cancer, cancer treatment, viral illness, primarily mumps, autoimmune orchitis.

These conditions are hard to quantify in terms of incidence and prevalence due to either low numbers, such as in the case of autoimmune orchitis or many confounding factors, such as in the case of cancer and cancer treatment you can't really tell them apart.

As you know, mumps has been a relatively rare condition since the two-dose MMR vaccination

program was introduced in 1989, with cases generally ranging from just a couple of hundred to a few thousand per year.

The 2006 outbreak started on a university campus in Iowa and quickly spread to the neighborhood states, and the CDC conclusion at that time was the cause of the outbreak was the combination between the college campus environment and poor rates of vaccination.

Although this was considered an isolated incident at that time, in recent years there has been a steady increase in the number of reported cases from 229 cases in 2012 to 6366 cases in 2016, with cases still being tallied for 2017 through 2019.

But as you can see, still high. This is most likely due to a decrease in the vaccination rate overall in the United States.

With this surge in mumps cases, we're also likely to see more cases of mumps orchitis in the near future affecting the male population.

Continuing on the acquired branch, we

have to talk about cancer and some of the relevant statistics of pediatric cancer. In 2018, it is estimated that almost 16,000 children were diagnosed with cancer.

The male pediatric cancer survivor rates of hypogonadism are as high as 26 to 36 percent. These particular statistics come from adult males with chronic hypogonadism following their pediatric cancer and cancer management.

It is outside the scope of my presentation today to discuss all types of cancer, however, I wanted to go over two examples. Non-Hodgkin's lymphoma is very common in adults with over 70,000 cases annually.

It is much rarer in pediatrics, however, it will still affect about 1000 children annually.

ALL, acute lymphoblastic leukemia, on the other hand, is rare in adult population but quite common in children with approximately 3000 new cases diagnosed every year.

I chose these two examples because the

rate of post-therapy hypogonadism can be as high as 83 percent in this population.

Moving on to secondary hypogonadism, Kallmann Syndrome is a condition characterized by delayed or absent puberty and an impaired sense of smell.

It is caused by several gene defects affecting gonadotropic production and the prevalence of this disorder is somewhere between 1 in 8000 and 1 in 30,000 in males.

There are other causes, genetic causes, of hypogonadotropic hypogonadism and more are added through ongoing research.

Many of these identified defects were categorized as idiopathic hypogonadotropic hypogonadism prior to the specific defect being identified. And they are usually differentiated from Kallman's by an intact sense of smell.

These conditions taken one by one are extremely rare, however, when you combine all of them, they have a prevalence of approximately 1 in 10,000 children.

In the acquired branch of secondary hypogonadism, we also have those intracranial disorders that disruption the hypothalamic-pituitary functions such as CNS tumors.

In the U.S., the estimated incidence of these tumors is around 5.6 cases per 100,000 per year for children and adolescents below 19 years of age.

Secondary hypogonadism will affect approximately 13 percent of the cases prior to therapy and a whopping 20 to 80 percent post-therapy depending on the location of the tumor and type of therapy.

Another overlooked cause of hypogonadotropic hypogonadism is traumatic brain injury, the incidence of which is between 1 to 300 per 100,000 per year in the pediatric population. The male-to-female ratio is anywhere between 2:1 to as high as 4:1.

And these patients are at an increased risk of pituitary and hypothalamic dysfunction resulting in hypogonadism with rates as high as

41 percent in the acute injury phase with 7.7 percent persisting past 12 months from the incident.

Secondary conditions will have a mixed picture as is the case of Prader-Willi Syndrome, which is a complex genetic disorder characterized by obesity, hyperphagia, mild to moderate intellectual impairment, and a distinct phenotype, such as narrow foreheads, small hands and feet, short stature, et cetera.

The prevalence of Prader-Willi is 1 in 15,000 live births with a 1:1 male to female distribution. And virtually all males with Prader-Willi Syndrome will have hypogonadism.

The hypogonadism was classically thought to be due to hypothalamic etiology as most of the defects in Prader-Willi, however, evidence emerged supporting primary gonadal failure as a significant contributor.

Another disease in this category is X-linked adrenal hypoplasia congenita, which is a disorder that mainly affects males.

It's a genetic disorder that will affected multiple endocrine tissues and often results in delayed puberty and a pubertal arrest.

The prevalence is approximately 1 in 12,500 live births and it is usually identified early in life due to adrenal insufficiency component that manifests in infancy.

I used the U.S. Census Bureau data from 2017 that estimates the total male population ages 12 to 17 at 11.75 million to come up with an estimated number of hypogonadism cases in this population.

The number varies according to condition from several hundred cases for age in Prader-Willi to close to 1000 for traumatic brain injury and idiopathic hypogonadotropic hypogonadism to several thousand for Klinefelter and cryptorchidism, and culminating to anywhere between 10 and 30,000 cases for all combined cases of pediatric cancer.

You have to understand that pediatric cancer statistics are pretty much all over the place

because a lot of the times they do not include the therapy portion.

A lot of the times they do not include specific age ranges so that's why I give a broad estimate of this number.

However, this conservative approach -- I took the lowest numbers of the incidence of hypogonadism in all the cases -- still brought my tally up to approximately 50,000 cases in the 12 to 17 age range at any given time in the United States.

Thank you.

MS. WOODS: Good morning, I am Corinne Woods, a drug utilization analyst in the Office of Surveillance and Epidemiology here at FDA. Today I will be presenting testosterone utilization patterns among pediatric patients.

In this presentation, I will briefly describe the databases used in the analyses, then I will describe the methods and results for the two analyses.

The first analysis was the estimated

number of U.S. male patients with dispensed testosterone prescriptions, and the second was an analysis of the diagnoses proximal to testosterone initiation among a sample of commercially insured patients.

The IQVIA Total Patient Tracker provided U.S. national estimates of the number of patients with testosterone prescriptions dispensed from U.S. outpatient retail pharmacies.

The IQVIA Health Plan Claims Data provided administrative healthcare claims for a sample of commercially insured patients for our analysis of diagnoses proximal to testosterone initiation.

We evaluated the number of unique patients who were dispensed testosterone prescriptions from U.S. outpatient retail pharmacies.

Please note that this data source did not capture events where injectable or implantable testosterone were administered by healthcare providers and doctors' offices or clinics.

We included four years of data in twelve-month increments from September 2013 to August 2017. We included male patients and stratified by age group.

We used a cut-off of 13 years old for contextual purposes to provide background information for this Advisory Committee.

These results show the estimated number of young male patients being dispensed testosterone prescriptions from U.S. outpatient retail pharmacies between September 2013 and August 2017.

Approximately 7400 male patients aged 17 years or younger were dispensed testosterone prescriptions in the year ending August 2017.

22 percent of these patients were aged 13 years or younger with a range of 21 to 27 percent during the time studied. 78 percent of patients were aged 14 to 17 years, ranging from 73 to 79 percent during the time studied.

In our second analysis, we assessed diagnoses and claims data among a sample of commercially insured male pediatric patients aged

19 years or younger, with at least one year of testosterone.

Our study goals for this analysis were to evaluate diagnoses associated with chronic use among adolescent males.

We selected male patients with at least one year of testosterone therapy, defined as the presence of at least five testosterone claims and either continuous testosterone therapy for at least one year or at least a year between the patient's first and last testosterone claim, and at least two testosterone claims per year on average.

We searched for any diagnosis of interest in medical claims from one year prior to testosterone initiation until one month after initiation. We aggregated these results from 2009 through 2016.

These claims include all testosterone formulations and they did capture events where injectable or implantable testosterone were administered to a patient in a doctor's office or a clinic.

These results are from a sample of 1649 commercially insured male patients aged 19 years or younger with chronic testosterone therapy, stratified by age group. And again, these age groupings are provided for contextual purposes.

Patients may have contributed more than one diagnosis of interest to these results, and therefore, the data may sum to more than 100 percent.

Among male patients aged 17 years or younger, claims for other testicular function were present for approximately one-third of patients as were claims for delay in sexual development and puberty.

Claims for lack of expected normal physiological development were present for approximately one-quarter of patients and claims for Klinefelter Syndrome were present for around 17 percent of patients.

Most of these diagnostic codes do not provide more granular information regarding the clinical research behind the testosterone

initiation or testosterone deficiency.

In conclusion, pediatric male patients comprised less than one percent of all male patients who received testosterone from retail pharmacies.

Among these pediatric patients, around 75 percent were 14 to 17 years old, with an annual range of 39 to -- sorry, 73 to 79 percent. The reasons for these patients initiating testosterone were not available.

Among pediatric male patients with long-term use, the most prevalent diagnoses were testicular hyperfunction or delayed puberty. However, many diagnostic codes were not informative enough to describe the cause of testosterone deficiency.

This concludes the presentation on testosterone utilization among pediatric patients.

CHAIR DRACKER: We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions

to a specific presenter.

Thank you. We'll try to satisfy the technical difficulties in a minute. We've got one.

DR. COOKE: David Cooke for Dr. Galescu.

I think it will be relevant to the question of efficacy measures as well but in the incidence or prevalence data of testicular failure, I wonder if you have the feeling for how much of that could be equivalent to subclinical hypothyroidism, where the definition of the impaired Leydig cell function is based on maybe a mild elevation of LH with the testosterone level in the normal range?

DR. GALESCU: As I said before, the statistical part of prevalence and incidence of pediatric hypogonadism is pretty much all over the place.

So, I'm not sure if some of the data includes cases that were misdiagnosed or cases that were soft.

What I can say is when I tried to do the tally up was with studies and statistics that took into consideration chronic persistent hypogonadism. How that was diagnosed I'm not 100 percent sure.

The data that I used, I tried to be consistent and not cite a lot of single peer review articles and I tried using mostly CDC data, cancer, National Cancer Institute data, data from meta-analysis.

So I'm hoping that when we discussed about hypogonadism in our presentation, we referred to chronic, persistent, adequately diagnosed pediatric male hypogonadism.

I hope that answers your question.

DR. SHARRETTS: I just wanted to follow up on what Dr. Galescu was saying. I think a lot of it depends on the diagnosis as well.

So, for example, in the post-cancer I think there's probably a spectrum. But in a diagnosis such as Kallman Syndrome or idiopathic hypogonadotropic hypogonadism, it's

unquestionable and the testosterone levels are near zero.

DR. HOEHN: Sarah Hoehn, not a pediatric endocrinologist. I have a question for I think Dr. Nguyen or anyone else.

It wasn't clear to me through any of these presentations or from the briefing documents how people know that the testosterone is not getting to supra-therapeutic levels.

I know they've talked about PK proving that the testosterone level goes up and is normal, but I haven't seen anything looking at whether or not it gets supra-therapeutic.

And it could be because this is the standard of care in terms of lab tests, in terms of how frequently they do it, but I wasn't sure. So my first question is about how do they know it's not supra-therapeutic?

And then the second question is if there's any data about aggression or any of those other issues if they do have data when it gets supra-therapeutic?

DR. NGUYEN: That's an excellent question and that's something I didn't fit into my presentation, but certainly for the adults, our key efficacy end point is what we call a responder, so when you measure PK measurements over 24 hours.

And it's a very intensive PK sampling and you average it. You are considered a responder if you fall within that normal range, which is usually between 300 to 1000 nanogram per deciliter.

The second part, the second hurdle so to speak, is that you cannot have CMAXs above various thresholds. For example, the first threshold is CMAX above 1500 and then 1800 and certainly 2500.

And there we actually count the number of outliers. So, for example, in a Phase 3 trial, that expectation is that you have no subject who has a CMAX above 2500.

So, we do have some very key safety parameters built in as far as qualifying to be

approved, so to speak. So that's how we capture the CMAXs.

DR. GALESCU: I'm going to try and give you a clinical pediatric perspective. Yes and yes.

Yes, the levels of testosterone goes high because the formulations of testosterone currently available are not in any way physiological. The clinical practice is eyeballing it more or less.

We start low and hope we don't surpass thresholds. The ranges of normal testosterone based on Tanner stage are very high and in clinical practice we aim to stay somewhat in the middle but, for example, testosterone injectable, it will skyrocket and then have a sharp fall.

That's not the way children naturally produce testosterone. So, yes, we do overshoot when we treat these kids with the current formulations and they do get aggressive and other issues, mood, stability, we advance their bone age.

All these things we need to be very careful of in clinical practice when treating with testosterone.

DR. HOEHN: Can I just ask a follow-up question directly related to that? So how frequently in the clinical practice are you checking testosterone levels?

DR. GALESCU: Again, based on the condition, first of all, the range of treatment, it could be every two weeks or it could be every month depending what you treat with. It's difficult to say.

In a cancer survivor patient that has frequent clinic visits anyway, it might be easier to monitor. In a patient that has hypogonadism, gets treatment but you don't have as intensive follow-up, it might be every month or every couple of months.

DR. HOEHN: Last question on this topic, I promise. Is it followed throughout treatment or if you have three standard levels, do you then stop checking?

Or is there some ongoing assessment throughout the duration of treatment?

DR. GALESCU: Again, case by case and based on whatever the condition that you're treating and the stage at which the patient is.

Because if the patient has not progressed at all through puberty, your role as a clinician is to take the patient through puberty in as physiological a manner as possible, which means at least two and a half years of progression.

So, the level of treatment will change, the level of monitoring will change as the patient progresses through puberty.

If the pubertal arrest because of the patient condition happened at a later stage, you might get away with just a couple of bringing him to Tanner stage 4, 5 levels and then just adequate maintenance.

DR. WADE: Kelly Wade.

Staying on a similar topic, I was wondering if you could expand a little bit more, Dr. Nguyen or Dr. Galescu, about what is known about

the pharmacodynamics of exposure with bone growth and advancing bone growth?

And I know your presentation mentioned C average and CMAX but I'm also wondering about variation and exposure in things such as semen.

Is there anything we know about the pharmacodynamics of safety in terms of advancing bone age that could be affected by dosage or exposures?

DR. NGUYEN: My answer would be actually pretty easy because the Phase 3 trials are in grown men so we are not worried about the bone age.

And the goal there is really just to maintain the serum levels in the normal range so the man can maintain his sexual characteristics that he has already obtained.

DR. WADE: I guess I would say maybe is anything known in the pediatric literature of exposure about testosterone exposures of other pharmacodynamic characteristics that may affect advancing bone age?

DR. GALESCU: There is pediatric literature supporting bone age advancement with testosterone use. It is usually directly related to dosage and levels attained.

So there is a dose response curve but there's, again -- and every time I have to mention this -- depending on which condition you're treating, Klinefelter will be very different from a cancer survivor patient that has been bombarded with cytostatics and radiation therapy, which both will have already impacted the growth plate significantly.

In those cases, you don't really know what's affecting what. But, yes, there is a dose effect proportionality between testosterone replacement and maturation of the bone plates, which is the physiological way boys grow.

CHAIR DRACKER: Peter?

DR. HAVENS: Thank you very much. I have a series of questions that get to the I say of extrapolation and I really appreciated the initial presentation concerning that question.

So, as some of the pharmacokinetics related extrapolation discussion centered around the fact that in adults there is a known normal range and a known above-normal range, which you've already discussed.

In pediatrics it seems like the normal range varies, not just with age but specifically within people. So, somebody's normal at age 13 might be different from somebody's normal at age 15.

So these are fundamentally different, making it impossible to extrapolate. Is that overstated?

DR. NGUYEN: Actually, I think you brought up an excellent point and that's why we included it in our background package as well as mentioning it in the presentation.

One of our challenges is to look at the disease manifestation's goals of treatment and can we extrapolate between adults and children? And maybe yes or maybe no.

So, I think you're bringing up

certainly one aspect of it that as we're thinking about it, it might be very difficult to extrapolate when we're looking at PK for the reasons you've stated.

DR. HAVENS: Thank you. Then the other question about extrapolation had to do with Table A2 in the backgrounder and the presentation on drug utilization.

It seems like adult males, and again, I'm not an endocrinologist either, oh my goodness, but with males it sounds like once you're identified with low testosterone, people would consider that a lifelong condition.

DR. NGUYEN: So if I may clarify, in the Phase 3 because all we're looking for is making sure when you give a man the investigational product, it's a testosterone product that does what it's supposed to do, which is to raise your serum T levels to the normal range and not overshoot.

The intended population are not the same as the men who are enrolled in this Phase 3 trial. And the intended population are men who

have genetic or structural causes of hypogonadism.

So you can see low serum testosterone level associated with many different conditions. Back in 2014 we actually brought it to an Advisory Committee to discuss what we call age-related hypogonadism because we do know that as men age, on average, their serum T levels decline.

But is that something that's abnormal? Is that something that you need to have hormone replacement? It certainly is nowhere as clear as a man who's had testicular cancer and has had his testes removed.

So, the intended population is really more towards the latter that I mentioned.

Does that make sense?

DR. HAVENS: Yes, but it gets sort of to the same idea that in adolescence there's a changing amount of testosterone that's appropriate by age and might be a variant among people.

And so when I was looking at the Table A2, other testicular hyperfunction delay in sexual

development and lack of expected normal physiological development.

I guess the question is if you just wait, will many of these people develop testosterone that's the right amount for them?

DR. GALESCU: I can answer that. In the pediatric population, there is a condition called IHH, classified as IHH, idiopathic hypogonadotropic hypogonadism.

A lot of things get bumped under this umbrella and you have the constitutional delay of growth. Again, these might be absolutely normal children growing at their own pace.

Yes, they're not going to be on par with their peers, yes they're not going to have the secondary sexual characteristics of their peers, however, they will catch up.

Unfortunately, these kids do end up being treated in clinical practice with testosterone products because of parental concerns, because of other issues, because of peer pressure, because of a number of issues.

So, we are not talking about those patients in this presentation and in this indication.

We on purpose left those people out because from a clinical and regulatory point of view, we do not consider those patients adequate for treatment with testosterone products because of the reason that you said.

If you wait, they will start the HPG axis on their own and they will produce enough testosterone. It might not be at 12, 13, it might start at 16, 17, but that's a variant of normal.

So we did not include those patients.

DR. HAVENS: So my question is what is the specificity of the diagnostic codes, the first three in Table A2 in the backgrounder, which incorporate 90 percent of use?

Are many of those people really IHH for which you say it's not really an indication? Does this make sense to you?

DR. GALESCU: In literature but not

anywhere in government statistics or NIH statistics, in just peer reviewed literature, the estimate of these patients is somewhere between 20 to 30 percent of the total patients treated with testosterone products.

I am generally quoting, you will have ranges that go up to 50 percent. Again, when I did my presentation and I came up to those 50,000 patients in the age range that we are looking at, those are strictly patients with confirmed hypogonadism, not constitutional delay of puberty.

DR. HAVENS: Thank you.

DR. GALESCU: And one more thing to answer your first question, usually in pediatrics we don't go necessarily by age, again because every child develops at its own pace.

We go by Tanner stages, and the norms of testosterone and the norms of treatment and the norms of monitoring are by Tanner stages and sexual maturation.

CHAIR DRACKER: I just want to remind everyone please state your name before asking your

question or making a comment, for transcription purposes.

DR. HAVENS: That was Peter Havens.

CHAIR DRACKER: Thank you, Peter.

MS. OSTER: Randi Oster. My question has to do with testosterone and the effect on sperm.

Could you comment on how testosterone affects the sperm count and what studies have been done to understand that the impact of the testosterone is not continued to be needed as the child grows?

DR. GALESCU: Unfortunately, I'm not aware of any sperm count studies in the pediatric population off the top of my head.

If testosterone physiologically is necessary for maintenance of sperm production, it is an internal regulation of the testes. So the testosterone effect on certainly cells to maintain and promote sperm production is there.

I know that it can be a double-edged sword obviously. Overtreatment can inhibit

production but in pediatric population, I'm not aware of any studies.

MS. OSTER: Can you comment on the adult population and what happens with testosterone and sperm production just so that if we have to extrapolate, we have that knowledge as a group? Thank you.

DR. NGUYEN: Speaking as a gynecologist, I'll do my best. Certainly, with exogenous testosterone injection we know that you do shut down that natural feedback where you produce LH, FSH.

So, certainly with overtreatment there is suppression of sperm production and certainly a very high exposure. Certainly, chronically it can lead as far as infertility. We certainly know that in athletes.

So I think that's an extreme end of that pharmacodynamic response but, yes, we do know that an adult male, who is looking to start a family, what have you, that testosterone replacement certainly may adversely impact his fertility.

CHAIR DRACKER: Randall, you had a question?

DR. FLICK: Forgive me for asking simple questions, another non-endocrinologist. So, you talked about the use of testosterone replacement based on pharmacy sales but maybe I'm confused.

Are these all injectable from outpatient pharmacies or are there children using other forms other than the injectable or the implantable?

MS. WOODS: Hi, this is Corinne Woods, the drug utilization analyst.

We do have some information about patients who received testosterone products from outpatient retail pharmacies, however, we did not break that down by formulation so we don't know what's topical transdermal versus what's injectable.

We do know that there is some injectable use but we didn't analyze that for this PAC.

DR. FLICK: I guess I was more

interested in knowing whether there are children who are using the forms that are typically used in adults.

And do we have any information about adverse effects, side effects, whatever, in that population? I assume not.

MS. WOODS: We don't have that analysis for this PAC.

DR. FLICK: Okay, and then my second question is it seems to me that in adults we can use a kinetic end point, serum levels. In children we have to use a dynamic end point, some physiologic change.

And the question that I would have for my endocrine colleagues would be if you're designing a study to look at the outcome of testosterone replacement in children, what is your primary outcome measure?

Is it testicular size? Is it growth plate closure? What is the primary outcome measure?

DR. GALESCU: You know, that's why you

guys are here. Okay, so you're right, in pediatrics we want a PD kind of outcome.

This may be a compound of certain ranges of testosterone level with clinical evidence of sexual maturation, with clinical evidence of growth, secondary sexual characteristics.

It can be a lot of things.

DR. FLICK: And again, forgive me for my ignorance, but as I read the briefing document the problem here is that these dynamic end points have enormous variation, which leads one to the inevitable conclusion that the sample size is going to have to be so large that it overwhelms the number of available subjects, which is obviously, again, the reason we're here.

But I'm just looking for a little bit of clarity.

This isn't the first time that anyone here as looked at studies regarding testosterone replacement in children for some reason or other, and I just wonder what the end points in those studies are for a person who doesn't read endocrine

literature?

DR. NGUYEN: Hi, actually if I may hold your question, we actually have Dr. Chan who will be presenting the management of permanent hypogonadism in boys.

And I think your questions can really be -- we'll have a much broader discussion on that.

CHAIR DRACKER: Bridgette, you had a question?

DR. JONES: Bridgette Jones, my question may also need to be answered in the afternoon. So one of the things that's been mentioned is the wide variability in testosterone levels, what's considered normal throughout puberty.

And I was wondering, is there any information about the correlation between testosterone levels and any kind of effect, so gain of secondary sexual characteristics?

What's the variability in the response in response to your testosterone level?

DR. GALESCU: There's no clear-cut --

there's obviously a dose response curve but it varies from patient to patient and from clinical scenario to clinical scenario. Each patient will respond differently.

DR. JONES: And do you see similar variability in adults even when it's used for other indications? Does anyone know? Is there a lot of variability in the response?

DR. NGUYEN: As far as correlation with either pharmacodynamic outcomes?

DR. JONES: Yes, between the actual testosterone level that's attained with treatment and whatever the clinical outcome that you're treating.

Do you know if there's --

DR. NGUYEN: I'm not aware. Certainly, as I mentioned in Phase 2 trials we do not correlate the responder levels to a specific clinical outcome.

So again, in the male it's rather simple, you're just looking to get the range of the C average into the 300 to 1000 range.

DR. JONES: Thank you.

CHAIR DRACKER: Dr. Portman?

DR. PORTMAN: So this is fun and I think it's a topic that goes beyond just this particular topic.

Speaking from a drug developing standpoint, what I wanted to ask is related again, as Dr. Flick and Dr. Haven have commented, to extrapolation.

So, how are we going to take this information that we have from adults and the approval in adults and use it in kids? So, with extrapolation it really should be used unless we can justify why we shouldn't use it.

And it reduces the exposure of children to research and it uses all the available information that we have to try to make drug development easier for kids.

So this is a difficult situation because you have heterogeneous etiologies of hypogonadism. In pediatrics the response is going to be different depending on the age.

Each individual etiology is very small so how are you going to take all this different group and pull it together from that standpoint? And then the response is going to be heterogeneous, as we've heard.

So the real question I have, then, if we're going to think about extrapolation is what is the efficacy end point? And that's been addressed.

But I mean in the context of extrapolation, what can we use from this long list of testosterone effects to use for efficacy, aside from just the testosterone level, which may be the only one we can use.

I don't know.

DR. NGUYEN: So, I'll jump in and certainly, the question you brought up and I think was brought up previously is one about discussion points to the panel this afternoon.

So if you could hold onto those thoughts, that's actually a very critical discussion that we're going to have just dedicated

to that point.

And as I mentioned, we do have our guest speaker who is an expert in this field, who can help inform us a little more.

CHAIR DRACKER: Christy?

DR. TURER: Christy Turer, UT Southwestern.

So, some of my comments, one, regarding extrapolation I think it is important to keep in mind what are the adult diagnoses? And we are not given those currently.

Secondly, one of the things that I bring to the pack is my experience with obesity and I'll say in the adult world, a lot of low T is driven by obesity.

And I did a quick PubMed search and it looks like we also know that children with obesity have some secondary hypogonadism and in fact, bariatric surgery reverses that.

So, in the comment about lifelong use, weight loss improves testosterone levels significantly. So, I think we need the adult

diagnoses to understand if extrapolation is possible.

We need to understand the role of obesity in children. It turns out NHANES actually does have testosterone all the way down to the age of six so you can get population-based levels and I think it would be prudent to exclude children with obesity to develop such population-based levels.

I didn't see whether that's already been published. And then third, we absolutely need long-term adverse events. These were not discussed but we are very concerned in internal medicine about cardiovascular outcomes.

This increases erithropoiesis, I'd be worried about stroke, it changes HDL levels, reduces them. I'd be worried about cardiac events. It also can increase gynecomastia and we have been seeing breast cancer in males in unprecedented rates.

So I absolutely think that this is a drug where we need evidence. And in terms of

extrapolation, a very big concern is in adults they're not going through puberty.

I think we've got a different scenario here so we need to be thoughtful about both what we're treating, the major differences from adults, as well as the long-term outcomes.

DR. NGUYEN: I'll comment on what the intended population is in adults.

You're absolutely right, we did not provide an exhaustive list of diagnoses, but the general summary point is those men with genetic or structural defects require lifelong testosterone therapy.

And I actually can comment on the obesity bit because we are aware, certainly, men with diabetes, obesity are receiving testosterone.

Those are not the intended population because frankly, we don't know if you just give those men testosterone that it's going to reverse their disease. In fact, as you mentioned, they lose weight, that's all they need.

They don't need to take testosterone and have all those adverse effects. So, I hope that helps sort of narrow down the adult population.

CHAIR DRACKER: Ethan?

DR. MCCUNE: Sorry, this is Susie, I'm going to cut in for a second. I apologize for the microphone issues that we seem to be having intermittently across the table.

If we can make do with what we've been doing until the break, we will fix it at the break. So thank you.

DR. HAUSMAN: Ethan Hausman, FDA. I just want to clarify for the Advisory Committee one or two nuance issues about extrapolation.

The disease presentation and progression and response to treatment between adults and adolescent or pediatric population does not have to be exact. You don't always have to use the exact same marker.

So, in the end, if we believe that the central issue is the hypogonadism, the task of the

Committee throughout the day will be to try to arrive at some sort of gestalt at what we think an appropriate pediatric marker could be.

It doesn't necessarily have to be the same as adults because we're in different physiological stages of development. So that's one thing.

And then the next job would be to identify a dose as Members have said today, investigating safety of course.

And just as input from before, I'd like to remind people that one of my specialties is actually pathology, it's clinical pathology, and there's a lot of clinical medicine in there.

And as we were going through or as I was going through, helping to put the background package together, the clinical pathology literature actually does address some specific markers, clinical markers, that are part of Tanner stage that people use in addition to bone age.

Testicular volume and the delta in testicular volume over the treatment period can

be used by some clinicians when they're treating patients.

It's different for the incident issue, disease X and disease Y may not be the same.

The second key issue is that you're going to be at a different starting point depending upon when you have arrest of puberty if you're talking about some sort of secondary issue that's causing it.

CHAIR DRACKER: Thank you.

DR. HAUSMAN: Anyway, that's it, thank you.

CHAIR DRACKER: Dr. Sayej?

DR. SAYEJ: Wael Sayej. I completely agree with Dr. Turer's comments about the obesity and a lot of the other risk factors associated with the testosterone deficiency.

Just from a general perspective, idiopathic hypogonadotropic hypogonadism is very common in adult males, about 40 percent of adult males, as far as I know, have some level of that.

And as far as I know, testosterone

replacement in that population leads to about 88 -- or 88 percent of those treated develop azoospermia, which is decreased production of sperm, which also, as far as I know, is irreversible.

So one of the recommendations or the comments or the advice that is given to adult males who are being treated with those medications is that if they are planning on having children, then this is something that's going to lower their chances of actually being able to have children.

So, if we are seeing that high of a percentage of patients, adult patients, developing azoospermia, without looking at extrapolation of data, can we assume that we will see the same level in the pediatric population, if not higher?

And the second I have which is a question is are there alternatives to prevent people who need testosterone replacement from developing azoospermia?

For example, in adults they use

chlomiphene citrate, which is a fertility drug. Is that an alternative that can be used in some of these patients?

DR. SHARRETTS: Hi, John Sharretts. I think I'll field that question. I'm not on the testosterone regulation but I am an adult endocrinologist.

So I think that fertility is really outside of the scope of this presentation. So, fertility is a complex condition and it's dependent on stimulation from the pituitary gland on the cells in the testes, and I'm just going to be very high-level on this.

And it requires testosterone levels within the testes that are much higher than testosterone levels that are in the circulation.

So, when we are talking about replacing testosterone levels to stimulate secondary sexual characteristics, that has no impact on fertility.

Or shall I say if anything, testosterone replacement inhibits fertility

because it's going to inhibit LH and FSH production by the pituitary gland.

And if there is a structural defect in the testes, it may not be possible to stimulate the testosterone levels or the sperm cell development in the testes.

So I think fertility, it's treated differently and it's outside of the scope of what we can talk about here.

So children who have Kallmann Syndrome, the treatment if they desire fertility is something very different and it's just something I don't think we can really -- I don't think we can get to it in the treatment of hypogonadism in kids.

DR. GALESCU: And just quickly, I wanted to remind you that many of the conditions that I went through today, they will have a baseline fertility issue associated with their disease, completely unrelated to the treatment of their hypogonadism.

So, when you treat with testosterone, many of these cases, you treat them so they can

obtain those secondary sexual characteristics so they can obtain growth, muscle mass, accrual of voice changes, all of the things that are considered male standards.

But their baseline disease will affect their fertility.

CHAIR DRACKER: We will take one more question and then we have a break at 10:45 a.m.

MS. OSTER: Randi Oster. I actually have two questions so I'm sorry about that.

If we did nothing with these 50,000 cases that you've brought up, please describe to me when they're 30 years old their voice level, how they look, and what actually happens? So that's my first question.

And my second question is reading the documents, we have seen that many times parents want their children to go through the puberty and there's a lot of peer pressure.

And one of the outcomes of this testosterone can be acne as well as mood disorders as well as these other things.

And so my question is what research has been done when someone is taking testosterone as well as Accutane, or as well as an ADHD medication?

And how does that affect overall what is happening with that child?

DR. GALESCU: I'm going to try and break down in two answers. Hopefully I can reply.

Most of these conditions, depending on the state that you start treatment at, some of the cancer patients, some of the other conditions will actually progress through puberty up to a point and then rest and stop progression at that point. And then they require treatment.

So wherever they stop, be it Tanner stage 1 or 3, that's where they'll be as an adult without testosterone supplementation. You don't progress, this is the physiological way of accruing secondary sexual characteristics.

So you will talk about -- an untreated patient will be juvenile in all aspects, body size,

voice, hair patterns, everything, forever like an early teen.

Your second question I honestly don't know. So you're right, the peer pressure part has been studied extensively. It is complicated.

Yes, you will have instances of acne but usually, the patients that I personally dealt with were much more concerned about growing, about developing muscle mass, about having facial hair, about having a deep adult voice as primary points of focus about peer pressure, rather than the acne issue.

I don't know what the drug interaction would be.

CHAIR DRACKER: Thank you. I just want to reflect for a minute.

What's very interesting is that over the years when I've listened to a variety of different subjects we've discussed, we often talk about it in just the limited context of treatment of children, and yet, all of us on the Committee realize that these children graduate from our care

and become adults.

And we forget that the treatments we sometimes provide today become disorders that we don't deal with tomorrow. And we rely on our adult colleagues to try to maintain these patients.

And hypogonadism is no different really in many cases than hypothyroidism which doesn't go away. And unfortunately, all of us are limited in the scope of what we do in trying to take care of these children who graduate into adulthood.

And it's frustrating at times, just like with congenital heart disease, these children that we fix become adults and the adult don't know how to really deal with them.

So, it's a complicated issue regardless of whether we're discussing just hypogonadism or any other disorder that we discuss.

So I think it's interesting and I think all of us are realizing that it's a problem when they do become adults, and we need more information and long-term follow up.

We are going to start promptly at 11:00

a.m. again. I just want to remind everyone to please fill out your lunch requests so we can get that in.

I also want to remind everyone not to discuss any of the proceedings if you're a Member of the Committee. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:48 a.m. and resumed at 11:05 a.m.)

DR. DRACKER: The first speaker for this session is Dr. Chan who will discuss landscape abuse. Thank you, Dr. Chan.

DR. CHAN: Good morning. My name is Ming Chan and I'm a pediatric endocrinologist at Boston Children's Hospital. I was going to be co-presenting with Dr. Stephanie Seminara from Massachusetts General, but she had a death in the family and was unable to attend today. It would be great to have the perspective of an adult reproductive endocrinologist. I did train with Stephanie from my research years and my fellowship for many years, so I did absorb some things. I'll

try to answer some of the adult questions as well. But again, I'm a pediatric endocrinologist.

This is our disclosures. So I'm going to recap some of the topics that have already been discussed, but repetition can be helpful and review basic male reproductive endocrine physiology, talk about causes of hypogonadism in boys, discuss how we diagnose these conditions and try to distinguish between them, often unsuccessfully, and then talk about the management issues that are the main focus of today's presentation.

So to briefly recap reproductive endocrine physiology, we often talk about the hypothalamic pituitary gonadal or HPG axis. And the hypothalamic populations in question are the neurons in the hypothalamus that make a hormone called kisspeptin which, in turn, stimulate GnRH neurons to make GnRH in a pulsatile fashion. This, in turn, triggers the pituitary gland to release FSH and LH which circulate through the bloodstream, and in the case of boys, the gonads to make testosterone. That's the primary product, the

hormonal product of the gonads. It's converted peripherally to DHT as well as through the aromatase enzymes to estradiol and some of the important properties of testosterone are mediated by estradiol.

The reproductive endocrine system is remarkably dynamic across the life cycle, so even before birth there is remarkable activity of the reproductive endocrine axis which is important for a number of developmental features that I'll come to in a moment.

There's a perinatal dip, but then the activity resumes in infancy and proceeds through what we often call the minipuberty of infancy in boys lasting about six months, give or take. And then there's a long period of relative quiescence through childhood. We'll sometimes call this the juvenile pause and then the re-emergence of activity at the time of puberty and persistence of that activity through adulthood.

One thing I didn't put on this slide, but it's worth mentioning is that this timing of

pubertal initiation varies tremendously, that there is about a four-year variation in just normal pubertal timing, not to mention some of the variants, both precocity and delayed puberty.

So what are the effects of androgens during this life cycle? In the first trimester of fetal development, it's responsible for virilization of the external genitalia and so the genitals start from primordial structures that are bipotential and depending on whether androgens are present or absent, they will develop of the male or female pathway respectively. It also has a role in internal male genital structures and stabilizes Wolffian duct structures that give rise to the epididymis and other structures.

During the second and third trimesters after the genital development is complete, there is an on-going role for testosterone in encouraging and driving the growth of the testes as well as the descent of the testicles from the abdomen eventually into the scrotum and particularly that final step of traveling from the inguinal ring to

the scrotum is a testosterone-dependent process.

There are also poorly defined effects on the brain that we know of because we know that there are differences between boys and girls in terms of behaviors, sexual orientation, gender identity and we know that testosterone and androgens have an important role of precisely what those mechanisms are or unknown.

So during the pediatric years, I mentioned the minipuberty where there's that activity of the axis during infancy and for the most part we really don't understand what the role of the minipuberty is. There's some speculation, but little direct evidence.

And in childhood, it's not as if the system is completely shut off. There are very low levels of testosterone being produced during childhood, during that juvenile pause, but what's not known is whether this has any important physiological role. But then at puberty, as we've discussed, there are a number of changes induced by testosterone including hair growth, deepening

of the voice, the growth spurt which is driven both by testosterone and by estradiol, genital development, increased muscle mass, decreased fat mass.

And then in adulthood, ongoing use of presence of testosterone is important for maintenance of libido, erectile function, muscle mass and strength and an important thing that I'll get to in a moment is bone health.

And as I mentioned, testosterone is aromatized estradiol and many of testosterone's effects physiologically are mediated by estradiol and in particular the growth effects are largely driven by estradiol. There is a contribution directly from testosterone. The maturation of the growth plates and eventual closure of the growth plates is exclusively driven by estradiol. Acceleration of bone mineralization is largely estradiol-dependent, so testosterone does have some direct effects.

And in adulthood, maintenance of bone mineralization and slowing of that rate of decline

of bone mineralization is critically dependent on the presence of estradiol.

So I'm going to recap some of the causes of testosterone deficiency in boys. The causes that are typically permanent include primary testicular insufficiency and I'll get into subcategories in a moment, as well as causes of persistent or permanent hypogonadotropic hypogonadism. This can be due to pathology of the hypothalamus or pituitary or both. And then this entity of idiopathy hypogonadotropic hypogonadism.

And then I think very relevant in the discussion will be the self-limited or reversible cause of delayed puberty in boys foremost of which is constitutional delay which I'll describe more in a moment, and then functional causes of hypogonadotropic hypogonadism.

So to go through these causes starting first with causes of primary testicular insufficiency, Klinefelter Syndrome again, congenital anorchia, also called Testicular

Regression Syndrome, formerly called Vanishing Testes Syndrome which we don't really use as a term much anymore.

And then certain disorders of sex development, also called DSD. These are so-called intersex conditions. And then acquired causes that have mentioned, chemotherapy, particularly alkylating agents, radiation mumps, trauma, torsion, surgical removal of the testes for any reason.

So to dive into each of these in a bit more depth, Klinefelter Syndrome, as was mentioned, is the presence of a Y chromosome and two or more X chromosomes. And so this is a karyotype showing the presence of an extra X chromosome in an otherwise XY karyotype.

So the classical form of Klinefelter Syndrome you have 47 chromosomes and 2 Xs and 1 Y chromosome, but variants include XXXY, XXYY, mosaicism, et cetera. And all of these are generally considered Klinefelter Syndrome and its variants.

The clinical features are highly variable but may include a smaller genitalia, tall stature, challenges with learning, socialization, sometimes frankly psychiatric disorders in childhood, gynecomastia. In adulthood, there's a well-described increased risk for features of metabolic syndrome such as hypertension, Type 2 diabetes, obesity. And almost inevitably these men or late adolescents develop testicular insufficiency.

Typically, puberty starts at a normal time. Children progress through puberty to various stages, sometimes completely, sometimes partially before the testicular insufficiency and testosterone deficiency kicks in.

As was mentioned, the prevalence of Klinefelter Syndrome is probably somewhere anywhere between 1 and 500 to 1 in 700 studies of live male births and studies that have looked at newborns and done karyotype analyses. And historically, this has been under diagnosed and often diagnosed late.

And so this is a graph from a review article from Claus Gravolt that shows the age at diagnosis for men with Klinefelter Syndrome and you can see that there is a peak at birth for prenatally diagnosed Klinefelter Syndrome, but the main peak is in the 30s when men are typically presenting for infertility and childhood diagnosis is relatively rare. But this is changing.

The widespread use of noninvasive prenatal screening to look at chromosome has led to dramatic increase in prenatal diagnosis of Klinefelter Syndrome and I think these types of graphs are going to change dramatically over the next several years.

So as I mentioned, in Klinefelter Syndrome the puberty typically starts at a normal time that would be appropriate for the child, but then the hypogonadism, the primary hypogonadism emerges at some point, typically late adolescence or early adulthood, although there's a fair amount of variability.

The question has been raised whether

there might be some partial testicular insufficiency, even in those minipuberty ranges or during childhood and this becomes relevant in discussions about use of testosterone treatment in these age ranges.

Just to show you some examples of the data that are out there, it's fairly inconsistent. So this is looking in infants, so this is one article that shows the chronological age in months on the X axis and the testosterone concentration on the Y axis. And the arrows bracket indicate the typical range for newborn boys and you can see that some of the individuals with Klinefelter Syndrome have testosterone in the typical range and others are below that range.

This is another study looking again at the normal range shaded in gray and the testosterone measurements for the dots in the boys and you can see that many, but not all of them, have testosterone in the normal range. Some of them fall below.

This is yet another study -- or the boys

with Klinefelter Syndrome are those blue dots among the gray dots of a normative sample. And in this study, most of the boys are actually in the higher end of the normal range for testosterone in infancy. So again, the data is inconsistent. I think from this I'd take away that some, but not all boys with Klinefelter Syndrome may have testosterone deficiency in infancy. And in childhood for the levels already low to start with it becomes next to impossible to demonstrate whether the boys with Klinefelter Syndrome are even lower than that.

I'm going to mention briefly testicular regression syndrome. This is where an individual with XY chromosomes and typical male appearing external genitalia are found to have absence of the testicles. The cause of this is not entirely clear, but it's thought that it had to have happened after the first trimester because in the first trimester if you have testosterone deficiency, you have effects on the external genitalia and these individuals have normal male external genitalia. So the loss must have happened some time during

the second or third trimester after genital development was complete. But what the cause of that loss is unclear. It's been postulated that it could be bilateral testicular torsion, at least in some cases. Again, it's not entirely clear. This is a relatively rare condition and is fairly recognizable by the lab pattern showing primary gonadal insufficiency in a newborn boy who has again otherwise normal appearing male external genitalia.

Intersex conditions, also called DSD, or disorders or differences of sex development are defined. The DSD term was defined when it was coined as congenital conditions in which development of chromosomal gonadal or anatomical sex is atypical.

Just a brief mention that the nomenclature is somewhat contentious. Intersexes come in and out of favor. Not everyone likes the DSD designation so we always to be a little bit cautious in discussing these conditions. But I will use the term DSD.

The conditions that can be associated with male hypogonadism are just a subset of DSD, but they include conditions where there's partial testicular dysgenesis that the testicles don't form fully properly. Disorders of androgen synthesis, so biosynthetic defects and testosterone production are disorders of androgen action, namely androgen insensitivity syndrome where the androgen receptor is mutated.

You can have issues where the testes are appearing in an XX individual who would normally have ovarian development and this can either be completely testicular or oval testicular where there's a mix of ovarian and testicular tissue and oftentimes these gonads are dysgenetic and also don't produce full amounts of testosterone.

There can be conditions where the Y chromosome is mosaic or chimeric so present in some, but not all cells of the body and this can frequently result in gonadal dysgenesis as well, occasionally ovotesticular DSD.

These are rare conditions. Because

they're so rare the prevalence estimates are challenging, but overall, they are not common conditions at all.

And in order for them to have presented in this way, there had to be some degree of testicular insufficiency during that first trimester to have affected genital development and so testicular insufficiency later in life is an inherent part of these conditions that present this way.

Also, it's worth mentioning that some of the conditions confer a fairly high risk of germ-cell tumor and prophylactic gonadectomy is often done for those scenarios in which case the children are now surgically gonadally agonadal on top of their inherent biological testicular insufficiency.

There are various acquired forms primary hypogonadism that have been reviewed, chemotherapy, radiation, which can actually either cause primary hypogonadism if it's affecting the testicles and can also cause secondary hypogonadism

if radiation includes the hypothalamic pituitary regions. Infections are relatively rare. Injuries such as bilateral torsion affecting both testicles are also quite rare.

And then as I mentioned, there are conditions where bilateral orchiectomy is done either for treatment of bilateral tumors or for prophylaxis of intersex conditions that are at high risk for germ cell tumors.

Moving on to the hypogonadictropic causes of testicular insufficiency in boys, there is congenital hypopituitarism usually seen in the context of other pituitary hormone deficiencies or combined pituitary home deficiency. There have been a number of transcription factors that have been implicated in pituitary development and mutations in the genes in coding those factors can cause hypopituitarism.

The presentation is going to depend somewhat on what axes are affected, but you can have any or all of the pituitary hormones affected. And the presentation can be variable. It can be

that because of the gonadotropin deficiency they present with micropenis and torquism because of deficiency of testosterone in the second and third trimesters. Because of growth hormone deficiency and ACHT deficiency they may present with hypoglycemia. They can have features of congenital hypothyroidism. They may be recognized because of growth failure due to growth hormone deficiency.

And because the gonadotropin axis is affected they can have absent or delayed sexual development and infertility later in life.

Acquired forms of hypopituitarism include tumors or other masses, craniopharyngiomas, for instance, surgery in the region often to manage those tumors, cranial irrigation as I mentioned, traumatic brain injury has been mentioned, and infectious causes such as Langerhans cell histiocytosis, hypophysitis, tuberculosis. These are relatively rare causes.

And then moving on to the entity that has been termed idiopathic hypogonadotropic

gonadism, I think that I'll come to constitutional delay in a moment, but generally I do not use this term to encompass constitutional delay.

It comes in two flavors, as has been mentioned. There's the form with an intact sense of smell and the form with an absent sense of smell which is called Kallmann Syndrome. And these are generally due to defects in the ability to either make GnRH or respond to GnRH and the underlying pathophysiology is that some of the genes affect GnRH neuronal development and their migration from the olfactory placode into the brain or they are unable to make GnRH or receive or make the signals that tell the GnRH neurons to make GnRH such as kisspeptin.

And so the common phenotype is that they have a deficiency in LH secretion and as a result hypogonadism. It can exist on its own or sometimes in the context of a broader syndrome such as CHARGE syndrome. And typically, they're going to be caught because they're failing to enter puberty and they present with delayed puberty, though

occasionally you can catch the boys in infancy because if microphallus cryptorchidism and sometimes they go undiagnosed and present later.

So moving on to constitutional delay, this is distinguished from IHH in that it's a self-limited delay in pubertal onset. So puberty is late to start, but it does start and seems to progress normally. By statistical definitions, this is going to affect two to three percent of children. We don't actually understand the pathophysiology and so our definitions are strictly statistical. If you enter puberty more than two standard deviations below the population mean, we're going to call you delayed. We don't know why you're delayed, but we're going to call you delayed and so by definition it should be two to three percent of the population has delayed puberty.

This is among the most common reasons for children to come to the pediatric endocrine clinic, oftentimes for concerns about height and growth, not necessarily puberty per se though often

all of those together. And I'd say largely and this is the teaching that it's a benign developmental variant of normal. They're just kind of the tail end of the normal distribution curve. I'm not sure I fully agree with that and there's some hints in the literature that there may be long-term consequences in terms of attaining height, peak bone density, psychosocial outcomes which are significant, can be significant during adolescence and may have long-lasting sequellae into adulthood. Though I'd say that the literature is suggestive, but not conclusive on this.

And then finally, functional causes of hypogonadotropic hypogonadism are not an inherent pathology within the reproductive endocrine axis, but a normal physiologic response to the stress. And so these stressors can include chronic illness or inflammation such as Celiac disease, IBD, under nutrition, excessive exercise. Interestingly, the male reproductive endocrine axis seems to be a little more resilient to these stresses than the female axis and so hypogonadism due to, for example,

excessive exercise is relatively infrequent among male athletes where it is fairly common among female athletes.

And then it's worth keeping in mind that there are hormones and other drugs that can suppress the reproductive endocrine axis so high levels of prolactin, high levels of glucocorticoids that you would see in Cushing's syndrome and then use of sex steroids exogenously or endogenous ectopic production of sex steroids or autonomous production from the gonads can suppress the hypothalamic pituitary portions of the axis through negative feedback.

Glucocorticoids, whether endogenous or exogenous, will induce hypogonadism and then opiates are also an important suppressor of the reproductive endocrine access.

So looking at some of the -- to put this into context, how common are each of these presentations or each of these causes. This is unpublished data we have from a retrospective chart review that we did at Boston Children's Hospital

of patients seen over 15 years for delayed puberty. And we had data on close to 1,000 boys and just asked what were the eventual diagnoses for these kids. And so by far, constitutional delay is the most common and other studies have suggested up to two thirds, three quarters of boys presenting for delayed puberty have constitutional delay.

The second most common in our cohort was the functional suppression. I think we have to take this with a grain of salt because we are a large medical center with a lot of chronic illness and so this is not going to be reflective of what you see in the general population. I think the functional causes are going to be much smaller. But the other causes are relatively uncommon, so idiopathic hypogonadotropic hypogonadism is only one percent of the patients in our cohort having a structural lesion or known pathology of hypothalamic pituitary region and two percent hypergonadotropic hypogonadism only two percent.

And then other syndromes, again,

probably a result of being at an academic medical center where we get a lot of referrals, that four percent is probably an exaggeration compared to the general population.

All right, so when we have the patient with delayed puberty presenting in the clinic, how do we evaluate them? How do we diagnose the underlying cause?

So it does very much depend on when the hypogonadism occurs as was mentioned before. If the hypogonadism is present during the first trimester of development, as I mentioned, that will cause atypical development of the external genitalia that can result in conditions including hypospadias, incomplete scrotal development, ambiguous genitalia, and this is an example of the scale that we use as pediatric endocrinologists to describe varying degrees of under-virilization in boys born with -- or individuals, XY individuals, born with atypical external genitalia.

If it occurs during the first and second trimesters, again, sometimes, but not always, it

can be recognized by undescended testes or micropenis in an infant newborn boy. Later on, it is thought that even during the minipuberty there is some importance of the activity of the HPB axis for ongoing penile and testicular growth. And so these are studies in infants that showed some correlation between serum testosterone and penile length and growth.

In adolescence and adulthood, the adolescent is again typically where we'll see them because of absence of pubertal onset and absence of the pubertal growth spurt and so they are noticing that their peers are having their growth spurts and shooting past them in terms of height and they're lagging behind.

Occasionally, you'll see someone who enters puberty, but then has a stalled or delayed presentation and that can be another manifestation of more partial hypogonadism. And then in adulthood again, adults may present because of a loss of libido or erectile dysfunction, loss of muscle strength and athletic performance, and a

vague, but fairly reproducible decreased sense of well-being and infertility is again another common cause of seeking consultation.

So we've worked them up and we have typical laboratory findings. If you are evaluating a child when the HPG axis would normally be active so that is during the minipuberty or during the pubertal years or beyond, if you have primary testicular insufficiency this is pretty readily recognized by the fact that you have low products in the testicles, so testosterone, AMH, inhibin B may all be low if you measure them. And the hallmark is that because of the loss of negative feedback, you have elevated gonadotropins in a hypogonadotropic hypogonadism pattern that really definitively points to a testicular process.

It gets more complicated when you're looking at hypogonadotropic hypogonadism. You're going to see low testosterone, but the question of what is the appropriate testosterone for a given age range is something that's already been discussed and it's a challenging topic. And the

gonadotropins may be frankly low or they may be in the normal range, but inappropriately so because given the hypogonadism, the normal response should be for the loss of negative feedback to result in hypergonadotropic hypogonadism, so normal gonadotropin levels give you a diagnosis of hypogonadotropic hypogonadism as well.

This is now speaking to the challenge in evaluating the reproductive endocrine axis in a prepubertal boy where the axis is normally relative quiescent. There is a range that you can see if they have primary testicular insufficiency. If you measure AMH, you can often see that AMH is low because AMH is actually relatively preserved during the juvenile pause, but it requires that the Sertoli cells are affected. If they're unaffected, then AMH will be normal.

And this is looking at the gonadotropins. This is a study in anorchic boys across a range of ages and years on the X axis. And on the Y axis is measurement of LH. And you can see that there is the activity during the

minipuberty. There's activity at puberty. And these individuals are hypergonadotropics as expected. But during the juvenile pause, some of them have low gonadotropins, some of them have gonadotropins in the kind of typical pubertal range and some are frankly hypergonadotropic. And so there is some variability. So you may or may not be able to diagnose primary testicular insufficiency during that juvenile pause when the axis is relatively quiescent.

Hypogonadictropic states are essentially impossible to diagnose during the juvenile pause because you can't distinguish whether the gonadotropins are low because they're normally physiologically low or because they are pathologically low.

So one of the big challenges that we face in the clinic is, as I showed before, constitutional delay is by far the most common cause of a boy presenting with hypogonadotropic hypogonadism, but it's very challenging to distinguish this from the more persistent form of

IHH. And so the common features is that they present with delayed puberty. They're both diagnoses of exclusions so if you've ruled out functional causes you've used out organic causes and they're characterized on labs by low sex steroids and low gonadotropins.

And the difference is really what happens in the future that the child with IHH will fail to achieve normal reproductive endocrine function by whatever arbitrary cutoff age is used. Typically, 18 is used in most definitions, but again, that's an arbitrary cutoff. Or in contrast, the constitutional delay child will achieve puberty spontaneously before this cutoff age.

And so the problem is that these are both retrospective diagnoses and that doesn't help you distinguish with a child in front of you what's going to happen in the future. And obviously, the prognosis is very different between these two conditions and if you knew how they are going to end up, you might approach them differently in terms of your management. The pathophysiology also is

presumably different that these are qualitatively different. Puberty either happens late or it never happens at all, although there are some nuances there that I won't get into.

And so for decades, pediatric endocrinologists have tried to identify tests to distinguish between IHH and constitutional delay. People have looked at LH at baseline, overnight, stimulated by GnRH or GnRH analogs. People have looked at testicular function. People have looked at inhibin B, AMH, and a number of other tests. And unfortunately, none of them is really fully sensitive or specific in distinguishing IHH from constitutional delay.

And so for example, I'm showing some data on studies that have looked at inhibin B as a way to try to distinguish. And as is typical for a lot of these studies, this is the first study that shows these very promising results. These are the IHH children and these are the constitutional delay children. This is inhibin B on the Y axis and there seems to be this very

clean separation between those with IHH and those with constitutional delay. But then the follow up study comes along and you start to see some overlap and then this is a study in adults with IHH showing that a fair number of them have inhibin Bs in the normal adult range. And so again, inhibin B along with all these other tests is not able to cleanly distinguish between a constitutional delay and IHH.

Some research that Stephanie Seminara and I are conducting is trying to develop a physiologic test that may actually help. You may recall that I mentioned that kisspeptin stimulates the body to make GnRH and individuals with IHH, the pathology is generally at the level of the GnRH neuron, so we hypothesized that the kisspeptin stimulation test would be able to help distinguish IHH from constitutional delay.

And this is data from an initial study we did in 15 children presenting with the late or stalled puberty and we saw three patterns where we had children who responded robustly to

kisspeptin, those who didn't respond at all, one children who had this very small response to kisspeptin.

And the challenge is now we have to wait until they all reach 18 to find out what the eventual diagnosis is. And so we don't have that data ready to present yet. Hopefully soon, to really test the validity of this test, whether it's a useful predictor. But suffice it to say at the current point in time, we do not have good tests to predict who among the children presenting with delayed puberty will eventually have a permanent condition versus a self-limited condition.

My hunch is that we may get close when we have functional testing like this layering on some baseline clinical characteristics, possibly genetic testing. We may start to get close, but I think ultimately there are some individuals where we're just going to have to wait and see what happens.

All right, which brings us to management. So I'm going to recap briefly some

of what has been said before about the different formulations of testosterone that are available. The mainstay of treatment in pediatric populations is the use of the injected testosterone esters. Enanthate and cypionate are what are most commonly used. Undecanoate is available for adults, but is not commonly used in the U.S. for treatment of delayed puberty. It is fairly commonly used either on its own or in combinations with mixtures of esters in Europe and the U.K.

And the reasons that it's attractive are that the dose is very easily titratable. You can draw up as much as you want in the syringe and that's the dose that you give and you have a whole range of doses available to you. As we come to some of the transdermal concerns, with the injections you have no concerns about cross-contamination of household members and other people who might come in contact with the child. And it's typically given anywhere from once a week to once a month and that intermittent dosing can be convenient for some families and also for issues

of adherence in remembering to get the treatment on a regular basis.

Actually, I stand corrected. I had put on here that these are the only forms approved for pediatric use, but the pellets as well. So testosterone cypionate is approved for use of really specifically hypogonadism and more permanent conditions and clearly diagnosed conditions. Testosterone enanthate also has the indication of delayed puberty which can be seen as encompassing constitutional delay as well.

The oral formulations just recently became available, so testosterone undecanoate just was approved for treatment of men, adult men with hypogonadism. And there have been some studies, historical studies that have been done in children which seemed like it worked find in those populations as well.

The transdermal formulations are less popular. The trans-scrotal patches do work, but usually you present that as an option to a patient and they're not enthusiastic about the idea.

The transdermal patches that you put on other parts of the body very frequently cause skin irritation often leading to discontinuation. One study I saw set an incidence of ten percent of the skin irritation. What I've seen is that it's much more common than that. You can use topical glucocorticoids to try to prevent that irritation, but most people just don't want to be bothered.

The transdermal gel is probably the second most commonly used form in pediatric populations. And the challenge in using it in pediatrics comes from a few points, one that I've mentioned that the way it's formulated in the packets or the pumps, it's difficult to titrate it and give the small doses that you want to give for an initial pubertal induction in boys. We do worry about inappropriate use by the boys either giving themselves inappropriate doses or not letting it dry off properly, risking cross contamination for family members, as well as peers who they may come in contact with.

And so for older adolescents, we will oftentimes switch them to gels because they don't want to continue with injections, but I would say for the most part for initial pubertal induction, people are using injections, but there are people who will use the gel for initial pubertal induction as well.

There are the buccal patches, the subcutaneous pellets that I mentioned. These are rarely used in pediatrics, the pellets especially because of the issues of dose titration are challenging at the very low doses that you want for initial pubertal induction.

So switching to some lessons that we can possibly extrapolate from adult care, possibly not, there have been studies that have addressed some of the questions that come up how quickly do you see the effects of testosterone, at what doses or serum levels do you start to see the effects. And again, these are all data from adults.

These are studies that followed the progression of symptoms in hypogonadal men after

starting testosterone treatment and found that you get normalization of serum testosterone relatively quickly in a matter of months, excuse me, these are all with -- these are studies with the topical transdermal gel formulation of testosterone. And most of the physiologic changes happen on the order of three to six months, so changes in body composition, the normalization of hematocrit, effects on the prostate, effects on the psychosocial outcomes largely take about three to six months. The effects on bone density take longer, about two to even three years to peak.

And then looking at different doses of testosterone and at what levels you start to get normalization, this was a study done by Joel Finkelstein at MGH where they took healthy adult male volunteers, put them on a GnRH analog to suppress endogenous reproductive endocrine activity and then simultaneously gave them varying doses of testosterone gel ranging from placebo to up to 10 grams of gel of the 1 percent gel daily.

And so what they found is that they

could identify certain thresholds of the doses that would cause prevention of some of the symptoms of hypogonadism. So changes in body fat were effectively prevented by doses of five grams or above which achieved an average serum testosterone of around 400 or 500 nanograms per deciliter.

They also had layered on another arm of the study where they simultaneously treated them with an aromatase inhibitor to prevent conversion of testosterone to estradiol and we were able to ask of these effects of testosterone which of them were mediated by estradiol and which weren't. For body fat, the effect was partially mediated by estradiol and partially by testosterone directly.

When they looked at lean mass, the muscle mass primarily, they found out a lower threshold was needed, that a dose of 2.5 which achieved average serum testosterone between 300 and 400 nanograms per deciliter was sufficient to preserve lean body mass and this was an entirely testosterone effect. Estradiol did not seem to have a role in mediating that effect.

And then when they actually looked at strength, an even lower threshold was sufficient to maintain muscular strength with average serum testosterone levels even dipping down into the 200 nanogram per deciliter range.

So just to address one of the questions that came up, I'm not aware of any comparable studies that have been done in pediatric populations to determine what levels of testosterone correspond with appearance of which secondary sex characteristics. And I think there's going to be a combination of both dose and serum testosterone level and the duration as well that we know that the secondary sex characteristics continue to develop well after adult levels of testosterone are reached. You look at a college senior compared to a college freshman and they look different and that's the testosterone effect. Even though the levels are the same through that time period, it's the duration of effect over the years that makes a difference as well and those are very difficult things to disentangle from each

other.

So in adult men, there are guidelines on the management of hypogonadism and use of testosterone treatment and these are some of the recommendations. At baseline to assess what the degree of pubertal development is, to look for signs of insulin resistance, to evaluate for at baseline breast development, to monitor for gynecomastia, to do a testicular examination, look at genital development, and do to basic anthropometrics, and to follow how these change with the initiation of treatment.

There are some concerns that there can be an increase in risk for prostate cancer though this has not been borne out in studies that have formally looked at this. And as has been alluded to, there is a boxed warning for increase in cardiovascular risk for use of testosterone in adult men.

So moving back to the kids, when do we start treatment with testosterone? In the pediatric populations, there are no consensus

statements or guidelines on how to do this. There are review articles that are largely based on expert opinion, a few studies that have looked at this.

So in the individual who has hypergonadotropic hypogonadism and primary testicular insufficiency, for example, the boy with anorchia and you know they're never going to make testosterone on their own, when do you start treatment? You can look at the gonadotropins. Remember from that graph before there is that dip in gonadotropins and when you see the gonadotropins start to rise, you know that the body is producing the endogenous signals to induce puberty. It's just that the testicles are unable to respond to that because they're either nonfunctional or absent.

And so that rise in gonadotropins can be a clue as to roughly the time to start treatment in those boys. And the boys with hypogonadotropic conditions you don't have this clue and we have to base it on a number of factors. We don't have

any way of telling when puberty really would have started for these individuals. So we look at the population averages. Boys on average start puberty around 11 or so. We look at the family history, were the parents early, late, average to enter puberty themselves. We factor in there is a discussion of psychosocial factors, how keen or not is the patient and his family to start testosterone treatment.

And I do want to say that this is a significant reason for people to come to the pediatric endocrine clinic. It is a significant reason for pediatric endocrinologists to treat and whether that's appropriate or not is a matter for debate, but I would note just personally say that sometimes a degree of distress is very real and that testosterone treatment can be very helpful for psychosocial reasons. And again, that is a common reason for myself and my colleagues to treat boys with delayed puberty regardless of the cause.

So what dose to start? And the concern is that has been brought up that too high a dose

will cause overly rapid skeletal maturation, premature closure of the growth plates, and compromise of adult height. What's not clear is how much, how long, how early this becomes a problem. We do know that boys with precocious puberty can end up short because they start puberty too early and close their growth plates early. There have been use of testosterone to cause early end of growth in boys who are concerned about tall stature. And so we know that if we push the system enough we can cause early growth plate closure and compromise of height. But again, how much is not clear.

And so a lot of the studies that studied testosterone in the early days when it was being used for treatment of delayed puberty, were actually fairly encouraging regarding the safety of testosterone with regards to growth plate closure. So these doses used doses anywhere from 33 milligrams to 200 milligrams given every 3 or 4 weeks for anywhere from 3 to 20 months. So a lot of these doses and durations were much higher

and longer than what we would typically use today to treat boys with delayed puberty. And none of these studies demonstrated significant bone-age advancement. I'm actually a little skeptical of some of them at the very high doses, but that's what's out there in the literature.

Again, this is just really based on teaching and personal experienced and anecdotal experience that the typical starting dose that people will use is using one of the testosterone esters, enanthate or cypionate, at a dose of usually 50, sometimes 25, every 4 weeks or month as the initial starting dose. And then every three to six months advancing the dose.

I would say that most people do not monitor serum testosterone in using this treatment and just treat empirically. Safety labs are rarely, if ever, followed. The concept being that this is meant to be providing physiologic levels of testosterone, not pharmacologic levels.

And so the dose, as I mentioned, is advanced about every six months or so and it's

roughly doubled every six months to gradually achieve adult doses over a two to three year time course. Depending on the condition, you may increase the dose first or the frequency first. There probably isn't much of a right or wrong, but it may vary depending on what you think you're treating.

And the monitoring is primarily based on growth first and foremost. So looking at the growth chart, looking at pubertal growth acceleration is the main tool that we use as pediatric endocrinologists. We will also frequently, but not always, monitor bone age along with this to get a sense of how quickly things are progressing and whether the bone age is advancing proportionately to the degree of growth.

We'll also monitor secondary sex characteristics, ask about sexual functions, sexual drive, but I would not consider these outcomes that were primarily targeting for intervention. I think we're really mainly targeting the growth and the height. We expect

all of these things to happen and they almost inevitably do and so it's almost a given that you'll rise in appearance of secondary sex characteristics rise and erections and so on.

And again, during this phase, my experience and both myself and talking to my colleagues is that very few people are following serum testosterone concentrations. People are very rarely monitoring safety labs. Again, the concept being that this is a physiologic replacement at levels that are doses below what you would use in adults.

So I'm actually going to venture into fertility despite our caution that it may be beyond the scope of this discussion because this is actually one of the debates going on in the field and so for individuals with hypo -- so actually backing up, the individual with primary hypogonadism are rarely going to be able to achieve fertility on their own. Or for the individuals with hypogonadotropoic hypogonadism will have normal testicular functions, just absence of the

signals to the testes. They can often achieve fertility when they're treated with exogenous either gonadotropins or GnRH to replace the missing gonadotropins.

And so while we use testosterone for initial pubertal induction, at the time fertility is desired, then those patients are typically switched over to treatment with gonadotropins or GnRH to achieve spermatogenesis.

And the question that has arisen is that this is not physiologic, right? So what normally happens is that the gonadotropins start to rise, particularly FSH. You start to see some increase in testicular volume and then the serum concentrations of testosterone start to rise. And there has been a theoretical concern raised that if you invert this order have testosterone go up first for the gonadotropins, could this compromise future fertility.

There is not a lot of data on this, and the data is conflicting. So there's one study that looked at adults with IHH, looked at

spermatogenesis induction with exogenous gonadotropins and tried to identify factors that predicted the success. Overall, the success rate is on the order of 80 to 90 percent of men treated with gonadotropins can achieve spermatogenesis and fertility. And what they found in this one study is that prior use of testosterone predicted less likelihood of achieving fertility.

Another study looked at the same thing using GnRH treatment instead of gonadotropin treatment and found no effect of discernible effect of prior testosterone use. These are retrospective studies. These are not randomized studies and so there could certainly be confounders of why some men got testosterone versus others that could -- and it could be not that the testosterone itself was affecting things. Or it could be the other way around that in the other study there may have been differences between the men who got testosterone or not and how they were managed. Subsequently, that may have conferred better chances of fertility. Hard to know when you just

have these two studies with conflicting results.

There was one small study that was done, again, at the MGH Reproductive Endocrine Unit where they used GnRH pump therapy for many years to induce fertility in men. And this is a study pre-treating these men with FSH alone, recombinant FSH, prior to initiation of GnRH therapy which is going to cause rises in both FSH and LH. FSH alone is not going to cause a rise in serum testosterone. It's really just going to focus on the Sertoli cell and seminiferous tubulus components of the testes.

And what they found was a hint that did not quite reach statistical significance of higher sperm counts in the men who were pretreated with FSH compared to those who were just started on GnRH pumps straight away.

I believe all of these men had received prior testosterone treatment and so that was not a factor that we could look at in this study.

So all of these as kind of hints as to the possibility that initial treatment with FSH and gonadotropins may yield somewhat better

fertility outcomes later in life, but I think far from definitive results.

So that was the typical boy with complete absence of pubertal development for whatever reason. I'm going to switch gears to talking about treatment for Klinefelter Syndrome. Again, there are no consensus statements or guidelines for management of Klinefelter Syndrome and testosterone replacement. But the goals of care are again to complete pubertal growth, induce secondary sex characteristics, improve bone health, sexual function, and cardiovascular health.

I put a question mark after cardiovascular health because it's one, not entirely clear to what extent hypogonadism is the cause of the increase risk for cardiovascular risk factors in adult men with Klinefelter Syndrome, much less whether testosterone treatment would affect those.

And then in the pediatric population, there's been a lot of attention to potential

psychosocial and neuro-developmental outcomes in the boys with Klinefelter Syndrome and I'll come to that again in a moment.

But because of the kind of differing goals of care, different opinions on what testosterone treatment does and doesn't do for boys with Klinefelter Syndrome, there's a really wide range of when boys will get treated and when treatment will start for their Klinefelter Syndrome.

I think the most classical is really using criteria similar to treatment of hypogonadism in adults where you want to see a frankly low testosterone, below the normal adult range and frank symptoms consistent with hypogonadism. The challenge being that adolescents are not always great at articulating the symptoms of hypogonadism or recognizing them.

So slightly softer criteria would be testosterone maybe be not frankly low, but in the low or low-normal range; elevation of LH showing that at the very least you have the subclinical,

if not frankly clinical, pattern of hypogonadism; and either symptoms of hypogonadism or on your exam an arrest, failure to progress in terms of pubertal development. And this is somewhat subjective.

Some people will treat once they see evidence of the LH rising and start treatment at that point, perhaps thinking that the writing is on the wall, this child is headed towards testicular insufficiency, so let's stay ahead of it rather than waiting until you get frank symptomatology.

There are some arguments that testosterone treatment could be started at the first signs of puberty with the thought that there is some subclinical hypogonadism that's present even at the early ages, even though the boys on serum measurements in terms of pubertal development seem to be doing just fine.

There have been arguments before puberty and even in infancy that I'll come to in the next slide.

So there has been a lot of interest in treatment of Klinefelter Syndrome with

testosterone and other androgens, not so much with the goal of inducing puberty, but improving some of the sometimes fairly severe neuro-developmental and learning issues that these children face.

So this was a study done by a number of people, some in the audience, looking at use of oxandrolone which is a non-aromatizable analogic steroid, so it's going to have solely androgenic effects. And this is in pre-pubertal boys with Klinefelter Syndrome treated for two years with oxandrolone and at a range of ages, but all pre-pubertal.

And so there were some physical effects that were seen. These included lower percent body fat, lower triglycerides, but some that are not welcome such as lower HDL cholesterol. There were some modest improvements in some, but not all measures of motor function, anxiety, depression, social, interpersonal problems. There was advancement of bone age and I think most concerningly in this pre-pubertal population, it did cause earlier onset of endogenous reproductive

endocrine function actually resulting in frankly precocious puberty in about a quarter of the boys in the oxandrolone treatment group. So I think cause for concern.

And then extending it even further, people have advocated for use of testosterone treatment in infants with Klinefelter Syndrome. Again, as I mentioned before that the infant boys, there's mixed data on whether there's actual testosterone deficiency, but there have been a number of observational studies, largely coming from one group that have looked at retrospectively at boys who got treated versus not treated with testosterone as infants and looked at neuro-developmental outcome for those individuals and found that those in the testosterone treatment group did have better neuro-developmental measures.

Now it's important to recognize that these are observational, not randomized studies and so confounding is a huge, potential source of bias.

There is one of my colleagues, a pediatric endocrinologist at Colorado Children's Hospital, Shanlee Davis, conducted a pilot randomized controlled trial in infants with Klinefelter Syndrome and she just presented that data at the recent Endocrine Society meeting. And what she found is that the boys with Klinefelter Syndrome who are treated randomized to placebo had higher fat mass and lower lean body mass compared to age matched boys without Klinefelter Syndrome. And those who were treated with testosterone did not experience those differences that they were indistinguishable from the age match norms without Klinefelter Syndrome suggesting that testosterone may have some benefit in this age range.

I think that again, kind of a note of caution, it's not entirely clear whether testosterone deficiency is even present in infancy, so we have to consider is this a physiologic replacement of a subclinical testosterone deficiency? Or is it a pharmacologic treatment to try to reverse some of the features of

Klinefelter Syndrome that may or may not be mediated by testosterone. Again, I think it would be helpful to know exactly what we're doing when we're thinking about treatment of these boys and these infants.

And then finally, to mention some uses of testosterone that are common, but not for permanent causes, so I mentioned constitutional delay and I would say this would be probably by far the most common reason for treatment as was mentioned before. The diagnosis codes, unfortunately, don't distinguish between these various cases, so we don't have that data. Again, it is formally an approved indication for testosterone enanthate and the idea is to induce secondary sex characteristics and really to induce that pubertal growth spurt. And I would say primarily for psychosocial reasons.

There is that specter because we can't distinguish between constitutional delay and IHH that the child could actually have IHH in which case you really would not want to delay treatment

or defer treatment and we don't know, we can't distinguish between those two conditions and I often present this as an insurance policy to families that at least this will keep your child from falling further behind regardless of the underlying cause of their delayed puberty.

There is some evidence, though it's not clear that treatment with testosterone may actually accelerate the onset of endogenous puberty, cause the child's own puberty to occur earlier. We often colloquially call his jump starting puberty with exogenous testosterone. This is really, I think, based mostly on anecdotal experience.

I would say we actually did a provider survey recently where the majority of pediatric endocrine providers believe in this phenomenon, but the data to support it is relatively limited.

This is the best study that I'm aware of. This was a randomized study of testosterone treatment of boys with delayed puberty where 50 were randomized to no treatment and 150 were randomized to testosterone treatment. As

expected, testosterone resulted in more rapid growth, more rapid genital development. These are expected effects of testosterone, but what's interesting is that testicular volume which is not a direct effect of testosterone, this is going to be driven by the gonadotropins and endogenous reproductive endocrine activity.

Testicular volume was higher in the testosterone group compared to the untreated group suggesting that testosterone may have either accelerated the progression through puberty or actually caused puberty to occur earlier in some of these boys. It's worth noting that 4CCs is the cutoff for defining whether a child is pubertal or not, and so about half the individuals in the group are actually early pubertal and half of them were pre-pubertal based on the mean testicular volumes that were reported.

So again, it's a little hard to distinguish between whether it causes those already in puberty to progress faster or those not in puberty to enter puberty. But this is about the

most suggestive data that I could find in the literature to support this concept that many people just anecdotally subscribe to.

There is off-label use of testosterone treatment for transgender use, so these will be individuals with XX chromosomes and designated a female sex at birth who assert a masculine gender identity. And testosterone is used to induce male secondary sex characteristics, to affirm their male or masculine gender identity. The Endocrine Society guidelines recommend treatment starting at age 16 which is the model that was developed by the group in The Netherlands, but the most recent statement acknowledges that treatment earlier than 16 may be appropriate and just from our center and other centers I have met with, treatment is often started at age 13 or 14.

It's worth noting that though this is a relatively small group of individuals right now, we are seeing an explosion in the number of children presenting for gender care at our gender centers across the country and many, but not all of them,

are seeking testosterone treatment. The growth is largely in XX individuals and so this does represent a change in the demographics of the people presenting in our clinics.

Testosterone is often used for treatment of infant boys for micropenis which may be due to an identified organic cause and will often receive one or two short courses of about three months treatment of testosterone. The pediatric urologist will frequently give a dose or two of testosterone prior to things like hypospadia surgery to enhance the growth of the penis to give them more tissue to work with at the time of surgery. And it's unclear whether this makes any difference in the long term. This is the one study that had Ns of three in each group. These are boys with hypogonadal conditions, some of whom were treated in infancy. The other groups were not and all were treated as adolescents and they all ended up with adult size penises, raising the question of whether micropenis treatment in infancy has any effect on long-term outcomes.

And then finally, it's worth mentioning that there is elicit use of testosterone and other anabolic steroids, particularly among athletes and body builders. The CDC Risk Youth Behavior Survey in 2017 reported that 3.3 percent of boys and 2.4 percent of girls in the high school age range reported use of anabolic steroids. Fortunately, at least according to the DEA, most of this is not coming from misprescription or misappropriation of testosterone from the U.S. They said that it is mostly coming from outside the U.S. and being smuggled into the United States.

I will end there and happy to engage in the discussion.

DR. DRACKER: Thank you, Dr. Chan. We don't have time for questions. We're going to take a lunch break. At three o'clock we will have time to ask further questions.

Dr. Chan, thank you. That was excellent. You're the reason I'm glad I refer patients to others that know much more about this than I do.

(Whereupon, the above-entitled matter went off the record at 12:04 p.m. and resumed at 1:03 p.m.)

DR. DRACKER: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes 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 that you may have with the sponsor, its product, and if known, its direct competitors.

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

financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, speak only when recognized by the chairperson. Thank you for your cooperation.

The first speaker is Varuna Srinivasan. Did I say that correctly? No. Sorry. I tried.

DR. SRINAVASAN: You did. Good morning. Sorry, good afternoon. Thank you for

the opportunity to speak today.

My name is Dr. Varuna Srinivasan. I'm a physician with a Master of Public Health from Johns Hopkins University. I'm a Senior Fellow at the National Center for Health Research which analyzes scientific and medical data to provide objective health information to patients, health professionals and policy makers. We do not accept funding from the drug and medical device companies, so I have no conflicts of interest.

The FDA estimates that more than a thousand adolescents currently meet the indications for use of testosterone replacement therapy, TRT, for development of secondary sexual characteristics and/or to stimulate puberty in certain conditions. To ensure that safe and effective hormonal replacement therapies are being used in pediatric populations, we recommend the following.

All testosterone replacement therapy products for adolescents should be based on adequate and well-controlled clinical trials in

pediatric patients. This is true for new testosterone formulations intended for this population and also for products currently on the market.

As discussed today, it is well known that testosterone can stimulate aggressive behavior, as well as serious adverse events. And of course, puberty can develop in a somewhat unpredictable pattern. For those and other reasons, clinical trials must have appropriate comparator groups and long followed periods for measurement of clinically meaningful functional endpoints and monitoring of unanticipated effects. In addition to this, known side effects such as premature closure of epiphyseal plates and infertility should be investigated in the long term.

Pediatric Research Equity Act exemption for TRT medications is likely not appropriate because of the number of adolescent boys given TRT each year.

We cannot rely on full extrapolation

of adult data for approval of TRT for pediatric population. As stated in the document, many of the TRT medications currently used in the adult population were approved not based on their impact on clinical science and symptoms, but rather on their effect on serum testosterone levels. This may be appropriate in an adult male who has already achieved puberty and develops secondary sexual characteristics and for whom maintenance of serum testosterone levels may be the goal of TRT use. However, this is not an appropriate endpoint in a pediatric patient for whom puberty and development of secondary sexual characteristic is the intended outcome of medication use.

It is essential to consider the risk-benefit profile for individual medications and intended uses. IQVIA administrative claims data suggests that there is currently substantial off-label use of TRT medication in pediatric patients. Proposed uses of these medications in children need to be carefully studied in well-designed clinical trials as noted above.

As FDA labels indicate, potential side effects of testosterone treatments in adult include increases in cardiovascular and hematological diseases such as stroke, venous thromboembolism, and increase in red cell mass.

Further study must determine if these risks may be seen in pediatric populations and determine what dosage levels are safe for which adolescent. We urge the Advisory Committee to consider these points while submitting their recommendations to the FDA today. Thank you.

DR. DRACKER: Thank you very much. Are there any other speakers for the open forum?

We will continue with the presentations. Next speaker is Alan Rogol.

DR. ROGOL: Thank you and good afternoon. That is who I am. I am from the University of Virginia. This is year number 45 for me there and in addition to the things there I've been involved with the Pediatric Endocrine Society as its secretary and at the Endocrine Society as its vice president. So it's more than

just the academic part.

These are the companies that have asked me to put together what I put together and so as part of my disclosure, those are the names of the companies.

So the agenda today is background, the physiology of the HPG axis in boys. I'm going to go over rather quickly, most of it's already been done. Estimate the number of adolescents who may require testosterone. Again, the numbers that I will show are very much the same, so we will go through those relatively quickly. Obviously, questions can be asked later on and I'll spend a lot of time on the challenges and designing and operationalizing studies of testosterone therapy in adolescents.

So let's get going. You've seen this slide before. The two lines that are underlined are important. They've been gone over before. Please, however, bring your eyes down to the bottom of the slide, limitations of use: safety and efficacy of X in males less than 18 years old have

not been established and I think that's a key point to make about that slide.

This is one of my favorite slides. I've taught four decades from it. We've talked a lot about growth at puberty. The upper right hand corner is nutrition and genetic potential. We didn't talk very much about that, but again, how fast somebody grows, how tall they are, how they go through puberty has a lot to do with genetic potential and nutrition.

Gonadal steroids affect growth at deficiency. They affect growth of the specific sex organs and they work as well on growth through the growth hormone axis. That's already been gone over, but I want to put all of the other things into perspective.

So you've seen this before. Ming and Stephanie's favorite molecule the K of KNDy, kisspeptin, is up at the top. Notice on the right next to that is estrogen, so when we talk about testosterone, we're going to have to talk about estrogen because most people do, in fact, have

aromatase.

The right side on the bottom is the compartment for spermatogenesis. I will come back to that. And then the Leydig cell making testosterone, you've gone through its physiology. It has a developmental physiology that Ming talked about in utero, minipuberty and then puberty as an adolescent and then as an adult.

So testosterone is a molecule that works by itself, but most of the time is a precursor. If you put your eyes up toward the top from 5 alpha reductase dihydrotestosterone is an important marker for the external genitalia. Aromatase making estrogen has a lot to do with body composition, bone that Ming brought up, and in fact, the closure of the epiphyseal plate. So if you don't have estrogen or if you don't have estrogen action, no matter how much testosterone you have, the growth plates will not close. And that's an important point when we talk about testosterone.

This is a slide with a little bit more physiology in it, but it is important from the point

of view of this is a daily testosterone pattern, multiple samples through the day. The vertical axis are the levels of testosterone and those are numbers you haven't heard of today. Ten on this scale is 300 on the scale you heard about this morning. And 24 on this scale is about 700. So between 10 and perhaps 30 would be the normal levels. This is what they use in Europe and around the rest of the world. So those are in SI units.

You will notice that there is a diurnal variation in testosterone. It is greater in the young, the blue dots, than in the older, but there is, in fact, a diurnal variation and what Ming didn't mention this morning if you really carefully go over it, at times in early puberty, a boy may have on the units that you're used to may have a value of 40 nanograms per mil in the afternoon, but in the morning have 300 or 400. What is he? Is he a man with a 400 or is he a boy with 40? So those things are important when we think about if we're going to measure testosterone, when do we measure it? If we're giving testosterone

exogenously, when do we measure it? Depending on the pharmacokinetics.

I'll bring that concept out as we talk about some of the difficulties of actually doing these kinds of studies.

So this is a little bit complicated slide. I'll walk you through it. We'll just take the top part. We'll leave the girls alone. So when the males, as Ming mentioned this morning, testicular volume of 4 mils or greater is the first indication of -- external indication of puberty that means gonadotropins are being secreted.

Sixty-eight percent, this is just plain old statistics are within one standard, the central portion, within one standard deviation you get down to 14 percent; and two, you get down to 2.3 percent. What we're looking at is the difference or the dividing line between the blue arrow looking that way and the tan arrow or the brown arrow looking that way. And so that's the issue of when they have delayed puberty.

And notice the title of the slide. This

says nothing about why. It doesn't say about physiologic. It doesn't say about pathologic. It says because of the statistics, 2.3 percent of males above the age of either 14 or 13.7 was a number that Ming brought up this morning, will have the late puberty, period. It doesn't say anything more than that.

And so, if you look at the population of boys, these numbers have been gone over before, but the blue numbers says there are about 8 million boys in this age range period. And then if you take 2.3 percent of those, we'll go through those numbers in just a bit.

So thus for a 14-year-old boy, 2.3 percent will have delayed puberty and as Ming talked about, and I will show you some numbers, there are about 65, 70 percent of those will have constitutional delay of growth in puberty which is essentially transient hypogonadotropic hypogonadism. Not permanent, but transient. And so clearly, those with delayed puberty diminish as the years go by and if you take an estimate that

I made, you can see what I did. I just reduced it by 50 percent each year. We're talking about somewhere in the ballpark of 60,000.

And so carrying that on a bit, I put in all the assumptions that I made. This relating only to 14-year-olds. I've halved the percentage and I took the 65 percent from two large studies. So there is the reference from Belgium on the slide and in the handout.

So if we go then to Klinefelter Syndrome, uncannily, or if we both looked at the same data, the data that you saw today was about 1,000 and that's how I made that particular calculation. We all agree, so there's really no sense at this point of discussing it further.

And then with the Kallmann's, what I did was took the 1 in 10,000 because Kallmann's is probably 1 in 10,000 for boys and maybe 1 in 20,000 or 30,000 for girls. And so the number that was brought up this morning was 1,000. I'm not going to argue the difference between 838 and 1,000.

So this is the second slide that was

essentially shown this morning. And what I showed about five or six slides earlier and the difference with this one is I have put a gray box around spermatogenesis. So spermatogenesis does occur. It is testosterone dependent. However, it is very different than testosterone that swims around in the circulation. Testosterone intra-testicular that affects spermatogenesis is between 50 and 100 fold higher. So it is majorly high.

And if you give testosterone and give me the audacity to say what's swimming around in the testes is likely what's swimming around in the rest of the body if you're giving it exogenously, there is before you even start, there is an issue about whether spermatogenesis, in fact, could occur.

On the other side of the coin is male contraception. So in male contraception what one is looking for is normal males giving them a contraceptive and then seeing what happens to spermatogenesis. And so most of the trials have been giving exogenous testosterone and a

progestational agent. And the amount of testosterone, yes, is supra physiologic, but it's not like what the athletes take. So in your mind, you have to balance those two factors together.

So the 800-pound gorilla in the room is CDGP versus IHH. CDGP being common, IHH being not so common, and please remember that CDGP is not on the label and IHH, in fact, is on the label. So that's a major difference right now.

The differential diagnosis can be difficult. Ming told you about that. Both may be familial. I will go over the growth curves. I know many of you are not endocrinologists, but you are pediatricians, and so we'll go over some growth curves just to show that there might be some subtle difference and the very early signs of pubertal maturation may be helpful, but they also may not tell you anything.

So this is a growth curve that most of you who do pediatrics are used to. And this starts at age 2, so the left hand most number is about age 2 and what this child does is sort of falls

off a little bit from the curve. I'll show you his baby curve in just a second. And then does fall off from the curve around age 14. Why? He falls off from the curve because the growth spurt is built into that curve at the average age. So if you're growing pre-pubertally, when you should be accelerating in your growth, you are going to apparently fall off the curve. So he's treated with testosterone, the start. And you can see where the first arrow, the first vertical arrow is.

And the second vertical arrow is -- oh, stop his testosterone. Okay, and then what happened? He had his growth spurt. So he had his growth spurt at the wrong time and it looks like he's accelerating in his growth and he's really not. He is going in fairness, boys of 16 and 17 don't grow that rapidly. Boys of 13 and a half and 14, do.

So you can see where he started on the left hand corner at somewhere just below the 50th centile and he winds up at age 18 his near adult

height is about the 50th centile. So the falling off and the speeding up have more to do with statistics than they have to do with this kid who knew how he should grow, he just didn't figure out the right time for him to grow.

His baby curve is this one, so on your left hand side is zero and these are lengths, remember, on this curve you're measuring length not height and then you can see slowly, but surely, over the first 36 months he is falling off. That's quite common in CDGP, but it doesn't make the diagnosis for you and most of the time most of us who do pediatrics don't have these kinds of curves unless they're our own.

And then some recent data that will be published pretty soon shows that on average if you look at height -- now we're looking in height SDS. So the average, if you're the average height, you're zero on this chart. And if you will look at the target height, that means how tall mommy and daddy told you to be. There are ways of calculating, not important, and so mommy and daddy

told you to be perhaps just a little bit below zero, that is average. And then birth, 6 months and 12 months, you apparently fall off as I showed you for that individual. And then eventually, you kind of stabilize at maybe minus half NSD.

But notice at pubertal age when you're going to start because you haven't had the beginning of the pubertal spurt, you are going to appear much -- not much, but further below eventually to catch up. So if you have a curve like this, it's terrific, but probably well under one percent of our kids that we see in clinic would come with a curve like I showed you previously.

And so this one is a little bit different, but not much different. That's why it's hard. So this is the growth curve for a boy with IHH, isolated hypogonadotropic hypogonadism. Could be Kallmann Syndrome and he is on the 50th centile at age 2 years. That's the absolute left hand point. You will notice that before, the year or two before the testosterone arrow is, he fell off his curve, but then once he got testosterone,

he caught up and wound up again pretty much on the 50th centile. So those are subtle differences. Those are in kids that you obviously don't have a genetic IHH diagnosis that Ming was talking about before.

So that might be helpful, but in a population base, the kind of kids that the pediatric endocrinologists in this room and I see usually you can't make the separation between the two diagnoses.

So then I'll switch over to the -- if you're going to treat them, what are the principles of going about treating these kids?

So you want to lead to or restore serum T levels. We were told that the kids with anorchia, the kids with IHH, have very, very low T levels. Kids with Klinefelter's may have anywhere from low to absolutely normal levels. And again, the point is made you want to be in the normal range for age. That's what you talk about first, but these kids are delayed, so you want to be stage of pubertal development. If you're in Tanner 2

which is relatively early genital development, at age 15, you don't want to be a 15 year old who most of them would be in Tanner 5 by that time. So that's a subtle, not so subtle, difference between those of us who deal with kids and those of us who deal with adults.

And you want to administer only to those that are transiently, recognize that word again, or permanently hypergonadal and again as we said, it doesn't matter whether you're primarily or secondarily hypogonadal.

What are the goals? As was brought up it's mostly pharmacodynamics rather than pharmacokinetics, so you want linear growth. You want a normal physiologic growth spurt whatever that is. That's got a wide range, both in amount and in time. Normal progression of secondary sexual characteristics, some boys go through puberty in two years, others take four or five. So again, there's variability across that.

Growth of the testes during androgen therapy is an important thing because those without

testes obviously can't. Those who have IHH will not have growth in their testes. Those who are delayed in puberty and have some LH, but more importantly, FSH function will have growth in their testes and that's actually one of the endpoints that most of us clinically would use. So we would treat a boy with CDGP until his testes got up to be eight or ten ml and then stop therapy. His testosterone levels will continue to rise, the only difference being that those are endogenous and not exogenous.

But the important point here is that despite the fact that you're giving a negative feedback regulator, testosterone, which is probably really giving estrogen because of its conversion, despite that, you are not suppressing gonadotropin secretion, but in fact, the robust gonadotropin secretion happens, overcomes the block. And so that's very, very different than permanent hypogonadism whether secondarily from the head or primarily from the testes.

Again, you want the acquisition of

pubertal and then adult body composition. Most boys, as they become men, don't reach their adult body composition until they're in their mid-20s. That includes bone and the regional distribution of body fat as well as muscle.

And the last point has been made and I'm thankful that it has been made, but if you go back to the old literature in the '40s, one of the reasons for treating kids, this is before the Kefauver business in Congress, was for their psychosocial aspects.

If you're a boy in high school, the most important things to you, in case you don't understand this, are not math and science. They're girls and sports. And so this is one of the psychosocial. They can't compete in sports as a boy who might be a man, a 12-year-man is the best Little league baseball player. He's 12 years old, but his physiology is more like 15 or 16.

So psychosocial development is important and even more important in Klinefelter's because they have great difficulties in that

particular sphere.

So the forms and dose ranges from previous studies, the mixed esters are cypionate and enanthate in Europe. Some of them use propionate as part of a mixed esters. Propionate is a very quick-acting one. We don't use it. You'd have to give it every three or four days. Testosterone enanthate, as was mentioned, there are testosterone pellets that was mentioned that are, in fact, approved and I was talking to Ming this morning and thinking about the 45 years I've been doing what I'm doing. I never remember talking about teaching or thinking about pellets in kids. They just don't use them in the United States. Yes, they are approved, but I'll bet the people who see the sales of them see very, very few, at least in this country.

So after a year, virtually all have growth spurt without unduly rapid bone maturation. That's confirming what Ming said this morning. And a few studies carried out to near adult height, no loss of height compared to predicted adult height

or initiation of -- to predicted adult height at initiation of therapy nor deviation from the family height.

So if you understand that Scottie dogs have Scottie dog puppies and Great Danes have Great Dane puppies, it depends how tall your parents are where you wind up. And so we sort of calculate what mommy and daddy told us to be and then we look at it and see if we're in the same range.

So there are a number of studies that have gone from 200 milligrams intramuscularly for 4 months. That's an adult dose given to a teeny weeny kid and 50 to 100 for 12 months that Ming brought up this morning and actually the dose really hasn't affected in the studies that have been done, haven't affected near adult height.

So let me go through these. Okay, we discussed this a little bit, but I want to bring out a couple of more points. Physiology notes pulsatile GnRH and gonadotropins at all ages, testosterone concentrations are very low except that minipuberty and at puberty and we talked about

the gonadotropin levels. But again, it sort of doesn't matter if you're not getting it in a pulsatile way, if you're getting it in long acting or short acting, the end point is simply the same. Now, that is adult sexual development and near adult height within the normal range.

Then, testosterone levels are easily measurable for greater parts of the day and become like adult in late puberty. So yes, you now have adult levels, but when do you measure it? If you're in the morning, it maybe one thing. If you're in the afternoon, you may be in transition. So levels are very difficult. We can measure them. That's not the hard part. The hard part is interpreting what those levels mean as you are giving testosterone exogenously.

So as with many other long-acting drugs, HCH being a long-acting LH, you really don't necessarily have to follow physiology. Long-acting insulin works, although insulin is secreted in a pulsatile manner.

So T levels follow multiple different

following -- multiple different TRT drugs and doses don't mimic physiology, none of them do. Yet, multiple forms administered by any of multiple roots are able to mimic pubertal maturation and what do we use to track the adverse effects?

Well, look at those things that I've listed there. Those are exactly the same lists as what we use for efficacy. So height velocity excessive, very difficult to determine. Bone age maturation is excessive, a little bit easier for us to deal with. Adverse behavioral effects, we would get those adverse behavioral effects at least as clinicians, we would get them as talking to the kid, talking to the parents, what the parents have heard from the school teachers. That's the level. These are not psychological inventories that have been vetted and looked after by people who understand that kind of stuff.

Acne, that was brought up. But again, kids going through puberty have acne and did we cause acne by bringing the levels up two years too soon, and two years later they would have had acne

anyway.

T levels are the ones that I want to stop on here and that is when and what to measure. We brought up today whether you're concerned about AUC, C average, or the peak? Well, if it's a peak, when do you measure the peak. If you gave it four days ago, you'll have one peak or you'll have one level. If you gave it the same drug 14 days before, you would have a different level. Same kid, same body, just measured at a different time. To do a complete pharmacokinetic study over 28 days is heroic.

Okay, clinical trials. Conditions associated with a deficiency or absence of endogenous testosterone. We mentioned primary hypogonadism and then isolated or as Ming brought up some syndromes that we have that, in fact, have multiple pituitary hormone deficiencies.

The PMR on the NDA says a trial of testosterone replacement therapy in pediatric males ages 14 years and older, and I'll bring up some points about the kids who come to see the

general pediatric endocrinologist, with a deficiency or absence of endogenous T due to primary or hypogonadotropic, meaning secondary, hypogonadism.

Identifying the patients, the correct patients, remember CDGP is not on label, IHH is. They can have nearly identical clinical presentations. Ming talked about it and I did. Both will respond. CDGP is not on the label, and most of us, in fairness, assign a final diagnosis at either age 18 or a little bit before.

Most cases with constitutional delay will display testicular growth, etcetera, before age 18, but the cut off is age 18. You have hypogonadotropic hypogonadism if you haven't started puberty by age 18.

Challenges, many, so a small percent of the adolescents get to the specialist early. The other ones who want something done right now, and I will tell a 30-second story.

I had a kid come see me probably 30 years ago. At the end of August, he was short and

underdeveloped. The end of August is important because he was short all summer long, but he was starting school, and so I talked to him.

I talked to his parents, sent the parents out and started to, was going to examine him. He was sitting on an examining table taller of course than I am, and I asked him, you know, essentially, "How can I help you?" and he said, "I'm starting high school. I need balls and hair down there by Monday," and that is essentially what was on his mind and on the minds of many of these kids, so it is a psychosocial problem for some of these kids.

He was the only one that had the courage. In seeing thousands or 1,000 kids probably like that, he was the only one who had the courage to tell me that, however. And many 14-year-old patients, including my own, have already started T treatment.

The kids who come to see me have to get over the energy barrier of talking to you all as pediatricians. Mommy is pushing. The kid is

pushing, etcetera, but once they get to see me, they are very -- and Ming, or anybody else, David at an academic center, they are absolutely not the general population anymore. This is quite a skewed population.

The physicians do prescribe off label, although in my experience, very few pediatricians do prescribe this drug. Most of us are endocrinologists that do. It may not be for everybody.

But if I or one of the other physicians prescribe it, they're sure to get the drug. In a trial, they might not get the drug right away, and what's on their mind is they want the effects of this drug right away.

So in placebo controlled trials, there can be a perception of patient/family that there is an inferior arm, inferior meaning psychosocially inferior, not scientifically inferior.

He's going to get T. Almost all of the trials have it, but he may have to wait six months and he's not willing to do that.

With the newer formulations, it may be a little bit easier. We've got now transdermal, nasal, oral, and so it might be a little bit easier, but doing PK studies are not so easy with kids as I'll bring up just now.

So the subset for PK studies, because that's been brought up a number of times, for this, I kind of looked at my own experience and talked to two people, one in the UK and one is the U.S. who are in fact doing trials right now, so some of this reflects their difficulties in doing things contemporaneously.

So lack of direct benefit to the patients for doing a PK study, limited capacity to understand, especially the younger kids, inability to properly compensate patients and parents, and that doesn't necessarily mean money.

This is a big commitment if you're going to do PK studies to have the folks take off work, etcetera, and the difficulty scheduling because of school.

Most of the clinics, as opposed to those of us who deal with clinical research units where they're open on weekends, most of the clinics are not open on weekends and that is another barrier making it difficult.

And remember, this is not done in every little town. You're talking about a medical center which may be 50 or 100 miles away from where the folks live.

Klinefelter syndrome is difficult, the reason being only 10 percent are diagnosed. You've already heard about that. Again, as we project, half a decade and a decade in advance, with prenatal diagnosis, that may bring in more patients or not.

When to start, that was brought up. That's probably a very good question for our discussion at the end of today. What level is appropriate based on T, based on gonadotropin levels, and perhaps for Klinefelter syndrome and other primary hypogonadal conditions?

Perhaps bringing LH down to the high

normal range might be a very good way, but again, that's a very small population in comparison to the number of kids one would need to do proper trials.

There are multiple etiologies of IHH. Are they all the same? Those with syndromes are probably different than those without syndromes? What about development, which the brain, versus maturation, which is the body?

The behavior aspects, this is only the fourth time that issue has been brought up, and do you need controls? For CDGP, you certainly would need controls because they might just go ahead and do everything on their own. If you're certain about the hypogonadism, be it anorchia, be it one of the common syndromes, okay, you may be able to not need controls.

What are the exclusion criteria, not so sure, certain genetic conditions. Again, most IHH is a genetic condition, so that one would be okay, but what else goes along with it? Concomitant medications, this is a big deal, a

really big deal in those of us who do any kind of pediatric clinical trials.

So you've got nasal and inhaled glucocorticoids. You've got people with allergies. You've got people with atopic dermatitis that can give you problems. You've got kids --

ADHD drugs are really common, anti-psychotics not so common, mood stabilizer not so common, but you put that whole universe of drugs together, and if you have to exclude them, that takes out probably 10 or 15 percent, maybe even a little bit more of the possible population that you want to deal with.

So what are the outcomes? This is the same as when we were talking about safety. Height velocity or change in height SDS, that's easy. How far is the top of your head off the ground? That's pretty easy.

Body composition, not so easy. You just do skin folds. You do waist circumference. You do a DEXA scan.

Metabolic parameters may be a little bit more important, but we don't worry about it so much. If this is in the obese adult who has isolated or idiopathic acquired hypogonadotropic hypogonadism, it is a big deal because metabolic syndrome is pretty darn common.

And is the issue to initiate puberty, whatever that means, just getting started or really have the whole menu of puberty, the whole program of puberty going through until they become an adult, and then switched over to adult doses? Does it make a different whether it's CDGP or IHH? The answer, or at least my answer to that would be yes.

The psychosocial aspects, these are all published. That is not terribly well, but what they looked at was low self-esteem, distorted body image, impaired psychosocial development, increased anxiety, and the big one being depression. Those are all written about. Those could all be followed.

And the issue of course is if you don't treat with testosterone and they have some of these

already, do they get worse? If you do treat with testosterone, do they get better or perhaps do they get worse? And so this is a big deal in trying to put together a clinical trial.

So, to conclude and get ready for the questions, testosterone trials are difficult in adolescent boys. I probably should stop right there.

Distinguish CDGP from IHH at young ages, many boys seek therapy below the age of 14, and if we polled the peds endos in this room, my guess is a number of our patients are treated below the age of 14, certainly mine are.

Mechanics of trial participation can be difficult for families, especially if they involve pharmacokinetic studies. There are few patients with a lot of these things, but a few patients with IHH and a few patients with Klinefelter syndrome are diagnosed before emerging adulthood.

Then when they turn 18, then this committee, in fact, calls them adults and they can

go into any one of a number of adult trials or they're essentially already on label. If you're 18 with Klinefelter syndrome, you're on label.

So I use a lot of sports analogies and this is what we're talking about. This is perhaps two 14-year-old boys. One is a 14-year-old boy. One is a 14-year-old man. And so this is one of the issues that they are really most concerned about, that they're little, but more than being little, that they look like they're very much younger and they are treated that way.

And as you know, I come from the University of Virginia, and so one is obligated to use a quote from Thomas Jefferson because he sat up at Monticello with his spyglass and designed the University of Virginia.

And one, I have about 100 of them, but one that I thought was appropriate for today, this is to a doctor, Dr. Caspar Wistar in 1807. "The only sure foundations of medicine are an intimate knowledge of the human body and observations on the effects of medicinal substances on that,"

precisely the subject which we are dealing with today. Thank you so much.

CHAIR DRACKER: Thank you, Dr. Rogol. I'd like to tell everyone that public session is still open until 2:00. I'll close that when 2:00 arrives.

I'd like to push ahead and do the panel discussion if everyone is okay with that, so we don't need a break now. Is that all right with you? Okay.

Are there any clarifying questions before we get onto the -- yes?

MS. OSTER: I forgot this. This is Randi Oster. Would you please just clarify if I heard this correctly, that when you look at the cases of teenage boys, and you went through there were two million at 14, two million at 15, and it basically gets to eight million, but when you look at natural growth projections, you came up with a number that you said there's probably about 60,000 actually affected.

And I just want to make sure that I'm

understanding that because I want to compare that to the total number of cases that were presented this morning to be about 50,000 on the other side of people who have genetic issues, so I'm just trying to see the total population.

DR. ROGOL: Thank you. Let's disentangle that.

MS. OSTER: Yes.

DR. ROGOL: The slide 10 that I showed were the population of boys. That's got nothing to do with hypogonadism.

MS. OSTER: Right.

DR. ROGOL: That's where eight million came from.

MS. OSTER: Right, and then what you did is you took the 2.3 percent and you showed it coming over time, and at the end, you came up with a number which was about 60,000.

DR. ROGOL: That's the math, yes. That's the math with my assumptions that it falls off each year by a certain percentage.

MS. OSTER: And just restate what that

60,000 is. I just want to make sure I understand it. That 60,000 represent what?

DR. ROGOL: Boys with delayed puberty.

MS. OSTER: Okay, so out of the total population, there are 60,000 that actually have delayed, right? That's what you're saying?

DR. ROGOL: 2.3 percent of eight million, one percent would be 80,000. I'll go back and do the math, but that's about what it is.

MS. OSTER: Right, but that's -- okay, so that's the point. I just wanted to make sure we have the two populations clear. One is 60,000 that actually have delayed and the other number that we came up with this morning was about 50,000 who have the IHI or those other --

DR. ROGOL: No, I don't think there are 50,000 with --

MS. OSTER: Well, the other gentleman this morning presented that, so those are our two populations.

DR. ROGOL: Between the two of us, we need to come up with an appropriate number.

MS. OSTER: Yeah, but that's important. As we do the study, we have to understand what our total risk factor is.

DR. SHARRETTS: John Sharretts. I'll just comment on the number. I think ours was not meant to be an exhaustive number. It was an estimate, and it wasn't just causes.

I think what Dr. Galescu was trying to identify is children who have hypogonadism in the age of 12 to 17. And so some of those kids are going to have a structural cause of hypogonadism. Some are going to be delayed puberty.

But, yeah, so we have an estimate number, but, you know, I think the idea is that the number is in the thousands versus -- you know, what we were trying to get is an idea of what the potential population that participate in trials might be. That was the idea.

DR. GALESCU: And actually I was very pleasantly surprised to find out that we came to very similar numbers.

If you look at the breakdown of the

estimate of cases that I came up with, you will see that, for example, for pediatric cancer of all causes, I took the 26 percent of male cancer survivors to do the calculations, 26 percent, but the study that I cited ranged anywhere between 26 to 36.

So every one of the analyses that I did were using the lower margins to give you a conservative view of the number of patients. That's how I came to 40,000.

My colleague used a statistical approach assuming a normal population distribution of disease and came with 57,000. Those two numbers are extremely close together. Do not differentiate between the two of them. We are basically in consensus about the population.

DR. NGUYEN: Hi, actually I want to bring into the discussion a very important distinction just in case it's not clear.

I know we're dealing with similar numbers, but on the one side, we're looking at sort of a gross estimate of boys who may be eligible,

I should say who may be candidates for a trial to look at the treatment of hypogonadism with TRTs.

And those boys would be the ones with permanent hypogonadism versus the estimate we have where we're talking about constitutional delayed, 2.3 percent, as our statistical number, two very different populations.

And also there was a reason why we presented the drug utilization data and I think that needs to be taken into consideration when you're thinking about the size of trials.

CHAIR DRACKER: Dr. Chan, did you want to clarify something?

DR. CHAN: Yeah, so to elaborate on Dr. Nguyen's point that again, the first presentation were for diagnoses that are associated with what are thought to be permanent lifelong conditions.

Dr. Rogol and I were muttering that we feel that that's probably an overestimate, that probably relevant to that is the comment that

someone, the question someone had about how many of these conditions actually result in frank hypogonadism as opposed to subclinical or possibly transient causes.

I think the rates of hypogonadism after cancer chemotherapy, those numbers seemed a little high to me, and certainly after cryptorchidism. I rarely see a child who has frank hypogonadism because of cryptorchidism, and usually that's because of a surgical complication, not because of the condition itself.

It's a little complicated because some of the permanent causes can cause cryptorchidism, and so there's a little bit of a chicken and egg issue there as well, but my suspicion is that the diagnosable, identifiable permanent causes is probably south of that 50,000 number that was estimated.

Dr. Rogol's analysis was kind of all comers agnostic to underlying cause and does include constitutional delay, and so I think that the two analyses are fundamentally different.

And I think speaking to the target population of a study where there's an identifiable permanent cause, the number is probably considerably less than the 50,000. That's my hunch.

DR. GALESCU: I just wanted to clarify that my analysis also includes 12 and above, so you do have a little bit of a difference in age population.

Twelve and above because as it was mentioned, a lot of these patients by 14 already come for treatment, so, yeah, we chose 14, but the reality is they are getting treatment even before that, so I wanted to include -- so you're talking about at least two extra years included in my analysis.

DR. ALEXANDER: And I would just sort of add onto that point a little bit to clarify. So when we're talking about this indication, because we are talking about the idiopathic or the hypogonadism, whether primary or secondary, because that's the indication that is approved for

adults, we're sort of separating out the constitutional delay of growth because of the fact that that is a separate indication that isn't part of what we can, as FDA, potentially require sponsors to conduct.

So I understand sort of the confusion, but what we are asking for is sort of a focus a little bit more on the hypogonadism and what types of studies should we think about with regards to what we can require of sponsors to address, which is the hypogonadism indication.

And whether that involves studies that include children down to 12 years of age or would only sort of look at older kids, that's not limited currently.

So potentially the studies that we're talking about or that you would be advising us on this afternoon could include children that are younger than 14 years of age if you think that's important. It could include children that are 14 years of age and older.

But that's what we are trying to get

your advice on and what we want to focus on is the idea of what kind of studies would seem feasible and actually collect useful information for addressing the PREA requirement for these drugs that are currently labeled for primary and secondary hypogonadism.

CHAIR DRACKER: Many of you are adding a number of important points. I just want to remind you to please state your name so we get this information transcribed appropriately.

DR. ALEXANDER: Sorry, I'm John Alexander.

CHAIR DRACKER: Thank you. Christy, you had a question?

DR. TURER: Christy Turer. So a couple of questions. First of all, it seems like there is not a good set algorithm for how to address these disorders.

It sounds like it's more of an art form, but I do wonder if there is kind of a response, you know, between differentiating the CDGP versus IHH, if there's an optimal time to determine that.

You know, if you start therapy at this age, when might you expect to be able to differentiate the two, right?

Because a grand challenge here is even if FDA can't enforce studying something in a population in which it may be transient, what we're talking about is there is a hodgepodge at the beginning, so you get a whole bunch of people treated, and now you've got a really confusing -- you know, is this IHH? Is it the other?

And so, you know, it would be helpful if you understood an optimal time. If you could define a response at X time period beyond that, you could even do like an adaptive trial, but I'll leave that off for, you know, the later discussion, but is there an optimal time? Is there a general time frame at which you could differentiate them?

DR. CHAN: Ming Chan. There are kind of two or maybe even three questions embedded in that. First is the over time, does your diagnostic capacity improve? You know, the data that we showed was all comers with delayed puberty.

As you get older and older, then the children with constitutional delay are going to start entering puberty and they start dropping out of your denominator essentially, and the chance that you have something permanent becomes more likely the older you get without entering puberty.

We have some data from our chart review that suggests that there are still a substantial percentage of boys, for instance, who are still entering puberty between 16 and 17.

And so, yes, it gets more likely over time that you're headed towards a more permanent diagnosis, but you have to get pretty close to that 18-year mark to get close to certainty that there's still a substantial proportion of kids who still have constitutional delay even fairly far on.

So that doesn't necessarily help you all that much. It's more graded. There's no sharp threshold when all of a sudden you say ah, you must have IHH, and even that 18-year definitional cut off is an arbitrary cut off. There are some individuals who enter puberty after age 18 and they

just have really, really delayed puberty.

With regards to the treatment, I think that's a difficult question to answer. Thinking about it physiologically, there's not a lot of data to suggest that the timing of treatment matters much, but it may matter.

Thinking back to some of the data that exists about long term outcomes of delayed puberty and the effect on height and bone density, that those may represent optimal windows for initial exposure to sex steroids, but that's an interpretation and it's certainly not proven. So there's a hint that it may matter. I think the proof is still yet to come.

I think from the psychosocial perspective, then the age certainly matters as Dr. Rogol eloquently described, that the longer you wait, the more discordant the children are with their peers and the more the anxiety has built.

And I think for a psychosocial indication, sometimes it's hard to sell a delay, and then sometimes it really depends on the

individual and their family.

CHAIR DRACKER: Sarah?

DR. ROGOL: Al Rogol.

CHAIR DRACKER: Sorry.

DR. ROGOL: I just want to finish on that answer. The only thing I would add is a stopping point would be, as I mentioned, if you start and you don't know what your diagnosis is and their testes start to grow, you stop when their testes grow, so that would be something that would be a distinguishing physical exam finding, and that's essentially what we do.

CHAIR DRACKER: Sarah?

DR. HOEHN: Sarah Hoehn. I have two clarifying questions. I have one for Dr. Chan and one for Dr. Rogol.

My question for Dr. Chan is in your slides, you mentioned safety labs, but then it wasn't clear to me specifically what you meant by safety labs and then how often, if you were going to check them, you would check them, which is tangentially related to my question for Dr. Rogol

which is when you went to the Circadian rhythm of testosterone, if you were going to potentially design a study where you wanted to titrate testosterone levels to ensure that you are not achieving supra-therapeutic levels, then how often would you want to check those labs, and then again, what time of day would you check them, and would you standardize for each child or each person if they were checked at the same time of day? Those are my questions.

DR. CHAN: Ming Chan. So addressing the safety lab question, it's really drawing off of known physiological effects of testosterone and increasing hemoglobin and hematocrit and affecting lipid profiles, and then in some non-physiologic forms of testosterone causing liver enzyme elevations.

And so, for example, the guidelines for management of transgender individuals recommends monitoring all of those parameters, hemoglobin and hematocrit, LFTs, and a lipid panel every six to 12 months.

But in the pubertal induction and in treatment of boys with Klinefelter syndrome, even on adult doses, that's really not routinely done, again the idea being that it's a fairly psychologic replacement, at least in theory.

DR. ROGOL: Al Rogol. Directly addressing the question about Circadian rhythm, if the child is not on a drug, then 8:00 or 9:00 in the morning because we like to hit the peak. Most of the levels by Tanner stage are in fact morning levels of testosterone.

If you're on therapy, all bets are off because if you're on gel, you can measure it any one of the 24 hours. The levels are pretty constant through the day.

If you're on an enanthate or cypionate, you're going to be supra-physiological at day four, five, six. You're going to be infra-physiological at day 25, 26, 27.

And so we, as a rule, not as a rule, as a practice, do not measure testosterone levels unless they're not being treated if we're

interested in the physiologic level, and that's really uncommon.

DR. HOEHN: So I have a follow-up question to that which is then how do you ensure that you're not surpassing physiologic and achieving supra-physiologic if you're not checking the levels?

DR. ROGOL: Al Rogol again. How are we sure? We measure what I noted as PD levels, their height velocity, bone age change, but again, those are really blunt instruments because even physiology has a huge range, so none of those are perfectly helpful, but some of them may be.

If the growth velocity is much higher than I would expect, which has happened perhaps twice, I have measured the levels and I've been surprised at how low they were. This kid just decided to grow.

DR. GALESCU: Ovidiu Galescu. Just a quick point to that question. In fact, with the current formulations, you can pretty much 100 percent assure that you do exceed physiologic

parameters because that's how the IM shots work.

For the first five or six days when you attain C max, it is way above the physiological range, and in fact, by the time you repeat the dose, the range of testosterone is below what is considered therapeutic.

So in fact, the currently approved products view a yo-yo of testosterone levels in these kids where you see supra-physiological ranges in the first part of the therapy, and then a nadir with a nadir in the therapeutical points as well.

DR. COOKE: Can I weigh in maybe just a little bit? So, David Cooke. I think the way I think of clinically approaching it, and I think the way that most do, is basically a clinical extrapolation, right?

We know we take these kids from zero testosterone to an adult dose, whatever that is, and we make an assumption that as we're escalating the dose up, that when we're below the adult dose, the levels are acceptable.

You know, if we're using the monthly or every couple of week injection, there is that swing from high to low, but we assume that the levels are below what the adult replacement would be accepted to be, and that any side effects of hematocrit and things like that would be very unlikely.

So my practice is to start with the low dose and escalate up, and then when I get to the dose that I think is the right final dose, then do things like measure hematocrit and lipid levels to see at that adult dose now on this young adult, adolescent, are we having those side effects, and then maybe some measure of testosterone level with the caveat that you have to make a judgment based on the timing of the blood draw compared to the treatment you're giving.

CHAIR DRACKER: I'm going to close the public hearing now. It's 2:00 and then we'll proceed. Who else had comments? Go ahead. You can go next.

DR. MCGOUGH: Jim McGough. I have two

related questions and then a third. As you're sort of thinking of this, what do you sort of see as the duration of the trial if we were to have a trial? If you were to enroll the youth into the trial, how long are you thinking?

Clearly you need long-term outcomes, but to demonstrate the efficacy that you're looking for, is it four months, six months, two years, just what's your thought at this point?

DR. CHAN: Ming Chan. It really depends on the outcome that you're examining. After starting testosterone treatment, you'll start to see growth acceleration usually --

CHAIR DRACKER: I'm sorry. Could everyone speak directly into the microphone?

DR. CHAN: Sorry.

CHAIR DRACKER: We're having trouble transcribing.

DR. CHAN: That you'll start to see growth acceleration typically within six to 12 months of treatment and it will continue at a pretty good pace until the growth plates close roughly

two and a half, three years after you've started treatment with your escalating doses.

And in terms of, you know, other things such as hair growth and voice deepening, those are pretty much given outcomes, but those will, you know, occur roughly in the same time frame.

DR. MCGOUGH: So would it be fair to say that a trial of a minimum of six to 12 months would really be necessary to do this? I mean, is that fair?

DR. CHAN: Again, it depends on the outcome you're looking at, but if you're looking at a growth outcome, I'd say probably closer to 12 months would be --

DR. MCGOUGH: So, now, the flip side, and I'm also speaking as an IRB chair, is considering that the psychosocial needs of these kids are a driving concern, you know, have we considered the consequences of not treating kids at that age for six to 12 months should they get placebo, and not even to mention the complication that they go off label and get treated anyway?

But I think there's an ethical issue in terms of asking kids at such high risk to forgo treatment. So have you thought about that and really what have you thought about?

DR. CHAN: I think we'll take turns addressing this one. So in the clinical scenario, there's this question. The child with delayed puberty, you don't know what they have. They probably have constitutional delay and you're faced with this dilemma with this incomplete information about prognosis and diagnosis.

Do you treat this child with testosterone or not, or do you, you know, continue to follow them and reevaluate in, say, four to six months and revisit the question at that point? And that's the fundamental management decision that's faced in the clinic when this child presents.

And there are a lot of factors that go into that, the degree of psychosocial distress, who is really pushing things. Is the pediatrician worried? Is the parent worried? Is the child worried? Who are you actually treating? And, you

know, what's the degree of delay?

Do they, you know, look like they're on the verge of entering puberty and maybe the testicles are on the verge of hitting that four cc mark, or maybe they look like, you know, just from your impression, they look like an eight-year-old child and it looks like it's years away?

All of these factors come into that decision making process. So I think that right now, given that there is an open question of what the long-term benefits and certainly what the psychosocial benefits are, it's a little bit of an open question still.

So you could argue that there would be clinical equipoise between a treatment and a placebo group, but I think from a practical perspective, you have some families and individuals, patients who really want the treatment and would not agree to participate in a trial that could involve differing treatment for six, 12 months.

There are very few randomized studies of testosterone treatment of boys with delayed puberty, again, most of whom had constitutional delay, and they do suggest that there are psychosocial benefits to the treatment, but those are very small studies.

DR. MCGOUGH: And my last question, you talk about excluding kids on CNS meds, and my question of that is that just from a clinical trial purist point of view or is there, you know, a physiological reason why those particular medications shouldn't, you know, would muddy the waters too much?

I treat mostly ADHD kids. I've sent some for hormonal therapy. So is it -- are you concerned that those medicines are going to be messing up their axis or is it just the fact that we tend to want our samples pure?

DR. CHAN: So again, I'll take first crack and then I'll hand it over to Dr. Rogol. So, again, there are a few issues there. We actually see a fairly high incidence of ADHD among

the kids with delayed puberty.

And in our retrospective review, I didn't show this data, but we had about a third of the boys presenting for delayed puberty had a diagnosis of ADHD, much higher than we would expect. What that connection is and why that is, there is no data.

That's all a matter of speculation, but we certainly have no hesitation in treating those individuals with testosterone. I'm not aware of any adverse effects or interactions between, for example, ADHD meds or other medications.

I think also speaking to this is the experience in the transgender community where, unfortunately, the incidents of psychiatric comorbidity can be quite high. That is not viewed as, you know, a contraindication to starting testosterone treatment.

You know, that having been said, there's not a lot of data driving that, but I think from clinical experience, people have not had concerns.

And then the question of aggression had

been brought up before, and again, I think it hasn't been formally studied as far as I know, but anecdotally, I have not seen concerns.

And again, the thought is that overall, you're averaging out to physiologic levels. Even if at times you are reaching supra-physiologic levels, it doesn't seem to be a common issue that arises, and I'll hand it over to Dr. Rogol.

DR. ROGOL: Well, the short answer to your question is yes, and that comes in two bits. Yeah, as a clinical pharmacologist, you want to do clean trials.

That, to me, is less important, but there are data from ADHD drugs, from corticosteroids, whether they're given by inhalation or not, that they do affect growth, and growth is one of our end points.

Does that mean I wouldn't treat a kid? If I didn't treat a kid taking some of those drugs, it would be a third of my kids that I wouldn't be treating. So it's not the issue of treating. It's an issue of being able to interpret the information.

One final comment was when these kids come to you, and you talk about psychosocial stuff, what they tell you, "Everything is wrong because my fighting in school, my poor grades, I don't get along with my sister, it's because I'm small or because I'm underdeveloped," and they are absolutely convinced that the psychosocial issues are the most important. The parents are, and in part, they're right, so it's an onion. There are many layers to this discussion.

CHAIR DRACKER: Some of these discussions are pertinent to the questions we're going to be posing the committee, so what I'd like to do is just ask if there are any more questions that are related to clarification of things that have been presented?

If you have questions that really are more related to the discussions we're subsequently going to have, please hold that off. Ethan, is that what you were going to suggest?

DR. HAUSMAN: No, actually I had a comment to make to the committee, but it's going

to help frame this afternoon, so it's not for anybody to comment back right now.

First off, it's very gratifying to see the discussion that's being generated right now, but I have observed that it's somewhat perhaps artifactually being dichotomized into IHH and constitutional delay of puberty.

That's an issue when we are looking at enrollment, but to go back to the FDA data that was presented before from our metabolic colleagues, there are a number of conditions that are at issue because the indications of concerns were primary and secondary hypogonadism. IHH is one condition that fits in there.

The other thing to bring up is that as we hope the committee gets into this afternoon, there are multiple ways of doing trials. It's not just necessarily drug versus placebo. There can be dose ranging studies as well, and that's mostly -- I think that covers my comments.

I just want to make sure the committee didn't go down the rabbit hole of saying the topic

to be discussed is IHH versus constitutional growth delay. It's primary and secondary hypogonadism.

CHAIR DRACKER: Okay, Randall?

DR. FLICK: Dr. Rogol, you mentioned off label use. You said, "I and all of my colleagues treat with off label use." When you say off label, do you mean off label using the injectable in an off label setting, a child who is eight years old or it's not labeled for that, or you're talking about using a gel or some other form of testosterone?

PARTICIPANT: Both.

DR. FLICK: Both?

DR. ROGOL: Al Rogol, both, and the reason is nothing but the injectable is on label. And when I say off label, the dose isn't specified. So it's kids who have, in my, we'll see what the others say, bone age at least 10 and a half and usually very rarely under 12, irrespective of what their age is, whether it's 12, whether it's 14, whether it's 16.

DR. FLICK: So is there a sense in your

mind that any of the formulations available in adults would not be efficacious in a child?

DR. ROGOL: Al Rogol, no and yes. I would not ever use testosterone undecanoate injection, which is a 10 to 12-week, because you don't -- if a kid has got, I'm not supposed to say this, constitutional delay, you don't want to have him treated for all that long, so I wouldn't ever use that one.

The ones that are available to us, we considered, there are probably reasons not to, cypionate and enanthate the same, and the reason I use cypionate and enanthate first until we get to mid puberty is I know how to meter that amount of drug.

I don't know how to meter the gel that was brought up this morning because until you get to a single pump of the old Androderm container of 1.25 grams --

DR. FLICK: So, forgive me, but that's why I asked the question. So people are using gel, unless I'm hearing wrong, so how is this being done

currently?

DR. ROGOL: I can only speak for myself. I know a lot more people than I are using the gel. I never started the gel. I'm retired, and when I practiced up to five years ago, I used the gel only after halfway through puberty because I knew that was a dose that was reasonable.

DR. FLICK: I think it's helpful for the committee to know how these formulations are being used currently because they are being used currently.

DR. ROGOL: Well, we've got several people here that are currently treating patients. Let them speak.

DR. CHAN: Ming Chan. So this is just anecdotally talking to colleagues. For example, people have gotten around the gel issue by using it every other day at the lowest dose instead of using it daily. People have tried to find ways to essentially titrate the doses down to the doses that you want to use at the very beginning of pubertal induction.

And I agree with Dr. Rogol that I'm not aware of any reason to think that the child's response to different formulation would be any different to an adult's.

DR. FLICK: So, if I -- and I just want to carry this to the conclusion, forgive me, but we're really not talking about -- so if we look up here, it's about safety and efficacy, right, but we've really sort of established efficacy because we use this all of the time now. It's really about dosing and safety. Am I right? Okay.

DR. CHAN: Ming Chan. I agree with that.

CHAIR DRACKER: David?

DR. COOKE: I guess the only thing I would add just in case it's helpful to everybody is the one aspect of using gels as therapy is that there the serum levels can be useful because the testosterone level on a day-to-day basis, once you get to daily therapy at least, you know that represents the sort of average circulating testosterone level, whereas with the injections,

there's such a difference from two days after the injection to two weeks after the injection that the levels at these lower doses are pretty much meaningless, but with the topical, there the levels become a little bit more useful if you wanted to use that to guide your therapy.

CHAIR DRACKER: Kelly, did you have a question?

DR. HAVENS: Could I follow up on this question about titrating the dose that just came up?

CHAIR DRACKER: It's up to her.

DR. HAVENS: Well, you said you titrate the dose of the gel from daily to every other day. What end point do you use to titrate the dose? You've been doing it a long time.

We heard before that you titrate the dose by age until you get to a certain age. How do you do that if you're younger because you never mentioned a drug concentration? I'm trying to get to the extrapolation question later.

DR. CHAN: Ming Chan. The initial

experience was with injectable esters, typically cypionate and enanthate, and what was empirically found was that if you start with a dose somewhere between one-eighth and one-sixteenth of an adult dose, you seem to do pretty well, and then you gradually ramp up over time.

And so people have used that same principle to calculate the gel without any published data to support that, and I think often without using serum measurements to corroborate that because people weren't doing the serum measurements for the injected esters either.

DR. HAVENS: To a non-endocrinologist, what does "You do pretty well," -- that's my question. There was a long list between height velocity and ALT about doing pretty well. Those are the things you're looking at to mean doing pretty well, not overshooting height velocity, not whatever?

DR. CHAN: Ming Chan. So exactly right. So I'd say that the primary outcome that the endocrinologists have looked at are growth and

bone age.

DR. COOKE: David Cooke. And the progression of pubertal signs.

DR. HAVENS: Testicular volume. Well, that's been mentioned by different people.

DR. CHAN: Ming Chain. Testicular volume is tricky because it is -- so first of all, in individuals with primary hypogonadism, it's not a useful measure. The testicles are just not going to develop.

For the individuals with permanent causes of hypogonadotropic hypogonadism, the testicular volume growth, as Dr. Rogol mentioned, is driven primarily by FSH driving the Sertoli cell and seminiferous tubule complement, so it requires endogenous FSH production unless you're getting something like exogenous FSH or GNRH to drive testicular volume.

So testicular volume is really used for those individuals with constitutional delay to see if they're entering and progressing through puberty.

DR. WADE: Kelly Wade. I have two clarifying points, one along this discussion. I'm struggling to understand why we're using an IM formulation that leads to supra-therapeutic exposures and then low exposures for a physiologic hormone that has diurnal variation.

Is that simply a limitation in our formulations or -- I'm just struggling to understand why we're using an IM injection for a physiologic hormone that has diurnal variation.

And my second question is different, but I'm trying to understand kind of clinically meaningful outcomes. I'm trying to understand what the epidemiologic data says about the age at pubertal development.

Is a delay in pubertal development, is that associated with harm in bone mineral density or could that be associated with protection of cardiovascular health outcomes? I mean, is there -- what are -- the timing of puberty, how does that correlate with clinically meaningful long term outcomes?

And when we think about things like height velocity, what does the data show in terms of its association with a clinically meaningful long term outcome beyond just your final height?

DR. CHAN: Ming Chan. So the first question about why we use this dosing regimen that gives you supra and then infra-physiologic levels, it's really historical, that that was the formulation that was available and that's what people used, and it achieved the desired effect of accelerating growth, inducing secondary sex characteristics, which kind of in retrospect tells us that that diurnal variation, even though it's physiologically present, may not be physiologically significant.

With regards to the second question, what are the long-term consequences of having delayed puberty? I think there was some comment this morning about what the long term -- if it's never addressed, that you're going to appear -- you know, you'll never achieve secondary sex characteristics.

One thing that I don't think was mentioned was that bone health seriously suffers from hypogonadal conditions, which is an important thing to consider.

But the question of, you know, puberty at 11 versus 13 versus 15, does that make a difference? We only have indirect data to speak to that.

There are a population of epidemiological studies that have associated both early and late puberty with a number of adverse outcomes in adulthood.

Late puberty in particular has been associated with lower bone density for sure, and also increased risks of cardiovascular disease, increased risks of depression and other psychiatric issues.

These are purely association studies, and so don't speak to causality, but there have been some Mendelian randomization studies that have definitively shown, I think fairly definitively within the limitations of Mendelian randomization,

that it is later puberty that directly causes lower bone density. For the cardiovascular, it's less clear. For the psychiatric outcomes, it hasn't been looked at yet.

DR. ROGOL: Al Rogol. I just wanted to follow up on that. What you bring into the rest of your life as far as your bones are concerned are probably what you have at age 20 or 22, and so there's a window in which you can build bone, and if you skip that window, your bones will always be below average.

That doesn't mean you're going to fracture, but it means you're going to be below average. You need to have sex hormones, testosterone and estradiol, in that window of puberty to build the best skeleton you can build.

DR. COOKE: Dave Cooke, just one more thing to add to the question about the pharmacokinetics. For a child that is known to have primary hypogonadism, I would agree there is absolutely no reason to think there would be a benefit of the monthly injection.

But because, again, the largest pool of these kids that are treated are in that pool of is this just constitutional delay or is it IHH, in that case, there's at least a theoretical benefit of the monthly injection because as those levels drop to zero, that may be part of what allows their own endogenous puberty to progress.

Now, I haven't seen any data to say that the topical given daily to induce puberty or to treat constitutional delay would slow it down, but in theory, it could.

CHAIR DRACKER: Randall?

DR. FLICK: Randall Flick. This is for Dr. Alexander. So, John, I just want to make sure I understood you, and I probably misunderstood, but you talked about the kids with constitutional growth delay, and the adult formulations, the gels or whatever are not labeled for that use, but that doesn't mean that those children couldn't be a study population for pediatric labeling, is that right?

DR. ALEXANDER: Correct.

DR. FLICK: Okay.

DR. ALEXANDER: The idea would be that potentially -- I'm sorry. This is John Alexander. So the idea would be that what we're trying to do is specifically address the hypogonadism population because that's what we can require studies of in the younger population.

That does not mean that that population that has a constitutional delay, especially if the issue there is one of not really being able to distinguish those patients who have constitutional delay versus primary or secondary hypogonadism until after the fact, that doesn't mean that those patients wouldn't necessarily be eligible for the treatment.

But what we are mainly interested in though is the longer term, the patients who would require that sort of longer term treatment. So it doesn't mean they can't be participants. It doesn't mean that you couldn't collect useful information from that population.

DR. FLICK: And the regulatory framework allows you to create a new indication

without extensive studies?

DR. ALEXANDER: No, because what happens then is the requirement allows us to say in adults, you've studied your drug and you've sought an approval for use in treatment of patients with primary and secondary hypogonadism.

Therefore, we can require you to sort of address that same indication in the pediatric population as long as we don't think that the studies would be infeasible or for other reasons we would need to sort of waive any further studies.

Once we get into studying a new condition or a new use of a drug, then that's basically outside of the PREA requirements and that would all be something that we couldn't require the companies to do.

DR. FLICK: So maybe I'm hearing something that's in conflict with one another here. So you're saying that it's not labeled for constitutional growth delay, but you're saying you can study those patients, I guess, under the rubric that they are -- that's hypogonadism and it's not

defined at the time that the therapy is initiated. Is that right?

DR. ALEXANDER: So I would say that -- this is John Alexander again. I would say that the -- as long as you think that those patients would potentially get a benefit from that treatment in the clinical trials, there's no ethical reason that would sort of preclude them from being included in a clinical trial or study.

I don't think that that would be the basis then for labeling the drug to say that this drug works for constitutional delay of growth, but that information that you collect from them could potentially be used to support the labeling that we can require of sponsors for the patients who have primary or secondary hypogonadism. Does that help?

DR. MCCUNE: This is Susie McCune, and let me just kind of -- because on one hand, we're talking about the studies that can be done from a scientific and ethical perspective. I want to just take a step back and I think what we're talking

about is what we can do under PREA and BPCA, and you had the slide this morning.

So what John is talking about is that under PREA, if a drug is labeled for an adult indication, we cannot ask for a different indication to be studies in the pediatric population under PREA.

However, if we think that it's important to study a different indication, we can -- that can be studied under BPCA with a written request, but we can't mandate that study be done, so that's voluntary versus required. Does that help make sense?

DR. HAUSMAN: Ethan Hausman. I'm going to make one more clarification. FDA traditionally has not considered constitutional growth delay where kids will grow up into eventually be physiologically normal adults without any treatment, bearing in the mind the psychosocial aspects of delay. We're not saying that that's not an issue.

But because we have not traditionally

considered that a form of primary or secondary hypogonadism, that actually falls under a different kind of indication if it were ever labeled. So that indication at this point, we don't have a mechanism under PREA to require sponsors to do that.

Should we feel that it ever becomes necessary to study, we could have a mechanism for doing that de novo under BPCA under certain circumstances, but that would be elective. So we would never be able to force anybody to do that, but if they should choose to do it, that would be a fine thing.

DR. FLICK: But, I mean, I recognize that you're asking the committee to think about the study design which will by nature include primarily kids with constitutional growth delay.

DR. HAUSMAN: Not necessarily. Ethan Hausman again. I understand your question and this actually would be more of a question for the AC and our invited speakers to address later.

So the question then becomes what are

your enrollment criteria? As we saw the slide before, there are a number of conditions, and the bigger ones as we're talking about are constitutional growth delay, which is not the condition that we're setting the framework up to discuss, versus IHH, so that becomes a teasing out factor if we're going to try to tease out those two populations, but there are a number of other populations.

The other thing that came up earlier, I can't remember who said it, but there was discussion about, I think, only studying patients 12, 13, or 14 and above.

If we feel that we have a situation of primary and secondary hypogonadism, another topic again for enrollment criteria for the AC is what are the lower ages? What's the lowest age bound that you would like to enroll in this study and how do we properly identify those patients?

So I understand your concern and consternation, and if it makes you feel any better, we wrestle with these same issues every day.

DR. FLICK: I actually feel fine, but I just wanted to clarify, and I think we'll get into this later, and I apologize. We're maybe getting out ahead of ourselves. We'll come back to this, I'm sure.

CHAIR DRACKER: Go ahead.

DR. JONES: Bridgette Jones. I just have kind of more of a practical day-to-day type of question about access to these therapies. So one of the things that I think one of you mentioned was that the patients that come to see you, they're not your typical general population type of family.

And so since many of these therapies are being used off label, is there insurance coverage typically for these types of treatments, or are patients paying out of pocket, or does insurance coverage vary?

DR. CHAN: Ming Chan. Especially if there is a permanent organic cause that's identified, I have never encountered a problem with insurance coverage for the off label use of these

products. I think among the indications that I discussed, the one challenge can be transgender individuals, but other than that --

Every once in a while, you hit an insurance roadblock where they apply the adult criteria and say you need two first morning testosterone measurements and so on, and you just, you know, say this is a different indication. This is a permanent condition, and usually it's -- I've never run into a problem where insurance was denied in the end.

CHAIR DRACKER: Peter?

DR. JONES: Thank you. Yeah, I'm just trying to make sure that there's not a population of kids out there that aren't receiving treatment because there's no coverage or they can't afford treatment.

DR. COOKE: David Cooke, can I tack on for that as well? So I would -- I think the question about off label is a little bit loose here.

So for, you know, testosterone enanthate, it is indicated for hypogonadism in

children, and for those children, I would agree. There's a lot of extra paperwork. It's not always easy, but we do get coverage.

In those instances where I've tried to prescribe the topical gels which do not have treatment of kids as an approved indication, those I have often had insurance companies refuse because it's -- well, they don't tell me why. They just say they refuse.

So I think there is a little bit of an access issue there that is generated perhaps at least in part by the ones that do have an indication and do not.

CHAIR DRACKER: Go ahead.

DR. HAVENS: Peter Havens. Another issue of safety has been raised in terms of using the injectable long acting which is high and then low versus a gel which may give a constant amount.

And Dr. Cooke, you had mentioned that perhaps the infra-therapeutic or what -- it's hard to say that there's a therapeutic level, so I don't

know how to other -- the low concentration --

DR. COOKE: The nadir.

DR. HAVENS: The nadir, good, thank you. The nadir concentration might allow endogenous testosterone, allow you to see endogenous testosterone production in people with CDGP. Do I understand that right?

DR. COOKE: Correct.

DR. HAVENS: And in patients who have IHH or other biology that will not allow that, you won't see that, and I guess to the testicular size issue as well?

DR. COOKE: David Cooke. Yes, and I would actually maybe more broadly say instead of testosterone levels, activation of the HPG axis is what you can see with CDGP, but not in IHH.

DR. HAVENS: So then as we think about the population of interest to the FDA for PREA purposes and the relative safety of different preparations, the different preparations should be equally safe from that perspective in the IHH and other groups?

Is that -- well, you could argue that the gel wouldn't be as safe if you're hoping to essentially remove the testosterone and see what happens to the axis.

DR. ROGOL: This is Al Rogol. We need to think about a couple of other things as well. The gel in kids, transference is a big deal.

DR. HAVENS: Transcutaneous --

DR. ROGOL: Transference from the kid or the adult --

DR. HAVENS: Oh, oh, giving --

DR. ROGOL: -- to kids. So we've seen -- and it's because --

DR. HAVENS: Giving it to somebody else.

DR. ROGOL: -- precocious puberty and pseudo-precocious puberty based on transference from granddaddy to a baby or something. There are many cases. I've been involved in court cases because of that. So there are a number of considerations. The gel needs to be put on every single day. You have to remember to do it,

etcetera, etcetera.

The injections, the kids actually, when it's once a month, eventually we go up to once every two weeks, when it's once a month, the kids get used to it, but there are other considerations than just the pharmacokinetics.

And the corollary to that is I do not believe that all of them are equal, that you can just give any one of them. Yes, they're all virtually safe, but the side effects are probably dependent upon which you use.

What was brought up today and is never used is the one that's put in the mouth, the buccal one. Well, that's not used very much because the men get very much irritation of their gum line. So each one is actually different. The drug is the same. It's metered differently and it's presented to the body differently.

DR. HAVENS: And could I just make one other comment, that I appreciate having these amazingly brilliant endocrinologists here. Just hearing everybody's perspective really has been

helpful. Thank you all very much. I appreciate it.

CHAIR DRACKER: If there's no more comments, I think we'll take a break and start in 15 minutes, because I have a feeling the next session is going to be involved, so thank you.

(Whereupon, the above-entitled matter went off the record at 2:42 p.m. and resumed at 3:01 p.m.)

CHAIR DRACKER: Okay, we'll start with the questions posed to us. I just want to mention when you consider these points please try to think succinctly and specifically.

Try not to wax on philosophically or else we will be ordering Chinese takeout for everyone. So please try to be specific if you can.

John is going to lead the questions for me, which I was more than happy to let him do so. So, go right ahead, John.

DR. ALEXANDER: Sure. So this is John Alexander. I wanted to give a little bit of a charge to the committee because we have been talking

about a whole lot of different aspects of use of testosterone in the pediatric population both for constitutional delay of growth in puberty as well as for different causes of primary and secondary hypogonadism.

So we do agree with the concept that was expressed in the open public hearing earlier that if the intent was for us to look at a product and get it approved for constitutional delay of growth we would probably need controlled trials in order to do that and I think that's a little bit beyond the scope of what we are asking today.

What we are looking at today is we have a certain amount of information both from adults with the approval of the drugs for treatment of primary and secondary hypogonadism as well as the fact that we have an approved product already, albeit approved prior to the requirements for demonstrating efficacy of an approved product for treatment of children with primary and secondary hypogonadism.

And the idea here is what we want to

do is outline what are potential studies that would be feasible for evaluating new drugs potentially with new roots of administration and what we would sort of need to be able to sort of evaluate those drugs for use in this population for the genetic or structural causes of hypogonadism, the things that are basically going to cause permanent testosterone deficiencies.

So the questions that we have outlined are really questions to the committee to sort of think about in terms of the study design and think about in terms of what is possible to do in a clinical trial to get us useful data that would support the use of these products for labeling.

So the first question, and these are all discussion questions, is that the goal of a pediatric development program with testosterone therapy is to obtain evidence to guide the safe and effective use of such therapies in boys with genetic or structural causes of hypogonadism.

Therefore, in consideration of the information that has been provided today please

discuss the following, study design and study population, so eligibility criteria that you would use in a clinical trial, the appropriate efficacy endpoints, the appropriate safety endpoints, duration of safety, follow-up, and estimated trial sample size.

And then Question 2 is given the information provided today in this study design to the elements in Question 1 above please discuss the feasibility issues related to the conduct of such a trial, including the size of a population of boys eligible to be enrolled in the trial and recruitment issues.

And on that question I would make the specific point we have discussed a lot in terms of different numbers of patients that might be eligible.

I want to point out that FDA, at least in recent years, has been very used to dealing with rare disease populations so that we can when we have a population that is small but is seen by a certain group of sub-specialists can accomplish

trials even in conditions that are considered ultra-rare, the less than 1000 population.

So I think it's important to keep that in mind with all the discussions that we have had about numbers of patients that are available.

And then, third, given the known complications of testosterone therapy in pediatric patients, for example premature growth plate failure and short stature, what post-marketing safety evaluations you recommend and provide a rational for your response.

So I'll turn over the discussion to you. Thank you.

CHAIR DRACKER: I haven't even asked a question yet. Go ahead, you can ask your question.

DR. HAVENS: Peter Havens. Is a non-inferiority trial design acceptable to the FDA as a --

DR. ALEXANDER: So, yes, that's a potential, but recognize we are also still talking about the feasibility and when you get to a trial

that is a non-inferiority study then you have to sort of decide what is it that you are comparing and I do think that being familiar with non-inferiority trials from my anti-infective days the number of patients that you need sort of increases fourfold if you decide that you need to actually design the trial around meeting a certain small margin.

So that is something that is important to keep in mind, especially when we are talking about the patients who have basically a permanent cause of hypogonadism of testosterone deficiency.

Designing sort of what the margin would be would be sort of difficult, but --

CHAIR DRACKER: Okay, I'm going to read the question, but, again, keep this in mind, we don't have to answer everything for all forms of hypogonadism.

So I would think the goal is to keep it narrow and doable. Is that fair, John?

(No audible response)

CHAIR DRACKER: Okay. With that, the

goal of a pediatric development program with testosterone therapy is to obtain evidence to guide the safe and effective use of such therapy in boys with genetic or structural causes of hypogonadism.

Therefore, in consideration of the information provided today please discuss the following. First, study design and study population. Again, think narrow.

DR. HOLUBKOV: May I? Rich Holubkov, biostatistician. So maybe just a strawman or a knee jerk, but, again, it's a very -- obviously, we learned today it's a very heterogeneous population, lots of etiologies, differences in the extent, the trajectory, the timing of development, and the certainty of diagnosis, too, as well.

So my knee-jerk thing is reduce the noise. Now is this -- is the FDA -- As a committee are we thinking of kind of trying to smash all the etiologies together at one time? Would it be willing to take an etiology, and I am just talking, like strawman, recruit only ten or Stage 2 at age of 15 or 16, those with the most to gain with the

largest possible treatment effect and maybe making other criteria, which I as a biostatistician I should warn about in clinical trials, restricting it so it's as clean, so the outcome is as clean as possible?

Again, a narrow population. Is that acceptable? Would that be extrapolable you are looking for here?

DR. HAUSMAN: Hi. Ethan Hausman. If I understand your comment correctly, if we assume that the hypogonadism that we are looking at is pediatric hypogonadism of a permanent non-temporary variety then if the proper population from all the lists that were gone over this morning fits into that category it could be possible to actually design a study with keying for a limited subset of those patients and accepting some other, kids with some other indications into that population.

And because you are actually studying hypogonadism rather than the primary disease that had, in fact, caused it, then the data could be

acceptable in some fashion for those other groups on that list. That's your question?

DR. HOLUBKOV: Generically, yes. Just can we narrow and tailor or should we -- You know, there is other trial designs as you know where you do, you know, for example like a Bayesian trial where you study several sub-groups together and kind of share, try to share the information and to try to get them all at once.

DR. ALEXANDER: So I'd say that because what we are dealing with in this instance what we are intending to study is the effects of testosterone replacement.

In those individuals with these various conditions that we have sort of outlined that have primary or secondary hypogonadism I think for the most part what we expect is that they have sort of something that, they have a deficiency that is there that we are trying to provide a physiological replacement.

And so it almost doesn't matter exactly what the etiology is for most of them given that

there are some differences with some of the patient populations where they might have some residual endogenous testosterone that they provide themselves.

CHAIR DRACKER: I just would like to suggest though, depending on the nature of the hypogonadism all of the issues listed here are going to be quite variable.

So personally I would rather rely on the experts we have who see these patients all the time to see what narrow group might give us the most information, because otherwise I mean everything from efficacy to safety to duration, I mean all of those could vary quite a bit depending on what the cause of the hypogonadism is. Yes?

DR. MCCUNE: Susie McCune. I just wanted to really point out that what we are talking about are genetic or structural causes of hypogonadism that are "permanent," that we're not talking about the constitutional delay and number of the other etiologies.

We really are trying to narrow the

conversation there and if you want to narrow it further we can talk about that, but I just want to make sure that we are on the same page that we are narrowing the discussion to that.

DR. HOEHN: Can I ask a follow-up to what she just said. Sorry. Because I was actually making notes on the question I was going to ask and I was going to advocate the opposite, that we actually look at the constitutional growth delay because I think the people that are getting treated with the softest calls are for less physiologic, like absence of the testes, those that have the IHH. To me they are the ones that have the greatest risk of harm.

So if you look at what does the FDA need to be worried about it seems like it would make more sense to me that you are worrying about people that are being treated for maybe what is child preference, parental preference, and all of the majority of the children who are being treated for that versus those who have hypogonadism that have a clear physiologic indication for treatment Not

to disagree with the FDA or anything though.

DR. COOKE: David Cooke. Let me throw out a different way of simplifying this. You know, I think what would be a reasonable minimum to require would be PK data, just understand for each of the different formulations what are the testosterone levels that are generated.

We've got things to compare that to. We can compare it to the adult PK data, we can compare it to the changes in testosterone level through the course of puberty.

That I think would be a minimum and that I think is doable and a reasonable expectation. I will leave it to others to decide what the ends are for that.

I think in that the range of the population would be those boys that are presumed to have a diagnoses of hypogonadism that have essentially undetectable testosterone levels so we can see what the exogenous testosterone does to their levels.

It should be across the age range that

these children would be treated, which would be 12 to 18 potentially, and I think that would be a starting point.

Now I think the question about, you know, other measures of efficacy get more complicated and I am interested in what others think about those issues.

I think there are some safety issues that are worth discussing but we'll save that till Question 3, but I would be interested, you know, in, you know, what about just that simple proposal to just require PK data from the efficacy standpoint since we know what testosterone does in large part other than the safety issues.

CHAIR DRACKER: Do the other endocrinologists have a comment about that?

DR. CHAN: Just another point for consideration, that the timing of when the hypogonadism appears does matter as well, that depending on what outcome you want to look at that if it happens before puberty starts or while the child is in the process of puberty or after puberty

is done there may be different outcomes to look at.

But that wouldn't affect something that obliterates endocrine activity and you are looking at the pharmacokinetics, but, for example, the other thing to consider is whether there is partial reproductive endocrine activity left or if it's declining.

So individuals with Klinefelter's Syndrome they don't go to zero immediately, they gradually decline over years, and how to factor that in could complicate things.

DR. ROGOL: Al Rogol. I would add a bit to that. If that is what you are going to do and you don't know a kid is 12, 13, or 14, whether he has constitutional delay or IHH, in fact if you measure in his blood his T will be low and his LH and FSH will be low, his testes will be small.

Now that meets the definition of secondary hypogonadism. You don't know what he really has, but would it be that group that you could do your PK studies on?

DR. COOKE: David Cooke. I'm sorry, what age did you say, Alan?

DR. ROGOL: Pick it. I said 12 and up.

DR. COOKE: Well 12 I think would be problematic because from an ethical standpoint you can't, you know, diagnose constitutional delay in a 12-year-old.

But I mean the inclusion criteria I think could be worked out to decide what the right age group are. Certainly a child with anorchia at 12 would be an appropriate child to recruit for PK data.

DR. ROGOL: Yes. Those are easy data, but the question was for IHH sometimes till 16 you don't really know what they have.

DR. COOKE: I agree, but I would expect you would be able to recruit enough in a range of diagnoses to just get the PK data. And, again, this is the low bar, I'm just talking about the minimum starting point.

DR. CALLAHAN: David Callahan. I mean for the population wouldn't it make sense to use

what's in the package insert for the adults which I think it excludes the IHH, meaning the secondary patients they say it's from tumors, trauma, or radiation, and then the primary patients they list all the other, most of the other things we have been talking about as with the patient population.

So to me we kind of list the population and the question, genetic or structural causes, and then it's in the adult indication, use that same patient population to try to avoid this issue of kids with congenital, I mean constitutional delay.

DR. DELANEY: This is Angela Delaney. I think that is something that has to be decided because I think if you really want to use this pure definition that you are suggesting of genetic or structural causes of hypogonadism you can't even consider IHH because you won't be able to diagnose that at that timeframe.

So if you want to exclude that whole category and just focus on the other ones then that's fine, but that's a much smaller population,

so you'll have to keep that in mind as well.

CHAIR DRACKER: Yes, Peter?

DR. HAVENS: To that issue, one approach that I was thinking about when I asked the initial question was so if you can't decide who's got what until they are 18, if you design a study that would incorporate everybody that's a long enough study to be able to exclude people when you see the increase in testicular volume and other things that are specific to constitutional growth delay then you would be able to subtract them out of your primary efficacy analysis.

So you could do a study in a primary endocrine setting, give two active treatment arms, and by the time you could retrospectively make the diagnosis you exclude those people and you are left with the FDA population of interest. That's for you to figure out.

DR. MCCUNE: So --

DR. HOLUBKOV: I'm worried though whether -- Oh, sorry.

DR. MCCUNE: So just to kind of get us

a little bit back on track, because what we are talking about here are what are the studies that we can require under PREA, and we are limited to the studies under PREA that are the studies, the indication that is given for the adult population.

So and I know -- I understand your concern about the constitutional growth --

DR. HAVENS: No, I understand --

DR. MCCUNE: Let me just kind of finish this for one second.

DR. HAVENS: Yes.

DR. MCCUNE: The constitutional growth delay, but if we are concerned about off-label use in that population we can add information to the label about it not being indicated for that population because we don't have information, but right now based on PREA we can only require studies for the adult indication.

DR. HAVENS: Would IHH be in the adult indication? Yes.

DR. NGUYEN: Christine Nguyen. So I will clarify the confusion that is an adult label.

Prior to 2015 we actually had idiopathic hypogonadotropic hypogonadism, so IHH.

We removed the word "idiopathic" because there was so much off-label use for all various conditions associated with low serum testosterone levels, such as age related.

So IHH in its very purest definition is a genetic disorder and it would be on-label use in the adults, but we had to fix that "idiopathic" word because out in the community people just think idiopathic is just anything that's associated with low serum T levels.

DR. HAVENS: That was for adults. In adolescence is IHH a label used? As I understood from Dr. Rogol's presentation that CDGP is not labeled --

DR. NGUYEN: Correct.

DR. HAVENS: -- but that IHH is a labeled use. That's not true?

DR. NGUYEN: Correct. IHH is a genetic disorder.

DR. HAVENS: And is labeled in

adolescence?

DR. NGUYEN: For the testosterone products, the IM products and the pellet products, correct, yes.

DR. HAVENS: That's exactly my point.

DR. NGUYEN: Yes.

DR. HAVENS: And so those are -- That is labeled so you can do PREA for that, but the functional problem is when you get people you want to enroll in the study you can't tell if it's CDGP or IHH, so you have to take all comers and only later then you say the CDGP group doesn't count for the FDA label.

This is important because we have heard that if you delay treatment then that's unethical because of a) bone growth and b) psychosocial development.

So you don't want to exclude people with IHH who will count for the PREA and the FDA and to not exclude them, which is a big group, then you have to include the people FDA doesn't want but can exclude at the end of the study when their

testicular size starts to increase.

So that it allows you to do a functional study with all of the ethical problems that came up in the conversation handled because you can include them, and you don't have to exclude them at the beginning.

Otherwise you are going to have -- and you are still left with the population who don't end up retrospectively being diagnosed with CDGP.

DR. COOKE: David Cooke. Can I just ask what is the efficacy endpoint that you are proposing, because I the think that's the dilemma here?

If we are going beyond PK data I think the first thing for us as a group to identify is what's the efficacy endpoint because that's where the underlying diagnosis might impact it.

DR. HAVENS: Well, but --

DR. FLICK: Can I just say --

DR. HAVENS: Yes, go ahead. Sorry.

DR. FLICK: I'm sorry. Randall Flick. First we have to decide whether we need an efficacy

study before we decide what efficacy endpoint there is, and I think this is to your point.

DR. HAVENS: Right.

DR. FLICK: Do we really need an efficacy study? I will read from the briefing book, "A PK safety study to identify doses that match exposures in adult may be sufficient to provide evidence of effectiveness for pediatric population when there is evidence of similarity of exposure response relationships across the groups from other drugs in the same class or across drug classes."

I think we already know that these drugs are efficacious, what we don't know is what the dose equivalence is between the current formulation that's used in the population and the proposed formulation, the adult labeled drugs.

That I think is the fundamental question.

CHAIR DRACKER: I think that is the crux of the matter. I think from the FDA we need to understand what is the priority, is it the efficacy

or is it, as David suggested, the PK data for different formulations.

What is the priority of what we are trying to achieve?

DR. FLICK: Can I just follow that with one thing? Equivalence is guaranteed in this, okay. So non-equivalence would be an ethical violation, right.

So if you are treating these children and you know that you have a drug formulation that will treat them and you treat them in some way that is less than that then that's unethical.

So I am not sure how one would do that and, in fact, how would one design such a study to have an endpoint of let's say linear growth when the mechanism by which these children are approached is a dose escalation.

That is the way they are managed through dose escalation. So if you use -- No matter what drug you use you are going to escalate the dose until you get the desired effect, am I right?

DR. COOKE: David Cooke. You know, I

think maybe one of the extra challenges here is we've heard that testosterone treatment is going to increase the growth rate of these children.

But I think what hasn't maybe been said explicitly but it's important to say is there is nothing to tell us what the optimal growth rate with this treatment is.

So I don't know that you could design a study where growth velocity is the efficacy endpoint because I don't know what the best growth velocity is.

DR. HOLUBKOV: This can be numerically challenging as well, as, you know. Rich Holubkov.

CHAIR DRACKER: Could I just suggest if you are going to follow growth could it be a percent of predicted value?

DR. COOKE: I'm not even sure what you mean by percent of predicted value. I mean if you look at growth of the normal population there is a spectrum of growth rate across age, time, and puberty, so it would be very hard to pick a number.

I guess you could pick, you know, the

median growth rate mid-pubertal for a boy going through puberty at the average time, but that's kind of an arbitrary number. That's not really a health outcome.

DR. HOLUBKOV: The change in z-scores.

CHAIR DRACKER: Yes, Peter?

DR. HAVENS: Well, we're getting to the extrapolation issue again and so the question -- To extrapolate, as I understand it, you have to have a PK/PD relationship that's well defined in adults and that would apply in children.

And since the indications for treatment in adults is not growth and the indication for treatment that what we are talking about is growth then the intention of extrapolation completely breaks down because --

DR. COOKE: So --

DR. HAVENS: So I am interested to hear it from Dr. Cooke, who has been talking about extrapolation, and then I need to hear from the endocrinologist at the other end of the table, because as I have been listening I can't see how

to do that.

DR. COOKE: So, again, I would not focus on growth as the outcome. You know, we know that testosterone increases growth rate, but the real goal of testosterone therapy in this situation is to get these kids through puberty and have secondary sexual characteristics.

DR. HAVENS: Well, okay, but, you know --

DR. COOKE: I think that the --

DR. HAVENS: That's good, okay.

DR. COOKE: I think the comparison though --

DR. HAVENS: But that likewise --

DR. COOKE: -- so as I sort of was proposing, and I don't know that this is perfect, but as I was proposing the comparitors for the PK data are both with the adult PK data but also with the known changes in testosterone levels through puberty, right.

We anticipate that if you start, you know, with a certain dose of testosterone that is

lower than full replacement how does that mimic a Tanner 2 boy in puberty, which is what your goal would be as you initiate this.

So that's one of the comparitors that you can have to -- or at least that's how clinically an endocrinologist could then choose the right dose.

DR. HAVENS: Except all you guys said you don't use concentrations. I mean --

DR. COOKE: In large part because we don't have that data. And, again, I think the once a month injectable it's really hard to do that.

I admit that for some of these formulations that interpretation is going to be a challenge, but the monthly preparation actually already has the pediatric indication, so we are more talking about the other preparations that are given daily.

DR. CHAN: Ming Chan, if I could jump in. I think that something to keep in mind that hasn't, and maybe I didn't emphasize enough, is that a lot of the older studies use much higher

doses of testosterone than we currently use.

And even within current practice there is a wide range of people using starting doses how quickly they escalate. I have seen some guidelines with these very detailed every month you are going to increase the dose by a little bit, other guidelines that say just stay on the same dose for six months and then double it and then stay on that for six months and really approach things stepwise.

And I think the bottom line is that the outcomes are at least at first pass at kind of face value don't seem to be widely different between these approaches.

There is a lot of leeway in the goals of achieving growth acceleration, achieving an adult height that seems to be appropriate for that child's genetic potential, and achieving secondary sex characteristics.

There is a lot of leeway in terms of the dosing that allows you to achieve all of those goals and the rest of it is, as someone said maybe a little more art, and whether that art matters

in terms of fine tuning things no one really knows.

And I think that's actually a big part of the reason that we don't check the levels because it doesn't seem to matter that much.

DR. HAVENS: Which by definition, this allows extrapolation since, if the doses that are used in adults to get whatever endpoint they want might be too high to get the impact you want in bone or height or secondary sexual characteristics, if you could achieve that with a lower dose which might be safer than establishing a PK/PD relationship in this age group, would seem to be the fundamental need.

I mean, when I looked at the, at Finkelstein paper in New England Journal that you put up, it seemed like there was a broad range of testosterone doses that got sort of similar benefit.

And it made the point, that you all have made, that estrogen is really important for a big part of this. So it would seem that a dose finding, of what you just described is the need for a dose

finding study to identify the PK/PD relationships of interest.

DR. CHAN: Yee-Ming Chan. I'm not sure that's the point I was making.

We know that pre-pubertal boys have very low serum testosterone concentrations, we know that adult men have adult range testosterone concentrations and we know that across puberty you get from Point A to Point Z. And over a time frame of about two to three years roughly.

And the point I was trying to make is that, as long as that trajectory is broadly mimicked by the dosing schedule, the clinical outcomes seem to have come out just fine in terms of, again, growth, adult height, secondary sex characteristics, acquisition.

DR. ALEXANDER: So, I just wanted, this is John Alexander, I just wanted to make a couple of points here. We've been talking a little bit about extrapolation.

I do think of that as sort of more of a conceptual framework for sort of considering what

you are going to propose as sort of an appropriate clinical study design for this population.

Peter, I think you and I are sort of a little bit more used to the idea of what you do in anti-effectives where we can target a specific dose. It's fairly straightforward that you're sort of targeting a exposure that's higher than, say, what's needed for a Cmax over MIC for an antibacterial or something like that.

I think that when it comes to this situation, especially with replacement of endogenous testosterone, it sounds like there's a lot of variability in the amount of exposure that's seen from person-to-person.

Meaning, what concentrations that you have in an individual with testosterone, and that those all sort of result in the same ultimate outcome of getting secondary sexual characteristics that develop in these patients that otherwise have these permanent generic or structural causes of hypogonadism.

And so, when thinking about

extrapolation, I would sort of pull back from saying, okay, you have to have the dose response in the adults, sort of completely defined in order to do that. I don't think that you need to do that if what you're going to do is find a dose within the trial that sort of matches the exposure that you think is necessary in the adolescent age group for normal pubertal development.

And then what you do is you look at those patients and get an outcome that might be looking at sort of what their secondary sexual characteristics look like six months to a year later. Or the amount of the growth that they have.

Because we're not going to do anything that's going to be sort of identifying the optimal time. And this patient sort of achieved the target growth amount that we really wanted them to achieve.

DR. HAVENS: So a PK based study might be acceptable to the FDA?

DR. NGUYEN: Christine Nguyen, FDA. So, what I've been hearing from our experts here is, in clinical practice they're not monitoring

serum T concentrations for the various reasons.

And that you're really kind of titrating to a PD effect. Be it be growth or something else.

So --

DR. COOKE: Let me jump in. This is David Cooke. I would disagree with that. We are not titrating to a PD effect. We're escalating a dose according to a paradigm. That really is what we're doing.

We start with 1/8th of the adult dose and increase from there based on our own personal program. It's very unusual to alter that based on any clinical outcome measure.

DR. NGUYEN: And how was this paradigm structure in the first place, is it completely in --

DR. COOKE: That would be before my time.

(Laughter.)

DR. COOKE: No, I think the answer is --

(Laughter.)

DR. COOKE: So the answer is, we know that they go from zero to adult over two to three years. And so, the assessment was, let's start with a low dose and get to the adult dose in two to three years. So it really is just trying to mimic normal physiology.

DR. NGUYEN: So, do you follow the same algorithm --

DR. COOKE: Escalation.

DR. NGUYEN: -- for all kids then?

DR. COOKE: Right. I'm sorry, say again?

DR. NGUYEN: Do you follow the same dose escalation paradigm for all kids who need --

DR. COOKE: Yes.

DR. NGUYEN: -- this treatment --

DR. COOKE: Yes.

DR. NGUYEN: -- regardless of, and their response --

DR. COOKE: You know, there may be nuances here and there, but essentially, yes.

Just like we do when we start estrogen

in a hypogonadal female. We start with a low dose. A sixth, 1/8th of the adult replacement dose and we escalate the dose over two to three years.

DR. NGUYEN: Okay, but you're not following serum T concentrations, what are you following?

I mean, granting you're following this, kind of sounds like a kind of a fixed algorithm, if I may, but what monitoring are you doing as you are treating these kids, just giving them testosterone?

DR. COOKE: I mean, we follow their growth, we follow their pubertal development, but they grow faster, they start getting secondary sexual characteristics.

I think in the IHH versus constitutional delay thing we're trying to see whether their testes increase in size so we should stop it.

DR. NGUYEN: Right. Right.

DR. COOKE: But once we've --

DR. NGUYEN: But my --

DR. COOKE: -- made a decision to treat

we just escalate.

DR. NGUYEN: Right. But my point is, at the minimum, you're not measuring serum T concentrations, so if we're talking about a PK/PD study, I'm not sure, I feel like we're going to a space that's not even defined.

DR. COOKE: So, yes. So the reason why I would argue for that, again, is, no, I mean, actually, I guess I'm not sure.

So, when you give intramuscular testosterone, the bioavailability of the is essentially 100 percent. It's absorbed over some period of time.

The topical testosterone I think is a bigger question. So, there's a much smaller amount that is absorbed.

And if that differs from a 12, 13, 14, 17, 35-year-old, than that's important information. Then maybe going to 1/6th or 1/8th the adult dose is not the right thing, maybe it needs to be 1/20th because in fact, they absorb three times as much because their skin is thinner.

So that's where I think that PK data becomes more useful. You know, I don't know about the intranasal, I don't know about the buccal, but again, that's where the bioavailability may very well be different.

So understanding that difference I think is going to inform us in a way that we don't need for the intramuscular because we have experience with that.

DR. NGUYEN: Right. And I'm not saying that PK data would not be valuable, that's not what I'm saying. I think what I'm trying to get at is, what else would we need?

I just didn't want to, I personally will be, I will feel a little bit at lose if PK is all we needed to establish efficacy. If that make sense.

That could be one component certainly, but I, again, I think the goals of the therapeutic invention between adults and children are very different. I mean, as we already discussed.

DR. COOKE: I share your desire. I

think the challenge is we know what testosterone does, it's going to do it regardless of how we give it. Maybe a little bit faster, maybe a little slower.

But I'm really struggling with what your endpoint, your efficacy endpoint would be in a practical means.

DR. MCCUNE: This is Susie McCune. I just had a clarifying question for you. You talked about the escalation paradigm, I assume that that's for the IM. Is that true for other preparations as well in terms of the gel?

DR. COOKE: Yes, although less comfortably understood. But in theory, yes.

DR. MCCUNE: Okay.

DR. DELANEY: This is Angela Delaney. Can I tack onto that because what I was going to say is very much related to that.

I think in the context of this discussion I do agree that the PK data becomes the most important thing. I think we have to sort of backup for a second and remember that, we already

have the indication for the IM for this population.

So, as David said earlier, what we really are talking about are these other preparations. And I can't tell you how many times I've had the discussion with patients in which I say, well, there are these other formulations, but we just don't know the right dose.

We don't know how to give. We don't know, we assume, we make these assumptions, we extrapolate but we don't know.

And I think because the titration, with the gels for example, is such a challenge having that PK data. And I think we have to follow efficacy and make sure that the efficacy looks the same as what we expect.

And I think we have to look at safety things as well. But I think the real unknown is the PK question.

Because if we have that information, then with the proper indication to use this in kids, drug companies would be more likely to make formulations that are more titratable for kids.

And then you're benefitting the patients.

And that's the goal, ultimately. So, I do think that that makes a lot of sense.

CHAIR DRACKER: Jim is going to go first but I just want to suggest, that is really, would be considering perhaps having two treatment groups, gel versus IM testosterone. Which would be a way to do that.

And you can collect the PK data during the course of the study. For both preparations.

DR. COOKE: And which outcome, what's the outcome point that you're going to look at?

CHAIR DRACKER: Well, I agree with you that growth velocity is really variable, person-to-person, but development of secondary sexual characteristics would be more reliable, wouldn't it? Within the time frame.

DR. COOKE: What time frame are you talking about?

CHAIR DRACKER: So endocrinologist.

DR. COOKE: Right. So there you're talking a two to three year study, because that's

how long it takes to go from Tanner 1 to Tanner 4 or 5.

And I'm not sure that it's meaningful, if one preparation takes you from Tanner 1 to Tanner 2 in six months and the other takes you from Tanner 1 to Tanner 2 in nine months, because again, I don't know what the optimal time is.

I think the goal is to get there in two to three years to mimic normal physiology. But short of that two to three year time frame, I would hard pressed to say, what's the better regime.

CHAIR DRACKER: But if you are a guy, if what you do in clinical practice is, let's say a two to three year treatment period, why couldn't that be the period for the study?

DR. COOKE: You could, I'm just thoughtful about the ability to recruit enough kids in enough, now you're going to have to start getting different diagnoses because, again, this IHH versus CDGP throws in there. Because the CDGP kids are going to behave differently than the IHH kids.

And how easy will it be to recruit kids

for a clinical trial, for two to three years. In the numbers that you would need for the outcome.

CHAIR DRACKER: But you're still preparing, you're still providing a therapy for that two to three year period, regardless if they weren't on study, correct?

DR. COOKE: Yes. But treatment and studies are a lot different in terms of the expectation for the individual.

DR. HOLUBKOV: May I ask what that trial would be in terms of a positive ultimate trial, like equivalence at two or three years?

DR. DELANEY: That sounds like a non-inferiority trial to me which sounded, people did not seem enthusiastic about that before.

MS. OSTER: So, this is Randi Oster. I think it's important that we don't look at the obstacles for why we should be even figuring out what our study designs at this point.

I think we have to really figure out what is the best study design and then identify cost and time as an obstacle.

And so, in order to do that I'd like to just go back to, how do we come up with this study design and the efficacy endpoint becomes really clear when you ask the patient, why are they here. And if the patient is coming because they are saying, I want to grow, that's different than, I want to become sexual.

And so, yes, it might be easier for us to use the PK study for sexual identifications because we have the adult population. But I like the FDA, and for this Panel to think about, how that would read in the newspaper that the FDA approved a drug to increase sexuality of teenagers. And so we need to think about that as we're putting these things forward.

DR. MCGOUGH: Jim McGough. And stating I'm not an endocrinologist and I have to leave all the intricacies of this to those of who understand it.

But from a clinical trial point of view my, I guess my advice to the FDA, I don't think this can be a controlled study. I just don't see

how you cannot treat children for a duration that's going to be necessary.

Also, I think we know what testosterone does, as had been said. And my suggestion to the FDA is to be as broad thinking as possible.

I think what you want is the most parsimonious study that will get you the most data, such as the PK, and then you look at what we have. We know what this does in adults, we have normative data, we have historical data.

I mean, I think this is where, I think if you have a community like this design a horse you come up with a who knows what. And that's kind of what we're doing.

But I think my only real advice to the FDA is, let's be really broad here. If we're going to answer the question, there is not going to be a standard clinical trial.

We've got to really leverage everything we know across the developmental spectrum, across the biological spectrum. Do the small studies that we need to give us that extra information and then

really bank on what we already have.

And I hope then the agency can come to make the determination it needs to.

CHAIR DRACKER: Bridgette.

DR. JONES: No, it's --

CHAIR DRACKER: Oh, no, sorry.

DR. PORTMAN: So I, this is Ron Portman, so I agree with you. I'm a proponent of extrapolation. I think we can learn a lot from the adult data. I think PK is also important.

But we also have a lot of data on children who have been using these drugs. Or testosterone. So we can develop, I think, a single armed trial.

We can develop a counterfactual so we can look at, we can do trial designs where we can compare the patients coming into the trial against existing patients who have already been treated, that for which we have data. And can select those patients in a randomized way and compare them to the new patients coming into the trial. So that's another thought.

DR. FLICK: So, am I hearing from you folks that you're not comfortable without an efficacy study?

DR. ALEXANDER: No. I think the idea here is, what we're trying to do is sort of outline what do people look at as the, sort of the necessary elements that need to be defined within a clinical trial.

And I think that what I'm hearing, the discussion going back and forth about is, is getting information about PK and safety of a specific new formulation of testosterone sufficient or is there reason that we should need additional endpoints or have additional outcomes that we sort of need to evaluate, and if so, how do we do that?

DR. NGUYEN: Actually, I think what would be really helpful for us is, for those who are treating these boys, if we were to approve a new formulation. So something you have very minimal experience, if any.

And if we were to approve a pediatric indication, what sort of information would be

helpful to you if we were to approve a new dosing regimen. Do you want to see how the doses correlate with the range of serum T levels and that will help you guide your treatment of these boys, do you want to see some associate PD outcomes with those levels, what sort of safety outcomes do you want to see?

So that will be very helpful to us because ultimately the drug development program is designed to assist prescribers to treat their patients.

DR. CHAN: Yee-Ming Chan. I think it's, I'm going to speak both from my own impressions as well as what I can piece together from looking at literature when the initial use of testosterone in boys with delayed puberty was being studied. Which is well before any of our times.

That I think the primary, as has been said many times, if we are able to mimic that normal rise of testosterone, then all those outcomes happen in the desired way.

The concerns that people had raised,

and that continue to be, I think would be raised for any new product, are the safety issues. In particular, is there going to be overly rapid bone age advancement and the risk of early closure.

And a lot of the early studies in testosterone very much focused on that outcome. And the, you know, what was the predicted adult height based on bone age and how quickly was it advancing. And I think that would be a key outcome of interests to make sure that we're not overdoing it with the new formulation.

And then other more idiosyncratic safety issues that may arise from a specific formulation would be of inherent concern to any pediatrician, much less pediatric endocrinologist. But I'd say, the one specific safety outcome would be the bone age.

CHAIR DRACKER: Dr. Cooke.

DR. COOKE: David Cooke. Yes. From a efficacy standpoint, understanding how a new formulation compares to what the testosterone levels it gives really would be the useful

information. And again, then there is other safety issues that we'll hold off on.

DR. NGUYEN: So, just to clarify. Christine Nguyen, FDA.

Clarifying question to both of you. So when you're talking about the mimic and the rise of the testosterone levels, so we would be comparing to what is known for the testosterone, expected testosterone concentration through the course of puberty that's been obtained in the general population?

DR. COOKE: Yes, I think that would be a very useful comparator to understand how to apply this to mimic that normal rise in healthy boys.

DR. CHAN: Yee-Ming Chan, agree. And in broad strokes.

DR. COOKE: Yes.

DR. CHAN: I think that if you started the dose and you say serum concentration in the mid-adult range you would be very concerned.

DR. COOKE: Exactly.

DR. CHAN: If you had a, you know, which

would say be 500 nanograms per deciliter. But if you start a dose and you get testosterone measurements in the 20, 30 nanograms per deciliter range, people would be very comfortable with that.

DR. COOKE: Agreed.

DR. ROGOL: Al Rogol. I just want to remind us, no matter what we do, faster, slower, the kids all go through puberty eventually and it doesn't really, there's a lot of slop in the data.

The issue about going too fast would really be quite a minor one, in my opinion. Because we already know that giving 200 milligrams to start with, for four months, which was done in the early '80s, which is essentially an adult dose, put the kids through puberty in the same way.

They stopped after four months to be sure, but in essence, in those kids who had testicular function, it worked just as well.

So, there's a huge range in which you can go through. So I don't think a trial would be very dangerous at all.

And the only danger you would get into

would be starting too slow. The kids are too anxious. But that doesn't worry me from a safety point of view.

DR. HAVENS: But what you have said is, what you know and the rest of us don't know. Which is, you can start too fast.

So, it would worry you to start too fast. And so, when you said what this might do is make a drug company give you a formulation where you can get a small enough amount of gel to give you the right dose at the appropriate time, and that's if I interpret it right, why you said, what you would want to do is target the average something or other for that age or that Tanner stage, maybe perhaps better said. So those would be the things.

So, can I ask, how often do you measure -- and then, because from the bone film is when you can calculate the anticipated adult height, right? And so, how often do you do that and, that would be the question.

DR. CHAN: Yee-Ming Chan. So, in the, I'll answer two questions. The first question

about the, how frequently would you check bone age.

Routinely. If you're just following normal progress you check one a year because things just don't change that fast.

(Technical interference)

DR. CHAN: -- is that used, initial studies that used fairly high doses of testosterone, for a short period of time, did not seem to compromise adult height.

Yet we know that if we use pharmacologic doses for a prolong period of time, we can limit the amount of remaining growth for a child. But it takes a lot, seemingly, to really compromise adult height.

DR. HAVENS: And then one other question. You mentioned, you both mentioned algorithmic increases in the doses that you use. So my question, and you mentioned a bunch of algorithmic potential increases.

Do you guys both use the same algorithm?

And I don't mean that in a flippant way, I think you fundamentally share the concept that

you want to, what was your phrase, mimic adolescent, something or other, and there's lots of, I might mimic it differently than either one of you. And you suggest there were a lot of protocols, potentially, extant.

DR. COOKE: David Cooke. We haven't compared protocols completely, the gestalt I've gotten is that we very, very closely follow similar protocols.

DR. HAVENS: And could you write a protocol for a study that endocrinologists in five desperate political areas of the country would agree on?

DR. COOKE: If we knew the PK data.

DR. HAVENS: So, bringing you back, that's what you say, PK is good?

DR. COOKE: Yes.

CHAIR DRACKER: All right, Sarah? You throw your name tag so.

DR. HOEHN: Sorry. I said if Peter Havens talks one more time, I'm throwing it across the room.

(Laughter.)

DR. HOEHN: Just kidding. This is Sarah Hoehn. So, it seems like the things people want the most is not any efficacy data, but the PK stuff, the bone age and the safety labs.

So, just listening to everyone it seems like what would make the most sense, if you were going to do a study, would be to do a three year study, which doesn't involve any additional x-rays. Knowing that some families might not want additional x-rays that were simply study related.

But if the standard is already to get one x-ray per year for a bone age, you could still have that as part of the study.

And then you've heard about the potential for lowering the HDL and other safety labs. And clearly you're not necessarily going to change the treatment because the boys all need the treatment. But it could change how often you follow them or any dietary advice or anything you give them.

So, I just didn't know if people would

be satisfied with sort of a three year PK study, but then also looking at them long-term for the safety data. Which seems like would still fall under the PREA rules, if I understand correctly.

CHAIR DRACKER: Kelly.

DR. COOKE: David Cooke. Yes. You know, I think as we start thinking about safety issues then, as a starting point, a two to three year study to look at safety issues would be very reasonable.

DR. WADE: Yes. And I would just, Kelly Wade, I would really advocate, again, exactly what Sarah was just saying, which is, it seems like what we're really lacking here is dosing information based on pharmacokinetic information.

And we know that pubertal variation that is expected to occur across boys, but our dosing is not designed to achieve that in evidence-based fashion. We have a historic label with a, you know, that has an indication, but it's not based on data.

So I really think the effort could be put into the PK data that could be used over multiple

formulations. We may find a formulation that would allow some of this diurnal variation.

Than we would have informed dosing, be able to do maybe a dose minimization, because maybe even our 1/8th dose is too high, but really put our efforts into appropriate systematic safety collection of data. Because sometimes I think we don't find a safety signal unless we're specifically looking for it.

So I really would advocate along the theme of really thinking about safety data in a very systematic and strategic way. Maybe for things we weren't anticipating. And certainly beyond just bone age. And then a very careful collection of PK in a smaller number, that could be applied across different formulations.

CHAIR DRACKER: Since --

MS. OSTER: Just to interrupt.

CHAIR DRACKER: Okay.

MS. OSTER: I need someone to define this PK study, and just do it quick, because my understanding, I don't understand it enough and

I'm feeling a little lost. So someone take a moment to explain to me exactly what that is.

CHAIR DRACKER: David.

DR. COOKE: Give them testosterone, measure testosterone levels to determine the Cmax, the half-life, the area under the curve. Things that I'm actually not that familiar with. But understand what the testosterone levels are after an administration.

Obviously, the details of that depend on the formulation.

DR. FLICK: David, wouldn't this actually be a dose escalation study? You don't know what the safe dose is so you're going to have to start at a very low dose and escalate that dose until you achieve some level that you think is a target level.

DR. COOKE: Yeah, I agree. The complete study would determine whether there is linearity between dose delivered and the serum levels, yes.

CHAIR DRACKER: Since we're discussing

a study using standard therapy, correct? As standard dose escalation, we are basically monitoring whether PK values or whatever. You are always looking for safety endpoints if something should happen. Do you think a two to three-year study would be acceptable to your patient population?

DR. COOKE: It depends on what you're asking them to come back for the PK data for. If you're asking them for two days of lab draws every dose escalation, that's actually quite a burden compared to treatment.

CHAIR DRACKER: Would you need to do it that many, I guess, for a valid PK data?

DR. COOKE: That's getting beyond my area of expertise.

CHAIR DRACKER: What I'm trying to suggest is that you suggested doing a true study for two or three years that is involved and laborious and a lot to expect of the patient. If you're doing standard care with dose escalations similar to what other endocrinologists do, and

there's not a lot of variation.

DR. COOKE: Yes. If there aren't any extra study-designed interventions, yes, I think that would be acceptable to the patients to be enrolled in essentially an observational study.

CHAIR DRACKER: Because it seems like there is already somewhat of a standard of care.

DR. COOKE: Yes.

CHAIR DRACKER: So that being the case, we have a standard of care but we don't have a lot of information of what we've been doing for years and years and years. It seems like it's really more data capture that we need to do more than anything else.

DR. COOKE: I would agree, yes.

DR. PORTMAN: This is Ron Portman. It's not far-fetched to talk about a three-year study or a four or five-year study. That is something that we do all the time in drug development in pediatrics for safety, for the immunologic drugs, for JIA, or in cancer, in multiple different areas. This isn't beyond the

realm of possibility.

DR. HOLUBKOV: So are we talking effectively almost a registry of collecting carefully all standard of care data with no chance of modifying the paradigm for delivery?

DR. COOKE: For efficacy endpoint, yes.

CHAIR DRACKER: That doesn't address the duration of safety follow-up which I don't think we've really done adequate job of to see what happens to these people long term that we've given therapy for. I'm afraid to even bring up the sample size issue. God knows what that could ever be.

DR. COOKE: So do we want to start talking safety? That's question 3.

CHAIR DRACKER: Go ahead.

DR. SAYEJ: So just going back to the design study published, the pharmacokinetics really looks at how the body metabolizes and breaks down the drug and how does it excrete it from the body. That's important, I think, in whatever we decide to do.

We already know that the efficacy is

there. We know that it works so I don't think we need to focus so much on that. Our focus is going to be hopefully mostly on safety and how to determine between different formulations like Dr. Cooke has mentioned.

Going back to the study design, I mean, we know a certain population of patients are going to develop hypogonadism. For example, the cancer patients. 89 percent of ALL in non-Hodgkin's lymphoma patients will develop. That's a good study group right there. We know that patients with cryptorchidism are going to develop hypogonadism. That's another group right there.

The Klinefelter group is more difficult because less than 10 percent are being diagnosed in that age group that we're looking at. We can break this up into two arms looking at the intramuscular versus the gel. We can also break this into two arms, primary versus secondary hypogonadism.

We might have difficulty in getting enough patients for the secondary hypogonadism

group. But for the primary hypogonadism group, I think the patients are right there without a seasoned IHH or the CDGP patients.

DR. COOKE: David Cooke. I think it's probably not quite as simple as you're thinking in that within that primary gonadal failure group, there are those that -- as I was asking this morning, there are those that maybe have an LH level that's 10 percent above the upper limit of normal and the testosterone levels are completely normal. That's a different group to study than those that have complete gonadal failure where their LH is 50 and their testosterone is zero.

Children with cryptorchidism, you know, I haven't looked at that data very carefully but I'm expecting most of those are kids that have testosterone levels in the completely normal range with a mild elevation of LH. I question whether they actually need to be treated.

Similarly, a high percentage of patients with malignancy-treated induced gonadal failure, I suspect that includes a range of children

from those with testosterone levels that go from zero to the normal range. I don't know that you can just grab those groups of diagnoses that come up with very big numbers to generate a discussion about it to say that is going to be an easy thing to study.

DR. SAYEJ: Wael Sayej again. I'm a pediatric GI so I'm not an endocrinologist and I'm not seeing by no means that this is going to be easy to do, but this is a population of patients that we already know are being treated off label. Am I correct?

DR. COOKE: Well, I would say many of them are being treated on label because the vast majority are being treated with testosterone enanthate which does have a pediatric indication. The vast majority of children that have hypogonadism are being treated with that. A smaller number are treated off label with the other preparations.

DR. SAYEJ: Okay. So they already have an indication. All we're doing is comparing

different formulations to the original formulation in the same population.

DR. COOKE: Yes, that would be an investigation.

CHAIR DRACKER: So could I suggest again, just to get somewhere, that we consider a study which follows current practice, number one, with using efficacy endpoints that you currently use now for your therapy. Is that reasonable? And, thirdly, also use the same safety endpoints you currently use as well.

DR. COOKE: So --

CHAIR DRACKER: Correct?

DR. COOKE: David Cooke.

CHAIR DRACKER: Just follow through and then you can destroy everything I'm saying.

DR. COOKE: Okay. So as a starting point, yes.

CHAIR DRACKER: And the duration of safety follow-up you could do very similar to what is done by gynecology trials. You have long-term follow-up studies where you do monitoring

basically, which has never really been done which clearly should be done.

Then the sample size, that's a statistical requirement which I have no idea how we could even touch that issue. You do open enrollment until some statistician tells us how many we have to collect. It sounds like that's what we have some consensus for.

Go ahead.

DR. FLICK: So I wanted to ask David a question.

If I'm understanding correctly, the primary endpoint here is dose required to achieve a certain serum level. Right? So you're trying to find a new paradigm with a different formulation. Am I right?

DR. COOKE: So, I mean, the true efficacy endpoint is getting a child to go from Tanner 1 to Tanner 5.

DR. FLICK: I get -- yeah.

DR. COOKE: But, yes. I think once you get to that, then the nuanced efficacy is what is

the adult treatment, but I think we already have that data for the adults. Yes, if you go with Tanner 5 --

DR. FLICK: The discussion we had earlier was that the thing that is most beneficial is to find out what the proper dosing is with the gel formulation or whatever it is.

The question I had for you is there a substantial difference across the diagnoses with regard to the amount of drug it takes to achieve a certain response?

DR. COOKE: No, not that I'm aware of.

DR. FLICK: So the population could be all-comers essentially?

DR. COOKE: Yes. With the caveat of central deficiency but, yes. If a patient has complete hypogonadism, there isn't to my understanding a difference.

Now, I think the challenge here is, remember, we've kind of thrown this out that the adult reference range for testosterone is essentially 300 to a 1,000, maybe more like 250

to 800 on the new assays.

When we are inducing puberty and treating it, I don't know what the optimal level for that individual is and I don't have an outcome measure to tell me that. Within that 300 to a 1,000, or 250 to 800 range, I don't know what's best.

DR. FLICK: This is Randall Flick. Aren't the levels that you're measuring to ensure that you are not too high? It's really a safety?

DR. COOKE: A little bit of both. I think especially in the patients with Klinefelter's where I definitely follow levels because those boys have significant testosterone production so there I'm looking to see that I'm doing better than they were doing before I started treatment so I am looking to see that level goes up as well.

I think as we've been talking about with the intramuscular, it starts on an every four-week basis and then we kind of escalate the dose and escalate it to every three weeks and then maybe escalate it every two week.

As I get -- again, I'll just speak for myself but as I get to what I think is the adult replacement dose, then I start measuring testosterone levels to see where in that adult range I am with all the caveats of the timing after the dose affecting the level and the uncertainty of where in that 300 to a 1,000 range is the best.

Once I get up to what I think is at or near the adult replacement, then I do start looking at the levels to judge it.

DR. TURER: So the concerns that I have really have to do with the safety endpoints, in particular with the different formulations. I would really worry about the pump and the potential for abuse and diversion.

The other thing is transference. Getting up to the higher doses, something that we haven't really talked about a lot but if you think about like XYY not just aggressiveness, but any hypersexuality whether that is something that's tracked.

All of those things when I think about

the pump versus the injectable. I mean, injectable is a painful injection. Nobody is going to divert that, right? With the pump, that to me is a little bit of a different beast where you would really want to be thinking about safety endpoints specific to the product that would be a lot easier to use and distribute.

DR. SAYEJ: This is Wael Sayej again. Just a quick question to the endocrinology folks here. So we already have a pediatric-approved intramuscular injection of testosterone. What were their safety endpoints? None.

DR. NGUYEN: Christine Nguyen. Just to remind you --

DR. SAYEJ: So why are we --

DR. NGUYEN: Just to remind you, like the IM was approved, I believe, in 1953. If you look at the drug label for those products, there are no clinical trial data. There you have it.

I think a lot of experience with the IM injection is the amount of time it's been on the market and the clinical comfort level of using

them. Certainly as far as data, like trial data?

DR. COOKE: This is David Cooke. I would add that certainly the pediatric endocrine literature has numerous reports on use of the intramuscular testosterone and outcome measures mostly focusing on height because that's a prime focus of pediatric endocrinologist.

It's not like there's no literature regarding intramuscular but there was certainly not clinical trial data that led to its approval. There is minimal or no long-term safety data.

DR. CHAN: Ming Chan. Just to add to that, I did mention that what convinced the clinical community to use these as treatment and to feel comfortable with it, or the data on bone age, some of the safety labs.

DR. ROGOL: Al Rogol. Let me remind you something about levels. It goes under the rubric of Mother Nature is smarter than we are. If a man has a level of 745, well within the normal range, and another man has half that, is he half the man?

The answer is no because it has to do with the responsivity at the androgen receptor. It has to do with the CAG repeats in the androgen receptor, etc., etc. Mother nature balances the LH, the FSH, and the testosterone to be within a range.

Just because you are at 700 doesn't mean you're any different than another man at 350 because it has to do with a lot more things than just measuring one testosterone level and that's another problem that obviously is in this calculus and makes the variation much greater.

MS. OSTER: I also want to comment this morning. Dr. Galescu had on his chart that one of the outputs of this medication is odd behavior cognition and memory.

To your point that we haven't done any studies there and we're looking at children, or teenagers, that if they are in school, what is the impact on cognition, memory, behavior and mood, and what are the risks and benefits to going back to your point for the safety that we do need to

at this point capture some of that data before we move forward and have a product that can easily, if it is a gel, be transferred without knowing.

DR. CHAN: Ming Chan. This has not been very systematically examined in the literature as far as I've read. There is some data suggesting that having delayed puberty can have a negative impact on some of those more psychosocial outcomes.

I'm not aware of anything that has directly looked at cognition or learning. I think just anecdotally the impression is that there doesn't seem to be a major effect. More subtle differences would require a study to actually look at. If anything, the thought is that treatment may be beneficial if it's bringing things to a more physiologic level but, again, there's not a lot of data to support that.

DR. GALESCU: Yeah, so in my talk in the morning those were under the physiological roles of testosterone, not adverse events of treatment with testosterone. Just one quick point that I wanted to remind the panel because we keep

cycling back to the gel formulation. There are many other formulations to keep in mind.

Right now as pediatricians, and I'm strictly speaking as a former clinician, we struggle with formulations that don't have adequate pediatric doses. We don't know how much gel to put in a kid. We don't know in how many parts do we cut a patch of testosterone. Is it a fifth of a patch? Is it a third of a patch? We just don't know.

There are newer formulations that are coming up. Maybe oral products intranasal, intrabuccal. When we talk about PREA requirements, we talk about all of these products.

CHAIR DRACKER: So we have 20 minutes left to consider -- Ethan, two more questions? So have we provided enough of a nebulous framework for a potential study?

DR. ALEXANDER: I want to thank everybody. I think that this whole discussion has been extremely useful. I think it sort of reflects to the same type of discussions that we've had

internally, but it's helpful to hear sort of the deliberations of the committee and the types of things that you're asking for.

If I understand correctly, what I'm hearing mainly is concern about the dosing and what the safety effects are and, in particular, the long-term safety. Yeah, I agree we should go on and do the trial.

CHAIR DRACKER: We have a pattern of practice that has been used for many years. What we need to do is get more data with regards to what is being done and also have more data with regards to long-term outcome and effects which we don't have. If it ain't broke, don't fix it for now.

DR. ALEXANDER: Okay.

CHAIR DRACKER: All right. So can we go to question -- yes.

DR. WADE: Kelly Wade. I mean, I think the question back to the endocrine groups is we basically probably could create primary genetic condition on it but we can't do that big epidemiologic look at them because we don't have

the safety data being collected.

That seems like if there was a guideline from the Endocrine Society or something recommending certain safety standard laboratory testing, that would be easier, but right now there's not a standard of safety testing.

CHAIR DRACKER: And to see what safety signals we'd be looking at in other drug trials.

Go ahead, Kelly. That was Kelly. Sarah.

DR. HOEHN: Sarah Hoehn. I had pretty much the exact same point which I had written down that there is no standard safety data. I think there's hints of things and things like that, but I think the most important thing for the FDA to ask for is a standard approach for safety data and to get some data on that.

CHAIR DRACKER: Yes.

DR. NGUYEN: Christine Nguyen, FDA. I'm sorry. Just one last question to our clinicians. Just going back to mimicking the progression, the serum concentration through

puberty. In standard practice we don't measure serum T until they get near adult development. The true desired outcome is really getting the kids from Tanner 1 to Tanner 5.

I assume that there's been pretty strong correlation between the progression of serum T through puberty and the progression of Tanner 1 to Tanner 5. I mean, is that a confident relationship between those levels and the Tanner progression?

DR. DELANEY: There's not of normative data on that. I mean, you'll see variations and ranges depending on what study you look at, but the general ranges will look similar. Like anything else, there's a lot of variability.

Again, I think if the focus is on assuring the safety of the regimens that one would propose using, I think really when you're in the context of a study when you're looking at those levels, you're going to want to make sure that your kid is not in Tanner 4 level when you're only shooting for Tanner 2.

That's really what you want to see. You're not looking to get them to a specific dose or specific serum level that correlates perfectly with your dose.

DR. ROGOL: This is Al Rogol. Let me follow up on that quickly. Almost all of the levels for Tanner stage are cross-sectional data. There are no longitudinal data and what we're really talking about is in that particular boy. Yeah, there are data but all data aren't equal.

DR. DELANEY: Good point. I agree.

CHAIR DRACKER: All right. Should we move on, John? Is that okay?

Second question I think is a little easier. Given the information provided today in the study design elements in question 1, please discuss feasibility issues related to the conduct of such a trial in a population of boys eligible to be enrolled in the trial and leaving it open.

CHAIR DRACKER: Everybody is getting tired. I know that's what it is.

Yes.

DR. ROGOL: This is Al Rogol. The people that I spoke to that are actually doing trials they are recruitment issues if they are done in a center. There's one in Europe and there's one in the U.S. Some people have to come from a very long way away.

So if it were scattered around that these were easy to do, you go to your CVS and you get something done, yeah, you could do those trials easily. But just because you have the population doesn't mean that the population and the people doing the trial are in the same area code, the same time zone, or anything like that.

Recruitment, two people spoke to me about it. I have done trials like this a decade okay. That's really what the issues are. Recruitment of those with honest to goodness diagnoses whether it's genetically made or for vanishing testes, what we used to call vanishing testes, is easy.

You got them or you don't got them and the IHH often if you have a genetic diagnosis, then

you're sure they have IHH. Not so many people spread over a big geographic area and matching them up with one, two, five, 17 trial centers is going to be some classy logistics.

CHAIR DRACKER: I guess it would depend on the recruitment number that would be necessary.

DR. ROGOL: Indeed.

CHAIR DRACKER: That would have to be determined. Then try to go to larger centers with larger patient populations.

Let me get to question 3.

DR. CHAN: Ming Chan. I can just give some numbers associated with our experience recruiting boys and girls, or just boys with delayed puberty for our studies looking at the simulation test. This is actually specifically excluding people with known permanent causes, but if we go by our numbers, that's about half of the people with delayed puberty.

We can just take our numbers and double that to get the all-comers. So we would come across roughly about 50 so, if you double that, about 100

boys per year at a large academic medical center just needing kind of prescreening criteria and then you would have to factor in how many of those would agree to participate in this study.

CHAIR DRACKER: Okay. Yes, I'm sorry. Go ahead.

DR. PORTMAN: So one thing related to feasibility, trial feasibility that should be mentioned is a new trend both in Europe and the United States, pediatric clinical trial networks.

In the United States the IACT, the Institute for Advanced Clinical Trials, is putting together a group that have 40 now and hopefully 100 academic medical centers in the next few years. That industry will be going to these groups with their compounds to look for sites to do these trials. That's something that should be considered as well.

CHAIR DRACKER: Thank you.

All right. The third question. Given known complications with testosterone therapy in pediatric patients such as premature growth, plate

failure, and short stature, what safety evaluation period do you recommend? Please provide rationale.

DR. COOKE: David Cooke. I think the issue of final height will be easily answered by any study of two or three years. Frankly, I'm not very concerned about that outcome. I think the experience we have is fairly reassuring that a wide range of testosterone therapy is going to be safe from bad outcome.

I'm going to throw out two uncertain concerns that I think are more problematic to try and address, and they won't be addressed by a three-year study. The first is there was a report in adult patients comparing topical to intramuscular injection where there was a higher rate of cardiovascular events in the intramuscular group compared to the topical.

Hypothesize related to those big swings in testosterone levels. Obviously we don't really know exactly what it was. That raises the question about whether there is an impact on cardiovascular

health long-term. That would be a lot harder to study. Or, at least, a lot more expensive.

Then I think the other issue is the fertility aspect in those with, you know, the hypogonadism, whether that be those with permanent hypogonadism where the possibility for future assisted fertility might be impacted by a different regimen.

Or the children that get recruited that end up having constitutional delay where we really want to be sure that we're not impacting their future fertility. I think that would be another aspect that would be -- you could hypothesize as a safety measure.

I think neither would be particularly easy to figure out. Those are the types of things that I think would be new data that we really don't have that we really would like to have, but also I'm not sure how practical it would be.

CHAIR DRACKER: Yes.

MS. OSTER: This is Randi Oster. I agree sperm count is one of the safety evaluations

afterwards. I also would like to add the ability to make your own testosterone after you go through this, that we should test if there isn't an impact there.

I would also like to know about withdrawal symptoms. You know, what happens when they are no longer on the testosterone. Then to add to that, I would like to make sure that we understand the impact on things like acne, to take a look at that, as well as sexual interest.

Those are the issues that as we go forward I think as parents they will want to know the answers too on the impact of making this decision for taking this drug.

DR. COOKE: David Cooke. I think the question about sperm count, it dodges testosterone at the end of the trial. It's kind of problematic because that would only be valuable in those that end up having constitutional delay who aren't the target group.

They just might be brought in with the all-comers. It would be a very good safety thing.

I think the more problematic issue is those with idiopathic hypogonadotropic hypogonadism where sperm count would only be treatment with GnRH agonist or HCG, or something like that.

That, again, gets a lot more complicated and problematic. Constitutional delayed kids that are brought in, sure. Those, I think, would be good and important outcome measures.

DR. ROGOL: Al Rogol. Let me add a few. There are a number of trials in men with prostate cancer who get GnRH agonist and become absolutely hypogonadal very quickly. They have menopausal symptoms. They feel bad and there are all sorts of difficulties with them. They can't be given back testosterone because of their underlying illness.

Let's remember how old these kids are, 14 to 18. I just pulled that out of the hat. When do people have their cardiovascular problems? You're talking now about a 40 or 50-year longitudinal study. These are difficult studies to do.

Fertility would probably be a 20-year or more longitudinal study. Again, difficult to do. Can be done from an epidemiological point of view, but end would have to be way larger than what we're talking about.

DR. TURER: Christy Turer. We are starting to see heart attacks in 20 to 34-year-olds. I mean, my husband is an interventional cardiologist. He just cathed a 30-year-old last weekend. I think we're seeing them closer. It's a small number, I agree, but we are starting to see signals.

Also heart failure. That was one of the things -- another thing with the testosterone increasing sodium retention so there is some concern with heart failure. There's been a 50 percent increase in heart failure incidents in 20 to 34-year-olds.

I agree but I also think that it wouldn't preclude in the context of a registry that went into adulthood, particularly young adulthood, looking for a signal.

DR. ROGOL: Al Rogol again. I unfortunately, or fortunately, work with USADA, the anti-doping group. Yes, there have been heart attacks but many of those people who've had them are steroid abusers and if X is the right dose, 40X or 100X is what they take.

I doubt seriously -- although your husband may have the data. I doubt seriously that otherwise well people who just had testosterone or have just been getting testosterone for five or 10 years at proper doses did have these problems without something else underlying. I could be corrected.

DR. TURER: Right. There's other stuff going on that's causing this including the obesity epidemic, early onset hypertension, etc. Correct. But the addition of that on top of those things could potentially potentiate those occurring earlier.

DR. HOEHN: Sarah Hoehn. I just want a second what Dr. Turer said. We have seen MIs, myocardial infarctions, in teenagers 17 to

20-year-olds. Yes, they have multiple other risk factors including obesity and hypercholesterolemia, and a lot of other situations.

But I think that we are seeing a very different evolution in coronary artery disease. I think if we're starting to see that there are some changes in cholesterol and there's this large number of boys getting treated with testosterone, it's imperative to at least come up with something that you are monitoring, the markers.

We've heard about HDL and that's why I think those things have to be monitored. Not that testosterone causes myocardial infarction, but if you have someone who is a little bit overweight and they are struggling with puberty and they have a family history of high cholesterol and their cholesterol numbers get all out of whack, I think they are at risk for a myocardial infarction that could be fatal.

I think these things should be taken into account to at least get the data. Maybe after

three years you find that, gosh, nobody's cholesterol changed in any appreciable manner. That's good, but then you would have that data. It sounds like right now we don't have that data.

DR. FLICK: So David or some of the wiser folks here, it sounds like to me that the study -- the size of this study is going to be based on the safety measures rather than anything else so there has to be -- I think we have to have -- there needs to be clarity about what the primary safety outcomes are because a study will be designed around those safety outcomes. Am I right?

DR. COOKE: I would agree, especially if the safety is something different than final height.

DR. FLICK: That was to prompt us to say what are those safety outcomes.

DR. HOLUBKOV: Are there, in fact --do you have kind of a spectrum of rare outcomes, just a few?

DR. FLICK: That was why I asked the question is how frequently do we see premature

epiphyseal closure? How often do we see polycythemia? How often do we see you name it.

These things are probably rare events and it would require an enormous study to be able to say with any confidence that they are less frequently in the new formulation than in the old which is sort of the point of the question. It's going to be very difficult to pick up a safety signal when the outcomes are extraordinarily rare.

DR. HOLUBKOV: Would you consider having like just a data monitoring committee look at this with the appropriate statistical and clinical expertise and just --

DR. FLICK: Yeah. It comes down to post-marketing. I mean, isn't that what it's ultimately going to be is post-marketing?

DR. NGUYEN: Christine Nguyen, FDA again. Yes, post-marketing safety evaluations but, you know, there's a whole spectrum of ways to look at post-marketing safety.

You're right, there is the gold standard, say the cardiovascular outcomes trial

that we've seen in the diabetes program where you power to a safety endpoint and you exclude a certain risk versus the comparator.

Those are the large trials. Certainly we have trials that are based on observational databases where we pre-specify certain outcomes of interest. Certainly statistically we do power it for person exposure or what have you.

Then we have sort of the more streamline data collection sort of depending how big of a population we're dealing with and are we just trying to understand sort of the broader safety profile once this drug has been out there and used by these children.

You know, it can cover really any of those spectrums. The concerns about the large sample size really relates more to, as I mentioned, the gold standard dedicated safety trial to exclude a specific safety outcome.

CHAIR DRACKER: Yes, Ethan.

DR. HAUSMAN: Yeah, Ethan Hausman. The other benefit of post-marketing studies, even

given all the caveats it's after the initial study for which a drug gets approved, compared to the spontaneous reports that are submitted to the FAERS system, the data are relatively cleaner because these are patients who have qualified for a clinical trial in the first place.

They have rolled over to a follow-on study, a registry. It is my no means perfect data but it's a lot cleaner than the nominally random reports that are submitted to FAERS.

CHAIR DRACKER: So it is 4:40. Have we addressed the issues for you adequately?

DR. NGUYEN: Good enough for me. Thank you.

CHAIR DRACKER: You're welcome.

Thank you for letting me be your Chairman. Good luck to everyone. Hope to see all of you soon again. Thank you.

DR. NGUYEN: Actually, before we break, I want to thank everyone here for all your time, effort, thoughts, discussion. It's been extremely useful for us. We've struggled with this issue

actually for a while so we really appreciate your feedback and your input. Safe travels.

(Whereupon, the above-entitled matter went off the record at 4:41 p.m.)