FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC) MEETING

Virtual Meeting

Wednesday, June 28, 2023

9:30 a.m. to 5:24 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Chairperson)

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Anschutz Medical Campus

Clinician-Scientist, CPC Clinical Research

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Professor, Department of Biostatistics

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Vanderbilt University Medical Center

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Professor and Chair of Medicine

UT Southwestern Medical Center

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Executive Vice President and Chief Medical Officer

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Cambridge, Massachusetts

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Professor with tenure of Radiology (retired)

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CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

DR. LOW WANG: Good morning, and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. For media and the press, the FDA press contact is Chanapa Tantibanchachai. Her email is currently displayed.

Good morning, and thank you for joining the meeting this morning. My name is Dr. Cecilia Low Wang, and I will be chairing this meeting. I will now call the June 28, 2023 Endocrinologic and Metabolic Drugs Advisory Committee meeting to order. Commander LaToya Bonner is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

CDR BONNER: Good morning, and thank you, ma'am.

I am LaToya Bonner, the designated federal officer of the committee. When I call your name, please introduce yourself by stating your name and

affiliation. We will reintroduce our chair, Dr. Cecilia Low Wang. Please introduce yourself.

DR. LOW WANG: Thanks. My name is Cecilia Low Wang. I'm a professor of medicine and endocrinologist at the University of Colorado School of Medicine.

CDR BONNER: Next, we will have Dr. Michael Blaha. Please state your name and your affiliation, sir.

DR. BLAHA: Hi. Dr. Michael J. Blaha. I'm the director of clinical research at the Johns Hopkins Ciccarone Center for the prevention of heart disease in Baltimore, Maryland.

CDR BONNER: Thank you.

Next we will have Dr. Elizabeth Chrischilles.

DR. CHRISCHILLES: Good morning, everyone. I'm Elizabeth, or Betsy, Chrischilles. I'm a professor of epidemiology at the University of Iowa in Iowa City, Iowa.

CDR BONNER: Thank you, ma'am.

Next is Dr. Greevy.

DR. GREEVY: Good morning. I'm Dr. Robert Greevy, professor of biostatistics and director of HSR Biostatistics at Vanderbilt University.

CDR BONNER: Thank you, sir.

Next, we have Dr. Wang.

DR. WANG: Yes. Thomas Wang, professor and chair of medicine at UT Southwestern Medical Center in Dallas.

CDR BONNER: Thank you, sir.

Next, we have Dr. Yanovski.

DR. YANOVSKI: Hi. Jack Yanovski, chief of the Section on Growth and Obesity and the Intramural NIH-NICHHD program. I'm a pediatric endocrinologist.

CDR BONNER: Next, we will have our industry representative, Dr. Meininger. Please introduce yourself and your affiliation, sir.

DR. MEININGER: Sure. Gary Meininger, industry rep, chief medical officer at Sana Biotechnology in Cambridge, Massachusetts, and an adult endocrinologist.

CDR BONNER: Thank you, sir.

We will continue with Dr. Applegate. Please state your name and your affiliation.

DR. APPLEGATE: Good morning. Dr. Kimberly Applegate. I am a retired pediatric radiologist from the University of Kentucky in Lexington.

CDR BONNER: Thank you, ma'am.

We will have Dr. Coffey. Please introduce yourself.

DR. COFFEY: Yes. Hi. Good morning. My name is Chris Coffey. I'm a professor of biostatistics at the University of Iowa.

CDR BONNER: Thank you, sir.

Next is Dr. Tobias Gerhard.

DR. GERHARD: Tobias Gerhard, professor of pharmacy and epidemiology at Rutgers University. Good morning.

CDR BONNER: Good morning. Thank you, sir.

Next is Dr. Jones. Please introduce yourself and your affiliation.

DR. JONES: I'm Elizabeth Jones. I'm a diagnostic radiologist by training. I'm chief of Radiology and Imaging Sciences at the Clinical

Center , NIH, in Bethesda.

CDR BONNER: Thank you, ma'am.

Next is Dr. Martha Nason.

DR. NASON: Good morning. I'm Martha Nason. I'm a mathematical statistician at NIAID, NIH, also in Bethesda.

CDR BONNER: Thank you, ma'am.

Next, we have our acting consumer representative, Dr. Robotti; Ms. Robotti. My apologies.

MS. ROBOTTI: Yes. Hi. I'm Suzanne Robotti. I am the founder of MedShadow Foundation, the executive director of DES Action USA, and I'm normally the consumer representative on Drug Safety and Risk Management.

CDR BONNER: Thank you, ma'am.

Next, we have Dr. Weber.

(No response.)

CDR BONNER: Okay. We will move back to Dr. Weber, and we will go to our next group, which is the FDA participants, starting with Dr. Lisa Yanoff.

DR. YANOFF: Good morning, everyone. I'm Dr. Lisa Yanoff. I'm the deputy director of the Office of Cardiology, Hematology, Endocrinology, and Nephrology in CDER.

CDR BONNER: Thank you, ma'am.

Next is Dr. Kehoe.

DR. KEHOE: Good morning. I'm Theresa Kehoe, the division director for the Division of General Endocrinology in OCHEN, in CDER.

CDR BONNER: Thank you, ma'am.

Next, we will have Dr. Stephen Voss.

DR. VOSS: Good morning. I'm Steve Voss. I'm a clinical reviewer in the Division of General Endocrinology.

CDR BONNER: Thank you, sir.

Next is Dr. Mark Rothmann.

DR. ROTHMANN: Good morning. I'm Mark Rothmann. I'm the director of the Division of Biometrics II in CDER.

CDR BONNER: Thank you, sir.

Next, we will have Dr. Feng Li.

DR. LI: Good morning. This is Feng Li.

I'm the statistical team leader of DBII, CDER.

CDR BONNER: Thank you, sir.

Next is Dr. Alexander Cambon.

DR. CAMBON: Hello. My name is Alex Cambon. I'm a mathematical statistician in DBII.

CDR BONNER: And next, we will have Dr. Po-Yin Chang.

DR. CHANG: Good morning. This is Po-Yin Chang, epidemiology reviewer, CDER. Thank you.

CDR BONNER: Thank you, sir.

We will move back to our voting members, and see if we have Dr. Thomas Weber.

Are you online sir?

DR. WEBER: Yes, I'm here. Tom Weber, Duke University, Division of Endocrinology and Metabolism.

CDR BONNER: Thank you, sir.

That concludes my introduction. I will turn the meeting back over to our chair.

Dr. Low Wang?

DR. LOW WANG: For topics such as those being discussed at this meeting, there are often a

variety of opinions, some of which are quite strongly held. Our goal is that this 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 productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, Commander Bonner will read the Conflict

of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, ma'am.

The Food and Drug Administration is convening today's meeting of the Endocrinologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of

interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the committee 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; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 215559 for palovarotene capsules, submitted by Ipsen Biopharmaceuticals, Incorporated. The proposed indication is the prevention of heterotopic ossification in adults and children, females aged 8 years and above and males 10 years and above, with fibrodysplasia ossificans progressiva.

This is a particular matters meeting during which specific matters related to Ipsen Biopharmaceuticals' NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statement that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gary Meininger is participating in this meeting

as a non-voting industry representative, acting on behalf of regulated industry. Dr. Meininger's role at this meeting is to represent industry in general and not any particular company. Dr. Meininger is employed by Sana Biotechnology.

We would like to remind members and temporary voting members that if the discussion involves any other products at issue or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you. I will turn the meeting back over to our chair, Dr. Low Wang.

DR. LOW WANG: Thank you, Commander Bonner.

We will now proceed with FDA opening remarks from Dr. Theresa Kehoe

FDA Opening Remarks - Theresa Kehoe

DR. KEHOE: Thank you. Good morning. I

would like to thank our advisory committee members, patients with fibrodysplasia ossificans progressiva and their caregivers, members from the Ipsen palovarotene product team, and the FDA review team and colleagues for attending and participating in today's advisory committee meeting.

We convene this advisory committee meeting to discuss whether it is reasonable to conclude, based on available data, that palovarotene used chronically is a safe and effective drug in patients with fibrodysplasia ossificans progressiva, which we will also refer to as FOP.

In my comments, I will discuss the underlying disease, FOP, as well as the proposed therapy, palovarotene. I will review the development program for palovarotene, and then discuss the review issues encountered. And finally, I will close with the discussion and voting questions we would like the committee members to consider as the day moves forward. The FDA presentation will mainly focus on the efficacy of the drug and the statistical concerns raised

during the review of the application.

FOP is a rare, severely disabling congenital disease with approximately 800 confirmed cases worldwide. It is caused by a gain-of-function mutation in the activin A type 1 receptor, ACVR1, also referred to as the ALK activin-like kinase 2. This mutation renders the receptor constitutively active to ligands like the bone morphogenetic protein. The activity drives ectopic chondrogenesis and osteogenesis, leading to heterotopic ossification, or HO, in connective tissue, joints, and muscle.

Heterotopic ossification is the hallmark of FOP. It begins to manifest in early childhood. The formation of heterotopic ossification is episodic with events starting with soft tissue inflammation, often referred to as flare-ups. The accumulation of extra skeletal bone is cumulative and irreversible, causing restriction of movement, deformities, severe disability, and early mortality.

There are no approved therapies for FOP. At

this time, conventional therapy is aimed at symptom relief to treat the inflammation and to decrease the chronic pain. Attempts at surgical resection of lesions generally lead to reactivation of disease and new heterotopic ossification formation. The FDA review team held a listening session with patients and caregivers in May of 2019.

Palovarotene is a retinoic acid receptor gamma selective agonist, or a retinoid, that appears to interfere with ALK2-mediated bone formation indirectly. The proposed indication is prevention of heterotopic ossification in adults and children aged 8 years and above for females, 10 years and above for males, with fibrodysplasia ossificans progressiva. The proposed dosing regimen is oral capsules 5 milligrams daily with flare-up dosing of 20 milligrams daily for 4 weeks, followed by 10 milligrams daily for 8 weeks.

Nonclinical models demonstrated that palovarotene may prevent heterotopic ossification, and this is the first clinical development program for FOP. It consists of four different studies.

The natural history study was begun early in product development. The phase 2 Study 201 was the first treatment study. It was a placebo-controlled 12-week study with 6 weeks of therapy and 6 weeks of follow-up, evaluating a flare-up only dosing. Study 202 is the open-label extension, and ultimately it became the platform for evolving dosing regimen and imaging modalities, and Study 301 is the phase 3 study.

Discussions were held with the company moving forward in their development program as far as in preparation for phase 3. In general, FDA requires that changes in the biomarker be accompanied by a functional outcome. In the phase 2 trial, functional outcomes did not show change. Likely this was related to the short duration of the trials; however, in the natural history study, there were correlations between higher amounts of heterotopic ossification and worsening functional status, suggesting that whole-body CT for assessment of heterotopic ossification could be the primary endpoint, and decreases in

heterotopic ossification would have clinically meaningful benefit. This is the approach that was taken in phase 3.

The phase 3 Study 301 is a single-arm study using the natural history study as an external comparator. Subjects were at least 4 years or older at study entry. Palovarotene was dosed using the proposed dosing regimen, and there were weight-based reductions for children with open growth plates. The primary endpoint was annualized change and new heterotopic ossification based on whole-body CT.

Two events happened during the phase 3 program. First, premature epiphyseal closure has been a finding with other retinoid products; therefore, a bone safety monitoring program was put in place for all palovarotene studies. The FDA was informed that 9 pediatric subjects developed evidence of premature epiphyseal closure. After review, FDA instituted a partial clinical hold for subjects under the age of 14 because of the concern of the closure of the growth plates.

Shortly after the partial clinical hold, the second interim analysis took place. Futility was declared and dosing was stopped. The applicant then conducted post hoc analyses, which formed the basis of the efficacy determination in this NDA submission. I will note that dosing was restarted in subjects over the age of 14 and the palovarotene studies concluded in September of 2022.

During the review of the application in the last cycle, FDA was informed that additional data would be available, including all scans conducted through September 2022. The review team anticipated that the additional data may help inform the efficacy and safety assessments, leading to the postponement of the advisory committee meeting originally scheduled for October of last year.

That brings us to the issues that we will be discussing today. The first issue is that Study 301 essentially failed the prespecified primary endpoint. The NDA submission relies on post hoc analyses from Study 301 to support the

effectiveness of the chronic plus flare-up dosing regimen; therefore, the two issues for Study 301 here are the appropriateness of the reliance on post hoc analyses to support effectiveness and also the use of the external control group. For the first issue, the appropriateness of post hoc analyses to support effectiveness, I'm going to briefly summarize the statistical approaches used, and these will be discussed further in the FDA's statistical presentation.

The primary analysis used a Bayesian compound Poisson model with square-root transformation. The applicant stated that the model was chosen to be more appropriately accommodating for the high degree of variability in the volume of new HO, assessed by whole-body CT. Using that analysis approach, the primary endpoint failed to demonstrate efficacy; however, additional post hoc analyses appeared to show evidence of benefit. These were the Bayesian compound models without square-root transformation and weighted linear mixed effects model.

The second issue is the use of the natural history study as an external control. Now, this may be acceptable in circumstances where the natural history of the disease is well defined; the external control population is very similar to the treatment group; the concomitant treatments that may affect the primary endpoint are not substantially different between the external control and the trial population; and the results provide compelling evidence of a change.

The natural history study in the palovarotene application provides the best data to define the natural history of FOP. There are really no other concomitant treatments that would affect the primary endpoint, so we need to look at the similarity of control versus treatment populations. Over the course of the natural history study, subjects were allowed to transfer out of this study and into an interventional study if they met the inclusion and exclusion criteria. Eight subjects transferred to Study 201, 13 subjects transferred to Study 202, and

39 subjects transferred to Study 301. There were some differences in the groups noted. The natural history population is older with more advanced disease. Various analyses were done to further explore the impact of these differences, and you will hear more about that in the FDA statistical presentation.

One other key issue was the apparent increase in flare-ups. Retinoids have been associated with hyperostosis and calcification of ligaments and tendons. As well, musculoskeletal adverse events, including back pain, arthralgia, myalgia, and rarely reports of severe myositis also occur. There is a concern that some of these events may trigger or exacerbate flare-up symptoms, requiring prolonged use of higher FOP palovarotene doses. You will hear more about this in the FDA safety presentation.

That leads us to our discussion and voting questions. We have two discussion and two voting questions. In the first discussion question, we ask that you discuss the evidence of effectiveness

for palovarotene demonstrated in Study 301. In your discussion, we ask you to consider the following, the use of the post hoc analyses to support demonstration of efficacy and the interpretability of the results of the external control natural history study.

Our second discussion question, we ask your view of the flare-up events in subjects treated with the proposed palovarotene dosing regimen and the relevance to the risk-benefit considerations. We ask that you also comment on whether you have any other concerns with the other safety issues included in the meeting materials and slide presentations or discussed today.

For our voting questions, the first question is, does the evidence from Study 301 of palovarotene's treatment effect show the drug is effective in patients with fibrodysplasia ossificans progressiva? We ask you to provide the rationale for your vote.

The second voting question is, do the benefits of palovarotene outweigh its risks for the

treatment of patients with FOP? If you voted yes, to provide your rationale, and if you voted no, to provide the rationale for your vote and provide recommendations for additional data that may support the conclusion that the benefits outweigh the risks. I'd like to thank you, and we look forward to hearing from you today.

DR. LOW WANG: Thank you so much, Dr. Kehoe, for that overview.

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, 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 Ipsen's presentations.

Sponsor Presentation - Howard Mayer

DR. MAYER: Good morning, members of the advisory committee and FDA. My name is Howard Mayer, and I am executive vice president and head of research and development at Ipsen. We're pleased to be here today to share the data supporting the positive benefit-risk profile of palovarotene in patients with fibrodysplasia ossificans progressiva or FOP. FOP is an ultra-rare severely disabling disease in which patients form heterotopic ossification or the presence of bone and soft tissue, where bone

normally does not exist. Fundamentally, HO is the key pathophysiologic process that leads to disease progression and morbidity in these patients.

FOP is a genetic disease that typically starts in early childhood. Palovarotene would be the first and only disease-modifying therapy that has the potential to change the progressive trajectory of FOP. Palovarotene is an orally bioavailable retinoic acid receptor gamma selective agonist that reduces the volume of new HO, a hallmark of FOP progression.

Let me explain the mechanism of action. In normal cell signaling, bone morphogenetic proteins, or BMPs, bind to the ACVR1 receptor, also known as the ALK2 receptor. This induces heterodimerization with a type 2 receptor and results in phosphorylation of the downstream pathway mediators of SMAD 1, 5, and 8 that in turn associate with SMAD 4. These complexes then translocate to the nucleus, resulting in bone formation.

FOP is an autosomal dominant disorder that results in hyperactive BMP signaling by altering

the ACVR1 receptor response to legends. In nearly all cases, it is caused by an R206H pathogenic variant in this receptor. This activating variant causes dysregulation of the BMP signaling pathway, in part, by receptor activation independently of ligands, but also by being hyper-responsive to BMP and activin A ligands. Because of this increased receptor activity, additional phosphorylation of downstream mediators occurs, delivering increased BMP signaling to the cell nucleus with an appropriate physiological trigger such as soft tissue injury. This promotes ectopic chondrogenesis and osteogenesis and, in turn, heterotopic ossification.

Shown here is a simplified depiction of the proposed mechanism for palovarotene in FOP. By inhibiting chondrogenesis to regulation of BMP signaling, palovarotene modulates downstream SMAD signaling through activation of RAR gamma. This has been demonstrated in mouse models of HO and FOP, and confirmed in relevant cell lines.

Palovarotene was shown to reduce the

aberrant inflammatory response at the site of a lesion to inhibit heterotopic ossification and restore healthy tissue response to muscle injury. These preclinical data supported the clinical investigation of palovarotene in FOP.

Let me briefly walk you through the clinical development history. The efficacy and safety of palovarotene is supported by our clinical development program, which has enrolled 25 percent of the world's known population with FOP. FOP is an ultra-rare disease, and in 2014 when we initiated this program, there was limited information on FOP disease progression, including outcome measures that could serve as the basis for a clinical development program; therefore, we conducted a rigorous natural history study to prospectively characterize FOP disease progression. At roughly the same time, we began phase 2 studies to evaluate multiple palovarotene doses. Based on the critical unmet need and the results from our phase 2 studies, palovarotene has received orphan drug breakthrough therapy and rare pediatric

disease designations.

In 2017, we initiated our pivotal Study 301 to evaluate the efficacy of palovarotene using the patients from the natural history study as a control group. In December 2019, the FDA instituted a partial clinical hold due to the risk of premature physeal closure or PPC. Based on this, dosing was stopped in patients less than 14 years of age.

PPC is an important risk associated with palovarotene treatment, and therefore, we are proposing that the target population include females 8 years of age and older and males 10 years and older. This is based on a benefit-risk assessment that considered the risk of PPC, the skeletal maturity of patients, and the risk of developing HO.

The development of HO, an associated physical impairment, can occur in patients starting at birth, and these effects are both irreversible and cumulative, making early intervention critical to preserving a patient's ability to function over

time. The efficacy and safety data that we will present today support a positive benefit-risk in this proposed target population. In addition, our education and risk management program will provide physicians, patients, and caregivers the information to guide appropriate treatment and will emphasize that the decision to treat should be based on an individual benefit-risk determination for each patient.

The proposed indication for palovarotene is for the prevention of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with FOP. The data from the palovarotene clinical program support the proposed oral dosing regimen. Patients will receive palovarotene 5 milligrams daily or the weight-based equivalent. When symptoms associated with a flare-up are reported, or at the time of a traumatic event, chronic 5-milligram dosing is stopped and the flare-up dosing regimen initiated.

Patients will receive palovarotene 20 milligrams once daily for 4 weeks, followed by

10 milligrams once daily for 8 weeks. If flare-up symptoms persist beyond 12 weeks, patients can receive treatment extensions in 4-week increments. At the completion of the flare-up dosing regimen, patients resume chronic palovarotene dosing at 5 milligrams daily.

The totality of data we will share today demonstrates that palovarotene has a positive benefit-risk profile in support of approval for the treatment of FOP in the target population. FOP is an ultra-rare genetic condition that causes severe deformity and disability starting in early childhood and is associated with complete immobilization and early mortality. There are no approved therapies to treat this aggressive and irreversible disease.

Palovarotene was shown to reduce the volume of new heterotopic ossification in patients with FOP, demonstrating the ability to modify the underlying cause of disease progression and disability. Palovarotene has a well-characterized safety profile consistent with the well-established

profile reported with other systemic retinoids. For specific adverse events, the proposed risk management activities will inform and guide patients and physicians on the safe use of palovarotene. If approved, palovarotene would be the first and only disease-modifying therapy that reduces new HO and has the potential to change the progressive trajectory of FOP.

Here is the agenda for the remainder of today's presentation. All outside experts have been compensated for their time and expenses to be with us here today. We also have additional experts with us today to help address your questions. Thank you. I will now turn the presentation over to Dr. Brown.

Sponsor Presentation - Matthew Brown

DR. BROWN: Good morning. My name is Matt Brown. I'm a professor of medicine at King's College London, and I'm the chief scientific officer of Genomics England. I'm a practicing rheumatologist and have been involved in the care of patients with FOP and in FOP research for nearly

30 years. Indeed, the discovery of the causative gene in FOP, ACVR1, was made in collaboration between my own laboratory and Professor Fred Kaplan and Eileen Shore's North American group. I'm pleased to be here today to discuss the unmet medical clinical need in FOP because whilst over the last couple of decades, we've learned a great deal about the disease, we still have no approved treatments that can slow the relentless progression of this severely disabling condition.

As you've heard, FOP is a genetic condition that arises due to mutations in the ACVR1 gene. It results in mild skeletal developmental disorders, or patterning disorders, typically just abnormalities of the big toe, but more importantly results in episodic flares in which soft tissue inflammation occurs, and that soft tissue, instead of inflammation and instead of healing through the normal route, heals by the formation of new bone in the affected tissues, which we call heterotopic ossification, and which we measure through whole-body CT scans.

In the three scans on the right, you see whole-body CT scans of three different patients with FOP, age 4, 10, and 31 years of age, and the amount of HO measured is given in the box at the bottom. In the 4-year-old patient with FOP, you can see that there is no heterotopic ossification, although the eagle eye amongst you will see that the child has some abnormalities, including abnormal big toes and abnormal hip joints, which are typical of FOP.

In the next patient at 10 years of age, you can see that there's a considerable amount of heterotopic ossification that has developed in the chest wall, around the hips, and knees. In the chest wall, this will result in loss of mobility of the chest and a restrictive lung insufficiency, as well as scoliosis, and at the hips and knees, this results in difficulty walking and early requirements for assistance for walking and use of wheelchairs. By 31 years of age, the patient has extremely extensive diffuse heterotopic ossification affecting the chest wall, the hips,

knees, and ankles, and this patient will be severely disabled by this condition, almost certainly unable to be independently mobile, wheelchair-bound, and likely bed-bound.

So thankfully, FOP is an ultra-rare disease affecting only about 1 in 1.1 million individuals, and we think that there are fewer than 400 individuals in the United States. The most common symptomatic manifestations of it are flare-ups, and these occur starting in early childhood. They're characterized by the typical manifestations of inflammation; that is, they cause localized pain, swelling, erythema, warmth, and tenderness, and they occur in response to minor insults like minor bruising that can occur from iatrogenic injuries, such as, for example, in reaction to injections like vaccines, or local anesthetic, or in response to surgery, or sometimes occur just in response to generalized viral infections like influenza. In about half of the cases of the flare-ups, there is no apparent precipitating cause.

So on average, patients with FOP experience about two flare-ups per year, but this frequency varies considerably both between patients, as some patients have very frequent flares and some have much less frequent flares, and in individual patients they vary in frequency over time. So patients can have periods where they go for long periods of time without flares and then have lots of flares over a short period of time, and we really have no predictors at this point about those that have lots of flares or even the frequency of flares in individual patients.

So the critical thing, though, is that these flares ultimately lead to heterotopic ossification, which is irreversible. This new bone formation occurs in nodules, segments, or sheets of bone. The nodules where they occur under the skin can result in pressure areas and pressure sores, which are slow to heal and cause a lot of discomfort. When they occur around nerves, they cause entrapment neuropathies, causing chronic neuropathic pain, and when they occur around the

chest, as you can see in these images here, which is a common problem with FOP, they result ultimately in loss of chest wall movement, deformity of the chest, and ultimately thoracic insufficiency syndrome, which is a major cause of death in the condition.

This is a continuously progressive condition, and you can see in these diagrams five rough stages of the condition. In the early stages of the condition, under 10 years of age, heterotopic ossification and flares occur typically in the neck and in the proximal upper limbs predominately. Because the amount of HO that's deposited is relatively small at this stage, children affected require no or minimal assistance, but as the amounts of bone increase and progressively affects other areas of the body -- other areas as the legs, for example -- then disability increases, and the ability to walk reduces, increasing the need for using aids.

By late or severe disease, by this time

we're talking about people in their mid to late teens, the disease often affects the jaw, resulting in inability to chew and severe dental hygiene problems. When it affects more joints in the arms, patients become dependent for activities of daily living such as dressing, toileting, and eating; and when it affects more extensively at the lower limbs, patients then require assistance to walk, either pick-up frames or wheelchairs. And by 15 years of age, which I'd point out is still quite young, on average, patients are requiring certain assistive devices, indicating quite severe disability.

As the disease progresses, then the level of disability increases, and by 25 years of age, most patients are wheelchair-bound. Symptomatic thoracic insufficiency syndrome then starts to appear, and by end-stage disease, or later stages of diseases -- and here we're talking typically late 20s early 30s -- patients are severely disabled and frequently bed-bound. Kaplan-Meier analysis suggests that the life expectancy for the

disease is 56 years of age, but I personally think that's an overestimate, and I have yet to see a patient who's made it to 50 years of age.

For patients with FOP, the pattern and onset of physical impairment relates precisely to where heterotopic ossification appears and links clearly heterotopic ossification with the physical symptoms and disability in the condition. Presented here are the results of a global cross-sectional survey, which evaluated the onset of disability in 500 patients with FOP according to region.

So what you can see is that in patients who are younger than 10 years of age, they have already developed disability affecting the neck, upper back, shoulders, and chest. By between 10 and 18 years of age, the disease becomes generalized and affects all areas. And the point of this illustration is to show that there is a real need to treat patients early because once disability occurs in any of these areas, it is irreversible.

So how do we manage patients with FOP? As has already been mentioned, there are no effective

or FDA-approved treatments to prevent either flare-ups or to prevent the development of heterotopic ossification or to reverse it should it occur.

In surgery, for example, to remove either lumps of heterotopic ossification or to deal with deformity or disability issues, it is not recommended, as this results in major flares of the disease and precipitates extensive new heterotopic ossification, usually making the patient worse than the presurgical state.

Patients often use high-dose corticosteroids for short periods of time during flare-ups with the goal of reducing the severity and duration of the flare-up, ultimately with the aim of reducing the extent and quantity of heterotopic ossification that occurs. Unfortunately, we have no data to demonstrate that steroid use reduces heterotopic ossification or improves the long-term outcome of the patients with FOP. Given the lack of treatments for it, actually management of FOP is predominantly supportive and multidisciplinary

teams are involved in trying to provide patients with the best support possible to manage as they slowly lose physical ability.

To conclude, patients with FOP are in major need of a treatment that will slow down the formation of heterotopic ossification and will alter the trajectory of this severe debilitating disease. There are no treatments currently available for FOP, and without such treatments, patients are going to continue to suffer from the multiple and irreversible clinical consequences of heterotopic ossification and will lose significant function, require full-time caregiver assistance to survive, and will suffer early mortality.

So given the devastating and irreversible consequences of this disease, preventing even small amounts of heterotopic ossification would be a clinically meaningful outcome for patients, as it would allow patients to maintain mobility and function over time.

I'll now pass over to Dr. Marino. Thank you.

Sponsor Presentation - Rose Marino

DR. MARINO: Thank you, Dr. Brown.

Good morning. My name is Rose Marino, and I'm a vice president of clinical development at Ipsen and a board-certified pediatric endocrinologist. This morning, I will review the clinical data showing that palovarotene reduces the volume of new heterotopic ossification, or HO, in patients with FOP relative to untreated patients. Importantly, the observed reductions demonstrate palovarotene's ability to modify the underlying cause of disease progression.

Let me begin with the conclusions from our phase 2 clinical program. The results from our phase 2 studies, as well as nonclinical data, contributed to our understanding of FOP disease progression and informed the dose selection in our phase 3 study. Our phase 2 program assessed patients at the time of an active flare-up. Imaging conducted within 7 days of the onset of flare-up symptoms showed substantial soft tissue edema, muscle necrosis, and immature HO,

demonstrating that HO formation may begin even before clinical symptoms present. Thus, it became apparent that chronic daily treatment was required to ensure exposure to palovarotene at the very start of HO formation.

Multiple flare-up dosing regimens were evaluated in the phase 2 studies, and the emerging data suggested that higher doses over longer duration were required to maximally inhibit HO formation, especially for more severe flares. These learnings from the phase 2 trials informed that chronic daily treatment, in combination with increased flare-up dosing upon symptom onset, would provide the optimal approach to reduce HO formation.

Let me now introduce our natural history study. Key learnings from the natural history study played an important role in the selection of endpoints for our phase 3 trial. The NHS was a three-year, non-interventional study designed to characterize FOP disease progression and evaluate patient characteristics. 114 patients with FOP

participated, representing approximately 14 percent of known patients with the disease globally.

Data from the natural history study showed us that the measures used to evaluate functional outcomes in FOP were not suitable to demonstrate disease progression over the course of an interventional trial; however, it was clear that HO volume, a clinically meaningful outcome for patients, could not only be objectively measured but also showed changes over relatively short periods of time.

One of the functional outcomes measured was CAJIS, a physician-reported measure for assessing range of motion. CAJIS can be useful for a healthcare provider in the clinic to evaluate disease status and track a patient's function over the course of a lifetime.

This figure illustrates how CAJIS is scored using the elbow as an example. The schematic on the left shows a CAJIS score of 0, which corresponds to a range of motion between 90 and 100 percent. At this stage, there's minimal loss

of function. On the right is a CAJIS score of 2, which represents joints that are completely locked. In the middle is a CAJIS score of 1. As shown by the area shaded in yellow, a CAJIS score of 1 represents a range of motion between 10 and 90 percent, and this highlights the challenge with CAJIS as an endpoint to evaluate disease progression in clinical trials because a patient could experience an 80 percent loss of function, but their CAJIS score would remain unchanged.

Although CAJIS has its limitations, cross-sectional data from the NHS demonstrate that the worst the joint-specific CAJIS score, the higher the mean volume of HO within that region. These figures show individual patient total HO volume by CAJIS score. I'd like to highlight here that median new HO associated with complete ankylosis of the knee -- so a CAJIS of 2 -- is approximately 50,000 cubic millimeters. In contrast, a median new HO volume of just 18,000 cubic millimeters is enough to completely lock the elbow. These data support the utilization of HO

volume as the primary endpoint in Study 301 because even a relatively small amount of new HO in the wrong place can lead to a significant loss of function.

The design of our pivotal phase 3 trial was informed by emerging information from the natural history study. At the time, we considered the size, scope, and duration required to execute a randomized-controlled trial, but given our understanding that patient-reported outcomes were not sensitive enough to demonstrate change over the short term and that HO could serve as an objective endpoint that is sufficiently sensitive to demonstrate meaningful change, alternative trial designs were considered.

With the natural history study ongoing and almost completely enrolled, there was a desire to maximally utilize this large data set that was actively collecting HO data. Given these factors, in the setting of an ultra-rare disease, the natural history study was selected to serve as the control group for Study 301.

It's important to recognize that the natural history study included a number of key characteristics that support its use as a control group for Study 301. In both, the NHS and Study 301, HO assessments were obtained in a robust standardized fashion across all centers. For all whole-body CT scans, HO was first assessed by visual inspection in each of the 9 body regions. When new HO was identified in a region, each reader confirmed the borders of the HO on each low-dose whole-body CT slice and quantitatively assessed the total volume using MIM [ph], a fully validated software application.

To eliminate potential bias, all assessments were conducted in a controlled environment by two independent radiologists, with a third for adjudication, and all readers were blinded to clinical information. The assessments of inter- and intra-read variability demonstrated a high level of consistency between readers.

While enrollment of the NHS was completed before Study 301 began, both studies ran during

concurrent time frames, and all study sites from the NHS participated in Study 301. Throughout both studies, patients were treated with consistent standards of care and background therapy, which have remained unchanged. Symptomatic treatment of flare-ups was permitted in both studies, which primarily included the use of prednisone; however, it is important to note that there is no evidence to suggest that these medications would affect the primary endpoint results.

Both studies enrolled sufficiently similar patient populations, enabling valid efficacy comparisons. Presented here is the summary of the baseline demographics and disease characteristics. Patients enrolled into the natural history study were slightly older, with a mean age of 17-and-a-half years compared to 15 years in Study 301. In addition, total HO volume, CAJIS, and FOP-PFQ were numerically higher in untreated patients, which is not unexpected due to the natural progression of FOP. While we acknowledge the numerical differences in baseline

characteristics, multiple sensitivity analyses have shown that these do not impact the efficacy of palovarotene.

In summary, the primary outcome of annualized new HO assessed via low-dose whole-body CT scan is an objective measure that was obtained using equivalent imaging protocols in both studies. Both studies ran during concurrent time frames, and the same clinical sites that participated in the NHS also participated in Study 301.

Standard of care in this disease has remained unchanged and was followed in both studies. Both studies enrolled similar patient populations, enabling valid efficacy comparisons. In addition, the results were adjusted for baseline differences in potential prognostic factors, and altogether, these factors make untreated patients from the natural history study a valid comparator for Study 301.

Turning now to our pivotal Study 301, Study 301 is the first multicenter phase 3 study in patients with FOP and was designed to evaluate the

efficacy and safety of palovarotene. Enrolled patients received 5 milligrams of palovarotene daily or the weight-based equivalent when they are not experiencing a flare-up. At the time of a flare-up or a substantial trauma, the dose is increased to 20 milligrams for 4 weeks, followed by 10 milligrams daily for 8 weeks after that.

Main assessments, including whole-body CT scans, were conducted every 6 months. Results from Study 301 were compared with data from untreated patients from the natural history study. The primary endpoint was the annualized change in new HO volume, and as Dr. Brown described earlier, HO formation is a key characteristic of FOP, and it provides an objective assessment of disease progression.

Study 301 also included multiple secondary endpoints to evaluate the proportion of patients with any new HO, number of body regions affected, percent of patients with at least one flare-up, and flare-up rate. We also conducted exploratory endpoints to assess functional outcomes.

Based on the prespecified statistical analysis plan, three interim efficacy analyses were conducted. A futility assessment was conducted with the second interim analysis when all patients have at least 12 months of follow-up. The third interim analysis was prespecified after all patients had at least 18 months of follow-up, and the final analysis was preplanned after 24 months of follow-up but was not conducted due to the interruption in study drug administration. Thus, interim analysis 3 serves as the final analysis.

The primary endpoint of mean annualized new HO volume was assessed at all interim analyses, and for this we used a Bayesian compound Poisson model, which describes the likelihood of an HO growth event and the volume of HO growth per event. The Bayesian model also incorporated a square-root transformation of new HO volume per region. As such, it required that new HO volumes be non-negative.

Turning to study disposition, 107 patients participated in Study 301 and 114 in the natural

history study. The principal enrolled population includes patients who met all inclusion criteria and had a confirmed R206H variant. The primary analysis was conducted in the full analysis set, which includes all patients from the principal enrolled population who had at least one post-baseline HO assessment. The principal safety population includes all patients from the principal enrolled population who received at least one dose of palovarotene and all untreated patients with post-baseline follow-up.

Now, turning to the results, starting with the second interim analysis and the futility assessment, presented here is annualized change in new HO using the prespecified Bayesian model with square-root transformation. As seen in the area shaded to the left of 0.7, the model predicted a 4.9 percent probability that palovarotene would reduce annual mean in new HO by more than 30 percent on the square-root scale, which would translate approximately to a 50 percent reduction when not on the square-root scale.

As such, the futility boundary was crossed, and per the protocol, administration of palovarotene was paused and the study data were unblinded. In order to better understand the results at IA2, the raw data were analyzed and demonstrated a large difference between the groups. Palovarotene-treated patients had a 59 percent reduction in mean annualized new HO compared to untreated patients.

Additional analysis without the square-root transformation, including a Wilcoxon ranked-sum test and a weighted linear mixed effects model for wLME, all indicated a treatment effect favoring palovarotene. The large discrepancy between the Bayesian analysis with square-root transformation and the Frequentist statistics led to an understanding that the square-root transformation was inappropriately masking the treatment effect. Because of this, we repeated the primary efficacy analysis without the square-root transformation.

This post hoc analysis of the prespecified Bayesian model found that the probability of

success was drastically different. Without square-root transformation, the model predicted a 79 percent probability that palovarotene would reduce annual mean new HO by more than 30 percent. Furthermore, the model predicted a 99.5 percent probability that palovarotene would reduce annual mean new HO compared with untreated patients.

Based on the totality of evidence from the second interim analysis, patients 14 years and older reinitiated dosing with palovarotene. At the third interim analysis, the primary endpoint was analyzed using both the prespecified Bayesian and wLME models. Because of the partial clinical hold in December and the dosing interruption in January, all data from the primary endpoint were censored at the time of these interruptions.

The Bayesian model for the third interim analysis showed similar results as interim analysis 2. The square-root transformation continued to introduce a bias against palovarotene, inappropriately showing a diminished treatment effect. When removing the square-root

transformation, the model predicted a 99.4 percent probability that palovarotene would reduce annualized mean new HO compared with untreated patients.

Presented here are the patient-level data from Study 301 and the natural history study, with each line representing an individual patient. On the left are palovarotene-treated patients and on the right are untreated patients from the natural history study. And while the majority of patients in both groups developed new HO, these figures demonstrate that the overall volume was less in palovarotene-treated patients. Importantly, fewer patients treated with palovarotene had large volume increases in new HO, as shown by the dotted line compared with untreated patients.

To account for the limitations of the Bayesian analysis, we analyzed the data using the wLME model, which includes all data as collected. Based on this analysis, palovarotene-treated patients achieved a 54 percent reduction in mean annualized new age HO volume compared with

untreated patients.

Now focusing on the target population of females 8 years of age and older and males 10 years of age and older, we again see consistent results in favor of palovarotene. Palovarotene-treated patients achieved a 49 percent reduction in HO volume compared with untreated patients.

Next, we performed multiple sensitivity analyses to evaluate the potential concerns of relying on an external control to evaluate efficacy. First, we conducted a paired analysis of the 39 untreated patients from the natural history study who transitioned to palovarotene in Study 301, and thus contributed data to both studies. This analysis is important because these patients serve as their own control and allow us to evaluate palovarotene's impact on disease progression.

Overall, the 39 transition patients had a 52 percent reduction in mean annualized new HO with palovarotene when compared to their mean annualized new HO while receiving standard of care in the

natural history study. In addition, when looking at the volume of new HO over time in the 39 transition patients, we can see the positive impact of palovarotene on disease progression.

The whole-body CT scans were conducted at different time intervals between the two studies. These data show that the trajectory of new HO volume while on palovarotene was dampened through 18 months of follow-up, and since HO accumulates over time and is irreversible, the ability to minimize development before patients lose function is clinically meaningful.

We also conducted a matched pairs analysis. This analysis evaluated the change in HO volume in palovarotene-treated patients from Study 301 compared with untreated patients from the natural history study. All patients who crossed over from the NHS to Study 301 were excluded from this analysis. Each untreated patient was matched with a treated patient, to the extent possible, based on the distribution of propensity scores and a caliper matching algorithm.

As seen in this plot of the distribution of propensity scores by treatment, it shows the improvement in the comparability of the patient with respect to the age; age-adjusted baseline HO; sex; baseline CAJIS; and time since last flare-up after matching. The matched pairs analysis showed a 77 percent reduction in mean annualized new HO volume with palovarotene compared with untreated patients.

These data support that efficacy is not an artifact of confounding differences between patients in Study 301 and the NHS. In addition, multiple other sensitivity analyses support that untreated patients from the natural history study are a valid comparator for Study 301. Each of these sensitivity analyses consistently demonstrate that palovarotene reduces the volume of new HO.

Long-term data provide additional evidence supporting the efficacy of palovarotene. These analyses include all data collected through last patient/last visit and allow for the assessment of efficacy both on and off treatment. As described

previously, the primary endpoint results were censored at the time of dose interruptions. For the long-term analysis, we will refer to this as the pre-pause period. The interruption period provides an estimate of new HO volume among patients during treatment interruption and uses the last whole-body CT collected prior to dose interruption and the first scan after re-initiation of palovarotene. The post-restart period includes all patients who restarted palovarotene treatment and had two or more whole-body CT scans during this period.

Finally, we also performed an analysis based on the ITT period, which spans both on and off treatment regardless of whether patients started palovarotene treatment or remained off treatment. This analysis provides a conservative estimate, as it includes data while patients were not receiving treatment.

Turning to the results, the wLME analysis for the ITT period from baseline to last visit in Study 301 compared to the natural history study

showed a 45 percent reduction in the LS mean new HO volume in palovarotene-treated patients compared to untreated patients. Now looking at the bar chart on the right, this analysis of the raw data shows the mean annualized new HO volume by time period in the long-term analysis. The amount of new HO accrued during the off-treatment phase is greater than that accrued while on treatment with palovarotene.

Next, we looked more closely at the 17 patients that restarted treatment who had at least two whole-body CT scans during the restart. Here, we also see a substantial increase in the amount of new HO during the off-treatment period when compared to the time when these patients were receiving palovarotene treatment.

Shown here is an analysis looking at patients in Study 301 who had treatment interruption, the majority due to the partial clinical hold, and never restarted palovarotene. These data demonstrate that HO formation was blunted while on palovarotene with the return to HO

formation closer to what was seen in the natural history study when treatment was stopped. The consistency of results across these long-term analyses support that palovarotene reduces new HO volume.

Next, I will discuss secondary and exploratory endpoints. Study 301 was designed to show a reduction in new HO volume in palovarotene-treated patients compared to the NHS. While this was demonstrated, it was thought that a reduction in body regions with new HO in palovarotene-treated patients would contribute to this treatment effect. This was not the case, as shown here. This may be related to the mechanism of palovarotene to dampen rather than completely block BMP signaling.

In addition, although we do not expect palovarotene to impact the flare-up rate, we did observe more flares in palovarotene-treated patients compared with untreated patients. As Dr. Brown described earlier, literature reports suggest that patients with FOP experience

approximately two flare-ups per year. In fact, a detailed review of flare-up rates from multiple different sources, including a 500-patient survey, an ongoing clinical trial in FOP, as well as registry data from the IFOPA, report that patients with FOP experience between approximately 1-and-a-half to 2-and-a-half flare-ups per year. This suggests that the rate observed in Study 301 may be more in line with what would be expected in clinical practice.

The explanation of the differences in flare-up rate between Study 301 and the NHS could be due to the difference in how flare-ups were captured in the two studies, which may have resulted in an underestimation of flare-up reporting in the NHS. To better understand the clinical significance of this finding, we asked ourselves whether the observed flare rate in Study 301 was impacting the positive HO results.

Presented here is the volume of new HO in a subset of patients who experienced at least one flare-up in either study. This analysis shows that

among patients experiencing a flare, the volume of annualized new HO with palovarotene is substantially less than in the natural history study. The long-term data are also important when considering this finding.

Presented here are the data for the 17 patients with HO assessments in all three time periods. Through four years of follow-up, the benefit of palovarotene on reducing the volume of new HO is lower while patients are receiving treatment. Thus, the data from our study suggests that palovarotene's effect on HO formation will persist even in the setting of a flare.

Next, I will describe the functional outcome measures. Physician- and patient-reported outcomes, including CAJIS, FOP-PFQ, and PROMIS, were evaluated in Study 301 as exploratory endpoints. It is important to highlight that while these measures can track physical function over the lifetime of a patient with FOP, they are not sufficiently sensitive to measure change over the course of a clinical trial.

Presented here are mean total CAJIS score and FOP-PFQ worst score in palovarotene-treated and untreated patients. As expected, these assessments showed minimal worsening in untreated patients over this relatively short period of time, and thus are not sufficiently sensitive to demonstrate meaningful changes through two years of observation. As palovarotene treatment is not expected to improve these measures, reduction in annualized new HO observed that palovarotene treatment should result in preserved function if observed over longer periods of time.

Finally, I will review additional evidence from our phase 2 program that supports the treatment effect of palovarotene. Since Study 202 was an extension study and not powered to demonstrate efficacy via comparisons to the NHS, a matched pairs analysis was performed to better align these populations and aid in comparisons.

Here, I am focusing on Study 202 Part C, as this study most closely resembles Study 301. This analysis shows the mean annualized new HO volume

for 19 patients who received palovarotene in Study 202C compared to 19 matched patients from the natural history study who did not cross over to receive palovarotene. Patients were matched according to age; sex; time since last flare-up; age-adjusted HO volume; and CAJIS. Overall, there was a 43 percent reduction in annualized new HO volume in treated compared to untreated patients.

The long-term data from Study 202C provide additional evidence supporting the benefit of palovarotene. Presented here are the pre-pause, interruption, and post-restart data for the 9 patients from Study 202C who contributed data in all three periods. Consistent with the results presented earlier for Study 301, we again see that the rate of new HO volume is less while patients are receiving treatment.

In summary, the data from Study 301 demonstrate that palovarotene reduces the volume of new heterotopic ossification in patients with FOP. In the overall population, palovarotene-treated patients achieved a 54 percent reduction in new HO

compared to untreated patients. Sensitivity analysis have shown a consistent benefit of palovarotene and support that the NHS is a valid comparator for Study 301. And despite the higher rate of flare-ups reported in palovarotene-treated patients compared to the NHS, the overall volume of new HO was less with palovarotene.

Additionally, analyses of the long-term data from last patient/last visit, as well as evidence from Study 202C, provide supportive evidence of palovarotene's efficacy. Collectively, these data support that palovarotene modifies the underlying cause of disease progression and disability in patients with FOP.

Thank you. I will now turn the presentation over to Dr. Schranz.

Sponsor Presentation - Jennifer Schranz

DR. SCHRANZ: Good morning. My name is Jennifer Schranz, and I'm the global head of Rare Disease at Ipsen. I will present the safety profile of palovarotene, and then review our risk management activities that were developed to guide

physicians in their benefit-risk discussions with patients and families.

164 patients with FOP have received at least one dose of palovarotene across the development program. As outlined in the proposed label, we are recommending that palovarotene be initiated in a specific target population; therefore, I will focus my presentation on the 139 palovarotene-treated patients who represent this population. This includes patients from Study 301 and our phase 2 studies.

Mean exposure was approximately 3-and-a-half-years, and 78 percent of patients remained on treatment for more than 30 months. In addition, safety has been evaluated in more than 300 healthy participants and more than 700 patients from other indications. These results support the safety of palovarotene in patients with FOP.

I would like to begin with the results from our bone safety monitoring program, specifically focusing on the premature physeal closure or PPC. Premature physeal closure, although not a

life-threatening event, is an important risk associated with palovarotene treatment. In the target population of females older than 8 years of age and males older than 10 years of age, 13 palovarotene-treated patients have reported events of PPC. These include a continuum of partial through complete closure of the growth plates.

To characterize the magnitude of risk, we conducted a detailed review of the individual patient narratives, including radiologic and clinical assessments of growth. We found that growth does not generally stop upon initiation of palovarotene or diagnosis of PPC. In addition, some patients had signs of growth disturbance prior to the identification of PPC, suggesting that monitoring can form ongoing risk-benefit decisions.

Regarding potential, long-term consequences, no patient in Study 301 experienced a femoral angular deformity and there was no difference in leg length asymmetry between treated and untreated patients. The clinical consequences of FOP and

heterotopic ossification formation are severe, and thus for every growing patient, the potential risks of PPC need to be weighed against the benefits of reducing the volume of new HO formation and potential for preserved mobility. In summary, premature physeal closure is a risk associated with palovarotene treatment in pediatric patients with open growth plates and will be highlighted in a boxed warning within the prescribing information.

Turning now to general safety, palovarotene has a manageable safety profile. All patients experienced an adverse event. The majority were of mild to moderate intensity, with 25 percent experiencing a severe adverse event. Thirty-seven percent required a dose modification and 9 percent discontinued treatment due to an adverse event. Serious adverse events occurred in 41 percent of patients. There were no deaths across the FOP development program, either on study or within 30 days after discontinuation of therapy.

Consistent with other systemic retinoids, mucocutaneous events were the most commonly

reported adverse event. These events were generally mild to moderate, and they were manageable through dose modification and prophylactic skin care. Musculoskeletal events were also reported in more than a third of palovarotene-treated patients. It is important to note these events are also associated with the natural progression of FOP and are commonly seen in patients with FOP who are not receiving palovarotene.

Mucocutaneous events were the most commonly reported adverse events that led to a dose reduction. Overall, dose reductions were effective in managing these events and allowed patients to remain on treatment. Dry skin was the only adverse event that led to treatment discontinuation in more than one patient. All other events were observed in one patient each. These data support that the safety profile of palovarotene is manageable, and the majority of patients are able to remain on treatment.

Next, looking at serious adverse events,

presented here are the most common treatment-emergent serious adverse events that occurred in the target population. Coronavirus infection and premature physeal closure were the most commonly reported serious adverse events. In addition to the information and guidance provided to the proposed label, our risk management plan was designed to inform and guide patients and physicians on the safe use of palovarotene. These include an educational program to inform healthcare providers, patients, and their caregivers on the risks of palovarotene treatment.

Because FOP is an ultra-rare disease, we anticipate that treatment will likely be initiated by a specialist. Palovarotene will only be distributed through a single specialty pharmacy with pharmacists trained on the USPI, the educational program overview, and the educational materials. Each potential prescriber will receive an introductory letter describing the program and a set of comprehensive educational materials. Prescribers will need to confirm review prior to

prescribing palovarotene.

In addition, each potential patient will receive an overview of the key risks with supplementary educational materials specific to either females, growing pediatric patients, and their caregivers. All of these educational materials will also be available via the online product website for ease of access.

We are also planning a 10-year post-approval registry study with a target of enrolling at least 80 percent of patients treated with palovarotene. The registry study will be protocol-based with study site personnel trained in rigorous data collection, with periodic reviews of data quality to ensure completeness. The primary aim of the study is to collect and assess real-world safety data with specific safety endpoints, focus on pregnancy outcomes, PPC, and vertebral fractures.

The registry study will also further characterize the effectiveness of this treatment, including palovarotene's effect on physical function as per the measurements collected in our

phase 3 study. Although it will be conducted as a real-world study, sites will be selected and staff educated and trained on the importance of enrolling patients to characterize the long-term safety and effectiveness of palovarotene. In practice, after palovarotene is prescribed, patients would be enrolled in a clinic visit. Follow-up visits would occur on site or remotely according to routine clinical practice in order to limit additional burden on patients and their caregivers.

In conclusion, palovarotene has a well-characterized safety profile, consistent with the well-established profile reported with other systemic retinoids. Mucocutaneous events were most commonly reported. The majority of adverse events were mild to moderate, and patients were able to remain on therapy through dose reductions and supportive care. Premature physeal closure and teratogenicity are important risks of treatment and are clearly communicated with a boxed warning in the proposed label. We have developed a robust education and risk mitigation program to inform and

guide patients, physicians, caregivers, and pharmacists on the safe use of palovarotene.

Thank you. I will now turn the presentation over to Dr. Hsiao.

Sponsor Presentation - Edward Hsiao

DR. HSIAO: Good morning. My name is Edward Hsiao, and I am a professor of medicine at the University of California, San Francisco, where I direct the Metabolic Bone Clinic. I am one of about 20 worldwide clinicians specializing in FOP. In 2007, I met my first patient with FOP and was astounded by the huge amount of abnormal bone formation and the overwhelming effects of the disease. Since then, I have had the unique opportunity to care for more than 60 patients with FOP and have dedicated my research to understanding this disease and developing medical management strategies for patients. It is from this vantage point that I am sharing my perspective as a clinician on the use of palovarotene in patients with FOP.

It's important to emphasize that FOP is a

devastating disease. Patients need a treatment option that can slow its relentless progression. Throughout my career, I have cared for many patients with FOP, ranging from a couple of months old to those aged 50 and beyond. The discussions I have with my patients and their families are difficult. They quickly realize that the new bone formation affects all aspects of daily life.

There are no effective treatments to slow the life-altering effects of FOP. It is devastating to watch as their children lose the ability to accomplish basic activities of daily living that we take for granted, like being able to walk to the bathroom and wipe themselves after using the toilet, or being able to turn around to see something behind them, or being able to walk or eat on their own.

Patients also realize that the bone formation has other impacts besides mobility. They are unable to sit or stand comfortably from masses in their back, their thighs, or flanks, or they develop pressure sores from the bony protrusions.

As Dr. Brown discussed earlier, standards of care for our patients is limited to symptomatic treatment, as patients continue to progress over time. These changes are permanent. Thus, blocking any new bone formation is the critical strategy for slowing progression of this devastating disease.

Palovarotene is the first medication that has been tested in the rigorous manner to show a reduction in the amount of HO and FOP. This is a clinically meaningful outcome for patients. The data presented earlier show that palovarotene-treated patients achieve a 54 percent reduction in new HO compared with untreated patients. It is important that we understand the magnitude of this reduction and what it means for our patients.

To give context as to what these volumes mean, the increase of 20,000 cubic millimeters of annualized new bone that was formed in untreated patients is about the size of a Clementine. Now, compare that to the 9,000 cubic millimeters of annualized new bone seen in palovarotene-treated patients over this same time period. This equates

to roughly the size of a grape.

If we go back to the NHS data presented earlier, patients with an elbow CAJIS score of 2, which represents complete locking, have a median of 18,000 cubic millimeters of HO. Thus, limiting the new bone volume to 9,000 cubic millimeters instead of 20,000 in the elbow would potentially preserve the ability to move, perhaps allowing a patient to reach for items on a shelf, to wash their hair, or to brush their teeth. So although bone is still forming, the fact that palovarotene can slow this formation is very meaningful to patients because it would allow them to maintain their mobility and independence for more time.

As with any therapeutic option, it's important to weigh the benefits of treatment with the safety profile. Because bone formation in FOP is cumulative and irreversible, early intervention is critical to preserve a patient's ability to function over time. During the clinical development program, PPC was shown to be a risk with palovarotene treatment, especially in younger

children; therefore, this is an important risk-benefit discussion for pediatric patients and their families.

In Study 301, we observed a higher flare rate compared with the natural history study. Although the cause of this is not clear, the data showed that the volume of new HO remains less in patients receiving palovarotene regardless of the observed difference in flare rates. As a site investigator, a number of our patients have expressed that this is a tolerable risk if it would allow them to maintain the ability to move or to be independent for a longer period of time.

Finally, mucocutaneous side effects were the most commonly reported adverse event in the palovarotene clinical program. While these events were significant for some, most of the patients I cared for were able to tolerate the medication very well. For my patients who did experience these side effects, many were able to remain on therapy with topical emollients or following dose reduction. These considerations highlight the

importance of clearly communicating the risks of palovarotene versus the potential benefits of early intervention to our patients and their families so that treatment decisions can be made based on the individual's needs.

In conclusion, the totality of data showed that the benefits of palovarotene treatment outweigh the potential risks. Palovarotene represents an important treatment option for patients with FOP. It would be the first therapeutic option shown to slow the trajectory of this disease through a reduction in new HO.

Clearly, the medication may not be for all patients with FOP; however, as a physician who has cared for these patients for more than 15 years, it is my clinical perspective that all patients with FOP should be given the opportunity to consider whether palovarotene is right for them. For our patients, palovarotene represents the best chance to live a more normal life and to slow the relentless progression for a disease that currently has no other effective options.

Thank you. I'll now turn it over to Drew Sansone.

MR. SANSONE: Thanks, Dr. Hsiao.

My name is Drew Sansone, and I'm the vice president of Regulatory Affairs and Quality for North America Ipsen. I'd like to conclude this presentation by thanking the entire FOP community. The support and sacrifice of study investigators, personnel, and most importantly, the patients and their families, have made this program possible.

Thank you. We'd be happy to take any questions that the panel might have at this time.

DR. LOW WANG: Thank you so much for this presentation.

Before we proceed with questions, I'd like to invite our patient representative, Dr. Chaikhoutdinov, to introduce himself by stating his name and his affiliation.

(No response.)

DR. LOW WANG: Dr. Chaikhoutdinov, are you able to unmute yourself?

(No response.)

Clarifying Questions for Sponsor

DR. LOW WANG: Maybe we'll go ahead and move on.

We will now proceed to clarifying questions for Ipsen. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I'd like to take the chair's prerogative and start with the first question. I do have a question for Dr. Marino, and this is relating to slide 60 and 61.

It was noted that there was markedly higher annualized new heterotopic ossification volume during the interruptions, so off treatment, especially when looking at the next slide, which looks at the 17 individuals with data in all three phases. So I was wondering if you could please expand on that and what you think the implications are since there are no other treatments to transition patients to.

MR. SANSONE: This is something that we've looked into extensively, and we believe the reasons are multifactorial. I'll have Dr. Marino come up and discuss more.

DR. MARINO: Thank you. Indeed, unfortunately we did have to interrupt therapy for patients due to the reasons discussed in the presentation, but we continue to collect data, as we were restarting therapy in order to be able to assess this off-treatment time period.

What we're seeing on the slide is an increase in heterotopic ossification after discontinuing treatment, with a return to a

dampening of that formation back on treatment. To me, this shows that treatment is necessary, and to continue to have dampening of the heterotopic ossification, you need to continue the therapy in order to continue to receive the benefit.

DR. LOW WANG: Alright. Thank you.

Let's move on to the first question from our panel.

Dr. Nason, you're first.

DR. NASON: Great. Thank you. This is Martha Nason. I'm a statistician at NIH, and I have two questions about the analysis. The first is I couldn't tell whether the fact that some of the same people were in both the natural history and in 301 was accounted for in the analysis, explicitly since those are obviously not independent. I was just hoping the statistician could confirm whether that was included in the model.

MR. SANSONE: Let me ask Dr. Strahs to come up and address that question, please.

DR. NASON: Thank you.

DR. STRAHS: Good morning. I'm Andrew Strahs, head of global biometry for R&D at Ipsen. Yes, I can confirm that that was taken into account in both the Bayesian analysis and the wLME analysis. There was a random subject affect in both.

DR. NASON: Thank you. If you don't mind staying for a sec, I have one more question which you might be able to answer. I just wanted to confirm -- I was trying to make sure I understood the annualized part of the HO, and I believe it's different for different types of HO, so I just want to make sure I'm understanding correctly.

When it was an ongoing new HO, it was divided by the time interval that that was measured over; however, when it was a baseline HO, it was using the subjects age to annualize the data. Is that correct?

DR. STRAHS: Those are different. The endpoint that was studied in the study was new HO --

DR. NASON: Right.

DR. STRAHS: -- so it was total amount of new HO divided by time of observation. The baseline, which we often used as a covariate, was baseline total HO across all body regions divided by baseline age. We did do modeling both with that age-adjusted baseline and baseline, and we did not see a difference in using those two versions at baseline.

DR. NASON: Okay. With the one that's annualized by the interval, was their data from the natural history study alone just to show that was relatively constant with age, or did that seem to plateau with age?

DR. STRAHS: We do see that the the new HO volume does decrease with age. The cumulative HO does build --

DR. NASON: Fine, sure.

DR. STRAHS: -- for age, yes.

DR. NASON: But I'm just trying to figure out, especially given age differences between the populations, how the annualized rate might be impacted by that.

DR. STRAHS: We did do substantial analyses also including age as a covariant, and that did not change the observation of post hoc efficacy.

DR. NASON: Okay. Thank you.

DR. LOW WANG: Next, Dr. Coffey.

DR. COFFEY: Thank you. My questions are also related to the efficacy and the statistical -- Chris Coffey, statistician, University of Iowa. Sorry about that.

I think one of the questions that I have is I understand the problems that you ran into with your log transformation of the endpoint that led you to do the additional analyses. I suspect one of the reasons, though, that the log transformation was proposed originally was because, clearly, when you look at that plot of the outcomes skewed data, you have some really large increases on the left side, more in the middle, and then a few in the other direction at the end.

So my question kind of on the other side though, the way that you presented in multiple slides, like 6061 we just looked at and several

others, were annualized mean differences, which seems like that could potentially be biased in the other direction, where some of the really large differences could really skew the means towards the higher end as opposed to the medians.

So in trying to get a sense of the effect, if you looked at median effects in the groups, how would that compare, and have you looked at that?

MR. SANSONE: I'm going to have Dr. Strahs come back up and address those questions, please.

DR. STRAHS: First, I'd like to clarify that it was a square-root transformation and not a log transformation.

DR. COFFEY: Thank you.

DR. STRAHS: Second, our observation was that the medians behaved similarly to the means, and interestingly, we were worried about the effect of extreme value. So one sensitivity analysis that we did -- and I could pull up CO-47 to look at the individual patient annualized new HO. One analysis that we did was we took everyone who observed greater than 100,000, and we replaced that with

100,000. We were concerned that an extreme value could be influential, and we found very similar results. FDA subsequently extended that analysis and varied the cutoff, and also produced very similar results.

DR. COFFEY: Great. Thank you.

DR. LOW WANG: Next, we have Dr. Yanovski.

DR. YANOVSKI: Thanks. Jack Yanovski. I have one question that, again, it's asking for supplemental analysis to what's been shown. The discussion has been about children between 8 and 14 potentially being different from children who are older than that age.

Have you analyzed the data, and can you show us an analysis of how the amount of FOP developed in those different age groups through the study and the different areas? That would be, of course, compared to this historical control group, as well as to the on-and-off treatment. Do you have those data for the age group 8 to 14 versus older children, older people?

MR. SANSONE: We do, and I'll ask Dr. Marino

to come up with the data.

Dr. Marino?

DR. MARINO: Sure. Thank you. We have done several subgroup analyses to look at different age groups, which also helped us determine our indication population of the 8/10. And what we're showing on the slide now are the age cutoffs of those that are in the non-target population, those less than 8/10, the 8/10 to 14, and the greater than 14; and what we see is consistent efficacy across all age categories here, understanding that these are subgroup analysis with smaller numbers.

DR. YANOVSKI: Thank you. That's my only question.

DR. LOW WANG: Next, we have Dr. Wang.

DR. WANG: Thanks. I just wanted to follow up on Dr. Coffey's question on this issue of the square-root transformation, as I recognize that this will be probably a topic of discussion given the efficacy results. If you could just explain so that I make sure I understand correctly; your feeling is that the reason that the square-root

transformation in retrospect was inappropriate is because of the different frequency of the CT scans in the treated group versus the non-treated group, as square roots aren't additives, which seems like a very reasonable point.

I guess my question is, this would have been known when you prespecified the analysis that the frequency of the CT scans was different. Was that considered when you considered the options, and how specifically did you settle on a square-root transformation to account for skewness or other problems with the data, as opposed to an alternative similar to those that you chose in the post hoc analyses?

MR. SANSONE: I'm going to have Dr. Strahs come up and walk you through some of the evolution of our analysis and how we came to be with the square-root transformation.

DR. STRAHS: The square-root transformation was actually a relatively late addition. The concern was that large amounts of HO in a small number of patients could mask a finding of

efficacy, and we include an example in the briefing document that demonstrates this. But ultimately, once we adjust -- so this bias was not appreciated before the unblinding.

When we do a sensitivity analysis that artificially equalizes the visit structure, though, we see very little difference between with and without square-root transformation. Both yield approximately a 40 percent reduction in new HO with a probability of efficacy both over 90 percent. At least in the Bayesian analysis, ultimately, square-root transformation, once you adjust for the bias, makes very little difference.

DR. WANG: Thank you.

DR. LOW WANG: Next, Dr. Blaha.

DR. BLAHA: Hi. Mike Blaha, Johns Hopkins. My questions have to do with -- could we pull up slides, let's start with CO-57, and they have to do with the series of sensitivity analyses and just trying to follow them. In particular, I'm going to zero in on propensity score adjustment.

Just here, I guess it looks very consistent

across these, but if I understand right, the sample size is changing considerably across these studies, and I struggled a little bit to follow exactly the difference between the matched pairs analysis, and the propensity score analysis, and the propensity weighted analysis, if those were all shown, and maybe you could comment on that. But before that, let's go back one slide if you don't mind, and I'm going to do the same on my screen, or actually back two slides, to CO-55.

This whole issue, I'm just trying to follow the sample size that came up here, and I'll follow up with one final question about the propensity matching here. It shows before matching, there's definitely some differences between the NHS and the 301, and then this showed that after matching, of course, we have more similarities. But the sample size has changed again here, and even the 61 and 58 were different on the prior slide; it was 62 and 58, so I was getting confused.

If I could ask the group to give me a quick comment, maybe at least on this slide, how these

sample sizes are arrived at. And then after that, one follow-up question about what was in the propensity adjusted model. But maybe a quick question about the differences between analysis on the multiple sensitivity analysis slide, and then the sample sizes on this slide.

MR. SANSONE: I'll have Dr. Strahs come back up and talk about those analyses a bit.

Dr. Strahs?

DR. STRAHS: The 62 dropped to 61 because one subject did not have time since last flare-up populated, so that subject was dropped for the propensity score weighting analysis.

DR. BLAHA: Okay. Then this slide, before matching, we have 61 and 58, and after matching, we have a pair of 39. Could you just walk me through again about how we arrived at these numbers?

DR. STRAHS: Sure. It was based on caliper matching using the propensity scores for the five variables that Dr. Marino mentioned. I believe it is time since last flare-up; baseline CAJIS; the age-adjusted baseline; HO; sex; and age.

DR. BLAHA: So then, I guess 19 participants were not able to be matched, I guess, from 301 into the matched pair group?

DR. STRAHS: That's right. That's right, only those that were able to have a matching within the caliper were included. That's how we go from the numbers on the left to the 39 on the right.

DR. BLAHA: Okay. Sorry, a final question. Can you just list the things that were in the propensity model again? I just want to confirm how you entered baseline HO into the model. That's a critical variable and understanding the change.

DR. STRAHS: Right.

DR. BLAHA: How did you get to that?

DR. STRAHS: In this analysis, we used the age-adjusted baseline HO, which was the total volume of HO at baseline divided by the baseline age. We've done other analyses where we've included just straight unadjusted baseline, and in that modeling, we really didn't see any difference between them.

DR. BLAHA: Difference between the results,

not difference between the --

DR. STRAHS: Right, different results; yes, different analyses. But more regression analyses in the ITT analysis that Dr. Marino mentioned, we didn't identify one as having any more predictive value than the other.

DR. BLAHA: That's the end of my questions. Thank you.

DR. LOW WANG: Thank you. Next is Dr. Gerhard.

DR. GERHARD: First, a quick follow-up to Dr. Blaha's question from a second ago. In the propensity score weighted model, you then include that the 61 and the 58 didn't have to match within the caliper, so just a quick follow-up.

The actual question was for the transition period analysis, so that's slides 51 to 53; and either for Dr. Marino, and maybe for Dr. Hsiao as well, this is the analyses that takes the people that were in the natural history study and then switched over to the 301, and the argument was made that these might be specifically important because

it's a within-person comparison.

To me, a lot of alarm bells go off because the reason that people switched at this specific point in time might be particularly because they were doing poorly and had an increase in HO prior to switching, and then you'd basically just see a regression to the mean.

So I would like to understand a little bit more, for those patients that switched, what triggered to switch from the natural history study to join Study 301, and was that because they were doing particularly poorly at the time? Is there any data that you have to extend that would shed some light on that? Thank you.

MR. SANSONE: I'm going to start by asking Dr. Marino to come up and begin to address those questions.

DR. MARINO: As Study 301 was enrolling, the natural history study was ongoing, and all patients that were still within the natural history study were invited to participate in Study 301, as well as the general FOP community. We had advertised on

clinicaltrials.gov and through the IFOPA, so we were making sure that we weren't selecting patients out of the NHS into Study 301. We didn't collect specific data or reasons why people left the NHS to come to 301. We did do an analysis to look at their HO formation when they left, and it did not appear that they were doing worse, if you will, in NHS compared to 301, which I think was one of your concerns.

To give maybe a little bit more clarity, we do have one of our PIs who participated in both studies, who could give you a little more of an idea of how his patients transferred and for what reasons, so I'll ask Dr. Hsiao to come up and give his perspective.

DR. HSIAO: Yes. Thank you very much for that question. I think as one of the site investigators, there were multiple reasons that patients gave. I want to emphasize that what we did was offer the option of transferring to 301 to every subject in the natural history study.

A number of patients were considering

different factors, including travel time, and for many, whether or not there was increased risk in terms of having to travel through the airports and potentially have trauma or difficulties from the traveling itself, as well as difficulties on the family side. Especially for families with young children, you can imagine that having to come on site requires a lot of effort, a lot of caretakers that need to come on site, and so a lot of these different types of factors were often cited by the subjects.

DR. GERHARD: Thank you. That's very helpful.

DR. BROWN: If I could just --

DR. GERHARD: I just wanted to follow up, though, also on the statistical follow-up question.

DR. STRAHS: Yes, I can confirm that the weighted analysis used all of the 58 and the 61 subjects, and there it was an attempt to include everyone but make more comparable by using weights to make the propensity scores, distributions between the full set, more similar. So I can

confirm your question.

DR. LOW WANG: Thank you.

I just wanted to state that we'll shorten our break to 10 minutes, so we have five more minutes for the last two advisory committee members to ask their questions.

So next is Dr. Weber.

DR. WEBER: Thank you. This is for Dr. Marino. Comments were made about dose reduction --

DR. LOW WANG: Would you please state your name? Sorry about that.

DR. WEBER: Sorry. Tom Weber -- I'm sorry -- from Duke. This is for Dr. Marino.

This is the question. Comments were made about dose reduction during the study, and looking at the packet, I see how those are kind of guided. But I had a question specifically whether dose reductions during this trial specifically were analyzed as to how it affected HO efficacy because that could have real-world implications in terms of, if it's approved, dose reductions and how it's

going to work. So if you can address that first question.

MR. SANSONE: I'll ask Dr. Marino to come up and address the question around dose reduction.

Dr. Marino?

DR. MARINO: We did have dose reductions, mostly because of adverse events of skin reactions. We didn't do an analysis, per se, looking at the dose reductions in particular, but what we're seeing in our efficacy, and what we're showing you, is including all of those dose reductions. So what we would expect in the real world would likely be what we saw on the trial, given that we did see dose reductions based on mostly the adverse events, so I don't have an analysis to show you for that particular question.

DR. WEBER: Okay.

My second quick question is, I know that the con meds such as prednisone don't affect the national history, but certainly they have potential adverse skeletal and other consequences. So do we have any data on con med, specifically prednisone,

dose reduction during the trial and whether that can provide an indirect benefit in that regard?

DR. MARINO: Most of the patients did receive prednisone, although not all of them, so we can give you a slide just to give you a sense of who received and for what flare-up; so about three-quarters of the patients in the natural history study and about two-thirds in Study 301. Usually, it's a short course. It's only 4 or 5 days, and they stop prednisone. So we did not do a formal analysis, but in reviewing data over the last several years, patients weren't reducing or not reducing based on their steroid use.

DR. WEBER: Okay. Thank you.

DR. LOW WANG: Thanks.

So we have two minutes left before the break, so we have time for one more question by Dr. Greevy.

DR. GREEVY: This is Robert Greevy. Thanks for squeezing me in for a question. Could you bring up slide 47, CO-47? In this particular

slide, it shows both positive and negative changes. I like this slide a lot because it shows all the data. Are negative changes physiologically possible, or is this more an indication of just measurement error in assessing HO?

MR. SANSONE: This is something that we've given a lot of thought to, and let me have Dr. Marino come up and provide an explanation.

DR. MARINO: So at the beginning of the trials, when we were designing Study 301 and the read paradigm of looking at heterotopic ossification, we didn't anticipate that we'd actually see all of these reductions. We saw them in both the natural history study -- it's maybe hard to see on the right -- and we saw them in Study 301. It was 5 percent of the patients in the NHS and 29 percent of the patients in Study 301.

What I can tell you is we've looked at this both radiologically, and what we see is that -- and I'll show you an example of a picture of what HO looks like at baseline and how it could reduce over time. So the radiologist didn't read negative HO

or smaller HO; they just read HO. And what we did is we subtracted the baseline from the subsequent time points; therefore, if you had a smaller amount measured after baseline, you would have a net negative reduction.

This was an observation, as I said, that we saw more in palovarotene compared to the NHS patients. Could this be something that palovarotene is influencing? It's possible, but I don't really have data that can show you that definitively. Given the mechanism of action of palovarotene, it could be influencing both the catabolic and anabolic phases of HO, or it could also just be a part of measurement variability of the scans when you're measuring very small volumes of HO. So there could be a biologic plausibility. It's just something that the setup of the study wasn't designed to really look at.

DR. GREEVY: Gotcha. That's helpful.

A follow-up question might be for Dr. Strahs.

DR. LOW WANG: Very quick.

DR. GREEVY: It's super quick, just which analyses truncated those changes at zero? Because I know at least the Poisson model truncated them at zero. Did all the analyses do that?

DR. STRAHS: No. The weighted linear mixed effects analysis did not employ a square-root transformation and was able to use the data as observed as measured. So the only analyses shown in which negative was truncated at zero were the Bayesian analyses.

DR. GREEVY: Gotcha. Thank you very much.

DR. LOW WANG: Alright. Thank you.

We'll now take a nine-minute break until 11:40 Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. So we'll reconvene at 11:40 Eastern Time. Thank you.

(Whereupon, at 11:31 a.m., a recess was taken, and meeting resumed at 11:40 a.m.)

DR. LOW WANG: Okay. It's now 11:40. Before we start our FDA presentations, I wanted to

mention that we may have time after the open public hearing for Dr. Applegate's question.

Now, I'd like to invite Dr. Chaikhoutdinov to unmute his microphone.

Dr. Chaikhoutdinov, please introduce yourself by stating your name and affiliation.

CDR BONNER: Dr. Low Wang, please unmute your mic.

DR. CHAIKHOUTDINOV: Hi. I'm Dr. Marat Chaikhoutdinov. I'm representing my patients, FOP patients. My daughter actually has FOP.

DR. LOW WANG: Thank you.

We will now proceed with the FDA presentations, starting with Dr. Stephen Voss.

(Pause.)

DR. LOW WANG: It looks like we're still setting up audio and everything in the FDA Great Room.

(Pause.)

CDR BONNER: This is LaToya Bonner speaking. We'll take a brief break to address technical issues. Thank you.

(Pause.)

DR. LOW WANG: Thank you, everyone, for your patience. We can now proceed to the start of our FDA presentations with Dr. Voss.

FDA Presentation - Stephen Voss

DR. VOSS: Thank you. I will give an overview of the clinical studies.

The natural history study was a three-year observational study to gather information about FOP and possible endpoints for clinical trials. Study 201 and the first part of the extension study, 202, evaluated short-term palovarotene treatment of acute flare-ups with assessments of the flare-up site. Chronic dosing with higher doses for flare-ups was evaluated in the later parts of Study 202 and in Study 301, with assessments of long-term disease progression.

The natural history study enrolled FOP patients with no recent flare-ups. The study included annual assessments of disease progression, including whole-body HO by CT scan, the CAJIS scale, which measures restricted mobility, and the

FOP Physical Function Questionnaire, designed to measure impairments of function that are characteristic of the disease. The NHS also evaluated a subset of reported flare-up events over a 12-week period, with assessments of local symptoms and imaging of the flare-up site.

The NHS baseline data confirmed the clinical impression that, over time, patients with FOP tend to have progressive accumulation of heterotopic ossification, as well as greater restriction of the range of motion at multiple joints as measured by the CAJIS score. There was also a direct correlation of the total body HO volume with increasing CAJIS score. This is consistent with the view that restricted movement in FOP patients results directly from accumulation of HO around joints and supports the use of HO as a clinically meaningful endpoint in this disease.

The NHS enrolled 114 patients with FOP, about half of whom subsequently transferred into interventional studies as listed here. There were no prespecified selection criteria for these

transfers as long as the enrollment criteria of the interventional study were met. Study 201 enrolled patients with an acute flare-up episode with onset of symptoms within 7 days. Subjects were randomized into one of three treatment groups: palovarotene 10 milligrams for 2 weeks followed by 5 milligrams for 4 weeks; or palovarotene 5 milligrams for 2 weeks followed by 2-and-a-half milligrams for 4 weeks; or placebo for 6 weeks.

Following the 6-week treatment period, subjects were observed for six additional weeks. Enrollment was initially restricted to patients at least 15 years of age. Subsequently, the age was lowered to 6 years old with dose adjustments based on body weight for subjects with younger bone ages based on X-rays of the hand and wrist.

Prior to these studies, the best method of imaging and measuring heterotopic ossification was largely unknown. Study 201 included standard radiographs as well as CT and MRI of the flare-up sites. The primary endpoint was the proportion of

responders as defined by standard X-rays showing no or minimal new HO at the flare-up site at week 6. The secondary endpoints included the volume of new HO at the site and local symptoms of pain, swelling, and range of motion.

Study 201 enrolled 40 subjects with FOP with a mean age of 21 years. In two of the three treatment groups, the mean number of flare-ups in the year prior to enrollment was around two per year, which is consistent with published surveys. The rate was somewhat higher, 4.6 per year, at baseline in the higher dose group, the 10/5-milligram group. Most of the flare-ups treated in the study involved the hip or knee area, which are sites that are commonly affected. Most subjects presented with typical symptoms of pain, swelling, and stiffness.

At the end of the 6-week treatment period, only 2 out of the 40 subjects in the study exhibited significant new HO by X-ray of the flare-up site; therefore, this study did not meet this primary endpoint. New HO was detected in more

subjects at week 12 compared to week 6, and CT scans were found to be more sensitive than plain radiographs. At week 12, the proportion of subjects with new HO was somewhat lower in the two palovarotene groups compared to placebo. The mean volume of new HO was also lower in the palovarotene groups. The volume data were highly variable. Pain scores declined moderately in each of the treatment groups.

All 40 subjects from Study 201 enrolled in the open-label extension study, 202, and 18 additional subjects were later added. Part A of this study evaluated additional flare-ups, which were treated with the palovarotene 10/5-milligram regimen. Part B of this study introduced higher doses for flare-ups, 20 milligrams for 4 weeks followed by 10 milligrams for 8 weeks. Chronic daily dosing of 5 milligrams between flare-ups was also added for skeletally mature subjects in Part B, and then for all subjects in Part C. All doses were weight adjusted for skeletally immature subjects.

When chronic dosing was begun, the primary imaging modality changed from assessment of flare-up sites to annual whole-body HO measurements by CT. The method outlined here was used in all the studies, 202B and C, and Study 301, and the NHS. At the baseline of chronic dosing, HO volume was measured at each of 9 body regions, excluding the head. On post-baseline scans, HO was re-measured in regions where any new HO was apparent.

An unexpected finding was that many areas of HO actually reduced in size over time, the mechanism of which we do not fully understand The data were reported as total volume for each body region; therefore, changes from baseline could be positive or negative for each region based on the balance between areas of HO that were growing or shrinking in size within a certain region. Data were not recorded on individual HO lesions or the extent to which changes were related to new versus pre-existing lesions.

The endpoint of annualized new HO represents

the sum of changes from baseline across all body regions divided by the time interval between the first and last scans. The criteria for initiating flare-up dosing changed between Parts B and C of Study 202. We are mainly interested in the data from Part C because it ran in parallel to Study 301 and used the same treatment regimen. Flare-ups were treated with high doses for 12 weeks, which was extended if symptoms were persisting, and the cycle was restarted at 20 milligrams for intercurrent new flare-ups or a marked worsening of symptoms.

Under a protocol amendment, flare-up dosing was also started if the subject had substantial trauma, such as a fall which was considered likely to trigger a flare-up. The primary endpoint of Study 202 Part C was the annual rate of new whole-body HO. This was the same primary endpoint as Study 301; however, 202 was a smaller study that was not powered to demonstrate efficacy through comparisons to the NHS.

In December 2019, treatment of children

under 14 was stopped due to reports of premature growth plate closure. The following months, treatment of all other subjects was paused based on an interim analysis. Many of these subjects later restarted treatment after a pause of several months. The efficacy data have been summarized for three treatment periods. The pre-pause period represents data on treatment that were submitted in the original NDA. The subsequent interruption period represents a time interval that was mostly, although not all, off treatment, and the post-pause period represents a subgroup of subjects who restart a treatment and had data on new HO following the restart.

The 202C subjects had a mean age of 21 years, which is older than the subjects in the other studies, NHS and 301, and they had higher levels of whole-body HO at baseline, probably related to the age difference. In the pre-pause treatment period, the Study 202C subjects developed new HO at an average rate of about 19 cubic centimeters per year. In the off-treatment

interruption phase, mean new HO rose to about 26.8 cubic centimeters per year. Most of these subjects subsequently restarted treatment, and during this phase, the average rate of new HO was much lower, 6.4 cubic centimeters per a year.

Among these, there were 9 subjects in 202C who had data in all three phases. This group showed a pattern similar to the overall study, with the rate of new HO increasing from the pre-pause to the treatment interruption period, and then a decline following the restarting of treatment.

The phase 3 study, 301, was a single-arm study of patients with FOP who were at least 4 years old and without a recent flare-up within 4 weeks. All subjects received the same chronic plus flare-up regimen used in 202C. A total of 107 subjects enrolled and external control is provided by untreated subjects in the NHS. There were 39 subjects who participated in both studies.

[Inaudible - audio gap.]

DR. LOW WANG: We can't hear right now.

CDR BONNER: Correct. We will have a

temporary break until we address the technical issues in the Great Room. Thank you. This is LaToya Bonner.

(Pause.)

DR. LOW WANG: I can hear you now.

DR. VOSS: Okay. We're back.

NHS subjects tended to have more advanced disease at baseline, including a higher --

DR. LOW WANG: Apologies for interjecting. I don't see the slides. I don't know if those are being projected.

(Pause.)

DR. LOW WANG: Okay. I can see the slides now.

DR. VOSS: Okay.

NHS subjects tended to have more advanced disease at baseline compared to 301, including a higher mean volume of whole-body HO and slightly higher mean scores on other disease parameters such as the CAJIS index. This is consistent with the somewhat older age of the NHS subjects. In the pre-pause period of Study 301, annual new HO volume

averaged 9.4 cubic centimeters per year. [Inaudible - audio gap].

DR. LOW WANG: Again, we've lost sound.

(Pause.)

CDR BONNER: LaToya Bonner, DFO. We will take a brief break to address the technical issues. Thank you.

(Pause.)

DR. VOSS: I apologize for our technical issues. If everyone can see this slide, this is study -- can we go forward on the slides, about three or four more slides?

(Pause.)

DR. VOSS: Alright. Let's try to resume here.

The primary efficacy analysis of the phase 3 study was based on whole-body HO volume measured by CT scan, which was conducted every 6 months in Study 301 and every 12 months in the NHS. Scans were read using the same method as in Study 202C based on 9 body regions, and the scans from 301 and the NHS were combined at random for blinded

readings by two independent reviewers.

These are some baseline data on NHS and 301 subjects. Demographically, these two groups were similar, except that NHS subjects were, on average, about 2-and-a-half-years older at the time of enrollment. NHS subjects tended to have more advanced disease at baseline, including a higher mean volume of whole-body HO and slightly higher mean scores on other disease parameters such as the CAJIS index. This is consistent with the somewhat older age of the NHS subjects.

In the pre-pause period of Study 201, annual new HO volume averaged 9.4 cubic centimeters per year, which was lower than the rate in Study 202C. Similar to 202C, average new HO volume was higher during the interruption of dosing and lower again after treatment was restarted in the post-pause period.

This table represents the 17 subjects in Study 301 who had HO data in all three phases, showing the pattern of relatively low new HO volume on treatment before the pause, then an increase off

treatment, then low again after restart. There were 16 subjects in Study 301 who never restarted treatment after the pause but did have follow-up scans. This group had very low rates of new HO during treatment and higher rates after stopping.

That's my last slide. My biostatistical colleague, Dr. Alex Cambon, will now present in-depth analyses of the Study 301 efficacy data.

FDA Presentation - Alexander Cambon

DR. CAMBON: First, I will briefly discuss the study design and endpoints and then go over the prespecified analyses and results. Thereafter, I will focus on key efficacy review issues.

Study 301 was a single-arm study evaluating palovarotene for decreasing heterotopic, ossification accumulation in adult and pediatric subjects with FOP as assessed by low-dose, whole-body computed tomography or WBCT. The study was designed to compare with the NHS as an external control with similar enrollment criteria; however, the WBCT was assessed every 6 months in Study 301 and every 12 months in NHS. We will discuss

further the impact of this difference on analysis results.

There were 39 subjects who transitioned from the NHS study to Study 301. These subjects contributed efficacy data for both studies. Although it was an open-label study, the image readers were blinded to the source of the image. The images from the two studies were interspersed during the blinded reading process.

The protocol-defined primary endpoint was annualized change in new HO volume. We will also refer to it as annualized new HO in the presentation. The key secondary endpoint was the proportion of subjects with any new HO at month 12. The prespecified primary analysis for the primary endpoint was based on a Bayesian compound Poisson model. Under this model, the change in HO since previous WBCT scan was modeled as a compound distribution of the number of body regions with new HO and the new HO volume per region where a new HO occurred.

The method does not calculate the annualized

change in new HO for each subject directly; rather, it estimates the mean annualized new HO by multiplication of mean annual number of events and the mean growth per event, where the occurrence of a positive new HO is an event. The treatment effect was expressed as a ratio of the annualized new HO between treated and untreated subjects, which is estimated by the ratio of annual event rates multiplied by the ratio of the growth rates per event.

With the intent to reduce variability and increase study power, the prespecified analysis included a square-root transformation and change in HO since the previous scan by region for calculation of mean growth of new HO greater than zero; however, this turned out to be one of the key review issues. The study failed to show efficacy of palovarotene based on the prespecified primary analysis, with posterior probability of reduction in the annualized rate of HO equal to 0.65; however, additional post hoc analysis appeared to show evidence of benefit on the primary endpoint,

which I'll elaborate on later.

I will now focus on the key efficacy review issues, which is the appropriateness of reliance on post hoc analyses and the use of an external control to support effectiveness. I will now discuss issue 1, the appropriateness of reliance on post hoc analyses.

Post hoc analyses are generally considered hypothesis generating because it could inflate the chance of a false positive finding and raise concerns of potential bias caused by selection of analyses for the intended favorable outcome; however, in this particular context, FDA acknowledges that the prespecified primary analysis may not have been the appropriate method of analyzing the primary endpoint for reasons outlined in subsequent slides.

Acknowledging the limitations of the prespecified analyses, we think it is reasonable to consider alternative more appropriate analyses for assessing evidence of efficacy. We will discuss such analyses later. Before that, I would like to

briefly talk about the limitations of the prespecified analysis.

The applicant reported that the prespecified Bayesian analysis has a bias against palovarotene due to the more frequent assessments and the application of a square-root transformation on each incremental change of HO between CT scans. We acknowledge this limitation. The rate of growth in HO volume was estimated based on the square-root transformation of each incremental change in HO by reason between scans.

Since WBCT scans were not performed at the same time interval in the two studies -- they were scheduled every 6 months in Study 301 and every 12 months in NHS -- the prespecified estimation approach involves comparing the sum of the square root of each incremental change to the square root of the sum of each change. This might have contributed to the failure of the primary analysis.

Here we demonstrate how more frequent assessments could lead to a bias against palovarotene under the prespecified approach with a

square-root transformation. We show that 2 subjects with identical change in HO at one year could have different estimated annual new HO in the two studies. Suppose a new ratio of volume 200 occurs in a body region before month 6?, and then 200 more HO volume occurs from month 6 to month 12? The annual new HO will be 400; however, with a prespecified statistical model for Study 301, it would be counted as two events with growth rate of square root of 200 per event under the square-root transformation. For NHS, it will be counted as one event with growth rate of square root of 400. Therefore, the estimated annual HO will be 2 times the square root of 200, or 28.3, in Study 301, and the square root of 400, or 20, in NHS, respectively. This example illustrates that the prespecified approach may lead to a non-sensible difference in the estimated annualized new HO and a bias against more frequent assessment.

The applicant's post hoc Bayesian analysis without square-root transformation produced results that supported the efficacy with a high posterior

probability of reduction greater than 0.99 in annualized new HO in treated subjects compared with untreated subjects. Adjusting for additional covariance yielded similar results. The applicant also conducted a Bayesian analysis with the square-root transformation but adjusted for the visit schedule; that is, Study 301 visit schedule collapsed into a single 12-month WBCT to match the timing of the first NHS post-baseline WBCT. The results were also in favor of palovarotene with the posterior probability reduction rate of HO greater than 0.9.

We note that the inference for the Bayesian model could be affected by different specifications of prior distributions of the multiple parameters in the model, and the results could differ if influential priors are specified. Additionally, the model targeted only positive changes in HO and set negative changes to zero. FDA post hoc analyses, which we will show later, will focus on Frequentist methods analyzing the annualized new HO with minimal assumptions.

The applicant's weighted linear mixed effects model, or wLME, without square-root transformation and with a baseline annualized new HO as the only covariant, achieved nominal significance. We have replicated the results. In this analysis, the annualized new HO for each subject was calculated using the change in total HO volume from baseline associated with the longest follow-up, divided by the length of follow-up. The mean difference in annualized new HO between Study 301 subjects and NHS subjects was about 11 cubic centimeters per year.

The length of follow-up varied substantially among subjects and between studies. The wLME model accounted for the various followed-up lengths using a weighted approach. We note that the estimated treatment effect based on various lengths of follow-up could be difficult to interpret without the strong assumption of a constant rate of change in HO.

As most subjects had HO assessments on month 12 before the treatment pause, we conducted a

landmark analysis comparing the change in HO volume between Study 301 and NHS subjects during a 12-month observation period. This approach does not rely on assumptions on the rate of change. However, some subjects did not have changes in HO through a 12-month period, including 4 subjects in Study 301 and 11 subjects in NHS. Depending on how substances without 12-month HO change could be handled, there are different ways for performing the landmark analysis.

We performed the landmark analyses using different methods for subjects who did not have 12-month data to investigate the consistency of findings. For all these analyses, a robust sandwich estimator is used to account for heteroscedasticity and variance. Results from these landmark analyses, with different ways of handling subject without 12-month data and including different covariates, are consistently in favor of palovarotene.

The prespecified Bayesian model incorporating square-root transformation appears to

have a bias against palovarotene due to the more frequent assessments in Study 301. We conducted more appropriate analysis to compare the annualized new HO between treated subjects in Study 301 and untreated subjects in NHS. These post hoc analyses seemed to support that the annualized new HO of treated subjects was lower than that of NHS subjects. These analyses used regression adjustments to account for baseline differences between subjects in the two studies. Additional analysis methods based on matching and waiting to account for the use of an external control will be discussed in subsequent slides.

Now we turn to the second issue, the use of an external control to support effectiveness. Despite the limitations associated with using an external control rather than a randomized concurrent control, FDA recognizes that support for effectiveness can emerge using an externally-controlled trial when the following are met, as outlined in the FDA guidance on subsequent evidence of effectiveness: one, the natural

history of the study is well defined; two, the external control population is very similar to that of the treatment group; three, concomitant treatments that affect the primary endpoint are not substantially different between the external control and the trial population; and four, the results provide compelling evidence of a change in the estimated progression of disease.

The concomitant treatments in this population are not expected to affect the outcome of interest. The NHS study is the first study performed to characterize the disease progression and outcome. We will focus on whether the difference between the study population at NHS and 301 impacted the conclusion regarding efficacy, and whether the results are compelling enough to overcome the general concerns of potential confounding factors.

The enrollment criteria for the NHS and Study 301 were generally similar. The table presents baseline data for three cohorts: the 39 transition subjects who contributed to efficacy

data for both NHS and Study 301; 62 NHS subjects who did not enroll in Study 301; and 58 subjects in Study 301 who had not participated in the NHS. As shown, NHS subjects who remained in the NHS were older, with a mean age of 20.5 years, than subjects who transitioned to Study 301, with a mean age of 13.5 years, and other Study 301 subjects, with a mean of 14.6 years.

Consistent with older age, the NHS-only subjects tended to have more advanced disease with generally higher whole-body HO volume, a greater number of body regions with HO and higher scores on CAJIS, indicating a more severely impaired range of motion and physical function. Transition subjects reported a shorter time since last flare-up.

We consider the propensity score-based weighting and matching methods to reduce the effects of baseline confounding. They are the commonly used methods for analyzing non-randomized, studies. When the propensity score model is correctly specified and there is no other unmeasured confounding, the propensity score-based

methods could effectively reduce or eliminate the effects of measured confounding. The propensity score-based weighting uses the inverse probability of receiving treatment or control to create weighted samples that are comparable in terms of baseline covariates.

The purpose of propensity score matching is to match treated subjects with untreated subjects who share a similar value of the propensity score. Subjects with similar propensity scores are expected to have similar distributions and baseline covariates. We consider the following covariates based on clinical relevance and importance for this indication: baseline age; sex; baseline total HO volume divided by age; CAJIS; and time since last flare-up.

The FDA review team performed 12-month landmark analyses, including all subjects after propensity score-based weighting and matching Results from these analyses are consistent. The average difference in annualized new HO between subjects in Study 301 and NHS was about 14 cubic

centimeters per year after weighting. The covariate 3 presented in the table included all the selected covariates in the propensity score model, whereas covariates 2 and 1 excluded some covariates with missing data.

In the propensity score matching analysis, treated subjects were exactly matched on sex and age group. They were further matched with NHS subjects in a 1-to-1 ratio by the propensity score using the nearest neighbor approach. There were 61 matched pairs. The mean difference in annualized new HO among the matched subjects was about 16 cubic centimeters per year. The application of a propensity score-based matching method needs to consider a bias-variance tradeoff and whether the matched subset is still representative of the target population. When tighter matching on more covariates is requested, the number of matched subjects could be much smaller.

Balanced assessments showed the covariates were well balanced after weighting and matching.

This table represents the means and standardized mean difference between Study 301 and NHS after propensity score-based weighting for the average treatment effect. The standardized mean difference, which is calculated as the difference in means divided by the average standard deviation, is the most used measure for assessing balance. All the standardized mean differences are small, indicating the weighted subjects are comparable in these baseline covariates. We note that validity of conclusion on treatment effects from propensity score-based analyses relies on the unverifiable assumption that there are no known or unmeasured confounding factors that could impact the results.

The applicant performed analyses limited to subjects who transitioned from NHS to Study 301. One of the applicant's analysis compared the observations associated with the longest follow-up between studies. The other analysis compared the last 12-month change of HO in NHS with the first 12-month change in Study 301. Results from the two analyses favored palovarotene, and we were able to

confirm the results.

These within-subject comparisons complemented the between-subject comparisons by using subjects' own observations in NHS as a control, which may potentially have reduced unmeasured confounding. Interpretation of results from these analyses should consider to what extent the disease is expected to progress similarly as what was observed in NHS after these subjects transitioned to Study 301; however, the impact of disease progression when enrolled in Study 301 could not be fully assessed without a concurrent control.

Various methods that are commonly used for causal inference provided consistent results with the applicant's post-wLME method. It appears that a difference in annualized new HO between treated and untreated subjects was not driven by any systematic difference in baseline covariates that are expected to be clinically important; however, there is a residual uncertainty on the impact of unknown confounders on the study conclusion.

In summary, we acknowledge that there is a bias of the prespecified analyses for Study 301, and the bias had a great impact on the study conclusion. It seems reasonable to analyze the data using the more appropriate methods to better assess evidence of efficacy in this setting. Nevertheless, general concerns of potential bias caused by selection of analysis methods toward the intended favorable outcome remain legitimate.

Evidence based on external controls is most convincing when the treated and untreated populations are sufficiently similar and the results are compelling. Consistent results from various post hoc analyses, based on methods for causal inference, indicate that the difference in the primary outcome between treated and untreated subjects was unlikely due to any systematic difference in measured confounding factors; and as previously shown in Dr. Voss' presentation, the findings from the within-subject comparisons for subjects who restarted treatment after dose interruption, along with findings from subjects who

transferred to Study 301, may complement the between-subject comparisons and seem supportive of a drug effect. However, it remains unclear how much unknown or unmeasured confounding factors have contributed to the findings, given the lack of randomization, and whether the results are compelling enough to conclude a treatment effect, considering the specific context of this ultra-rare disease. This concludes the statistical presentation.

FDA Presentation - Stephen Voss

DR. VOSS: I hope everyone can hear me. I'm going to present an overview of some key safety issues for this application.

There are many known safety issues associated with retinoids. Most of those listed here are labeled as warnings and precautions for various approved retinoid medications. Several of these were observed in the palovarotene studies, and the safety profile appears to be characteristic of a retinoid.

Flare-ups were evaluated in the studies as a

possible issue related to efficacy and safety. It was anticipated that chronic dosing of palovarotene may block the initiation of some flare-up episodes; therefore, flare-ups were designated as an efficacy endpoint in Study 301. There was also some concern for safety because of the known association of retinoids with musculoskeletal adverse events, including myositis and hyperostosis.

This slide shows data from the phase 2 study, 201. Under this protocol, an index flare-up was treated for 6 weeks, followed by 6 weeks of observation. Any possible new flare-up at a different site during this 12-week period were not treated as new flare-ups but were recorded as adverse events of condition aggravated.

Among the three treatment groups, there were more subjects receiving the higher dose of palovarotene 10/5-milligram regimen who reported these new events, 62 percent; however, this group of subjects also reported at baseline having experienced more flare-ups during the year prior to enrollment.

This is similar data across all the phase 2 studies and natural history study in which subjects were treated or observed during the course of an acute flare-up. In the 12-week follow-up period, the incidence of a new flare-up or condition-aggravated event was 23 percent in flare-ups that were untreated in the NHS and slightly higher in events treated with higher doses of palovarotene, 36 to 37 percent; however, some of this difference may be related to differences in reporting of flare-up events in different studies, which I'll discuss in the next couple of slides.

In Study 301, the proportion of subjects with at least one reported flare-up event was slightly higher than in untreated NHS subjects, 67 percent versus 56 percent. The number of flare-ups per subject was also higher, so the rate of flare-ups per month in Study 301 was about twice the rate in NHS subjects, about 0.15 versus 0.07 new events per month. Among the 39 subjects who participated in both studies, the data were similar.

An important caveat to this finding is that flare-ups appear to have been underreported in the NHS. Compared to Study 301, NHS subjects were not followed as closely by investigators, and worsening of flare-ups symptoms was not systematically recorded as a new event as it was in Study 301. The recorded rate of 0.07 flare-ups per month in the NHS is lower than in a published survey in which untreated patients reported an average of about 2 flare-ups per year, which is about 0.16 per month.

In addition, data from the 39 subjects who crossed over from the NHS to Study 301 showed a low rate of flare-ups recorded prospectively during the last 12 months in the NHS, about 0.6 events per month. But when these same subjects transferred into Study 301, their retrospective recall of flare-ups during NHS was higher, 1.1 events per month for the same 12-month period.

Within Study 301, the rate of reported flare-ups was higher when subjects were receiving the higher doses to treat an initial or index

flare-up. Most of these new events occurred at a different location from the initial flare-up, while others represented a worsening of symptoms at the original location. By protocol, all these events were treated as new flare-ups that restarted the 12-week treatment sequence at 20 milligrams. Thus, many treatment cycles extended well beyond 12 weeks and included multiple flare-ups. The rate of flare-ups initiated during chronic dosing with 5 milligrams was relatively low, about 0.12 per month. During flare-up dosing with 20 or 10 milligrams, the rate was higher, about 0.33 new flare-ups per month.

We're not certain why flare-ups were reported more frequently during palovarotene treatment, particularly during the higher dose treatment following an initial flare-up. Anecdotally, some patients with FOP are reported to experience clusters of flare-ups at different sites in a short time. In some cases, this may be related to a rebound in symptoms following the withdrawal of prednisone that was used to treat the

acute symptoms.

Potentially, retinoids could cause myositis, resulting in a flare-up, or could cause adverse effects such as myalgia or arthralgia that could be misinterpreted as symptoms of a new flare-up. It's not clear to us from the data whether such mechanisms may have played a significant role or, if so, whether they would be affected by the dose level.

Also uncertain is whether the increase in reported flare-ups has any clinical significance in regard to disease progression. In both Study 301 and NHS, subjects who reported at least one flare-up develops, on average, much larger quantities of new HO compared to subjects who reported no flare-ups; however, the data were highly variable. Overall, there was a moderate association between the rate of flare-ups and the rate of new HO, and a somewhat weaker correlation between the extent of flare-up dosing with the rate of new HO.

Teratogenicity is a major safety issue for

palovarotene given the association of multiple retinoids with fetal malformations and other adverse pregnancy outcomes. In patients with FOP, the disease itself creates risks to mother and fetus as indicated in current FOP guidelines. It is expected, then, for palovarotene, the risk could be managed through education and enhanced labeling, including a contraindication for pregnancy and boxed warning similar to other retinoids.

Premature epiphyseal closure, or PPC, or closure of the growth plate, was anticipated to be a possible safety issue based on prior literature reports involving children treated with systemic retinoids usually at high doses for prolonged periods. The palovarotene studies included bone safety monitoring in pediatric subjects with open growth plates. This included periodic X-rays of the knee and hand and wrist every 6 months, measures of standing height and knee height, and measurement of femur and tibia lengths by CT.

In the phase 2 and 3 studies, PPC incidence was unexpectedly high and appeared to be highest in

the youngest participants, girls under age 8 or boys under age 10. In this group, 14 out of 25 subjects, or over half, were affected. In the age 8 or 10, up to 14 year-old, group, 13 out of 39, or one-third, were affected. There were no subjects at age 14 or older reported to have PPC.

Almost all the cases were first apparent on X-rays of the knee. Hand and wrist X-rays generally did not show large increases in bone age in the subjects who were developing PPC. No risk factors other than age could be identified, and levels of palovarotene exposure were not a consistent predictor of risk. Several of the affected children had not experienced any flare-ups, and therefore received only the lower chronic levels of dosing.

In the natural history study and Study 301, mean height Z-score was in normal range at baseline. At month 12, there were moderate declines from baseline Z-score, which were slightly greater in the palovarotene-treated subjects, and there were trends of slower growth in the children

who were developing PPC. Other growth parameters, including knee height and femur and tibia lengths, showed similar trends.

This slide lists two PPC-related potential concerns in addition to reduced height. Leg length discrepancies could, in theory, develop if there's asymmetric growth, especially between the growth plates of the right and left knee. This was assessed in the studies using femur and tibia length measurements on each side, and there was no evidence of any differences developing over time. Joint angulation deformities is another potential concern. This also did not appear to develop in any study participants, according to X-rays; however, the duration of treatment and follow-up in these studies was generally limited, so possible long-term effects cannot be ruled out.

When the PPC risk became clear, the partial clinical hold was put into effect for palovarotene treatment in children under 14. The main rationale for this particular cutoff was that it includes most children who have not yet reached at least

90 percent of adult height. This cutoff also includes most of the children in the palovarotene studies who had not reached at least 90 percent skeletal maturity, which was defined as a bone age of 12 years for girls or 14 for boys. Children with bone ages below these cutoffs received reduced doses based on weight, and nearly all of the PPC cases occurred despite the reduced doses.

The proposed target population of age 8 and above for girls or 10 and above for boys is estimated to correspond to about 80 percent of adult height on average. Below age 8 or 10, more than half the children developed PPC, and the risk is considered high. Above the 8- or 10-year cutoff up to 14 years, the risk related to PPC and growth appears to be somewhat lower than the younger children, though still a substantial risk, and that concludes FDA's presentation. Thank you.

Clarifying Questions for FDA

DR. LOW WANG: Thank you, Drs. Voss and Cambon for your flexibility with the technical issues, and of course for your presentations. I

also wanted to thank the committee members for your patience and understanding. We're a little bit behind schedule, but we do have ample time for questions, so let's plan to end our question-and-answer session by 1:15.

So we'll now proceed to clarifying questions for the FDA presenters. Just a reminder to please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We'll invite Dr. Applegate to start us off.

DR. APPLEGATE: Thank you, and I hope I'm not too diffused because I'm an imager, not an endocrinologist, and thank you for all the wonderful presentations. I wanted to ask about a question that was brought up in the prior session, but is, I think, still applicable that might explain some of the negative percent; like 5 percent of the subjects had decreased volumes on the drug treatment by CT measurements.

Is it possible that with better CT equipment, or with, I don't know, auto segmentation, or with different ways in which the bone volume is measured, could that explain why there's decreased volume? It doesn't make a lot of sense to me. That's my first part question.

My second part question is, have people looked at using MRI to detect cartilage before it becomes bone, and could they consider MR to detect PPCs earlier, and also for follow-up of complications, if that's a concern? That's my first question. Thank you.

DR. KEHOE: Thank you, Dr. Applegate. This

is Theresa Kehoe. I'm going to try to repeat because some of our sound in the Great Room is a little decreased.

So you are asking specifically about the negative HO that was seen on the CT scans.

DR. APPLEGATE: That were trended down. I can't make sense.

DR. KEHOE: Yes. We've thought a lot about that, about whether or not it simply is almost like a callous formation, is if you get bone that is formed, and then it consolidates as it's there longer and remodels. If that is some of what we are seeing on --

DR. APPLEGATE: Like myositis ossificans, yes.

DR. KEHOE: Okay. That has been some of our postulation of what we are seeing with the negative HO.

Then your second question was --

DR. APPLEGATE: Another hypothesis was, is there different equipment involved over time that's better, and has that been consistent in the

research study as another hypothesis? But I think your first idea is probably the better one.

Then the other comment is to try to maybe use MR for following this disease in particular because it can pick up earlier cartilage and follow-up PPC, or find PPC and follow it.

DR. KEHOE: Right. We would agree that following the growth plates radiographically in these children that are put on palovarotene would need to be very closely followed, and that would be something we would consider for labeling.

DR. APPLEGATE: Then may I ask one other question? It may be back to the Ipsen people, but it was in table 9 and figures 34 and 35. It suggested that -- and this is in the primary data, not on the slides; the information submitted.

Dr. Wang, I don't know if you will allow me to ask it now.

DR. LOW WANG: Actually, why don't we wait on that question for after the OPH.

DR. APPLEGATE: Okay. Thank you.

DR. LOW WANG: I did want to follow up on

the question about the negative HO volume. I wasn't sure; and this was mentioned in the briefing documents as well. Was the magnitude of the negative changes larger than the measurement error of HO using whole-body CTs? So just making sure that those changes were, quote, "real."

DR. KEHOE: Yes. I don't know. I would ask our colleagues from Ipsen if they know the measurement error from the CT, and whether those changes are within that error.

MR. SANSONE: I'm going to have Dr. Marino address that question from Ipsen.

Dr. Marino?

DR. MARINO: Based on the inter- and intra-reader variability assessments that we looked at, the variability is about 10,000 cubic millimeters. So some of what we're seeing was outside of that range. I think the waterfall plots could probably show individually where those ranges fell. So some were within and some were outside of that.

DR. LOW WANG: Alright. Thank you.

Our next question is from Dr. Yanovski.

DR YANOVSKI: Thanks. This is Jack Yanovski. I have two questions. The first is an analytic one -- and I should have probably asked it as well to Ipsen -- which is that I noticed that the standardization for HO is always to divide by age, but at least in some of the analyses that FDA presented, HO divided by age was in the same analysis as using age as a covariate. Isn't that overcontrolling? That is the first question. But more generally, is it actually the right way to control for the age HO relationship, to assume that it's fully linear? So shouldn't this have been modeled in a different fashion, in general?

DR. KEHOE: My colleague, Dr. Li, will answer, but my understanding was that divided by age was only done at the baseline HO --

DR. YANOVSKI: Yes, but still, that's assuming a linear relationship.

DR. KEHOE: Right. So Dr. Li will answer.

DR. LI: Hello. This is Feng Li. I'm the statistical team leader. For your question, we

examined the impact of different covariates. We included a total baseline HO as a covariate instead of the age standardized HO, and the results are pretty similar. Also, with matching and the propensity score weighting analysis, the purpose is to reduce the effect of the assumed model on the results. With the matched analysis, we are less concerned about whether the outcome model is not linear or non-linear, so that will give you a robust conclusion.

DR. YANOVSKI: Thank you.

My second, again, probably may not be something that FDA has examined, but again, I'm concerned about the timing in which the drug is being proposed to be initiated. What's magical about 8 in girls and 10 in boys as opposed to 10 in girls and 12 in boys? Do we have any analyses that really suggest that it's essential or different to start at that age as opposed to a couple of years later, when, presumably, the number of individuals at risk for early epiphyseal closure and perhaps other complications might be diminished?

So it's really a moving target question. At what age do we get to a point where the pre-existing HO is so severe, and how many people, really, and what percentage of the people have reached a point of severity of HO, where we think the game is already a problem -- or I shouldn't call it the game -- or the disease is already such a problem that we wouldn't want to delay treatment?

A related question is how many -- what percentage of the people in that 8 years, 9 years, 10, all the way through the age when epiphyseal fusion and other complications might not be a problem -- of those actually have none or very little gain in HO during the study period?

DR. KEHOE: Let me ask Dr. Voss. I think there is some, perhaps, arbitrariness to the ages that are being used. Mainly, we believe we would like to have a product that you could use for the youngest and to prevent HO from developing. I think Dr. Voss discussed why we chose age 14 when we initiated the partial clinical hold, and the sponsor has come back and justified why they think

the lower ages perhaps would be better, given the risk-benefit. I don't know that we have specifically done analyses on the younger populations. Perhaps our Ipsen colleagues have that information.

MR. SANSONE: I'd actually like to offer some additional perspective from one of our clinical experts. I'm going to call up Dr. Brown to start.

DR. BROWN: So as a clinician, I feel the age cutoffs are fairly arbitrary. I'd agree with you; however, the key thing is that in some patients, they are experiencing very rapid progression of disease in quite young age groups, and there the wish for treatment and the need for treatment is much greater than in other patients, where you do actually experience fairly mild disease early on, and then it catches up later on.

So I think the age at which you start treatment is very much something that's a discussion between clinicians and the individual patients and families to decide about, for example,

what the flare rate is, how fast the disease is accelerating, and whether there's any evidence of toxicity like premature physeal closure in the patients that have already been started on the agent. So I think it's something that actually should be handed back to the patients and to their families to be making the decision about.

DR. YANOVSKI: Is that the end of the Ipsen comment, or is there more?

MR. SANSONE: That's all. Thank you.

DR. YANOVSKI: Thanks.

I guess as a related issue, the chosen primary outcome, which of course the FDA accepted to be the CT measure, is not something that would be routinely available in clinical practice or likely to be entertained. So the question will fall back on, for that kind of analysis where we throw it back to the patient to select, what would be the criteria that would be applied? And if there's something else that's going to be used, then that should have been studied. Maybe that's more of a comment and less than a question for the

FDA, but thank you. That is all I have, but thank you very much for the answers.

DR. LOW WANG: Dr. Kehoe, did you want to comment on that or should we move on to the next?

DR. KEHOE: Well, I think we are all learning through this drug development program about FOP and the modalities available. We know that X-ray, DEXA, MRI, all of those were evaluated during this development program to try to look for endpoints that may be beneficial. How that will translate into the caregiver setting, I think we will continue to evaluate and struggle with.

What we know is that right now X-ray used currently is not helpful. That was what was known prior to this development program, but it is not sensitive enough when looking for the endpoints that we needed. So how to translate it back into the clinic I think is something that we will continue to have to discuss.

DR. LOW WANG: Thank you.

Let's move on to Ms. Robotti.

MS. ROBOTTI: Hi. Thank you. I wanted to

confirm something first.

DR. LOW WANG: Excuse me. Please state your name before you --

MS. ROBOTTI: Of course. Thank you. This is Suzanne Robotti. I wanted to confirm that the drug is supposed to be used daily throughout the patient's life, and also that the study average time on drug was about 30 months. Did I get that right? Anyone? Sorry.

DR. KEHOE: Yes.

MS. ROBOTTI: Okay.

DR. KEHOE: The drug is given daily in the 5-milligram dose, and then if there are symptoms or flare-up, the dose is increased.

Is that what you're asking?

MS. ROBOTTI: Yes. The intention is if the patient doesn't take it in 4-week or 8-week flights, as happened in the trial, of course, it would be every day, daily, for the rest of their life, presumably.

DR. KEHOE: Correct, at the lower 5-milligram dose, yes.

MS. ROBOTTI: Of course. Thank you.

Secondly, the flare-up is at the higher dosing. Of course, it's a concern. I'm sure it's a concern with everyone. I don't remember seeing any data that tested the 10 milligrams and the 20 milligrams that were optimal. And if you did test for that, were you testing to see if it stopped the next flare-up, or shortened that flare-up, or how did you measure the effectiveness of the dosing at the higher levels?

DR. KEHOE: Well, during the development program, the earlier trials, the 201 trial, actually used a 5-milligram and 2-and-a-half milligram, and then a 10-milligram/5-milligram flare-based dosing that didn't appear to be very effective. That is why the dose was increased to 20 milligrams and tapered down to 10 milligrams for the flare-based dosing. So we have seen data with lower doses, but not in the chronic plus flare-based dosing setting.

MS. ROBOTTI: So you said it wasn't effective. How do you measure that?

DR. KEHOE: Based on the radiographs that were done in the phase 2 studies. Dr. Voss will help me answer that question.

DR. VOSS: In the phase 2 study, the 201 study, the quantity of new HO at the flare-up site was lower in the two palovarotene groups compared to placebo, but the difference from placebo was not statistically significant, so it was not entirely clear whether there was effective reduction of the new HO with those doses.

When the higher doses of 20 milligrams and 10 milligrams for flare-ups were used, there was more data generated, so I think there was more of a comfort level developed about the effectiveness of the flare-up dosing at those dose levels.

MS. ROBOTTI: Okay. But it seemed to have kind of rebound flare-ups, potentially, so you're risking additional flare-ups. Do I understand that correctly?

DR. VOSS: It was found that there were more flare-ups during flare-up dosing, and we have been trying to figure out the reason for that and the

potential clinical significance of that. Perhaps I could show one of our backup slides, number 15, if someone could find that backup slide.

Okay. Great. So these are scatter plots of the number of flare-ups versus the annual rate of new HO for individual subjects in Study 301 and the NHS. On the left, in Study 301, you can see that there's a lot of variability. And the one subject that had, by far, the largest amount of new HO did report a lot of flare-ups, 13 flare-ups, but there were other subjects who reported more flare-ups and had very much lower quantities of new HO or even negative new HO, so there was a lot of variability.

On the right side in the NHS study, there were fewer flare-ups reported overall, and it was interesting that the three subjects with the largest quantity of new HO reported only 1 to 2 flare-ups. So I thought that was a little bit counterintuitive. I think these are all untreated flare-ups, so you may expect that patients reporting more flare-ups would have more HO, and that didn't necessarily happen in that study.

If we could just go to the next backup slide also, number 16, please. Ipsen analyzed the relationship of flare-up rates and new HO in these three studies. Study 301 is on the top, 202 is in the middle, and the NHS is on the bottom. And in all three of the studies, there was really not a strong relationship of new flare-ups with new HO. So that gives us a little bit of comfort in terms of a lack of evidence that more flare-ups mean more new HO in the treated group.

I think you expect to see somewhat of a positive relationship because we know that flare-ups often caused new HO, but there was not a strong relationship. And I think that if we had seen a stronger relationship, that would have been difficult to reconcile with the findings of the primary endpoint that showed that treated patients developed much less new HO compared to untreated patients.

DR. LOW WANG: Thank you.

I would like to move on to Dr. Weber.

MS. ROBOTTI: Thank you.

DR. WEBER: Yes. This is Tom Weber. This is for Dr. Voss as well on slide 84 of the presentation. Oh, it's the wrong slide. It's the height on the mean high Z-score change between the natural history study and Study 301.

DR. VOSS: I think that was 84 in the backup slides.

DR. KEHOE: The main slides, you mean.

DR. VOSS: The main slides?

DR. KEHOE: Yes, the main slides.

DR. VOSS: So we want slide 84 of the main slides.

DR. WEBER: Yes, that's it.

In the comparison between the two studies in terms of the natural history versus 301 in the age group 8 to 10 to 14, it looks like there is no difference in the change in mean height Z-score. I just had a question about the comparability of those groups and were they, again, allowing for differences between studies.

Were the baseline characteristics similar so that that would add some robustness to the

observation? There really wasn't a difference between treated and untreated change in Z-score?

DR. VOSS: I don't think I can answer that question. We didn't really look at that.

DR. WEBER: Okay. I'm just trying to get some sense because it looks like there's no difference between those groups, in that age group, between the two studies, correct, in terms of the change in Z-score --

DR. VOSS: Right.

DR. WEBER: -- 0.3 versus 0.36?

DR. VOSS: Yes. There was tremendous variability in the height data, in the Z-score data, and part of that is related to as the FOP patients grow older during their teenage years, many of them develop scoliosis and various deformities that can create havoc with the height measurements. So there was a lot of variability in all the data.

DR. WEBER: Okay. Thank you.

DR. LOW WANG: Thank you.

I did want to take just a few more minutes

for Dr. Applegate. I noticed that you lowered your hand, but if you would like to ask your question, we can take a few more minutes.

DR. APPLEGATE: Well, I'm not sure I can go to the right slide or anything because it's in the original. It's in documents that I took notes on a long time ago. I remembered there was some interesting subanalyses of sex and age, and it looked like, from table 9, that I know the women were older, but it just looked like there was more of a response in the men.

I didn't know if there was any puberty effect and if that had been looked at. You're all endocrinologists and you look at this very carefully. So I didn't know if you would have a comment about that and if it's still table 9 in the newer information. And related to that, peri-puberty, I'm sure that's something clinically that people are monitoring and taking into effect. That's my main question.

DR. KEHOE: Sure. I'm not sure that we looked at the pubertal effects specifically, so I

will ask our colleagues at Ipsen to respond.

MR. SANSONE: Yes. We'd be happy to add some detail to that. I'll turn it back to Dr. Marino.

DR. APPLEGATE: Thank you.

DR. MARINO: In looking at the differences between males and females, we didn't collect pubertal status, per se, in the trials, but we think the explanation for the differences has to do with the amount of HO that we saw in the natural history study.

So if you're looking at the slide now, the female patients in the natural history study actually had less than half of the HO that the males had, and the age differences did play into some of what we're seeing here. So it could be something to do with the age, but then when we look at the comparisons between the treated and the untreated females, the difference is less because the NHS, the untreated patients actually formed a lot less HO compared to the females in the treated trial.

Looking at the differences in males and females in the treated trial, they're pretty comparable, so it could be something to do with the age, but I also don't have much information in terms of either their pubertal status, or menstrual history, or anything of that to comment on.

DR. APPLEGATE: Okay. Thank you.

DR. MARINO: Sure.

DR. LOW WANG: Great.

I don't see anyone else's hands raised, so we'll now break for lunch. We'll reconvene at 2:00 p.m. Eastern Time. For panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members, with the press, or with any member of the audience during the lunch break. Additionally, please plan to reconvene at around 1:50 p.m. to ensure you're connected before we restart at 2 p.m. Thank you.

(Whereupon, at 1:17 p.m., a lunch recess was taken, and meeting resumed at 2:00 p.m.)

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

(2:00 p.m.)

Open Public Hearing

DR. LOW WANG: Good afternoon. It is now 2:00, and we will now be starting the afternoon session, and start with the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's 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 applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses

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

I do see a message from one of the speakers that there is an echo, and I just wanted to check with AV to find out whether or not this is something you can remedy before we start. you sound great to meet. Thank you.

AV TECH: You sound great to me. Thank you.

DR. LOW WANG: Okay. Alright. Terrific. Let's get started then.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes.

MS. OLSEN: My name is Megan Olsen, and I'm here today to share my family's story. I have no financial disclosures.

Our lives were permanently changed on September 11, 2022. That was the day we learned that our son Hayden had FOP. He was just 2 and a half. As this condition is progressive, you just don't know when the new bone will start growing or where. As a parent, you are constantly

consumed with a thought of if your child wakes up with an arm or a leg frozen in place. You freak out whenever they fall or get bumped. I never took Hayden to the park because I was so scared of him falling. A mother shouldn't have to worry about something like that.

Hayden has bone running from his right shoulder to his left hip. His chest walls are so encumbered by bone that he's always in severe respiratory distress. In 2011, he got sick with pneumonia and ended up in the PICU for 4-and-a-half months. The doctors had to put him on a ventilator his second day or he would have died. Eleven years later, Hayden is still on a ventilator 24/7, and beyond seeing his regular pediatrician, we see cardiologists, pulmonologists, OT pulmonologists, and audiologists, just to name a few.

Hayden's medical bill for the 4-and-a-half month stay in intensive care in 2011 was around $1.25 million. The 24-hour-a-day cost for in-home nursing that he requires due to his trach and his ventilator is upwards of $350,000 a year. The

financial toll is high, but so is the toll on Hayden's life. He doesn't live a normal life. He can't be independent. He's 23 years old and will start attending UC Berkeley in the fall. Even though being able to go to Berkeley was a celebration for us, Hayden will never have a true college experience. He can't live on campus, he can't go out with friends, and he can't even go on dates unless a nurse, his dad, or I are there; not a fun date when your parents are right there. When all his peers have graduated and are moving on to jobs, new locations, he is stuck at home. He is isolated, and it's hard for him to make friends and do things that other kids do his age.

While access to an approved treatment may not change his current condition, perhaps it can keep FOP from further progressing. Speaking to you today, I dream about if there had been treatments to stop his bone growth before it became so restricting, Hayden and our family would be living a much different world, a world where Hayden's father and I could work one primary job instead of

being a parent, a medical caregiver, and a full-time employee; a world without overwhelming medical expenses; a world where Hayden could live independently and pursue a career in relationships like his friends. I ask you to consider this world that you could give to other families like ours as you consider your decision today. Thank you.

DR. LOW WANG: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes.

MS. ROCKE: Hi. My name is Miriam Rocke. I am speaking on my own behalf as an individual living with FOP, and I have no financial disclosures.

I was diagnosed with FOP at around age 13, after several years of medical chaos, including two surgeries and chemotherapy for what they thought was cancer. At the time, I had several teachers and other adults in my life check in with me about

whether I was depressed because of the diagnosis. At the time, I didn't understand why. After all, it was an entirely physical disease, not mental, and we finally knew what was going on with me. But it turns out knowing that you have FOP isn't the same as living with it.

FOP is incredibly depressing and isolating. For one thing, you are obviously different. As a child, I learned that being barefoot in public meant people would comment on my weird toes. As a teenager, I was extremely self-conscious about the funny way I had of moving. More than once, I have accidentally offended people because they thought I was ignoring them when it was just that they were beside or behind me, and I can't turn my head to look at them.

FOP's rarity means it doesn't have the in-person social support that other medical conditions have. You can find local support groups for ALS, or cancer, or arthritis, and other people have at least heard of these conditions and know what they are, but FOP is too rare. And I don't

have much in common with age-based communities. After college, I tried joining a social group for people in their 20s and 30s. They all wanted to do outdoor activities like hiking, whitewater rafting, and rock climbing, where I had to use a wheelchair full-time. They were focused on building careers, where I was coming to terms with being unemployable. I essentially had more in common with 80-year-old retirees than with people my own age.

And lastly, one of the most discouraging aspects about FOP has been the lack of treatments. The condition is progressive, meaning it will get worse over time, and there's been no way to predict, control, or change the course of events. Over the years, I've lost the ability to walk, to stand safely, to drive a car, to play the violin, to put a jigsaw puzzle together, to hug another person, or even pet a dog.

FOP has been a powerful lesson in adapting to uncertainty and change, but at the same time, it's discouraging to look back at 10 years ago, or

20, or 40 and see everything I've lost, and daunting to look at the future and wonder when things will change again. And it really is when, not if. I'm mostly immobile at this point, but even so, I have something left to lose. Last year, I had a 3-month jaw flare-up that affected my ability to speak, swallow, and chew. I am lucky that it resolved well, but next time I may not be so lucky.

My hope is that future generations of FOP children won't have to learn the same lessons I did; that treatments like this one will prevent as much bone from forming, preventing as much loss of motion as possible, and allow them to just be kids. No drug is without risk, but I would like you to remember the cost of doing nothing. Thank you very much for the opportunity to speak to the committee.

DR. LOW WANG: Thank you.

Speaker number 3, please unmute and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing, for the record.

You have three minutes.

MS. ROYS: My name is Cathryn Roys, and I will be reading the testimony of Ashley Martucci today on her behalf. Please display her slide.

"My name is Ashley Martucci, and I am a person living with FOP. I have no financial disclosures. One technological advance I don't believe we've mastered is the Freeze Ray. Sure, we have simple, smaller tools focused on smaller scale solidifications, acne, blemishes, but I'm talking about full-fledged, you draw a toot [indiscernible], and in front of you stands a perfect statuesque figure of a once living, breathing, moving person before you. I can imagine this is what has actually happened to me. That's what it felt like.

"One morning you were left with the newly calcified status, and you must adapt every single aspect of your life to your new mobility; the next day, wake up and do it all over again. Living with your newly calcified body would mean you weren't able to reach the cabinets anymore in your

childhood home. It means not leaving a classroom to use the bathroom because most doors cannot be opened with a push of a button. The course of your life has been changed, and now you have to make the most of the time you have left. But remember the only rule; you can't move.

"I lived half of my life misdiagnosed. Living without the knowledge I have gene mutation, my childhood was full of contact sports, running, playing tennis, general education classes, much more than the average afflicted child might experience. I wasn't diagnosed until the 7th grade. Soon enough, no sooner than my 18th birthday, my arm was completely frozen at my side, my knee, my hip; and much later, but still within the confines of these past two years, my good arm decided it no longer wanted to leave my side.

"These months that followed allowed for icing my joints, crying on the couch, and sitting on a shower chair wondering where the hell I went wrong. I take about 20 pills a day to manage my

pain and a sleeping pill to allow me an hour or two of rest. I have also begun therapy and antidepressants due to the mental toll these past two years have taken on me. Quality of life has become a daily internal conflict for myself and others as members of this greater community, with my day with FOP tolerable enough to experience tomorrow.

"A few weeks ago, I traveled to a farm in my power wheelchair, a first for me, but it also marked the first time I cannot open my mouth wide enough to enjoy the sweetness of an apple, a far cry from the conflict of the fall prior where I could run through the orchards and pick single-handedly. Unfortunately, most of my life as I had known it had become just like that, a memory.

"I have lost much muscle to calcification, but I've learned new ways to function. I've learned how to get shirts on by aiming and tossing them over my head. After brief suffocation, I'm dressed. I've customized my fashion to include laceless sneakers that I can slide my foot in

without lifting a finger. I've learned how to balance on one leg to complete tasks like brushing my teeth.

"By losing I've also gained a lot of strength, strength to ask others for help, one of the toughest things to do as a human being, and today I'm asking for yours. Just because I'm a fighter, I'm fortunate to have met many other fighters through being a member of the rare disease community. I ask you to think of us today as you make your decision and stand beside us in this fight. Though just because one could be strong and persistent doesn't mean they're destined to a life of struggling. There are a number of people that have to fight this on the planet, and I ask for your attention."

DR. LOW WANG: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing, for the record. Please stick with the three-minute limit. Thank

you.

MS. BLACK: Good afternoon. I'm Margo Black. I'm a clinical nurse specialist in the program for Metabolic Bone Disorders at Vanderbilt University Medical Center in Nashville, Tennessee. Our clinical research is supported, in part, by Regeneron and clinical trials of garetosmab for FOP. I have no other disclosures.

I've been a nurse for 45 years. I've worked as an educator, a care coordinator, a clinical researcher with a variety of patients who have rare skeletal dysplasias. I want to tell you about my experience in planning the care for these patients with FOP. First, transport is quite a challenge. Patients often must sit straight up in their car. They must have a special oversized vehicle to transport special technology of the wheelchair, so planning with our parking team in advance is important.

I've rarely had patients with such high safety needs. It's critical that our patients with FOP have advanced planning for their needs, so I

must mobilize additional trained staff to assist the patients. For instance, our anesthesia team I alert in advance because if they do require intubation, because the neck is fused early, hyperextension of the neck is not possible, so most patients with FOP would require nasotracheal intubation, which is a highly specialized skill and not the usual standard oral intubation.

Patients with FOP have very difficult access to veins, so to perform a standard venipuncture or place an IV is complicated. We must use the most highly skilled IV specialist and use bedside ultrasound to minimize the risk of further tissue injury, and thereby more heterotopic bone formation. Their veins are quite deep and often difficult to access because muscle definition is not good.

Patients also require special consideration, with some patients having locked jaws, and therefore an increased risk for aspiration. I've seen children and adults with FOP who cannot grow, cannot kick a ball, children and adults who want to

play, and yet the risk of further disability is a terrifying thought. I have never had to go to sleep personally at night and wonder if I'd be able to bend over the next day and pick up something from the floor, hold a fork in my hand, wipe my own nose, wash my own hair, scratch my own itch, or play blocks in the floor with my grandchild.

It is a privilege for me to witness such a resilient group of patients and their families as they navigate life's difficulties. It's a resilient group of patients who are highly innovative and eager to connect with each other and share their experiences about solutions that work for them. Patients and families with FOP are strong advocates for research, so today I ask you to remember them as you make your choice. May we all unite to support and champion these challenges and needs of such a special group. Thank you for this opportunity.

DR. LOW WANG: Thank you.

Speaker number 5, please unmute and turn on your webcam. Speaker number 5, please state your

name and any organization you are representing, for the record. You have three minutes.

DR. FRIEDMAN: Thank you. My name is Dr. Clive Friedman, and I have a financial disclosure. I have received a grant from Ipsen to do an oral health survey on Canadian patients; however, today I am speaking on my own behalf as a practicing pediatric dentist who sees patients with FOP.

I'm in private practice and an assistant clinical professor at both the University of Toronto and the Schulich School of Medicine and Dentistry in Western Ontario. I'm a member of the International Political Council for FOP and on the Board of Directors of Tin Soldiers. I have attended family gatherings for FOP since 2008 in the United States, as well as internationally, and as such, have been privileged to have seen over 200 people with FOP. I am consulted on a weekly basis about oral health issues from people across the globe.

I would like to address oral health

implications for my patients with FOP, as well as for the many that I've consulted for over the years. Quality of life for people with FOP is severely impacted by their oral health. Mobility restrictions impact their oral health, and jaw ankylosis can begin from as early as 2 to 3 years of age, specifically if they experience trauma to the orofacial complex. A large percentage of individuals with FOP, by the time they reach 30 have complete jaw closure. Dental procedures, if done incorrectly, can be major triggers for flares.

Oral health is the entryway to overall health. Everything from one's ability to eat, smile, breathe, swallow, and speak is impacted, and this is only the start. Imagine for one moment being able to eat one day, and the next on a liquid diet for the rest of your life; speak for five minutes with your teeth completely together. You don't need to imagine further.

One of my patients, while on the trial drug, experienced trauma to his jaw and experienced considerable decreased opening; however, recovered

to almost normal opening while on the drug. Having a drug like this available that can help even one patient and change the course of that person's life is immense, even if the success rate is only in the region of 60 percent.

I live in Canada, and I'm aware the Canadian authorities have recognized the value of providing the current drug to our patients with FOP. Seeing this made available to the many patients in the U.S. would be indeed a welcomed opportunity. Thank you for your time and attention.

DR. LOW WANG: Thank you.

Speaker number 6, please unmute and turn on your webcam. Speaker number 6, please state your name and any organization you are representing, for the record. You have three minutes.

MS. DANZER: Hi. My name is Erin Danzer. I am speaking on my own behalf as someone living with FOP. I have no financial disclosures. Please display my slide.

I'm 25 years old, and I was diagnosed with FOP when I was about 10 months old. Growing up, my

FOP was very mild, so I wasn't as restricted mobility-wise. I was able to walk and run until I turned 20, when I had a flare-up in my right hip that affected my ability to walk. Now I'm an ambulatory wheelchair user. I can walk some, but with great difficulty, and ultimately, it can be very dangerous for me because of my balance, and it can be painful at times as well.

When I turned 22, I lost mobility in my jaw, and it locked, causing eating and being able to take medications very difficult. My day-to-day life entails being able to get out of bed safely, dressing, bathing, and other acts of self-care that I need someone to help me with. I'd say the hardest thing about living with FOP was having to adapt constantly to a new normal.

FOP is so unpredictable. In one night, I lost the ability to stand up straight that affected my ability to walk forever. I'm constantly grieving the old me and all the experiences I was able to have. If there was an approved drug that stopped bone from growing, I wouldn't constantly

have to grieve anymore. The chronic pain that I live with every day, I've learned to bear, but sometimes the pain grows so unbearable and it affects my ability to live my life to the fullest. Because of my limited range of motion, a fall could ultimately end my life since I would not be able to brace myself. Because my jaw is locked completely and I am unable to open it, I could choke on my own vomit.

I don't live a normal life. I've always had to think ahead whenever I go out. The hardest part of my day is eating and taking medications. Because my jaw is locked completely, I live off of a soft food and liquid diet. I can't go out to dinner with friends and family and order off the menu like everyone else. I can't enjoy food anymore like I used to. Eating takes a lot of preparation and thinking ahead because I have such a limited range of foods that I can eat, having to blend it, puree it, or chop it into tiny pieces. I can't pick up lunch at the cafeteria like the rest of my college peers. My nutrition declined

increasingly since my jaw locked a few years ago. Not only has it affected my physical health, but my mental health as well.

Accepting my FOP and everything that I've lost because of it has caused me to gain a new perspective on life. I am forced to navigate this world that isn't built for someone like me, but I adapt. Just knowing that it's too late for me breaks my heart, but I've come to terms with all of that that I've lost because of my FOP, and I'm grateful for all the memories and experiences that I've had.

With an approved drug, generations after me wouldn't have to endure these issues because the drug could potentially slow the bone growth. It's my hope for the future generations of those with FOP that they wouldn't have to endure any more flare-ups and can live a normal life. Thank you.

DR. LOW WANG: Thank you.

Speaker number 7, please unmute and turn on your webcam. Speaker number 7, please state your name and any organization you are representing, for

the record. You have three minutes.

MR. SUCHANEK: My name is Joseph Suchanek, I live in New York State, and I have no financial disclosures. I'm 30 years old in a body that is clearly not working for me. Like many 30 year olds, you want to be free and independent, get to do whatever you want, whenever you want, make mistakes, and be spontaneous and make memories. I'm not like most people. My body is 95 percent locked.

I lost basically every function of independence. My neck is fused upward, so I can't physically look down. I can't get a power wheelchair since I can't drive it without being able to look down. Even prism glasses won't help me see where I'm driving a wheelchair. I'm stuck with a person next to me. I can't go to the bathroom on my own, or get dressed, or even get out of bed, so I'm stuck with a person next to me.

I am 100 percent reliant on someone to live. I lost the ability to swallow anything, so I have a tube in my stomach. I have to drink formulas and

tubes to feed me throughout the day. A regular person can eat and drink [indiscernible], while I have to find a place to eat and prepare the feeding. I'm stuck with a person next to me since I can't do it no matter how hard I try.

If I was like most people, all my problems could go away with surgery, but my body repair mechanism is faulty. With surgery, maybe I could swallow again, but nobody knows the complication surgery could cause or even if it's worth the risk. I have to spit my saliva into a cup forever. I can't go on my own, and when I do it's only in limited windows of time since I'm stuck with a person next to me.

The other person is someone I have to fully trust and who understands me. I have no paid caregiver, so they have to like me enough to want to spend the day with me and assist me with every function. There are festivals I want to go to and places I want to see, but people are too busy with their own lives or just don't want to go, or maybe just not with me.

I can't be mad at anybody. All I can be is sad for not being able to get my desires met. I can blame others, but it's not fair. I can blame myself, and that's fair. I guess life isn't fair. I have to watch the world go by while seemingly everyone else does regular tasks with ease. It takes me longer to get ready, planning events out if it's wheelchair accessible, plus if something goes wrong. People can just leave the house in five minutes, and they go with little to no barriers, or worry what restaurant to go to and know the ice cream isn't good for you. But you eat it anyway since you can handle the aftermath of being lactose intolerant.

The most frustrating part out of all this is a solution that is hidden behind a thick piece of glass that I can't break. Many of these surgeries are physically possible, like to fix my swallowing or help me walk, or move my neck. My disease is a huge barrier. I am the problem. A doctor has to mutter the words, "there is nothing I can do" and I have to accept it no matter how hard it is to

swallow. Thank you.

DR. LOW WANG: Thank you.

Speaker number 8, please unmute and turn on your webcam. Speaker number 8, please state your name and any organization you are representing, for the record. You have three minutes.

MS. KIRCHHOFF: My name is Karen Kirchhoff. I'm the family services coordinator at the International FOP Association, and I have no financial disclosures.

As a physical therapist, I have enjoyed helping people improve their functional abilities for the past 20 years, but none of the injuries or conditions I've worked with have even come close in comparison to the extreme challenges faced by individuals with FOP.

The physical effects of FOP are very visually apparent when you meet someone confined to a wheelchair with very limited mobility, but what you don't see is the significant pain and dysfunction that takes place during each and every daily routine in their private lives: parents who

have to get up every 2 hours to rotate their adult child in bed at night because they can't reposition themselves without help; people who can't go to the bathroom or shower in privacy because they can't pull down their own pants, wipe themselves, or wash their own hair; people who avoid going out to a restaurant with friends because they have to push food through small gaps in their teeth because their jaw has fused. Even being able to scratch an itch or move stray hair blocking our eyes is a luxury those of us without FOP take for granted.

Now, there are assistive devices and tools that can help people with limited mobility to wipe themselves or brush their hair, but as I've quickly learned, these tools have not been redesigned in decades, and for the most part, only help those who actually still have a decent amount of mobility. Sadly, the reality is these assistive devices rarely work for those with FOP. Instead, they're forced to find alternative ways to adapt their routines, make homemade tools to assist them, or give up their independence completely and rely

solely on a caregiver.

For those who want to maintain their independence, it can take considerable time, effort, and monetary expense to find equipment that might help. And all too often, I've seen people with FOP spend months working towards a solution, or even years finding comfortable positioning in bed or an appropriate wheelchair seating system, only to be devastated by another FOP flare that causes more bone growth or changes their body position again, erasing all their previous efforts and rendering their solution or new equipment useless. Many have shared with me that living with FOP is a never-ending cycle of adjusting to a new but more challenging normal.

Now, most people with FOP outwardly seem to take this process in stride, but I know that it actually takes a significant toll on their physical health, let alone their mental health. Many have shared with me that they would be willing to put up with their current pain and physical limitations if they could just know they wouldn't progress any

further. Imagine going to bed not knowing if you'll be able to walk the next day or if the cheeseburger you had for dinner will be your last. This daily anxiety and fear that they live with is an equally debilitating part of living with FOP. They have no choice but to be resilient and to try to avoid those what-if fears.

But an approved drug could ease some of this burden and reduce their daily anxieties surrounding flares and mobility loss. And just as important, an approved drug could mean those living with FOP are one step closer to never having to adjust to another new normal again. Thank you for your consideration.

DR. LOW WANG: Thank you.

Speaker number 9, please unmute and turn on your webcam. Speaker number 9, please state your name and any organization you're representing, for the record. You have three minutes.

MS. GONZALES: Hi. My name is Alexis Gonzalez, and I have no financial disclosures. I am the sister of AJ, who is 12 years old and living

with FOP. In 2012, AJ was diagnosed with FOP at the age of 2 and a half when I was 14 years old. My brother was unaffected by FOP, except for his funny-shaped toes. He was an active kid who loved race cars, Mickey Mouse, and playing pretend superheroes. At that point, I was focused on transitioning into high school, what was I going to wear, and when were the cheerleading tryouts going to be.

Meanwhile, my dad was fired from his truck driving job because he called out of work to attend one of AJ's many doctor appointments, as my parents went from doctor to doctor trying to get a diagnosis. My parents had to file for bankruptcy, and our family of five moved into a small two-bedroom apartment. Behind the scenes, my parents were fighting to save our house and get AJ medically needing Medicaid to alleviate some of the medical costs.

Throughout my high school years, AJ began to see 10 specialists and receive various therapies. I thought he was getting the help he needed, and my

life would continue as planned. In 2016, AJ fell at my high school graduation party and had a flare-up that caused him to lose mobility in his back, neck, and shoulders. He was only 6 and a half years old. That one fall off of a slide took away his ability to raise his hand in school, wipe himself in the bathroom, and turn his head to see what is around him.

Our entire world was turned upside down. I was no longer AJ's big sister. I became his personal bodyguard and caregiver. At birthday parties, family gatherings, or trips to the grocery store, I made sure AJ would not get bumped into or fall. I tried to prevent FOP from taking anything else away from him.

AJ's diagnosis of FOP led me to go to Temple University and become a recreational therapist and child life specialist. During summer breaks, I went home and became AJ's aide so he could attend summer camp. I would not let anything get in the way of AJ participating alongside his peers, even if that meant I had to come home and pass up on an

internship or a job opportunity.

I graduated college in 2020 and moved back home during the COVID-19 pandemic. While both of my parents continued to work, I became AJ's full-time caregiver and homeschool teacher. For a year, my days and nights were dedicated to ensuring all of AJ's needs were being met. Now it's 2023, I'm 25 years old, and working at a children's hospital, but I haven't stopped being a bodyguard and caregiver for AJ.

While AJ has lost a lot, an approved drug treatment to slow down bone growth would help him keep the important skills and capabilities he still has so he can attend school, chew his food, dress himself using adaptive tools, and play adaptive sled hockey. It would give us time, time to grieve all he has lost, time to prepare for the future, and time for him to be a kid. I ask you to remember AJ's story and my story as you make your decision. Thank you.

DR. LOW WANG: Thank you.

Speaker number 10, please unmute and turn on

your webcam. Speaker number 10, please state your name and any organization you are representing, for the record. You have three minutes.

MR. EICHNER: Thank you. My name is Steven Eichner, and I have nothing to disclose. I was diagnosed very early about 3 years old, so I did not have a long diagnosis journey, but I've obviously lived the rest of my life with FOP. FOP is a bear of a disease, and those of us with FOP try to avoid poking the bear whenever we can. FOP creates both mental and physical anguish. It impacts every aspect of life. I can't reach the top of my head to wash my hair. I can't reach my feet to tie my shoes. I can't open my jaw to enjoy foods that I once loved.

For me, July 4th is a holiday of freedom. About 20 years ago, I started eating an Egg McMuffin on a trip from DC down to Virginia Beach. That was my last Egg McMuffin that I could eat with my mouth open. By the time I got to Virginia Beach, just a 3-and-a-half-hour drive, my jaw was frozen.

FOP has impacted my ability to earn income for my family. I've had many career opportunities that I've not been able to take advantage of because of the limitations of FOP. Being able to attend out-of-town meetings or being able to even get across town because I can no longer drive has limited my job opportunities.

FOP also creates a substantial economic burden. A two-story house doesn't work so well. I need a large van that's wheelchair accessible. That's also very expensive. As Karen mentioned earlier, there's a lot of adaptive equipment for one to acquire to meet needs that is all terribly expensive.

Palovarotene may not be a perfect drug in arresting bone growth, but it is one thing we did not have before. We're not looking for massive change. Every millimeter of bone growth we can avoid gives us just a little bit longer to enjoy the freedoms: one more summer camp; one more jump in the pool; or one more opportunity to throw a ball. You guys have the opportunity today to make

a decision to enable patients, their family members, and their caregivers to make the decision that's right for them, and I think it's vital that you make a choice that enables decision making at the individual level. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 11, please unmute and turn on your webcam. Speaker number 11, please state your name and any organization you are representing, for the record. You have three minutes.

MS. HOLLYWOOD: Good afternoon. My name is Suzanne Hollywood, and I have no financial disclosures. My husband and I have a 16-year-old son who has FOP. Joe was diagnosed when he was four, although the signs like funny toes and weird bumps on his head would come and go, but they were there from the day that he was born.

When his diagnosis was confirmed, our hope was there would be a drug to slow down or stop the progression of the disease until a cure was found. We've held on to that hope. When Joe was 10, we enrolled him in the palovarotene trial. My husband

and I carefully considered the risks and the possible positive outcomes of the drug. We discussed with Joe what was involved in participating in a clinical trial and how it may or may not slow down the progression of FOP. It was very important to us that he felt comfortable participating.

He was all in and excited, very brave for a 10 year old. Safety was our priority; next was maintaining Joe's mobility. We felt the side effects of this medication were minimal, although we knew there was a risk he may be shorter in stature taking palovarotene, but that was a risk we were willing to take in order to keep his mobility.

As parents of a child with a devastating progressive disease, you want to hold on to every precious moment of normal for them. Joe goes to school full-time and is on the honor roll. He's involved in clubs and activities and also plays piano and cello. Swimming is his favorite physical activity because he can move freely without fear of getting hurt. We live with the anxiety of the

slightest event setting off a flare-up but balance it with wanting him to be happy and have a healthy quality of life. Joe turned 16 this month, and like other 16 years olds hitting this milestone, he'll be getting his driver's permit.

In August of 2022, while we were at a birthday party, Joe tried to eat a cake pop. We realized he wasn't able to open his mouth wide enough to bite into it. I can't express the fear that my husband and I felt at this moment. We realized FOP was beginning to affect Joe's jaw. He repeatedly asked us, "It's going to be okay, right? Once the flare-up ends, I'll be able to open my mouth wide again?" I can't describe the feeling of helplessness I felt as a parent at that moment.

There aren't enough words to convey the importance of having a drug that will allow my son to continue to live his life and maintain his current mobility while we race for a cure for FOP. I want Joe to be able to follow his dreams and hit a milestone. Thank you for allowing me to speak today.

DR. LOW WANG: Thank you.

Speaker number 12, please unmute and turn on your webcam. Speaker number 12, please state your name and any organization you are representing, for the record. You have three minutes.

DR. LEVY: My name is Charles Levy. I'm a physiatrist who has been practicing for 30 years. I have no financial disclosures. As a medical specialist in rehabilitation, my job is to maximize the function and independence of patients.

Starting in 1996, I saw my first patient with FOP, and from this developed a focused interest in this most rare disease. Over the years, I've seen dozens of individuals with FOP, and in some instances visited patients in their homes as I got to know them and their families.

Individuals with FOP face an unrelenting episodic assault of heterotopic bone growth involving pain; advancing restriction and joint range of motion; limiting ambulation activities of daily living, including dressing, grooming, bathing, toileting; impacting intimacy, as well as

limiting chest wall expansion and posing hearing loss; and freezing the jaw, causing dietary and dental problems.

From a rehabilitation perspective, the distorted and nearly frozen postures found in later stages of FOP demand sophisticated rehabilitation assessments and often complex solutions to wheelchair seating and positioning needs. The expertise and customized equipment necessary to respond to the challenges of FOP are expensive and hard to find. By reducing the amount of extra bone, palovarotene shows promise to slow the relentless march of FOP and result in lesser disability and impairment, and increase function.

A word about the MOVE trial; in my reading, the outcome measures of the CAJIS, which is a relatively crude measure of joint range of motion, and the relatively short duration of the trial made it unlikely that differences in function and range of motion would be detected; however, the reduction of heterotopic ossification is significant and encouraging.

Palovarotene is an imperfect but important advance in the treatment of FOP. Palovarotene is associated with premature physeal closure and mucocutaneous side effects and arthralgias; decreased vertebral bone; mineral density; and content and strength. Because of the high incidence of premature physeal closure, I believe palovarotene should be restricted to those who have already reached skeletal maturity with only rare exceptions.

Despite its limitations, palovarotene has demonstrated ability to reduce the burden of HO and makes it an important tool in the physician's armamentarium to counter FOP and preserve functions. Patients and their doctors should have the opportunity to consider treatment with palovarotene to evaluate the risks and benefits and choose the paths that are right for them. The treatment landscape for FOP is evolving. I believe that palovarotene has an important role to play. Thank you for your time and attention.

DR. LOW WANG: Thank you.

Speaker number 13, please unmute and turn on your webcam. Speaker number 13, please state your name and any organization you are representing, for the record. You have three minutes.

MS. DAVIS: My name is Michelle Davis. I'm the executive director of the largest FOP patient advocacy organization, the IFOPA, and we serve FOP families from all over the world. I have no financial disclosures.

You've heard a lot about heterotopic ossification today. You likely think it means people with FOP can't dress themselves or are confined to a wheelchair, or require the support of a caregiver. That's only the beginning. What do people with FOP really lose? They lose the ability to not only enjoy a meal, but they struggle to maintain proper nutrition once a jaw locks. We have children and teens using feeding tubes because their jaws are already locked.

This is why reducing new bone formation as early as possible is so critical. They lose the ability to properly clean their teeth, which

results in tooth decay and creates more inflammation in the body that further exacerbates the disease. I once watched a dentist walk out of a meeting with an FOP patient in tears, shocked by the number of abscessed teeth the patient had.

They lose the ability to fully open their mouth if they're vomiting, which creates both a physical risk for aspiration and a constant state of anxiety about becoming sick. There has been at least one death in the community as a result of this. They lose the ability to ride in a vehicle because their body is fused in a standing position, and they can no longer sit. If they don't have the funds to purchase a highly customized wheelchair and van, then they are confined to their home. We have a 16-year-old already in this situation.

They lose the ability to break a fall with their arms. In the last two years, at least four people have died from head and neck injuries sustained during a fall. And one of the losses that really impact mental health, they lose the ability to wrap their arms around another person

and give them a hug.

As you've heard, the path and timing of FOP's progression is unknown. One woman describes walking up the stairs at night to go to bed and not being able to get back down the next day because her hip had locked overnight. This is why chronic dosing is critical. The daily anxiety and fear people with FOP and their families live with is an equally debilitating part of living with FOP, and the financial cost of caregiving, either hiring a caregiver or leaving the workplace to serve as a caregiver, is quite high.

The unpredictable progressive nature of FOP is why chronic intervention to slow the bone growth is needed. While families dream of a cure, what they want is for the disease to slow down, even just a little; and they are willing to, with their doctors, weigh hard decisions about the risks and benefits of a drug.

The approval of palovarotene, even if it doesn't complete the end of progression of the disease or eliminate all FOP symptoms, could at

least reduce some of the daily anxieties and promote better health outcomes for people living with FOP. Most importantly, approval of a drug now would slow bone growth and buy time for people living with this devastating disease while additional treatments progress through clinical trials. FOP is a complicated disease, and a cocktail will likely be needed to truly treat all aspects of the disease. We thank you for your attention to the safety of people living with FOP and the critical need to bring effective treatments to them.

DR. LOW WANG: Thank you.

Speaker number 14, please unmute and turn on your webcam. Speaker number 14, please state your name and any organization you are representing, for the record. You have three minutes.

MS. WALLACE: My name is Rebecca Wallace. I'm an FOP mom, and I'll be reading the testimony of Candace Hixson today on her behalf. Please display her slide.

"Hello. My name is Candace Hixson. I have

no financial disclosures, and I would like to thank you for the opportunity to share my personal testimony with you today. As I mentioned, my name is Candace, but my favorite people on earth call me Mom. One of these people is my 8-year-old son, Samson. Samson was diagnosed with FOP when he was only 7 months old. Words can't describe the feeling of being told there is nothing you can do to help your baby, so pick yourself up off the floor, go home, and hope for the best.

"As you can imagine, our lives haven't been the same since. Samson has lived all of his short life in a state of chronic pain. While it's encouraging that he is able to power through it on most days, it is also emotionally painful as his mother to know there isn't much I can do to help him. No child should have to just power through.

"FOP is aggressive and moves quickly. Simple tasks that we all take for granted can be taken from a person with FOP overnight. Before he was a year old, Samson had lost some range of motion in his neck and shoulders. By age 4, he was

having trouble dressing himself and putting on shoes because his ability to bend at the waist became restricted. When Samson was 5 years old, he lost the ability to move his dominant arm at the elbow. He woke up fine one morning, and by dinner time, as you can see in his pictures, he couldn't bring his fork to his mouth.

"You can also see in his photos that Samson's back is currently covered in extra bone, connecting his shoulder blades and preventing movement in his spine. His shoulders have very limited range of motion and his neck mobility has only recently been taken from him. He can't look at the sky, or look up into my eyes, or look down at his feet to see where he's going. He also seems to have new painful flare-ups almost every single day.

"When it comes to FOP, we never know what we will wake up to each morning and what might be taken from him by the end of the day. At an age where most children are becoming more and more independent and doing things like learning to ride

bikes, tie their own shoes, or even button a shirt, Samson is having those experiences ripped from him. When he has a fun day of playing, he pays for it with pain in his feet, back, and legs.

"My boy is full of sunshine. He is loud and rowdy. He loves with his entire heart, and if he loves you, you know it. He appreciates the beauty in sunset and flowers. He loves Legos, and Xbox, and to play with his brothers, and an approved treatment for FOP, something that would stop or slow the growth of excess bone in his body, would give Samson the opportunity to enjoy the funnest years of his life the way these years are meant to be spent.

"If a drug can slow the bone growth, Samson might be able to keep moving and use his one mobile arm, or maintain movement in his legs and hips so he doesn't have to end up confined to a wheelchair. It would give him the chance to try new things, to gain more independence before FOP has the chance to take more of his body from him. It would give me a peace in my heart that I haven't felt since before

FOP was a part of our lives. It would give Samson hope for a brighter future, full of opportunities to lead an independent life with less pain, and so much more of his sunshine. Thank you."

DR. LOW WANG: Thank you.

Speaker number 15, please unmute and turn on your webcam. Speaker number 15, please state your name and any organization you are representing, for the record. You have three minutes.

MS. NEWPORT: My name is Hope Newport, family services manager at the IFOPA, and I'll be reading the testimony of Suzanne McCloskey today on her behalf. Please display her slide.

"Hello. My name is Suzanne, and my 17-year-old daughter Erin was born with FOP. Erin was almost 3 years old when we finally got a diagnosis. For almost 3 years, we struggled to get answers to why she wasn't meeting her fine and gross motor benchmarks. We saw multiple specialists, including orthopedics, physical therapy, and craniofacial.

"It took a lump that developed on her chest

that got us an appointment with genetics at Seattle Children's Hospital. The diagnosis was brutal. To be told there was no cure, no treatment plan, we were left devastated and unsure how to navigate this rare diagnosis. For Erin, her abnormal bone growth concentrated on her spine, which started around the age of 3 years old. By 10, many FOP flare-ups signaled bone growth up and down her spine in conjunction with normal growth spurts, causing her spine to curve.

"From about age 3, she experienced horrible stomach pains that no GI doctor was able to diagnose. She was failing to thrive, not gaining weight, and experiencing painful flare-ups that affected the top of her head down to her hips. Unable to eat, her energy was nearly non-existent. During grade 2, she started missing substantial amounts of school. When she did attend, she would fall asleep in class. By the time she was 11, she had an ND tube to help aid with nutrition.

"She caught a common virus that normally doesn't require a doctor to intervene. She showed

symptoms on a Friday afternoon, and by Monday, she was in the ICU in respiratory distress. Because of the curvature of her spine caused by FOP bone growth, her lungs were unable to clear the excess mucus caused by the virus. She ended up with a tracheostomy and stayed in-patient for 15 months. She is now wheelchair-bound and 24/7 dependent on a ventilator, and needs daily treatment to clear her lungs. With the pandemic, in-home nursing was very limited. My husband and I sold our home over a year ago and moved away from the city because in-home nursing was very difficult to staff. We were told that the farther away from a main hospital we are, the better odds it would be to find nursing.

Erin not only had to adapt to the fast changes to her body, but she also missed out on her childhood. She was so sick all through elementary and middle school, by the time she was well enough to attend school, she should have been in high school. She tried attending brick-and-mortar schools, but by this time, students are on block

scheduling, which did not accommodate Erin's needs. She tried virtual school. Because school was virtual, it was more demanding and challenging compared to in-person school. That mode was not accommodating to her needs. We pulled her out of school altogether.

"During her in-patient stay for respiratory distress, I heard a lot about quality of life. In layman's terms, that means we now make decisions based on the amount of work needed compared to the benefits you'll receive. Not only did she have this brutal diagnosis that stripped her of her childhood, now we balance expectations versus what is reality.

"We've been through way more than we ever anticipated in these last 17 years. I'm slightly jealous that other patients can potentially have medication to help curb FOP bone growth. It's probably too late for Erin, but I would not want another family to go through what we've been through. To have a therapy for FOP is a step in the right direction. Thank you."

DR. LOW WANG: Thank you.

Speaker number 16, please unmute and turn on your webcam. Speaker number 16, please state your name and any organization you are representing, for the record. You have three minutes.

MS. NEWPORT: Hello. My name is Hope Newport. I will be reading the testimony of Dr. Ellen Elias today on her behalf.

"My name is Ellen Roy Elias. I'm a professor of pediatrics and genetics at the University of Colorado and the director of the Special Care Clinic at Children's Hospital Colorado. I have no financial disclosures.

"Today, I'll be speaking about several key barriers that patients I serve face, which prevents them from accessing routine medical care. As the director of one of the largest clinics in the country, where patients with medical complexity come for care, I've cared for 8 patients with FOP over the past 22 years, ranging in age from young infants to young adults.

"Today, I will be talking about two key

issues. The first is the inability to give normal childhood vaccines to children with FOP because giving intramuscular shots can lead to the development of FOP flare. We've developed a special way to give flu shots to our patients with FOP as a subcutaneous injection instead of an IM shot. This is important, particularly given the horrible respiratory season we witnessed this past year. However, it's not possible to give most childhood vaccines in this way, nor COVID vaccines, as the efficacy of subQ versus IM shots has not been studied. This leaves my patients enormously vulnerable.

"People living with FOP experience bone growth in all the muscles of their chest and abdomen, significantly compromising their respiratory health, which can make illness with influenza or COVID especially dangerous. Additionally, many of my patients have developed feeding and nutritional problems, which can be related to involvement of the jaw, the neck, and the upper extremities. This makes it difficult to

chew and open the mouth normally or to use the arms in normal fashion to bring food to the mouth. This has made it quite problematic for my patients to be able to eat normally in school.

"In other patients with different diseases, I often use high-cal formulas and feeding tubes to give patients good nutrition, but I cannot do that with my patients with FOP due to the need to avoid surgery at all costs. If there was an available drug which could slow down the growth of ectopic bone, patients living with FOP would have a better opportunity for more normal respiratory health and good nutrition. Thank you for your time and attention."

DR. LOW WANG: Thank you.

Speaker number 17, please unmute and turn on your webcam. Speaker number 17, please state your name and any organization you're representing, for the record. You have three minutes.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. My comment today will rely on my

research, expertise at Yale and Harvard, and in my current position, as well as my expertise on FDA policies. Our non-profit think-tank focuses on the safety and effectiveness of medical products, and we do not accept funding from companies that make those products, so I have no conflicts of interest.

Today's panel is here to focus on the science, and that's really hard. We've heard some heartbreaking stories, and just to remind you, FDA can only help patients when its decisions are science-based. So what are the benefits that we know about? The drug, unfortunately, did not meet its primary endpoint, and then the data had essentially been tortured to try to show a benefit, and they did find a significant benefit. But because of all the statistical manipulation, it's very hard to know whether these multiple comparisons really undermine the statistical significance. And since this is a decision to make about full approval, not accelerated approval, I'd have to say that the evidence standard for the FDA has not been met.

We know there are a lot of serious adverse events. We've heard about them, so we don't need to go through them. We know that a lot of patients had to drop out because of adverse events, sometimes serious ones. The adverse events caused dose modification interruption and discontinuation in a large number of patients, making it hard to evaluate the data, and we know that 100 percent of the patients had adverse events, and many of these are known to be -- almost all of these -- side effects of retinoids, including calcification of ligaments and tendons, back pain, arthralgia, myalgia, and rare reports of severe myositis; and in addition to that, depression, psychosis, and suicidal ideation, and even one patient that tried to hurt themselves.

The risk of flare-ups is not clear, and that's something that we really need to know more about. So any decision that's being made about this drug really needs to first clarify whether the drug itself can cause flare-ups, and if so, whether those flare-ups can cause more HO.

Then in conclusion, I just want to say that I'm concerned about the lack of information about the age of the patients. We know how old they ranged, the age ranges, but the sponsor did not tell us very much, particularly about the adult patients over the age of 25. We know there are quite a few of them. We know from the sponsor, from page 37 of their document --

DR. LOW WANG: Excuse me. Could you please summarize? Thank you.

DR. ZUCKERMAN: -- yes, sure; this is the end -- that the patients who are over 25 really had virtually no increase in HO, so the question is, what is the age range that should be suitable for this drug, both in terms of adult people over 25 and maybe even over 30? Are those ages too old? And also concerns about children, particularly under the age of 10, who might be more harmed than is necessary. Thank you very much.

Clarifying Questions (continued)

DR. LOW WANG: Thank you.

The open public hearing portion of this

meeting has now concluded, and we will not be taking further comments from the audience. I wanted to express my deep appreciation to our OPH speakers for sharing your experiences and insight.

We do have four minutes left in this session, so since we have additional time, we have a little bit of time to take any remaining clarifying questions, so please display M1 slide 5. I don't see any raised hands, so maybe I'll start with a question.

Just going back, this may be a question for Dr. Marino at Ipsen. For Study 301, I don't think it's been made clear what patients were eligible to restart treatment after the interruption. So really the question is, were the patients who restarted treatment comparable to those who didn't restart treatment, and could the treatment effect have been affected by differences in those populations?

MR. SANSONE: [Inaudible] -- thank you.

DR. MARINO: The patients who were eligible to restart, because we were still under the partial

clinical hold, was anybody who was over the age of 14. Because the time of the restart was really in March of when the COVID-19 pandemic really was getting going around the world, we had some temporary measures in place to ensure the safety of patients. They had to be able to comply with minimum safety assessments and be willing to have those assessments done in order to restart treatment, so it was those patients over 14 who were willing to restart. What I can tell you is that in Study 301, of the patients who were eligible to restart, 90 percent of those patients did.

DR. LOW WANG: And that population, were those characteristics looked at it compared to those who didn't restart?

DR. MARINO: We didn't look at them specifically, but they were just those patients who were older than 14. That was the only difference, was the older population.

DR. LOW WANG: Okay. Thank you.

It looks like there's a question from

Dr. Coffey, and go ahead, Dr. Coffey.

DR. COFFEY: The one question I have -- and this is maybe for both groups -- is there was the FDA slide that talked about the bias with the square-root transformation, and I think there was a great slide that showed if you had the same change over 12 months, but you measured it at 6 months versus 12 months, how you got a different value based on the transformation.

So with that in mind, one of the questions that I have is if you -- and the problem with that was because you did it every 6 months in 301, but every 12 months in NHS, was there an analysis done where you assumed -- kind of the same way the FDA example did -- that the 12 month was basically split into two chunks of 6 months?

So if you had an increase of HO by 400 at 12 months, and you split that into 200 and 200, and do an analysis that way with the square-root transformation to see whether that also gave you significant results, which given some of the concerns about the post hoc analyses -- and that

would still be a post hoc analyses, but it would at least be close to the intent of the primary analysis. Was that done, and if so, what were the results of that? And if not, why?

DR. MARINO: I could say that, yes, we didn't do the splitting. What we did was the collapsing, if you will, where we collapsed the 6 months into 12 months. And I'll bring that data up and ask my statistical colleague, Dr. Strahs, to walk us through that analysis.

DR. STRAHS: As Dr. Marino said, we did the analysis in which we took for the Study 301 patients all of the HO that was observed within the first 12 months, so from month 0 to 6, and then we added that to that observed month 6 to 12, and that resulted in a 91 percent chance of efficacy, and with transforming back to the standard scale, a 36 percent chance of efficacy, which was very similar to the 39 percent reduction in new HO that came when we did not use the square-root transformation, but used the same collapsed data set.

DR. COFFEY: So just to clarify the top one, the square-root transformation collapse over the 12-month interval, the only difference in that and your original prespecified analysis is that you just combined the 6 month and the 12 month as if you just had one 12 month in the treatment group, and then did the comparison. Everything else is exactly the same?

DR. STRAHS: Correct. It was for every patient, the same volume of HO, the same everything, except we collapsed the HO from month 0 to 6 and 6 to 12 into a pseudo month-12 assessment.

DR. COFFEY: Thank you.

DR. LOW WANG: Next is Dr. Greevy.

DR. GREEVY Yes. Can you bring up that last slide? Because I think there is an important piece of that square-root transformation being misunderstood.

Part of the issue with the square-root transformation causing problems is that timing issue; however, this sensitivity analysis addresses

that part of it. But there's another piece of the square-root transformation that's even more important, and that is, all those negative values are being set to zero to apply that square-root transformation.

Now, if you think about really small total body HO values, there's a measurement being taken at baseline and a measurement being taken at follow-up, and both of those measurements are taken with measurement error. So if you're thinking about really small changes, some of those are going to be negative just due to measurement error. So that delta, that changed score, has an error distribution to it. It has a measurement error distribution to it.

When you truncate to zero, you're changing that measurement error distribution and, in fact, you're inducing a positive bias in that measurement error distribution such that if you're trying to estimate the mean, that mean would be positively biased.

Now, if the treatment group has more people

with small values than the control group, you're then inducing a positive bias onto the mean of the treatment group so that square-root transformation, and in particular the truncation of those negative values to zero, is inducing a positive bias, and a differential positive bias if there's a difference in the prevalence of small values between the two groups. So in my mind, I'm really throwing out all the square-root transformation analyses because I know those are positively biased by design. Thank you.

Questions to the Committee and Discussion

DR. LOW WANG: Thank you.

I don't see any more hands raised, so because it's 3:04, I think it's now time to move on to the next part of our agenda.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I'd like to remind the public observers that while

this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

Let me give you an outline of the time schedule. So it's around 3:04 for right now. There are two discussion questions before the two voting questions. So we'll spend a little bit less than a half hour on each of the discussion questions, and if that works out, we'll have a 10-minute break from 4 to 4:10, and then we'll have time between 4:10 and 5:30 to go over the voting questions, and then ask everyone on the panel for explanation of the vote.

So if that meets with your approval, let me read the first question. After I read each question, we'll pause for any questions or comments about the wording of the question.

Question number 1 is for discussion. Discuss the evidence of effectiveness for palovarotene in Study 301. In your discussion, consider the following: A, the use of post hoc analyses to support a demonstration of efficacy;

and B, the interpretability of the results using the external control.

I'll open the floor now. Actually, any specific questions about the wording of the first question?

(No response.)

DR. LOW WANG: If there are no questions or comments concerning the wording, we'll open the question to discussion. Please raise your hand if you would like to make a comment.

Let's start with Dr. Greevy.

DR. GREEVY: I forgot to restate my name last time. I'm sorry about that. Robert Greevy, Vanderbilt University. The one thing I'll state just related to that last comment is I know the prespecified analysis is a flawed method. That square-root transformation, in particular the truncating at zero in order to apply that square-root transformation, that was flawed, and that happens. And in my career I've prespecified plenty of analyses that were wrong. Just because I prespecified it doesn't make it better.

So here, when I'm thinking about these post hoc analyses, I'm personally thinking of them as analyses, a whole bunch of analyses, that were trying to be correct analyses as opposed to the prespecified analysis, which I know it's incorrect.

DR. HSIAO: Thank you.

Next, Dr. Nason?

DR. NASON: Thanks. This is Martha Nason. I actually would say something similar. My gut reaction about post hoc or ad hoc analysis is always a negative one as far as it being the catalyst for a decision, or really the main evidence for a decision. In this case, though, I think everyone has shown, to my satisfaction, including the FDA's agreement, that there were problems with the prespecified, and that doesn't leave any choice, really, other than post hoc. So I do agree, it's reasonable in this case. It's just a question of which post hoc and how much flexibility is allowed there.

I agree very much with the points that have been made. I think the one that I initially feel

the most comfortable with is to adjust for the time intervals but still keep the square root. Of course, the point that was just made about those negative values is a real one, as well. I think in this case, bottom line, I do think it's reasonable, although I normally would have said no to that. Thanks.

DR. LOW WANG: Great. Thank you.

Dr. Wang?

DR. WANG: Thanks a lot. My comments actually really are quite similar, but it's probably useful to state it for the record, which is that, as the last advisor noted, I normally am very suspicious of post hoc analyses, but I do think of it a little bit differently here. As Dr. Greevy noted, the prespecified analyses probably never should have been prespecified because there were flaws that are obvious, and maybe obvious in retrospect. It would have been, obviously, more useful if they were noted previously.

So it becomes for me almost a philosophical

question. When you have a set of prespecified analyses that you can't really trust, do you really throw out the rest of the data? And that's why in this context, I am more willing to consider the post hoc analyses and consider whether there's a consistency across all the various post hoc analyses that would lead me to support the conclusion of efficacy and also place that in the context of a disease that is devastating and rare, and for which the generation of further prospective data would likely be very, very difficult. That's my comment.

DR. LOW WANG: Thank you.

Dr. Coffey?

DR. COFFEY: Chris Coffey, Iowa. I guess a couple of thoughts. One, I agree with, in general, the square-root transformation issue that Dr. Greevy raised, but I believe, if I remember, there were more negative values in the treatment group than in the NHS group, which that bias would have led to a higher average in the treatment group, which would have impacted it more and made

it harder to show an effect. So actually, the bias would be going against -- I'm basically saying that the analysis that they showed with the 12 months, even with the square-root transformation being significant, would be overcoming a bias that should be making it harder to show. I'm just saying that to say that I think that makes it, in some ways, even more convincing.

I do struggle a bit -- I mean, the one case, I don't think these two -- the A and B are not independent questions. And one reason, the whole reason, the post hoc analyses were needed in the first place was because of the use of the external control and, in essence, the controls not following the same timing schedule as the treatment group. Even with all the flaws of the square-root transformation, had this been done as a randomized control, I have a feeling that even that analysis would have showed benefit based on the results we've seen today.

So I feel like, in some ways, our challenge is not just a post hoc analyses, and it's not just

the external control, but in some ways those two are confounded with each other, and that part of the challenge is with this. I think although the evidence is strong, the point that was raised about -- I mean, technically, it's hard to claim that the criteria to use the biomarker, which would require compelling evidence, it's kind of hard for me even though I agree with the rationale used for the post hoc analysis.

Anything done after unblinding is very difficult. All of those p-values that were reported were compared to a 0.05 threshold. I don't have any idea what the type 1 error of this study is, and I'm not sure anyone does. I'm not even sure how many post hoc analyses were completely done.

So it is a bit of a conundrum, and just to say I struggle a little bit with that. Even though the post hoc analyses are consistently supported, I do have to wonder were others done that maybe weren't supported and we didn't see. It's really hard to know what the threshold of what we're

looking at is, and I think we do have to keep that in mind as we ponder this. Thank you.

DR. LOW WANG: I think those are incredibly important points, so before I make my comments, I'd like to go to Dr. Gerhard.

DR. GERHARD: Well, at this point, I don't think what I have to say is particularly new. I'm also generally quite skeptical of interpreting post hoc analyses, particularly in the context where there is a really devastating disease for which there isn't a treatment option. I think one has to be extremely careful to not approve treatment where there isn't sufficient evidence for efficacy because it actually doesn't help patients to have a treatment that isn't efficacious approved, even if there isn't an alternative.

Here, I am actually convinced that the evidence for effectiveness is strong. I think as discussed, the prespecified analyses I think was flawed. I'm really primarily convinced by the consistency through the various different post hoc analyses. They seem to indicate to me, and looking

at the raw data displayed, that there really is sufficient evidence there.

In terms of the external control, I feel quite good. Again, this is obviously a very unusual situation, where the trial in totality has a substantial proportion of the really worldwide patient population included, and the external control, compared to other examples that I've seen over the years, is quite well characterized, particularly when it comes, really, to the primary effectiveness measure.

The time scale is a little bit off, but that can be corrected, and the covariates that have been adjusted in various ways, in addition to take care of the, I would say, somewhat minor imbalances but real imbalances, to me were quite convincing. Again, this is not a gold standard trial, but it's probably also not what you can expect in a condition like this. So I clearly see evidence for effectiveness here.

DR. LOW WANG: Thank you.

Next, Dr. Blaha?

DR. BLAHA: Yes. Hi. Thanks. Mike Blaha, Hopkins. I think I'm going to say many of the same things that others have said, perhaps with a slight nuance and maybe slightly a more negative tone. But I'm extremely skeptical of post hoc analyses after unblinding, and I think, unfortunately, this whole discussion today, as many of us probably would agree, goes against nearly all the principles that we have of evaluating the trials, many of the trials that we're used to looking at and the development programs we're used to evaluating. So it's very tricky.

I agree that A and B here on the screen both raise a lot of concerns. I also have concerns about C, about the surrogate outcome, about the imaging measure. I have some concerns about that, too. So I agree with Dr. Wang that it comes down to really a philosophical question then, really, that's driven for me only by the rareness of the disease; otherwise, this wouldn't be much of a discussion. So I'm weighing the extremely challenging use of post hoc/post unblinding data

analysis against that dire need for patients. Thank you.

DR. LOW WANG: Thank you.

I think next is Dr. Weber.

Oh, actually I'm sorry. Next is Dr. Wang.

DR. WANG: Thanks a lot. I just had an additional comment in response to some of the thoughtful comments to my colleagues. First, to Dr. Coffey's comment, I completely agree. One of my normal concerns of post hoc analyses is type 1 error, and we don't get to see the analyses that were done that might not have been so supportive.

In that sense, I am a little bit reassured by the fact that the FDA did their own set of independent analyses, and my read of the FDA's statistician's conclusion was very similar to the conclusion from the sponsor in that, to the extent that you can make the conclusion for post hoc analyses, the weight of the evidence seemed to favor efficacy.

The second comment I'll make is just my impression. Sometimes a picture is worth a

thousand words, and there was a slide shown in the last session that was plotting the number of flares by HO progression. It was shown for a different purpose, but in looking at that slide, I was really struck by the fact that the scale on the axis for HO progression was completely different for the treatment arm compared to the natural history study. The treatment arm, the scale for that, the access was much lower. So I really did get the sense, even just stepping back and looking at the forest, that there was less progression in the treated patients. I know that's more of a descriptive impression than a statistical one, but, again, it supported my impression across all the various post hoc analyses that there was a difference.

DR. LOW WANG: Thank you.

Next, Dr. Weber?

DR. WEBER: This is Tom Weber. I share many of the concerns that folks have spoken about the post hoc analyses and the external control. Having said that, I'm reassured, I think as Dr. Wang just

mentioned, about the independent analyses, including the landmark analysis by the FDA, which showed basically similar results, so that's reassuring.

Then the other thing I was going to mention is, again, you've got an external [indiscernible] disease, which advances. I know the FDA raised in discussions initially with the sponsor about doing a randomized trial, a placebo-controlled, but from an equipoise standpoint, I think that would be very difficult to achieve. So I think with all of the issues we have in this progressive disease, I think the analyses that we've seen so far seem to be justified.

DR. LOW WANG: Thank you.

Next, Dr. Applegate.

DR. APPLEGATE: Thanks. This is just a really quick point that someone else --

DR. LOW WANG: Would you please state your name? Excuse me.

DR. APPLEGATE: Oh, yes. Sorry. Kimberly Applegate. Just a quick point that someone else

really already made; that I'm in a world of mostly observational study in imaging, and, really, someone said a picture is worth a thousand words. I think when we're looking at the evidence, which is based on CT volumes, I think that's important. I've done a lot of research in these sorts of studies. So I just want to say, to counterbalance some of the negative comments, I've lived in a world where we look at Fryback and Thornbury hierarchy of evidence rather than randomized-controlled trials for our study. So I'll just leave it at that. Thank you.

DR. LOW WANG: Thank you.

I don't see any other raised hands, so I'll go ahead and make a few comments as well.

I really appreciate what everyone has said. My personal comments mostly mirror what has been said. The prespecified analysis method, using the Bayesian method with square-root transformation, didn't seem appropriate for the visit schedule and for capturing that reduction in the new heterotopic ossification volume. I was much more reassured by

the consistency of the sensitivity analyses and the various methods accounting for confounding.

I think the post hoc analyses were performed after unblinding, so besides being problematic in and of themselves, the fact that it's unblinded is problematic. But I think that in this situation, there were these problems with the prespecified analysis and it's a very rare condition. So I'm less concerned, especially because the FDA analyses were consistent.

The external control population from the natural history study did appear to be appropriate, even despite those baseline differences, including the older age. The lower rate of flare-ups in the natural history study did appear to be consistent with underreporting, as was presented. So having said that, I realize there's unknown confounding, potential for bias in both of those instances.

Does anyone have any further comments? I think there may be a hand raised by Dr. Greevy?

DR. GREEVY: Yes. Thank you. Robert Greevy, Vanderbilt University. One thing we

haven't talked too much about yet is effect size and those effect size estimates and confidence intervals. Most of the analyses are estimating an absolute effect around 10,000 cubic millimeters less in the treated arm, which is about a 50 percent difference over the course of a given time period. Those confidence intervals are fairly wide, though, so that can be as big as 20,000 or as small as 500. So I am interested in some of the clinical experts sort of weighing in on that sense of a range of effect sizes.

The one thing I'll note, if we go all the way back to Study 201 and look at the effect size that was taken between the treated arm and the placebo arm, back when it was randomized data, that effect size is still around about 10,000 cubic millimeters. So I looked back at that because the one place where there was a randomized trial done at one point in time, a very big confidence interval there because the trial didn't get very far. But at that point in time, the point estimate was pretty similar to the post hoc analyses that

we're seeing now.

DR. LOW WANG: Thank you. Cecilia Low Wang. I did want to follow up on that comment because the measurement error of the whole-body CT was 10,000 cubic millimeters, so I think that's something to keep in mind when thinking about the effect size. We're just about within that measurement error, so I'd love to hear more comments about that.

So the next person with their hand raised is Dr. Coffey.

DR. COFFEY: I guess one additional thing that's been bothering me a little in trying to interpret this, and I would also be curious about getting other's thoughts on, particularly the statisticians on the panel, is related to the external control in the treatment population, about over a third of the participants in the 301 study are also in the natural history study.

So in some ways, it's the same people that are at different points in the progression of the disease. I worry a little bit that no matter what

kind of fancy statistical tools are used to try to come up with propensity score and matching, or other things, it's going to be impossible to completely eliminate unknown confounders like differences and just the progression of disease over time.

So in some ways, I feel like one of the things we haven't heard much about today, other than sensitivity analysis in that subset, was how that might impact the findings, either positively or negatively. I would also be curious just to get thoughts from others on how big of an impact that might have on interpreting these results.

DR. LOW WANG: Thank you.

Dr. Yanovski?

DR. YANOVSKI: Hi. Jack Yanovski. I want to make one comment about the use of the post hoc analyses, which has already been made, which is there's no adjustment for the multiple comparisons undoubtedly done, and we just have no idea how many there were; and therefore 0.03 and 0.04 p-values are suspect, at a minimum.

The second is really that practically everything wound up being wrong about the way these trials were conducted. They didn't standardize their procedures between what was supposed to be the control group and the intervention, and then misspecified a statistical analysis, which we're now trying to jury-rig a way around. And I agree, the first analysis was flawed, and no doubt about it, but now we're stuck with the fact that after study data had been locked, the analyses were done.

Then despite the FDA's recommendation of getting some placebo-controlled data, that was not what was followed. And even in rare disease situations, which is something that I'm fairly familiar with, there are possible ways of getting placebo-controlled data even in a condition like this, where as long as there's equipoise, one might take the same group, even on open-label therapy, and then randomly assign them either to remain on therapy or be placed on a placebo for a certain number of months. That would have been much better than this forced discontinuation, which was because

of adverse events that were easily predicted to occur in kids who are still growing with open epiphyses.

So I'm very concerned about the use of the results from the external control for multiple reasons, and I think the study designs were very much not ideal, so I'll just leave it at that. Thank you.

DR. LOW WANG: Thank you.

So are there any other comments? Let me see if I can see. Yes.

Dr. Nason, please go ahead.

DR. NASON: Thanks. This will be a little repetitive, but I just wanted to jump in because when I spoke at first, I was really focused on just the adequacy of the post hoc analysis, so I really just wanted to lend my support to some of the other things that have been said about the issues with the external control, I suppose, and I have much the same reaction to that, especially worrying about the people who were in both and were dropping out of the natural history in order to be in the

intervention arm or the intervention study.

So I just wanted to make sure my comment earlier had really been focused on the post hoc analysis and whether that was something that was appropriate here. And I do believe it is, but having said that, I don't want that to be misconstrued as my not having misgivings about this or being worried about the actual strength of efficacy evidence.

DR. LOW WANG: Thank you.

Are there any other comments about part B on question 1, so the interpretability of the results using that external control?

Dr. Gerhard?

DR. GERHARD: This is maybe more a clarification question to the sponsor because it came up in some of the comments. In my understanding, the propensity score adjusted analyses -- and I'm not sure whether the kind of standard multivariate adjusted analyses -- and in my understanding, they included the patients that switched from the natural history to the 301 study,

but I could have been wrong. That's how I read the slides, which, again, gave me a little reassurance because their analyses did include everybody, including the switchers. There are some analyses that are limited to only those that didn't switch. But it would be nice to have that confirmed.

DR. LOW WANG: Alright. Thank you, and the last call for additional comments before I summarize.

I think I see two hands up, so Dr. Greevy.

DR. GREEVY: Robert Greevy, Vanderbilt. One comment that I did want to respond to was the question of multiple comparisons has come up a couple times. I just want to make sure we're thinking about that carefully.

The way we think about multiple comparisons is if you're analyzing a bunch of independent or modestly correlated outcomes, then your type 1 error is going up because you're analyzing all these different things. Here, we're analyzing one outcome a bunch of different ways, so that thinking about multiple comparisons is different.

What we're worried about is cherry-picking in the sense of I think what I'm hearing is what if there was a whole bunch of analyses done, and only the ones that looked good were chosen? So the concern is cherry-picking more than multiple comparisons.

I do think the many different analyses, especially the ones done by the FDA, were chosen specifically to address concerns and weaknesses of the other analyses, so they did seem pretty well chosen to me in that regard. But one thing I do want to say is I'm not too worried about the 0.05 p-value as much as I think about those confidence intervals. That's why I said, in my mind, the analyses are consistent in the sense that those point estimates are kind of hovering around that 10,000 cubic millimeters effect. The confidence intervals are pretty big. It's 10,000 plus or minus 10,000.

The way that I understand it, we're not ruling out clinically trivial effects. We might be ruling out zero, and if you're skeptical of those

confidence intervals and make them a little bit bigger in your head, maybe you're not ruling out zero; but whether or not you're ruling out zero in your mind, we're certainly not ruling out really small effects.

So that's why I'm interested in if anybody has a clinical take on that of whether the wide confidence interval is going to impact your decision.

DR. LOW WANG: Would anyone on the panel like to comment on that question that Dr. Greevy just raised?

Go ahead, Dr. Blaha.

DR. BLAHA: Yes. I'm Mike Blaha. I don't have clinical experience to comment on this disease state. In that discussion about confidence intervals, I am going to keep in my mind that this is an imaging surrogate of what matters to patients. Now granted, it's part and parcel of the disease state, but it is a wide confidence interval on a surrogate for which we hope makes clinical impact. So that's not really an answer, but it's

part of my interpretation as well as I think about things. Thank you.

DR. LOW WANG: Thank you.

I'd like to invite Ipsen to address some of these questions.

DR. STRAHS: Andrew Strahs, statistician at Ipsen. I can address the question earlier about the propensity scores. All of the propensity score analyses that we've talked about, including the matched pairs and the weighted analyses, only include the subjects who participated in exactly one study. They do not include the 39 patients who transferred from the natural history study to Study 301.

DR. LOW WANG: Okay. Thank you.

I see a couple more people with comments, so Dr. Wang?

DR. WANG: Just my quick take on the effect size question, which I think is an important one, but as Dr. Blaha mentioned, we're already dealing with the surrogate. Secondly, I do think the clinical point that it's not just the amount of HO

but it's where it's located, and in certain joints or areas, the significance is a lot greater. In the end, I don't know that I can use the size of the effect in an absolute sense. It doesn't sway me too much one way or the other. I agree that it may be that we're only dealing with a drug that has a modest effect on HO, but given the breadth of the confidence interval, it could also be over 10,000, in which case, by all measures, that seems to be a significant amount of HO included in the upper part of that confidence interval. So overall, it doesn't sway me positively or negatively.

DR. LOW WANG: Okay. Terrific.

Last comment by Dr. Weber.

DR. WEBER: This is Tom Weber, and just a couple comments. I think in regards to the clinical significance, I think the sponsor had mentioned about clementine versus grape size, and where it's located can have an effect. So understanding the width of the confidence intervals and how big the effect is, I think 10,000 could be an effect.

The other comment about the surrogate, I think Dr. Blaha and others have raised the question about a surrogate and whether or not how important that is in terms of trying to understand. I guess going back to the natural history study, it's published that there's a strong correlation with the CAJIS scores, as well as with the other functional outcomes. So it's not perfect in its correlation, but I think that it needs to be stated as well.

DR. LOW WANG: Great. Thank you.

Let me summarize if there are no other questions or comments. Oh wait; there's one other comment.

Ipsen, go ahead. Is this to address some of the concerns raised?

DR. STRAHS: It is. I just wanted to clarify that we have been very transparent about the analyses done without the square-root transformation. We have shared essentially all of the analyses that we have done, and subsequently FDA produced these same analyses themselves. So I

want to assure the committee that this was not a case of us having to work hard to find evidence of efficacy. Essentially, we passed the futility boundary unblinded, and we saw more or less the waterfall plot that we showed in the presentation. Thank you.

DR. LOW WANG: Great. Thank you.

So let me summarize. There are a number of different issues we are considering here, so please, if you strongly disagree with the summary, let me know. I think this was a really active discussion regarding the evidence for effectiveness for palovarotene in Study 301.

Regarding the use of post hoc analyses to support a demonstration of efficacy, what I heard is that panel members felt that the prespecified analyses were flawed and willing to consider the post hoc analyses, especially with the different frequency of visits between Study 301 and the natural history study, as well as the consistency of findings from the analyses by the FDA.

However, the fact that the post hoc analyses

were performed and that we're kind of relying on them, including after unblinding, is problematic. So there are questions about whether the p-value of 0.05 was appropriate, especially with multiple comparisons; were the data cherry-picked; the large confidence interval; the effect size; and the fact that this is a surrogate endpoint.

In terms of the interpretability of the results using the external control or the natural history study, what I heard is that the panel generally felt that this seemed to be well characterized and appropriate, especially because of the rareness of FOP, but there was concern expressed about subjects enrolled in multiple studies and the lack of a placebo-controlled study that was recommended by the FDA.

Does anyone have strong comments about that summary?

Go ahead, Dr. Nason.

DR. NASON: Thanks. I just want to add a tiny bit more about the external control. I think the one thing that you didn't say is that I still

do have concerns about the potential differences and biases amongst people who would have chosen to be in the natural history, but for whatever reason of their own have chosen to move on to the interventional trial versus those who would not. That's inevitable in an observational study, I suppose, but would have been not a problem if there was some randomization to placebo or something similar. So I just thought that was one thing that still does concern me about the external control.

DR. LOW WANG: Thank you. That's fair.

So now let's move on to question 2, which is also a discussion question. Question number 2, first I'll read the question, and then asked whether or not there are any issues or questions about the wording, and then I'll open up the floor for discussion.

Question number 2 is discuss your view of the flare-up events in subjects treated with the proposed palovarotene dosing regimen and the relevance to benefit-risk considerations. Also comment on whether you have concerns about other

safety issues included in the meeting materials and slide presentations, or discussed today.

Any questions or issues about the wording of this question?

(No response.)

DR. LOW WANG: Okay. I don't see that there are any issues with that, so now we'll open the question to discussion. Please raise your hand if you would like to comment.

Go ahead, Dr. Blaha.

DR. BLAHA: Yes. Hi. Mike Blaha. This is a difficult one. I think there's almost a separate question, is do we believe that there are more flare-ups, I guess, in the active treatment group because of the notion that maybe they're undercounted or underappreciated in the natural history group, but it does give me some concern.

Again, I'm coming back to this idea of a surrogate endpoint. The things that matter to patients the most, it seems like in this disease data, is of course progression of the disease, but also symptomatic episodes. Is it plausible that

you might have more, at least in the short-term, symptomatic flare-ups in the treatment group? I'm not sure, but it's something I think I at least need to be thinking about as I think about what matters to patients in this disease.

This is tricky. It's tricky. The reason why we need to use a surrogate here is because in the time frame of this trial, with the amount of patients we have, we can't appreciate symptomatic benefit, I guess, on any of the measures that were listed in the exploratory outcomes because, presumably, in the couple years of a study, you can't see any difference.

This is a drug that you'll need to take for life to see a benefit, so this possibility of an increased flare-up did catch my attention, although I also appreciate that there might be undercounting in the natural history group. But anyway, as I think of what matters to patients, I think I do have to take this into account.

DR. LOW WANG: Great. Thank you.

Next, Dr. Applegate.

DR. APPLEGATE: I just wanted to agree with what was said and also to restate a concern that I mentioned earlier about puberty, and perhaps there's some information embedded in what's already been collected about the effect of the hormones in both the girls and the boys. How that relates to the bone deposition, heterotopic bone, I don't know.

Then further, I don't know if it's appropriate to ask if the subjects taking this medication can be followed more closely because of concerns about safety that have been raised by the panelists and by the FDA. That's a question for you. Thank you.

DR. LOW WANG: Thank you.

Dr. Weber?

DR. WEBER: This is Tom Weber. In regards to the flare-up, I guess what I'm reassured from the data as presented by the FDA, I believe, is that there was no correlation between the number of flare-ups and the progression of HO. In listening to the public comments today, what really struck me

was fear and actual progression of the disease, and that really is where the rubber meets the road.

I mean, again, symptomatic and flare-up events are important, but what came through was that. Again, the lack, at least based on the data analysis and the flaws as we've talked about as they are, it was reassuring to see not a correlation between the flare-ups and progression of the HO.

DR. LOW WANG: Thank you.

Next, Dr. Wang.

DR. WANG: Yes. Related to the last comment, I try to distinguish in my head --

DR. LOW WANG: Excuse me. Could you state your name?

DR. WANG: Oh, sorry. Thomas Wang. Related to the issue of surrogate endpoints, I try to make the distinction in my head between surrogate endpoints that are just markers of morbidity and mortality versus surrogate endpoints that are considered part and parcel of the biology of progression of a disease and really an etiologic

factor. In that sense, in cardiovascular disease, for instance, we accept LDL as a surrogate endpoint for approval because of the convincing evidence, the overwhelming evidence that LDL is part of the progression of ischemic cardiovascular disease.

So in this case, if we can accept that heterotopic ossification is the principal mechanism by which this disease progresses, it makes me more comfortable with this surrogate endpoint and more willing to weight this as opposed to against some of our concerns about some of the other safety signals that we may or may not be seeing.

DR. LOW WANG: Great. Thank you.

Dr. Greevy?

DR. GREEVY: Robert Greevy, Vanderbilt. Dr. Strahs will have to correct me if what I'm saying is wrong. But if I understood the Bayesian model correctly, it's jointly modeling flare-ups and HO, and if the model's allowing those to be correlated, then the HO estimates are effectively getting penalized by a greater prevalence of flare-ups in the treatment arm.

Table 4 in those supplemental materials that we were sent is the one that addresses the time interval question about the square root, where we're saying if we just use 12 months for both, what do we get? A subtle thing you get out of that table is you get the Bayesian analysis without the square-root transformation. So I've been thinking of that as sort of the flare-up penalized analysis. It's the analysis that's penalizing for those flare-ups, and instead of about a 50 percent reduction, we're seeing about a 60 percent reduction if you're assuming, well, flare-ups should be associated with more HO, so I'm going to effectively shift my estimate a little bit to account for that. Thanks.

DR. LOW WANG: Thank you.

Dr. Yanovski?

DR. YANOVSKI: Yes. I actually want to raise the possibility that some of what was termed flare-ups were actually directly related to the mechanism of the medication; that we know that it can cause adverse events, myositis, et cetera. I

wonder if, in fact, there was some extra treatment in the treatment group applied because of actual retinoic acid receptor-related issues as opposed to typical flares, and in that case, increased flares are simply a measure of the fact that you're using medicine that has effects. So for that, I'm not concerned nearly as much by the number of flare-up events that were observed because I suspect some of them were not going to be as much disease-causing as other etiologic causes of flare.

I also think the other safety issues that we obviously have to think about, the one that is uniquely pediatric in nature, is the one I'm most concerned about, which is the premature epiphyseal closure. Now, such individuals that have this terrible disease have a lot more problems to worry about than exactly how tall they get to be. So it's a relatively minor concern once the children are of sufficient size, and that's why the youngest kids certainly cannot, unfortunately, be treated with this medicine, with the ideal medicine that will be applied quite early and prevent all the

progression of FOP, and whether the right cut for beginning it, as specified in the proposal, or not, is actually a question. That I still don't have a really good sense to know whether you could get virtually the same, or almost as good, outcomes in the long term, waiting another year, or to avoid more of the closure of epiphyses that's premature. So I'll stop there. Thank you very much.

DR. LOW WANG: I do have a question I wanted to bring to the committee, and that was just the question about premature physeal closure. We know that it can cause height loss, but I think I read in the materials that it can also cause deformity. So I wondered what's the significance, or besides height loss, what else are we worried about with premature physeal closure?

DR. YANOVSKI: Yes, that's a very good question. Mostly in people with premature puberty who have extra sex hormones, so finish their growth early, such individuals typically do not have much deformity, although of course spine deformity can occur during puberty, and therefore that's

accelerated. But for the most part, it's mostly the effects on height, and a disproportion may occur because spine growth and limb growth are differentially regulated in the presence of when the growth plates are closing. So it is possible that that might lead to disproportion more than anything, but there could be some deformity maybe in this condition uniquely, I think is a concern.

DR. LOW WANG: Okay. Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Thank you. So --

DR. LOW WANG: Could you please state your name for the record?

MS. ROBOTTI: Suzanne Robotti. Thank you. Since flare-ups are not directly correlated to HO increase, at least not on a 1-to-1 basis, it' not at all clear. I'm concerned about treating them so aggressively. And this could just be my lack of a medical background, but higher drug dosing generally increases side effect risks, and without a clear benefit to it, I'm not comfortable with what I heard as the explanation. Those doctors

with much deeper knowledge than mine can clarify that if they want to with me.

I also wonder how well the drug is tolerated. In Study 301, the dropout rate was pretty significant; 12 dropped for adverse events; 31 withdrew consent; 15 others dropped out because of other. So there's some reason to be dropping out, and it was mentioned travel is difficult, and challenging, and risky, but that's a lot of dropout.

And nobody here has mentioned -- or at least I didn't hear it -- the side effect of vertebrae bone strength, BMC or BMD with a higher onset of vertebral fractures, which I would have to think is a confounding factor as HO progresses, so a lot of questions. Thank you.

DR. LOW WANG: Great. Thank you.

I'd like to invite Ipsen to address some of these concerns that were raised by the panel members.

DR. STRAHS: Thank you. Andrew Strahs, Ipsen. I just wanted to make a clarification based

on Dr. Greevy's comment. In the Bayesian analysis, the event is event of new HO volume greater than zero. Those Bayesian analyses do not use information about flare-ups. And I'd like to turn it over to Dr. Marino to comment further on other questions.

DR. MARINO: If I could, I'd like to bring up a slide to address the concerns about the dropout rate. Oh, I'm sorry. I cannot bring that one up, but I can talk to you about the dropout rate in the briefing book, where you were concerned about the significant numbers.

What we have to remember is that table also represents the patients who were continuing on the trial just for safety. Those were the less than 14-year-old patients. We allowed patients to stay on the trial off treatment to continue to follow their growth and safety. So about 30 percent of the patients that we saw who ended the trial early actually did so because they weren't receiving any treatment. They stayed in the trial for some time, and then decided to leave. So it wasn't just about

patients dropping out because they couldn't or did not want to receive the therapy any longer.

In terms of to address some of the concerns about the potential longer term sequelae of the premature closure, and just to address that, what we also saw in the trial was that the closure, when we said premature closure, doesn't mean that the growth plates were completely closed. We caught the PPC for the majority of patients in a partial state and were able to watch the growth after the patients came off therapy.

In fact, in our target population, we did see that about half the patients who had the diagnosis of PPC had reached an adult height within the normal range, and the others were still growing after stopping the palovarotene as well, and that some of the concerns we looked at, even in the long turnover, the 3 or 4 years, were some of the angular deformities we were monitoring, which we didn't see any, as well as the leg length discrepancies. So I hope that gives a little more information.

DR. LOW WANG: Great. Thank you.

Dr. Chrischilles?

DR. CHRISCHILLES: Yes. Hi. Elizabeth or Betsy Chrischilles, University of Iowa. I just wanted to maybe add one more point to the discussion so far, and in preface to that to say that my thoughts have been following along the same pattern that Dr. Yanovski expressed with respect to the flare rate and also with respect to the well-characterized safety profile consistent with other retinoic acid agents that are already on the market.

What I wanted to add to the mix was the statement by the sponsor, of their intent to host a post-approval registry. It was something that was touched on only briefly in the presentations, so it's not quite clear what all would be monitored and how it would be monitored in that registry, but I find that a reassuring way to really keep track of these safety concerns that we really just don't have the adequate power to really quantify. Thanks.

DR. LOW WANG: Great. Thank you.

Dr. Applegate?

DR. APPLEGATE: Kimberly Applegate. I don't know if it was addressed or not that premature physeal closures could be partial or complete, and they can cause significant deformity if the bone crosses the growth plate in some areas. I think the data that was presented said 6 percent of the subjects had PPC, so they would need to be followed. Again, it can be diagnosed earlier if we have MRI, which is the gold standard. It can be a fast MR, but that's the way to go; so yes. Then the normal way to treat it is surgery, but obviously that can't be done. Thank you.

DR. LOW WANG: I don't see any other raised hands, so maybe I will make a few comments, and then see if there are any other last comments.

I agree with almost all of what's been said and appreciate their critical comments from the panel members. I also appreciate the FDA and the sponsor's comments. I am concerned about the possible higher incidence of flare-ups, but even

though there isn't a strong correlation with new heterotopic ossification, as was presented, they can still cause significant morbidity and reduced quality of life. So it's possible that this higher incidence is actually related to the known side effects of the retinoid class of medications, but it's not really clear from the data that were presented.

So in terms of other safety concerns, addressing the second part of this question, I have two concerns. These have been mentioned already, but I wanted to emphasize the second because I haven't heard other panel members mention this. One is the premature physeal closure in subjects younger than age 14. The other is really the rebound or accelerated new heterotopic ossification formation after discontinuing the study drug. To me, the latter is very concerning and needs to be understood better, and definitely needs to be part of that benefit-risk analysis for patients and families because there are quite likely situations where the medication cannot be continued.

Are there any other comments for this discussion question?

I do see a raised hand by Dr. Weber.

DR. WEBER: This is Tom Weber. I guess to the question, I think one of the panelists brought about the bone question, about fractures and decreased bone mineral content, and looked at table 23, which went over some of that data, and retrospectively assessed by the sponsor, which did show perhaps some potential concerns for a decrease in bone mineral content, vertebral strength; and knowing the track record of retinoids, that would be something -- I know the question or the issue of a post-approval registry was raised, but that would be one of the things obviously to capture because of the potential concerns. So there are some issues that need to be addressed, particularly when it comes to long-term therapy that we need to capture and understand better.

DR. LOW WANG: Great. Thank you.

If there are no other comments, let me try to summarize, and as with the previous summary,

please, all questions and comments are appreciated.

In answer to the specific question regarding the flare-up events in subjects treated with the proposed palovarotene dosing regimen and the relevance to benefit-risk considerations, the panel was reassured by the lack of strong correlation between flare-ups and new heterotopic ossification as presented by the FDA, but this also raised the concern about treating at a younger age, and then relatively aggressive treatment with chronic dosing and flare-up dosing.

Then with regard to whether the panel has concerns about other safety issues included in the meeting materials, et cetera, there were concerns raised about the premature physeal closure for those younger than age 14, vertebral fractures, and then also concerns about decreased bone mineral content, and the need for closer follow-up and long-term follow-up was raised by several panel members.

Are there any other comments about this summary?

Go ahead, Dr. Greevy.

DR. GREEVY: Robert Greevy, Vanderbilt. You also brought up the point of a really interesting analysis that happened of the on drug, stopping drug, restarting drug having that rebound effect. Do we have the numbers on that? Can I see those numbers again? I hadn't thought about it in that light of thinking of that as a rebound.

DR. LOW WANG: Yes. I don't know if FDA would like to present that. I remember which slide it was in the Ipsen presentation, slide 60 and 61.

(Pause.)

DR. LOW WANG: I'd like to invite Ipsen, and if you could throw up slide 60 and 61, that would be terrific. I actually don't know if that's possible. Oh, there you go.

Go ahead.

DR. MARINO: Are we unmuted?

DR. LOW WANG: Yes, I can hear you now.

DR. MARINO: Okay. Great.

We are presenting slide 60, and we have 61 if you'd like to see it next. Here, what we're

looking at is the ITT, which is on treatment, and then the entire on treatment and off treatment, the entire study, and on the right is on treatment, followed by off treatment, followed by on treatment.

What we're seeing, or what we've interpreted the data to tell us, is that it's not necessarily a rebound in the off treatment necessarily, but their HO goes back to what was expected and seen in the natural history study. So I think of a rebound as going beyond what would be normally expected or what would be in an untreated state. So our interpretation of this is that the 20,000 is right around what we saw in the natural history study, which was 20,000, or just about 20,000, that we're looking on the left side of the screen.

DR. LOW WANG: Will you please go to slide 61? I think that actually shows the 17 individuals who are in all three phases.

DR. MARINO: Correct. That is the 17 patients who are the same patients followed throughout. Again, you see the reduction on

treatment and the 29,000 higher than the average in the NHS, but very wide variability given the small subset in these patients.

DR. LOW WANG: Okay.

Are there any other comments from the panel members?

(No response.)

DR. LOW WANG: Alright.

I think what we'll do right now, then, is to take a quick 10-minute break. We'll have the two voting questions after the break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break, and we'll resume at 4:13 Eastern Time.

(Whereupon, at 4:03 p.m., a recess was taken, and meeting resumed at 4:13 p.m.)

DR. LOW WANG: It is now 4:13, so we will now proceed to question 3, which is our first voting question. Commander Bonner will provide the instructions for voting.

CDR BONNER: Thank you, Dr. Low Wang.

LaToya Bonner, DFO. Questions 3 and 4 are voting questions. Voting members will use the Zoom platform to submit their votes for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote.

After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce the voting will begin. A voting window will appear where you can submit your vote. There will be no discussion doing the voting session.

You should select the radio button that is the circular round button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on

the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including the rationale of their vote.

Are there any questions about the voting process before we begin?

(No response.)

CDR BONNER: Since there are no further questions, I will hand the meeting back over to our chair, Dr. Low Wang.

DR. LOW WANG: Question 3, slide 4, it looks like that is up, and let me read the voting question. Question number 3 is, does the evidence from Study 301 of palovarotene's treatment effect show that the drug is effective in patients with fibrodysplasia ossificans progressiva or FOP? Provide the rationale for your vote.

Are there any issues or questions about the wording of the voting question?

I do see a raised hand. Dr. Nason?

DR. NASON: Thank you. Martha Nason. I'm just struggling with the word "show." That's a bit of a vague word to me as far as strength of evidence, and I was just wondering if the FDA had anything they could say about how to interpret that word.

DR. LOW WANG: Dr. Kehoe or other members of the FDA? There you go. Okay. Great.

DR. KEHOE: This is Theresa Kehoe. We are just considering the results of Study 301 here, and in the data that's been presented, whether you believe the drug is effective. I don't know that we thought much about using the word "show."

Does that help?

DR. NASON: Not entirely, but I suppose if it's the best answer, then I'll have to go with that. Thanks.

DR. LOW WANG: Dr. Weber, go ahead.

DR. WEBER: This is Tom Weber. What about revising it to, "show the drug provides adequate effectiveness?" Just a way to adjust the wording,

and there may not be a way to do it.

DR. KEHOE: Well, ultimately, the question is what are your conclusions about the drug's effectiveness as seen in Study 301?

DR. LOW WANG: Dr. Coffey?

DR. COFFEY: Chris Coffey. My question maybe follows a similar line. When you say our thoughts on the effectiveness from Study 301 in terms of effectiveness and kind of an absolute scale compared to any other clinical trial, or effectiveness given the results of the study in the context of it being a rare disease?

DR. YANOFF: Hi, everybody. This is Lisa Yanoff. I think, informally, we want to know do you think this is a positive study, period, end; not in the context of this or that. I think you may be overthinking a bit.

Could you provide some clarification on -- Dr. Nason, what is your concern about the word "show"?

DR. NASON: I guess I just don't know how much evidence to take it with. Certainly, if it

said "prove," I would certainly know what to answer, but "show" is weaker, so I don't know if I should interpret it as I am convinced versus do I think, probably, because there's a difference.

DR. YANOFF: You have to make a yes or no call --

DR. NASON: Right.

DR. YANOFF: -- and we'll leave it to you on how convinced do you feel you need to be to make a yes or no call. So there is no gradation here. Does the study show it's effective or does it not.

DR. NASON: Alright. I'll try. Thanks.

DR. YANOFF: Yes. Unfortunately, that's the decision that FDA is faced with, a yes or no decision, so we hope you can help. Keep in mind that your comments are often more important to us than your vote, so maybe don't worry so much about your vote, Dr. Nason, but just provide the best you can with your vote, and provide your rationale, and that will be very helpful to us.

DR. LOW WANG: Thank you, Dr. Yanoff.

There's also a question from Dr. Applegate.

DR. APPLEGATE: Kimberly. This may be overthinking it. The evidence is looking at Study 301, but also, in my mind, we're comparing what we were given, which is also the natural history study.

DR. YANOFF: When we say Study 301, we mean the study with its accompanying comparator group.

DR. APPLEGATE: Okay. Thank you. That's all I need to know.

DR. LOW WANG: Great. Thank you.

Seeing no further questions or comments concerning the wording of the question, I'll turn it back to Commander Bonner so that we can begin the voting on question 3.

CDR BONNER: LaTonya Bonner. We will now move the non-voting participants to the breakout room.

(Voting.)

CDR BONNER: LaToya Bonner, DFO. Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. LOW WANG: Great. Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also --

CDR BONNER: Just for a second, Dr. Low Wang, I'll go ahead --

DR. LOW WANG: Oh, sorry.

CDR BONNER: -- and give the voting results live for the record. Sorry about that.

For the record, LaToya Bonner. Due to technical difficulties, we had to receive one vote via email, so when it comes to the voting results, we have 10 yeses, 4 noes, and zero abstentions.

I will now turn the meeting back over to our chair.

Dr. Low Wang?

DR. LOW WANG: Great. Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record, and you may also include the rationale for your vote.

Let's start with Dr. Chaikhoutdinov.

DR. CHAIKHOUTDINOV: I am Dr. Chaikhoutdinov. I voted yes, and the reason is because we don't have any medication for the treatment of this very disabling disease. Secondly, it showed some effectiveness. It's, of course, not perfect. Third, it's better to have a short person than a person with immobility, even if it has premature physeal closure. Thank you.

DR. LOW WANG: Thank you.

Dr. Chrischilles?

DR. CHRISCHILLES: Yes. This is Betsy Chrischilles. I voted yes, and my reasons for doing so were, first, the consistency of findings across many appropriate sensitivity analyses, including the somewhat natural experiment afforded by the treatment interruption, which allowed some individuals to be observed before the interruption while on treatment, during the interruption of treatment, and when they resumed treatment thereafter.

My second reason was the quality of the external control group, in my opinion, afforded by

its use of the same clinical centers; the same imaging reading center; the same standardized disease progression outcome endpoint; the almost concurrent time periods for the study; and the ability to adjust the results for baseline differences. So those were my reasons for voting yes.

DR. LOW WANG: Thank you.

Please state your name and your vote into the record, Dr. Blaha?

DR. BLAHA: Yes. Hi. Michael Blaha. I voted no on this one, and I tried to factor out, a bit to the extent that I could, the rareness of the disease, and tried to look at the body of evidence and really determine if this provided persuasive statistical and clinical trial evidence to me, and that there was a benefit for these patients that was beyond a reasonable doubt in my mind, and I couldn't come to that conclusion, based on these data that I saw today.

I felt we emphasized maybe a little bit too much today in the discussion perhaps some of the

statistical features, some of the things that we could try to correct, so to speak, by switching to different modeling. I was more concerned about the things we can't correct; for example, the comparison to an external control group, the natural history control group; the fact that patients are moving in and out of studies; and a relatively small sample size that we're looking at here.

I actually did find, for example, the propensity matched analysis somewhat persuasive. I liked the analysis of the patients who were on and off, and on the drug again, then I reminded myself that it really was talking about less than 80 patients, or maybe 17 patients, in the latter analysis, and I just didn't think that reached a level of being convincing for helping patients.

I did look to try to see if there's any symptomatic benefit for patients or something that I could hang my hat on, where these patients were really clearly given a benefit, and I had to resort to an imaging endpoint. While part of the disease

process, I just wasn't a hundred percent convinced that that imaging endpoint with a certain amount of calcification -- of course we have experiences of calcification in other disorders, too -- was enough for me to say that there was an unequivocal benefit for these patients.

So I would say that it would be a tragedy if this wasn't studied further. I think this is such a great opportunity here to take what we've learned and really study this in a rigorous way, but that's what led to me voting no in this case.

DR. LOW WANG: Great. Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I voted yes, the drug is effective. I don't know how effective. I've seen enough consistency between the analyses to lead me to believe that some people with FOP will get some benefit. My understanding of the disease leads me to believe that small increments can be important to patients.

Every FDA advisory committee I have ever sat on -- and it's been a few -- we, the committee,

have complained about the poor data, and we will continue being asked to make difficult decisions as long as we accept data we don't feel is clear. I voted against many drugs solely because the data just wasn't clear enough, but I don't have the stomach for that with this drug and with this population. There is a small window because the damage accumulates, and small differences can make big differences, so I voted yes.

DR. LOW WANG: Thank you.

Dr. Weber?

DR. WEBER: Yes. This is Tom Weber. I voted yes. Although the post hoc analysis obviously is inherently flawed and there are confounders that we can't adjust for, I do think that the overall totality and summary of the data do support adequate effectiveness in reducing the primary endpoint in patients with FOP.

I do think the endpoint is appropriate based on the pathophysiology of the disorder and the association with specific outcomes in terms of joint contractures, as well as patient-reported

outcomes, and I'm reassured by the independent analyses and, as was previously mentioned, the sensitivity analyses, which showed a consistent picture, at least directionally, and similar amount, so that's why I voted yes.

DR. LOW WANG: Thank you.

Next on the list is me. My name is Cecilia Low Wang, and I voted yes. So despite problems, as has been mentioned, with post hoc analyses, in general, and the fact that these were performed after the data were unblinded, I felt that the post hoc analyses were appropriate in this instance, and with propensity matching and with trying to account for confounding factors, et cetera, the results were convincing and consistent as performed by the sponsor, and especially because these were confirmed by the FDA as well. In terms of the new heterotopic ossification, I was convinced about that efficacy endpoint, especially since it's thought to correlate well with functional assessments.

Let me move on to the next person.

Dr. Applegate?

DR. APPLEGATE: Yes. Thank you. Kimberly Applegate. I also voted yes, and I won't repeat what others have already said very eloquently. No study is perfect, and we're weighing benefit-risk. What I would like to see is that all of these patients, since there aren't that many, participate in a registry like any child in a cancer registry. That would be my big ask, so with that, thank you.

DR. LOW WANG: Thank you.

Dr. Wang?

DR. WANG: Thanks. Thomas Wang, and I voted yes. I voted yes despite the clear imperfections in the body of evidence that we have. In fact, I can't really remember the last time that I have voted in favor of something where the primary endpoint was not met. In this case, though, I felt that the evidence that the prespecified analysis was so flawed as to be biased consistently against finding a positive result, that I had to rely more on the post hoc analyses than I ever would and normally do so, and in that sense felt that the

consistency and totality of the analyses conducted, not just by the sponsor but also by the FDA, and in the sense that the selection of the post hoc analyses were appropriate to address the concerns about the prespecified analyses, led me to this vote. Thank you.

DR. LOW WANG: Thank you.

Next is Dr. Gerhard.

DR. GERHARD: Tobias Gerhard. I voted yes. In the context of the rare disabling and progressive disease with no approved treatment option on the market, the data generated by Study 301 exceeds, in my opinion, the threshold necessary to demonstrate efficacy.

The prespecified analysis approach I believe was quite clearly flawed, and thus justifying looking at post hoc analyses, which obviously is generally a red flag. But given that the post hoc analyses, both from the sponsor and from FDA, were consistent and convincing, I was willing to consider these. On the side of the external control group, I think while clearly not optimal as

an approach, the external control group was quite high quality and sufficient to make these inferences on efficacy in this context.

DR. LOW WANG: Thank you.

Dr. Yanovski?

DR. YANOVSKI: Jack Yanovski. I voted no for basically the same reasons as Dr. Blaha mentioned. There were just so many things about the experiment that left me unsatisfied. That's not to say that I don't believe that there might well be significant benefit from this approach, but I think that there's a lot more that needs to be done before I would be convinced.

DR. LOW WANG: Thank you.

Dr. Greevy?

DR. GREEVY: Robert Greevy. I voted yes. I see this data as not being at the level of a randomized-controlled trial, but also not being at the level of a pure observational study. It's sort of in-between, where it was part of an experiment. But we don't have any benefits of randomization, but we do have the ability to adjust for some

observed covariates, do a bunch of sensitivity analyses, and have measures taken under experimental conditions, in particular the HO volume, which I thought was a really nice outcome. I think it had a chance to have power and had a nice association with functional outcomes.

That said, the effect range, even by these analyses, is observed around 10,000 cubic millimeters of mercury, and could be as high as 20, and could be as small as in the hundreds. So if I was going for the threshold of trying to rule out small effect sizes, then it wouldn't have met that threshold. But given the circumstances of this disease, rare population, severely debilitating disease, and no other treatment available, I had a lower threshold for being persuaded.

DR. LOW WANG: Thank you.

Dr. Coffey?

DR. COFFEY: Yes. Chris Coffey. I voted no mostly because as the question was worded, it was to assess the effectiveness of the drug as shown in this study. I think, as has been raised, the

concerns for post hoc analyses, analyses that were done after unblinding, exist for good reasons. Even though the analyses that were presented were convincing, the medical literature is filled with examples of studies with similar positive results, that when followed up in a randomized clinical trial did not hold up because of unmeasured biases or unmeasured confounders in the studies.

So because of that, I don't feel that it meets the typical standard for effectiveness, which was mostly the way the question was worded. Had the question been, does it meet a standard of effectiveness adequate, given the rare disease spectrum, I would have probably voted differently. Thank you.

DR. LOW WANG: Thank you.

Dr. Jones?

DR. JONES: I voted yes, marginally.

DR. LOW WANG: Can you please state your name and your vote?

DR. JONES: Oh, sorry. Elizabeth Jones. Yes. Sorry. I voted yes, and I was right on the

margin. I think the effectiveness is very small. This is very problematic. The disease seems to have a considerable variability. There's a short duration of the study, and all the imperfections that we mentioned with the surrogate measure and lack of placebo. I did have a lot of concerns about the analysis. I finally decided, based on the post hoc analysis, even given that there are problems doing that, that I was convinced that there was a small benefit, so ultimately I voted yes. Thank you.

DR. LOW WANG: Thank you.

And last is Dr. Nason.

DR. NASON: Thanks. Martha Nason. I voted no. As was apparent from my question beforehand, I struggled with the word "show," and I decided to think of it as show conclusively for myself, and I do not think that the evidence here, given all the open questions and the flaws in the analysis and the design, show conclusively. There's just too many open issues.

I do agree the prespecified analysis was

flawed, and therefore the post hoc analyses were really the only choice and appropriate in that sense; however, I don't think because of that, we can really lower the standard of burden of evidence too much just because there was a bad choice initially. So in a sense, there's a bit of a higher bar, to me, given that it was post hoc.

Certainly, as Dr. Blaha said, I believe this should absolutely be studied further. I'm optimistic that it works. I hope it works. I think it probably does work. I just don't think we were able to see evidence today that really was convincing or conclusive. Thanks.

DR. LOW WANG: Great. Thank you.

I think all of the panel members have stated their votes and their rationale, so let me summarize. We had 10 panel members who voted yes and mentioned the fact that FOP is very rare. It's debilitating and progressive, and there are no other treatments available, and that the evidence was convincing for treatment effect after interruption. So actually that start/stop/start

data was convincing; the quality of the control group, as well as the consistency of the analyses by the sponsor and the FDA, and the appropriateness of this endpoint of new heterotopic ossification. Among those who voted yes, the need for long-term follow-up was mentioned and the fact that the vote was definitely affected by the fact that this is such a rare condition and so severe.

So four panel members voted no and were concerned that aside from the rareness of the condition, the body of evidence was really not strong enough to show efficacy. There are statistical and design issues, including a lack of a placebo arm. There was no symptomatic improvement, and this imaging endpoint wasn't enough, and this drug should be further studied and that more data were needed.

Now we will move on to question 4, which is our last voting question. I'll read the question first, and then, again, pause to see if there are any questions about the wording before we open up the vote.

Voting question 4, do the benefits of palovarotene outweigh its risks for the treatment of patients with FOP? If you voted yes, please provide the rationale for your vote, and if you voted no, provide the rationale for your vote and provide recommendations for additional data that may support a conclusion that the benefits outweigh the risks.

Are there any specific questions about the wording of the voting question?

(No response.)

DR. LOW WANG: I don't see any questions or comments about the wording, so now we'll begin the voting for question 4, and I'll turn it back to Commander Bonner.

CDR BONNER: Thank you, Dr. Low Wang.

We will now move non-voting participants to the breakout room.

(Voting.)

CDR BONNER: Thank you for your patience. LaToya Bonner. The voting has closed and is now complete. The voting results will be displayed.

(Pause.)

CDR BONNER: This is LaToya Bonner, DFO. For the record, for question number 4, 11 yeses and 3 noes. We had to retrieve one vote from the email due to technical difficulties.

Now, I will turn the meeting back over to our chair.

Dr. Low Wang?

DR. LOW WANG: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also include the rationale for your vote.

We'll start with Dr. Chaikhoutdinov.

DR. CHAIKHOUTDINOV: This is Dr. Marat Chaikhoutdinov. I vote yes because the medication showed benefits and outweigh benefits against a risk of complications. The most common complication, as was noted, are dry lips, dry skin, both patients with FOP has this condition all the time. The medication is very important during puberty and also during, particularly for girls,

menarche.

As my observation, my daughter became very disabled. She was able to go to school. She completed college. She got a college degree, and then when she's 13, menarche came, and she became disabled, and now she's on a ventilator. She has family hypertension and all these kinds of complications. From the beginning of this trial, we also tried Accutane [indiscernible]. Accutane was one of the medications that was recommended for FOP, and we tried, but I don't know how that was effective, but we did it.

She was doing fine before menarche. She had some problems, but not significant. This medication might give, and I believe it can give options for families to go through and try this medication. The complications are very mild, I believe. It's possible to be managed with the dose reduction, which they did it, and then basically the patients were doing ok. Interruption could be also done. That's my opinion. Thank you.

DR. LOW WANG: Thank you.

My name is Cecilia Low Wang, and I voted yes. So despite the risks for premature physeal closure and potential increases in flare-ups and vertebral fractures, I believe that the potential benefits of the study drug to reduce new heterotopic ossification outweigh those risks.

I felt the open public hearing comments were incredibly compelling. We really have no other alternatives that might alter this disease course, but this drug might. So ideally, I'd like to have a longer term follow-up study for Study 301 and a placebo-controlled trial. But given the rare nature and severity of this debilitating condition, I feel the benefits outweigh the risks.

I do feel that it's incredibly important to mitigate the risks through careful selection of patients and in-depth risk-benefit discussion with the patient and family about the potential risks of that premature physeal closure; the potential increases in flare-ups; potential increases in vertebral fractures, as well as the other side effects; and lastly, that increase in the new

heterotopic ossification seen when the drug is interrupted.

Let's move on to the next panel member, Dr. Jones.

DR. JONES: Elizabeth Jones. I voted yes. Although I believe the benefit is small, the risks that we heard about I think can be managed carefully, and the patient's going to require a lot of additional follow-up, and testing, and monitoring, but I think you can screen for premature physeal plate closure with MR, and Dr. Applegate has mentioned that, and monitor bone mineral density, and try to moderate the various adverse effects. I think those things can be managed, so even though the benefit is small, I ultimately thought it had a positive ratio.

DR. LOW WANG: Thank you.

Dr. Chrischilles?

DR. CHRISCHILLES: Yes. Elizabeth Chrischilles. I voted yes, and I concluded that the benefits do outweigh the risks along several different lines of thinking that helped me come to

that conclusion. First, I think there's reason to suspect that the apparent increase in flare is either A, not real and a result of under-ascertainment in the natural history study, and/or B, real but not really meaningful in terms of disease progression.

A second consideration is that the safety profile for the drug is largely consistent with other approved retinoids and manageable with black boxed warnings for PPC and pregnancy. Third, the special pediatric issue of PPC can and should be addressed as part of the individualized benefit-risk decision making by patients and their providers. Fourthly, the point value of delaying or slowing the progress of this profoundly painful, intrusive, and unrelenting rare disease is clear. And lastly, finally, a post-approval registry is planned by the sponsor and will be valuable for quantifying the safety issues over time. Thank you.

DR. LOW WANG: Great. Thank you.

Ms. Robotti?

MS. ROBOTTI: Thanks. This is Suzanne Robotti. I voted yes. Our committee read and saw a lot of emotional testimony, and I understand it cannot be overestimated how horrific HO FOP is and what a toll it takes on the family. But the public testimony focused on how bad HO FOP is, not on how good palovarotene is.

Wanting a drug to work does not mean it will work, and it can harm. We don't have clear data that this drug works, and the side effects are significant. A hundred percent of participants had significant side effects. Fifty percent had dropout rates during the trial. The endpoints changed, and the new ones reset after it was unblinded, and the FOP flare-ups were a higher number than anticipated.

All that being said, I'm swayed by the hopeful data interpretation that the sponsor has offered and the FDA seems to be supporting. I'm swayed by the immediate need. This is a retinoid, and the many significant adverse events that retinoids can cause are already well known.

I heard that the sponsor is planning a registry. I don't believe that registries belong with the pharmaceutical company. Registries are an important data source, too important to be housed where there is such a clear conflict of interest in sharing data. I ask the FDA to enter this drug into the iPLEDGE program with HO FOP listed as an exception. Once the drug is approved, even if the indication is only for rare disease, doctors can try using it for something else.

We are supporting this drug based on some assumptions. I ask the FDA to please require confirmatory trials, and please require that they be done on a reasonable schedule with clear deadlines and clear endpoints. Thank you.

DR. LOW WANG: Thank you.

Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. I voted yes as well. I think there are clearly significant safety concerns with this drug, but given the severity of the disease, the benefit I think pretty clearly outweighs the risks in this decision. As

we've seen, patients and their caregivers with FOP are incredibly involved in their care and I think will be able to discuss these difficult trade-offs with their doctors.

I think it will be important to have a robust registry program because there is clearly much to learn in the clinical management of the drug in different populations and clinical contexts. So I think that will be important. As one of these speakers in the public comment period said, I think this is imperfect but important progress for patients with FOP.

DR. LOW WANG: Great. Thank you.

Next we have Dr. Yanovski.

DR. YANOVSKI: Jack Yanovski. I voted no basically because if I couldn't convince myself that the studies proved benefit, I can't assume that any risk would be acceptable. That doesn't mean that I don't believe that there's a possibility for this drug to be very helpful in the future; it just needs more conclusive data. I think those could come in a variety of sorts.

It's clear that the perfect RCT placebo control is not going to be done in this rare disease, but there are other alternatives. Even among those that are already recruited and using the medicine in the studies, there could be a placebo-controlled withdrawal phase, for instance.

There also are significant questions, for me anyway, about what's the right age at which this drug should be commenced. What is the severity of the disorder? At which point should it be commenced? We have no data as to how the relative progression occurs. We know that the most severe patients tend to get more severe. So should this drug not be limited to people who have the most severe consequences at an early age or whenever they appear as getting worse rapidly? I really don't know.

I think there are a lot of unknown questions in the study design that up to now have not been adequate for me to have a good sense as to who should be treated, when they should be treated, and if they should be treated. Thank you.

DR. LOW WANG: Thank you.

Dr. Wang?

DR. WANG: Thanks. This is Thomas Wang. I voted yes. I voted yes despite the imperfect body of data because of the benefits that were discussed in the last question. There are risks. As noted previously, I think the risks are largely predictable, based on the drug and related drugs. Overall, I think balancing the benefits against the risks relies on taking into account the context, and context has been described as one of a debilitating and progressive disease. I was also moved by the testimony of the families, and the caregivers, and patients who've been really impacted by this disease.

I'd also, lastly, like to acknowledge the sponsor. The sponsor has contributed to the knowledge of this rare disease to the studies that have been done since 2014, and I would hope that if the drug is ultimately approved, that the sponsor will continue contributing to that knowledge in the ways that have also been discussed. Thank you.

DR. LOW WANG: Thank you.

Next is Dr. Weber.

DR. WEBER: This is Tom Weber. I voted yes. The severity and inexorable progression of this devastating disease with early mortality does warrant the availability of palovarotene to patients with FOP, based on the risk-benefit assessment. Although the benefit may be small, I do think that the risks are acceptable and can be managed.

The issue with premature physeal closure and decreased height, I was reassured by the data that the target, or the approved population, seemed to be less of a concern based on the data that was presented today in that regard. I'm also reassured that the target population of providers will be prescribing this and have fundamental knowledge in this disorder and in the pediatric endocrinologists, rheumatologists, and bone specialists, and will be able to apply that knowledge in an appropriate way in risk-benefit assessment discussions with patients and their

families in terms of the drug.

Again, I also agree with the sponsor and I applaud them for starting a registry. I think gathering the safety outcomes are important, and I would also recommend that gathering data with regards to dose reductions and effects on outcomes, including patient-reported outcomes, are going to be important to confirm the positive impact of the drug on this disease.

DR. LOW WANG: Great. Thank you.

Dr. Coffey?

DR. COFFEY: Hi. Chris Coffey. I voted yes. While I do have concerns about how convincing the data on benefit is, and there are concerns about risks, I do feel that based on what we know, at least as of today, the benefits do outweigh the risks. In particular, as noted in one of the prior presentations, and I think we iterated during the open public hearing, any reduction here would be meaningful, so I think that kind of bar for the benefit-risk ratio here is not that hard a barrier to cross if there's any suggestion of benefit

relative to controlled risk. Thanks.

DR. LOW WANG: Thank you.

Next is Dr. Applegate.

DR. APPLEGATE: Yes. Kimberly Applegate. I voted yes, and I agree with what's been said prior in terms of the benefit-risk. There's, in my mind, more benefit than the described risk, although we know it's imperfect data that's been presented. I think the patients and their surrogates presented very compelling information to us.

I think it comes down to an ethical assessment or a judgment of thinking about justification of the benefit for something that we don't know fully what is going to happen with the risks and giving that option to this patient population. However, again, I will really push for having, what others have said, registries so that we can know as much as we can without burdening people, with data capture, but really understanding what happens to this patient population. It's a small population, so we want to know what happens, and also perhaps get better CT methodologies going

forward with auto segmentation to understand those volumes better. I'll just make a plea for that and other points that have already been made. Thank you.

DR. LOW WANG: Thank you.

Just a reminder that if you voted no, please provide provide some recommendations for additional data that might support a conclusion that the benefits outweigh the risks.

Next is Dr. Blaha.

DR. BLAHA: Yes. Hi. Michael Blaha, and I voted no, which probably isn't surprising and followed the last question. I also thought that Study 301 didn't provide enough persuasive evidence for me to be certain that this was an effective therapy.

My vote isn't entirely out of concern of adverse effects, although I do think there's potential for adverse effects here, as others have discussed. It's just as much, if not more, just a concern about the the database for efficacy, and I'm just not sold on that. By all counts, in

almost any other scenario, I think we'd all consider this to be data that justifies a pivotal trial, rather than this being the pivotal data for therapy in a disease state. Although we want it to work, it's just so hard for me to say that this works, based on the data that I'm seeing with all the detail discussion we had about trying to find that benefit.

So I just hope this isn't the last word on this therapy as far as high-quality data. I know once a broad label is granted, it's harder to do studies, but hopefully in creative ways, we can think of doing studies to try to show some patient-centered outcome improvement, and symptomatic improvement, and one of these other scales that's validated in this disease state, and show benefit on that, and show benefit on disability, or hospitalization, or something that matters to patients, even if I guess that's against historical controls. And something beyond just saying it reduces the imaging evidence of calcification would give me a lot more confidence.

So I think, and I'm sure the company will be anxious to do that, to try to look beyond an imaging endpoint, and show at some point something persuasive that does something for patients is what I would ask for. Thank you.

DR. LOW WANG: Thank you.

Next is Dr. Greevy.

DR. GREEVY: Robert Greevy. I voted yes. Interestingly, Dr. Blaha's comments perfectly captured my feelings even though he voted opposite as me; that under different circumstances, this would be the trial that we looked at, or the evidence that we looked at, that made us go, "Oh, wow. Yes. Please do the next study," as opposed to, "Yes, we want to approve this medication."

I think I, along with a lot of us, am weighing the risk-benefit and delaying access to the medication in order to gather more evidence. And certainly my sense of saying yes is very conditional, as many people have stated, under the assumption that more evidence is going to be collected.

Dr. Robotti's comments really resonated with me as well, that just simply creating a registry possibly under the sponsor's control that's only collecting adverse events really feels insufficient in this case. One of the things that Dr. Cecilia Wang brought up that I just want to circle back to again is the data that we were presented did show this possible rebound effect; that by accident, we got this data that ended up being quite compelling, and convincing us that the medicine was really working in these 17 people, but also opened up that question of what happens if you stop the medication for a while?

So being able to assess the practical efficacy in a population that might not be a hundred percent compliant, or not as compliant as an experimental population, is going to be really important. I just want to emphasize the magnitude of that rebound effect, a big confidence interval, because there's only 17 people, but they were close to 30,000 cubic millimeters of mercury when stopping the drug. That's 10,000 more than the

people that's standard and not on the medication. That's on par with our treatment effect.

So the question of that rebound effect I think really is something that, along with the other possible side effects, needs to be addressed if the drug is allowed to go forward. Thank you.

DR. LOW WANG: Thank you.

And Dr. Nason?

DR. NASON: Martha Nason. I voted no. My reasons are very parallel to those that Dr. Blaha and somewhat Dr. Greevy just gave as well. I felt I needed to be consistent with my vote that we did not have sufficient evidence yet of efficacy or effectiveness, so certainly that influenced my vote on this risk-benefit ratio.

I do think further study of the effectiveness will also allow a careful tally of the flare-ups while taking steps to avoid any sort of differential underreporting to really nail that issue down. And as far as delay of access, I certainly am sympathetic to that, and the public commentary was very moving. I agree with all my

colleagues on that. But I would hope maybe that in collecting more data, the company would want to get as many people as much data as they could, and people who were interested could join one way or another the study and kill two birds with one stone in the sense of having some access, but really get that important data we need before it's turned over to a licensed drug and a registry. Thank you.

DR. LOW WANG: Great. Thank you.

I think we've heard from all of the voting members, so let me try to summarize the committee's comments. We had 11 panel members vote yes. The panel was, in general, swayed by the efficacy data versus the risks, which were not felt to outweigh the potential benefits despite acknowledging the imperfections in the data. This is in the context of a very severe disease with inexorable progression.

There are significant safety concerns acknowledged, but it was felt that these could be managed, and the need for close monitoring and long-term follow-up was emphasized. For some panel

members, that yes vote was qualified by the need for stronger efficacy data and the concern about increased heterotopic ossification with medication interruption.

There were three panel members who voted no, and the rationale was that the available data are not sufficient, and that more conclusive and stronger efficacy data are needed, ideally to include functional and possibly quality-of-life endpoints, so more patient-oriented outcomes. There are also concerns about safety expressed, and furthermore, lots of open questions that aren't addressed by the available data, including the right age to start the drug.

So I just wanted to say that I very much appreciate the hard work and preparation by Commander Bonner and the staff at the FDA to plan for and organize this meeting, and I sincerely thank all of the panel members for your diligence, your comments. I thank the sponsor and the FDA for your detailed and thorough presentations, and the individuals who spoke during the open public

hearing, for your important contributions to the meeting, and lastly, to members of the public for attending.

So before we adjourn, are there any last comments from the FDA?

DR. KEHOE: Yes. Can you hear me now?

DR. LOW WANG: Yes.

DR. KEHOE: This is Theresa Kehoe. We'd really like to thank our panel members for the robust discussion today, and we've heard your concerns, and we'll take them back and continue to work on the application. I'd like to thank all our open public hearing speakers and their families for their very important impact and messages today, and to thank the FDA review team for their hard work on the application. Thank you.

Adjournment

DR. LOW WANG: Thank you so much. We will now adjourn the meeting. Thank you.

(Whereupon, at 5:24 p.m., the meeting was adjourned.)