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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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OPEN SESSION
OF THE
JOINT MEETING OF THE PEDIATRIC ADVISORY COMMITTEE (PAC) AND THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

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May 11, 2018
12:00 p.m.

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, MD 20903

PAC MEMBERS:

MARK HUDAK, M.D.	Chair
DANIELLE BOYCE, M.P.H.	Voting Member
MARY CATALETTO, M.D., FAAP	Voting Member
MELODY CUNNINGHAM, M.D.	Voting Member
ROBERT DRACKER, M.D., M.H.A., M.B.A., CPI	Voting Member
PETER HAVENS, M.D., M.S.	Voting Member
MICHAEL WHITE, M.D., Ph.D., FACC, FAAP	Voting Member
RONALD PORTMAN, M.D., FAAP	Non-Voting Member

EMDAC MEMBERS:

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JAMES D. NEATON, Ph.D.	Voting Member
THOMAS J. WEBER, M.D.	Voting Member
PETER W.F. WILSON, M.D.	Voting Member

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

JATINDER BHATIA, M.D., FAAP	Temporary Voting Member
DAVID COOKE, M.D.	Temporary Voting Member
KATHLEEN NEVILLE, M.D., M.S., FAAP, FCCP	Temporary Voting Member
JOSHUA PAHYS, M.D.	Temporary Voting Member
HAN PHAN, M.D.	Temporary Voting Member
MARIEANN R. BRILL, M.B.A., RAC, MT(ASCP)	Designated Federal Officer

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FDA PARTICIPANTS:

SMITA B. ABRAHAM, M.D.
Clinical Reviewer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

MARY THANH HAI, M.D.
Acting Director, Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

DONNA L. SNYDER, M.D., FAAP
Pediatric Ethicist/Team Lead
Office of Pediatric Therapeutics
Office of the Commissioner

MARINA ZEMSKOVA, M.D.
Clinical Team Leader
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

SUSAN McCUNE, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner

SANDY WALSH
Press Contact

OPEN PUBLIC HEARING SPEAKERS:

KAREN FREEDMAN
Parent

DR. DAVID BLAUSTEIN
Parent

ROSA LUTTRELL
Parent

AMER HAIDER
Founder, Growing Stronger, Supporting Dwarfism

ANTHONY MOSCATO III
Patient

PINCHAS COHEN, M.D.
Leonard Davis School of Gerontology
University of Southern California

RAVI SAVARIRAYAN, M.D.
Murdoch Children's Research Institute
Melbourne, Australia

SETH FRITTS
Global Genes

MORRYS KAISERMANN, M.D., Ph.D.
Parent

JACOB BLAUSTEIN
Patient

CATHLEEN RAGGIO, M.D.

SAMANTHA OZAN
Parent

OLGA MAROHNIC
Parent
Chair, Hispanic Affairs Committee
Little People of America

SARAH CATHERINE CREWS
Parent

AIDEN COCKRELL
Patient

KRISTINE DIGERONIMO
Parent

SHAHZADI MUNIR-ISRAR
Parent

HANK FUCHS, M.D.
President, Research and Development
BioMarin Pharmaceuticals, Inc.

ALECIA COCKRELL
Parent

DENIS BRONNIKOV, Ph.D.
Parent

SATYABRATA JENA
Parent

MICHELLE KRAUS
Advocacy Director, Little People of America

JAMIE HARVEY
Cofounder, MAGIC Foundation for Children's Growth
CEO, International Coalition of Organizations Supporting Endocrine Patients

JILL BLAUSTEIN
Parent

CHANDLER CREWS
Patient

REBEKAH BAILEY
Patient

ESTEFANIA GONZALEZ
Fundación ALPE Acondroplasia

SHARON MOSCATO
Parent

RON ROSENFELD, M.D.
Consultant
BioMarin Pharmaceutical, Inc.

AMANDA TUMBIOLO
Parent

MUNIRA SHAMIM
Parent

LACI EGGERTON
Parent

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M E E T I N G

(12:05 p.m.)

DR. HUDAK: Is this on? Okay. We will get started for the afternoon session. So as a reminder to everybody in the audience, again, the discussion this morning was in closed session and confidential. None of the information specific to the discussion this morning can be raised during this afternoon's session.

As a reminder, nothing went off this morning; you're all in great compliance with the instructions to silence your cell phones, etc., so do that again.

And where is Sandy Walsh? I'm supposed to identify Sandy Walsh as the FDA press contact. Okay. Well, we'll get to that later.

All right, so we will do introductions again this afternoon because the audience may be different. So let me start. Where did we start this morning, the left or the right?

(Off microphone response.)

DR. HUDAK: All right, so let's start on the right and go around the --

DR. PORTMAN: I'm Ron Portman, pediatric nephrologist on the PAC and the Industry Representative.

DR. NEATON: Jim Neaton, a biostatistician from the University of Minnesota on the EMDAC.

DR. BURMAN: Ken Burman. I'm Chief of Endocrinology at

MedStar Washington Hospital Center and professor at Georgetown University.

DR. BLAHA: Hi, my name is Michael Blaha. I'm with the EMDAC. I'm a cardiologist at Johns Hopkins.

DR. BUDNITZ: Dan Budnitz with the EMDAC. I'm a medical officer and epidemiologist with the CDC.

DR. LOW WANG: Cecilia Low Wang. I'm an endocrinologist. I'm an associate professor at the University of Colorado, and I'm a medical safety officer at CPC Clinical Research.

DR. COOKE: I'm David Cooke. I'm an Associate Professor of Pediatrics and Director of the Pediatric Endocrine Clinics at Johns Hopkins.

DR. PAHYS: I'm Josh Pahys. I'm an orthopedic spine surgeon at the Philadelphia Shriners Hospital for Children.

DR. HAVENS: Peter Havens, pediatric infectious diseases, Medical College of Wisconsin, member of the Pediatric Advisory Committee.

DR. CUNNINGHAM: Melody Cunningham, pediatric hematology, oncology, and pediatric palliative care, University of Tennessee, Memphis, and a member of the PAC.

DR. DRACKER: I'm Bob Dracker. I'm a member of the PAC. I'm in pediatrics hematology, oncology, and transfusion medicine, Syracuse.

MS. BOYCE: Danielle Boyce, Patient Representative for PAC.

DR. HUDAK: Mark Hudak. I'm Chair of Pediatrics, University of Florida College of Medicine in Jacksonville and a neonatologist.

MS. BRILL: Marieann Brill. I'm the DFO.

DR. WHITE: Michael White, pediatric cardiologist, vice chair for our IRB at the Ochsner Health System, Ochsner Clinical School, New Orleans, Louisiana, and a member of the PAC.

DR. WILSON: Peter Wilson, EMDAC, endocrinology, preventive cardiology, Emory.

DR. WEBER: Tom Weber, adult endocrinologist, Duke University, Durham, North Carolina, and a member of EMDAC.

DR. EVERETT: Brendan Everett. I'm an adult cardiologist from the Brigham and Women's Hospital and Harvard Medical School in Boston, and I'm a member of EMDAC.

DR. CATALETTO: Mary Cataletto. I'm a pediatric pulmonologist, and I also do ped sleep medicine. I am a member of the PAC.

DR. BHATIA: Jatinder Bhatia. I'm a neonatologist and nutritionist at the Medical College of Georgia, and I'm a temporary voting member for the PAC.

DR. PHAN: Han Phan, pediatric neurology and sleep medicine. I'm a temporary member of the PAC. I'm also a clinical research -- guest researcher for CDC and clinical consultant for CDC.

DR. NEVILLE: I'm Kathleen Neville. I'm a pediatrician and pediatric clinical pharmacologist and Professor of Pediatrics at Arkansas Children's Hospital, and I'm a temporary voting member for the PAC.

DR. SNYDER: I'm Donna Snyder with the FDA Office of Pediatric Therapeutics, and I'm a pediatric ethicist.

DR. ABRAHAM: My name is Smita Abraham. I'm a clinical reviewer for the FDA in the Division of Metabolic and Endocrine Products.

DR. ZEMSKOVA: I'm Marina Zemskova. I'm clinical team leader in the Division of Metabolic and Endocrine Products.

DR. THANH HAI: I'm Mary Thanh Hai, Acting Director, Office of Drug Evaluation II.

DR. HUDAK: Okay, thank you. So a few bookkeeping items here. So just to remind everybody today that, you know, this is one of those meetings where the topic may elicit a variety of opinions from speakers and among audience members, but the goal of this meeting is to have a fair and open forum so that these issues can be discussed and individuals can express their opinions freely without interruption. So as a general reminder to everybody around the table, that speakers will be recognized if you put your name tag up like this, and I'll get around to you, I hope, eventually.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that all the

Committee members take care that their conversations about the topic at hand take place only in the forum of the meeting. We are aware that members of the media may be anxious to speak with FDA about these proceedings; however, FDA will refrain from discussing anything in this meeting until it ends. And so the Committee is reminded to refrain from discussing any meeting topics during the break. And I'll pass now to Marieann who will talk about the conflict of interest.

MS. BRILL: Good afternoon. The Food and Drug Administration is convening today's open session of the joint meeting of the Pediatric Advisory Committee and EMDAC 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 this open session 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 the Advisory Committees' compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 is being provided to participants at this meeting and to the public.

FDA has determined that members and temporary voting members of these Committees 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 Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest or when the interest of a regular Government employee is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from the employee.

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

Today's agenda involves discussion of drug development for treatment of children with achondroplasia. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this open session.

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

With respect to FDA's invited Industry Representative, we would like to disclose that Dr. Portman is participating in this meeting as a non-voting Industry Representative acting on behalf of regulated industry. Dr. Portman's role at this meeting is to represent industry in general and not any particular company. Dr. Portman is employed by Novartis.

Ms. Danielle Boyce is participating as the Patient/Family Representative, which is a voting position.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committees of any financial relationships that they may have regarding the topic that could be affected by the Committees' discussions.

Thank you.

DR. HUDAK: Okay, thank you. All right, so we will proceed to the FDA discussions.

MS. BRILL: No, recognition of service.

DR. HUDAK: Recognition, I'm sorry. Recognition of service. Dr. Susie McCune.

DR. McCUNE: Good afternoon. Good afternoon. Sorry, there we go. And do you have my slides for me? I really appreciate you letting me talk to you for a moment today. Usually, our Pediatric Advisory Committee meeting, when we had this originally scheduled in March of -- March 22nd, we would've done this piece associated with just the Pediatric Advisory Committee Safety second day, but unfortunately, the weather had something else in mind for us. So I really want to thank everyone for their patience and flexibility associated with scheduling this EMDAC/PAC meeting. I really apologize for the fact that we needed to cancel the meeting in March.

But the Advisory Committee meeting was really organized to obtain maximal input from the public and discussion by the AC, and given all of the travel issues associated with the snow or -- well, it really wasn't much snow, but it was lack of airplanes. We postponed the meeting so that really we could optimize the potential for discussion, and as you know, nothing moves terribly quickly in the government, so rescheduling this meeting within a little over a month has really been challenging for all of the PAC logistics members as well as all of the PAC members, and we really appreciate your willingness to travel twice within the month of May for us.

I would also really like to thank the following

individuals for helping and coordinating the meeting with the Division of Metabolic and Endocrine Products, to Dr. Thanh Hai and all of her staff for all the work that they've put into this, as well as all of the staff from the Office of Pediatric Therapeutics, including Marieann Brill, Sheila Reese, Shivana Srivastava -- sorry -- Euneka Joseph, and Amy Odegaard.

I would also just remind everyone, as you've already heard, that the discussion that went on this morning, it was a closed session and should not be discussed this afternoon.

And I'd like to take just a couple of minutes to go through, first, some announcements of Committee members and then do a required announcement of the noncompliance letters that we usually do associated with a Pediatric Advisory Committee meeting. So Kathy, I said I wasn't going to do "next slide," but okay, there we go.

So clearly, being pediatricians, we have to have the cute slide. So we really want to give a heartfelt thank you to the members who are rotating off, and we want to say hello and welcome to two of our new members. Dr. Cnaan is not here with us today, but I just wanted to let folks know that we really appreciate her service, and she is rotating off the Committee. Now I understand why folks had trouble this morning. Okay. The next person, and I'm not going to read these, you can certainly read them for yourself, we have very distinguished members of our Advisory Committee, but we have been very

fortunate to have Dr. White with us since 2013, and I just wanted to give Dr. White a token of our appreciation.

(Applause.)

DR. McCUNE: And we were really kind of afraid yesterday evening when we got the notice that his flight had been cancelled, that once again Dr. Hudak wasn't going to be able to make it to join us, and Dr. Hudak has been on and off the Committee for quite a while. I remember back when I was doing PAC safety presentations when you were on the Committee, but certainly this round, the service on the PAC since 2013, and we really appreciate your chairing and being a part of the PAC for all of this time.

(Applause.)

DR. McCUNE: Okay. And, first, we want to welcome Danielle Boyce, who is our new PAC member and is our Patient Representative, and I can't tell you how important this is for our Committee -- patient and parent input, especially related to pediatric issues, is critically important for us, and we really value her input on the Committee -- and then Dr. Portman, who has joined us from Novartis as the Industry Representative, are the two new members of our Advisory Committee. And I think this is my last slide.

So we are obligated to let you know about potential noncompliance letters. There are 2 noncompliance letters that have been posted for CBER, 28 that have been posted for CDER.

The website lists the sponsor, product, a copy of the noncompliance letter, the sponsor's response, and the status of the PREA requirement. And I just wanted to let you know that since the last PAC meeting when we met, there are no updates; in other words, these are still the same 2 from CBER and 28 from CDER that we presented at the last PAC meeting.

And I believe that's it for me. Thank you.

(Off microphone comment.)

DR. HUDAK: It's good? Okay, thank you. All right, so now we go to the presentations by FDA; we have two. I think Dr. Abraham does double duty and gives a presentation for 20 minutes followed by Dr. Snyder.

DR. ABRAHAM: Good afternoon. My name is Smita Abraham, and I am a clinical reviewer in the Division of Metabolism and Endocrinology Products. On behalf of the review team, I would like to thank all of you for being here today. The objective of our open session this afternoon is to host a robust and interactive program to identify the therapeutic goals of the achondroplasia community.

During my presentation I will provide the clinical background for achondroplasia and also provide a brief regulatory background for drug development at the Food and Drug Administration.

Achondroplasia is the most common form of dwarfism and is an inherited, autosomal dominant, short stature skeletal

dysplasia. Achondroplasia is caused by a gain of function mutation in the fibroblast growth factor 3, or FGFR3 gene, a negative regulator of endochondral bone formation.

Clinical features of achondroplasia include short stature with reported final adult height in women and men of approximately 4 feet; disproportional growth with individuals characteristically having long narrow trunks and shortened extremities, especially in the upper arms and thighs. Similarly, individuals with achondroplasia can have larger heads out of proportion to their body size. And one last characteristic feature is that of short hands and broad fingers exhibiting a trident appearance at birth.

Individuals with achondroplasia are at risk for multiple complications because of their abnormal bone growth. Complications occur in multiple organ systems as is described in this and the following few slides. The most severe complications are usually neurologic in nature and are often a result of the decreased size or diameter of the craniocervical junction and spinal canal. Foramen magnum stenosis can lead to cervicomedullary cord compression, and when symptomatic, this cord compression can result in sleep apnea, disordered respiration, myelopathy, and in 5 to 10% of cases, sudden infant death.

Other neurologic complications, also typically from the altered size of the craniocervical junction and spinal canal,

include internal hydrocephalus, intracranial hypertension, and spinal stenosis.

Musculoskeletal complications can include a thoracolumbar gibbus, which is also described as a wedge deformity in the lower back vertebrae, tibial or lower leg bowing, and joint hyperextensibility and hip flexion contractures. These joint mobility issues can and often lead to the development of spinal stenosis in childhood and adulthood.

While complications can be specific to and only involve one organ system, more commonly, medical complications are a result of one or more organ systems acting together. The musculoskeletal and neurologic impairments of reduced chest circumference with altered function, upper airway obstruction, and cervicomedullary cord compression occurring in combination can result in obstructive sleep apnea or chronic respiratory insufficiency.

Less severe but more common complications that occur in individuals with achondroplasia include recurrent ear infections, conductive hearing loss, speech delay, developmental motor delays, and dental abnormalities.

Age-specific mortality is increased in individuals with achondroplasia. Increased mortality in infants and toddlers is due to sudden death, as described previously, and increased mortality in adults is reported as related to an increased incidence of cardiovascular and neurologic diseases.

Although individuals with achondroplasia encounter many physical complications, the combination of impairment in body structure and function presents challenges in performance of activities of daily living. Specifically, children encounter problems with mobility, self-care, hearing, and the availability of adaptive aids at school to address, for example, use of heavy doors or high doorknobs and inadequate desk sizes. Socialization can also be challenging at all ages. Ultimately, these issues can affect children's performance at school and overall education.

Moving on to a discussion of growth velocity rates in achondroplasia, the table presented here shows birth length and growth velocity data; however, these data represent one population of individuals with achondroplasia and should be considered approximate.

Starting with birth length, although it appears that the mean birth length of term individuals with achondroplasia and those of average stature are similar, the two birth lengths are statistically significantly different. In a separate cohort, not shown here, birth length of individuals with achondroplasia was reported to be 1.6 standard deviations below the mean of average stature infants.

In infants with achondroplasia, the growth velocity is approximately 20 cm per year as compared to their average stature cohorts who grow at approximately 44 cm per year. The

differences in growth rates are apparent throughout childhood with a slightly less dramatic difference between the ages of 2 to 10 years and an increased difference again seen during the pubertal years. Whether or not children with achondroplasia experience a pubertal growth spurt is controversial.

As seen on the previous table, the height gain in children with achondroplasia is particularly limited during infancy and puberty, two periods of rapid linear growth. Also, it is reported that an overall decrease in the fluctuation of the growth rate throughout childhood in individuals with achondroplasia contributes to reduced final adult height.

Height velocity curves highlighting the 5th, 50th, and 95th percentiles from 0 to 16 years of age in children with achondroplasia are represented by the solid black lines compared with data for children of average stature represented by the dotted lines and shaded section, which in the 3- to 16-year-old group, represents the 3rd, 50th, and 97th percentiles of growth. In both boys and girls, the 50th percentile height velocity in achondroplasia is comparable to the 3rd percentile of height velocity in children of average stature.

There is no cure or specific treatment for achondroplasia. Available supportive treatments aim to prevent or treat complications of achondroplasia.

Other therapies specifically aimed to increase height have

been tried. Growth hormone therapy trials have been done; however, no clear long-term treatment benefit has been established, and growth hormone therapy is not approved for achondroplasia in the United States. Surgical limb lengthening is reported to add 15 to 30 cm to standing height. However, use of this procedure is controversial as individuals may need to undergo repeat procedures, experience wound complications, as well complications related to stretching of non-skeletal tissues, including nerves and blood vessels. Last, the cosmetic effect of long legs and short arms might not appeal to some individuals.

I will now provide a brief background of drug development at the FDA.

To be approved for marketing, a drug must be safe and effective for its intended use. Effective is defined as demonstration of substantial evidence. As quoted in the Code of Federal Regulations or C.F.R., "substantial evidence consisting of adequate and well-controlled investigations . . . that the drug product will have the effect it purports or is represented to have under the condition of use prescribed, recommended, or suggested in the proposed labeling." Safety is considered in the context of whether the benefits outweigh the risks.

For product approval, data must support that that the benefits of the product outweigh its risks. Benefit is defined

as a positive impact on how the patient feels, functions, or survives. Being able to describe the clinical benefit is essential to making a decision about the favorability of the benefit-risk profile of a product.

Demonstration of efficacy and safety of a product comes from adequate and well-controlled investigations. These trials adhere to the principles of good clinical practices. Generally, robust trial designs that allow us to achieve a more accurate estimate of efficacy and safety consist of a control group, a randomization procedure of the study participants, choice of an appropriate population, and choice of an appropriate primary efficacy endpoint. The primary efficacy endpoint ideally is a direct measure of how the patient feels, functions, or survives.

Ultimately, the FDA evaluates the benefits and risks for the population, the provider evaluates the benefits and risks for a patient, and the patient evaluates the benefits and risks of drug therapy in terms of their own personal values.

At this time I will present discussion points that we would like the Committee to address with regard to drug development for the treatment of achondroplasia.

Number 1: Considering the various manifestations of complications of abnormal bone growth in achondroplasia, discuss potentially clinically meaningful study endpoints in the development of drug products for achondroplasia.

Number 2: For the potential clinical study endpoints proposed in the discussion of Question 1, discuss whether there is a specific age for which treatment initiation should be considered to most effectively increase height, reduce disproportional growth, and/or decrease the incidence and/or severity of achondroplasia complications. In your discussion, please also comment on whether there is a pediatric, age-specific subpopulation that should receive priority for the investigation of drug treatment.

Number 3: Discuss the design of a clinical trial that will generate robust evaluation of the efficacy and safety of a study drug in the intended population. In your discussion, please consider whether a randomized, placebo-controlled trial is required to allow for such evaluation, and discuss the strengths and limitations of the trial designs proposed.

And last, Number 4: Considering discussion from the first three questions, comment on the required duration of a clinical trial that will allow for an adequate assessment of long-term efficacy and safety of the drug. In your discussion, consider the durations for core, extension, and postmarketing phases of the trial.

Thank you for your attention. This concludes my presentation.

DR. SNYDER: Good afternoon, everyone. I'm Donna Snyder, and I'm with the Office of Pediatric Therapeutics, and I'm a

pediatric ethicist. The purpose of my presentation is to provide information on the ethical principles that guide pediatric research as we discuss programs in achondroplasia.

Here are the topics that I plan to cover during the presentation: the basic ethical framework in pediatrics, low risk and higher risk pathways for pediatric product development, choice of controls in pediatric research, and considerations for studies in achondroplasia.

The basic ethical framework in pediatrics is as follows: Children should only be enrolled if scientific and/or public health objectives cannot be met through enrolling subjects who can consent personally. Absent a prospect of direct clinical benefit, the risks to which children are exposed must be low. Children should not be placed at a disadvantage by being enrolled in a clinical trial. And vulnerable populations unable to consent, including children, should have a suitable proxy to consent for them.

An important concept when considering research in children is the principle of scientific necessity. This states that children should not be enrolled in a clinical trial unless necessary to answer an important scientific or public health question about the health and welfare of children. The practical implication of this is that there needs to be a balance of risk and benefit to determine whether it is appropriate to initiate pediatric studies. The study must be

capable of answering the scientific question. The study must have an appropriate sample size; it may need to include blinding and a control group to answer the question. And, of course, the study must be a public health benefit to children.

The principle of scientific necessity includes a requirement to enroll -- I have to go to another slide. The principle of scientific necessity includes a requirement to enroll adults prior to children unless children are essential to answer the scientific question. In the case of studies in achondroplasia, studies in children are essential because of the many manifestations of achondroplasia that present in childhood.

Additionally, risks in this research should be minimized. Research procedures that are not necessary should be eliminated if they don't contribute to the scientific question.

When an IRB reviews a protocol for potential approval, the IRB is charged with evaluating the risks and benefits against the importance of the knowledge that's expected to be gained as a result of the subject participating in the research. Adults may participate in research solely to contribute to knowledge gained as long as adequately informed of the risk, but for children there are additional protections that limit the amount of risk to which children can be exposed to on the basis of contributing to knowledge alone. These protections are found under 21 C.F.R. 50 subpart (d) in the Federal Regulations.

IRBs must evaluate research in the context of these regulations.

Essentially, research in children can be thought of in terms of research that provides a prospect of direct benefit to children or does not provide benefit. For research that does not provide direct benefit, the risk of participation must be low, either minimal risk, categorized as 21 C.F.R. 50.51, or no more than a minor increase over minimal risk, or 21 C.F.R. 50.53. For situations that constitute a minor increase over minimal risk, the children must have a disorder or condition, and the research or intervention must be reasonably commensurate with expected medical situations. Although the research does not need to directly benefit the child, the research must contribute to generalizable knowledge about the child's disorder or condition.

If a child directly benefits from participation in the research, higher risk can be tolerated. The risk and benefits need to be at least as favorable as any alternative treatments. This research is approved under 21 C.F.R. 50.52 in the Federal Regulations.

For all research conducted in children, permission of a parent or guardian and the assent of the child must be obtained.

This slide includes the criteria from the Federal Regulations I discussed on the previous slide but in the order

that they appear in the Federal Regulations. The first three criteria have been discussed. The fourth criteria is reserved for situations where a research study does not meet the criteria described, is more than a minor increase over minimal risk, and offers no benefit to the child but may be ethical to conduct. Such a study could not be approved by an IRB and would require review by a federal panel.

Now we'll move on to discuss some of the concepts that come into play as we evaluate research under the regulations, the first being direct benefit. Direct benefit in a study refers to the effect of the intervention on the child and whether that intervention improves the health or well-being of the child; for example, providing a drug to treat a disease may result in a direct benefit, but the additional medical care that may be provided as part of the study is not a direct benefit of the research intervention.

For interventions or procedures, whether the procedure is part of clinical care or if the procedure or intervention impact on medical care will also weigh in to whether there's direct benefit to the child.

Direct benefit is based on the structure of the intervention. The dose must be sufficiently large and the duration of therapy of sufficient length to see an effect from the treatment.

And, finally, in considering direct benefit, the level of

evidence needed to make a determination that the child might benefit needs to be considered. For example, for a rare disease that only occurs in children and for which there are no other alternative options, nonclinical data may be sufficient to support direct benefit and to initiate studies in pediatric patients, but for a disease that occurs in both pediatric and adult patients and where there are alternative therapies available for pediatric patients, we might require adult data on efficacy prior to allowing studies in children.

Another important concept is that of minor increase over minimal risk. The concept of minor increase over minimal risk was developed by the National Commission in the late 1970s as part of their report and recommendations on research in children. The Commission defined minimal risk as a risk that is normally encountered in the daily lives of healthy children. Examples such as a physical exam in a doctor's office or a single blood draw through a peripheral needle might be considered to be minimal risk.

The Committee defined minor increase over minimal risk to be a risk that goes slightly beyond the boundaries of minimal risk and poses no significant threat to the child's health or well-being. In situations where the risk is a minor increase over minimal risk, the children must have a disorder or condition that will be studied, so healthy children could not be enrolled. Minor increase over minimal risk is a limit of

risk that a child may be exposed to if there is no direct benefit to participation in the research unless there's a review by a federal panel, as previously mentioned.

When evaluating risk in a protocol, all the interventions and procedures in the protocol need to be evaluated separately to determine if they meet the requirements under subpart (d). This is a concept called component analysis. The concept of component analysis was also supported by the National Commission, and the concept is included in the preamble to the final rule for subpart (d) published in the *Federal Register* in 2013.

The concept is fairly simple. Interventions that may result in a prospect of direct benefit are considered under 21 C.F.R. 50.52, and those that do not result in a prospect of direct benefit, under 21 C.F.R. 50.51 as minimal risk, or no more than a minor increase under minimal risk, under 50.53, unless reviewed by a federal panel.

One of the concerns of not applying component analysis -- this doesn't -- this clicker is very persnickety. One of the concerns of not applying component analysis to all the interventions and procedures in a protocol is that if a component analysis is not applied, we might allow a procedure or intervention in a trial to move forward that exceeds the allowable risk. Examples of procedures that exceed the allowable risk are the use of central lines in the placebo arm

of a study or liver and kidney biopsies for research purposes. A federal panel review would be required if there was an ethical justification for including these procedures in a protocol.

I included this slide to provide some context of the level of evidence required for pediatric studies. Although FDA has defined by statute that two adequate and well-controlled trials are needed to establish effectiveness for therapeutic products, FDA also recognizes that data from one adequate and well-controlled trial may be sufficient in some cases, especially if there are other supporting data and has been flexible in interpreting this statute. This flexibility has been applied when approving products for rare diseases considering that the population for study for these diseases may be limited.

The choice of control group is an important consideration when designing a clinical trial. These considerations are applicable to both adults and children. In general, research subjects in the control arm of a study should receive an effective intervention. However, a placebo or no treatment is acceptable in some circumstances such as when there is no established intervention, or if withholding the intervention would only result in a temporary relief of symptoms or mild discomfort, or if the use of an established comparator would not yield scientifically reliable results and use of placebo would not add any risk or serious or irreversible harm to

subjects.

The choice of control group is an important consideration when designing a clinical trial. These considerations are applicable -- oh, I'm sorry. I already did that one. This slide expands on the choice of control groups. We've already discussed some of the considerations of the placebo control.

If an active treatment control is used, design considerations include whether we expect the experimental treatment to be superior or non-inferior to an existing therapy. Non-inferiority trials often require a larger sample size than superiority trials. In the case of achondroplasia, there are no alternative treatments for comparison. Historical retrospective control might be considered. These study designs are not ideal because of the inherent biases when comparing noncurrent data. The population chosen for comparison may not be representative of the treatment group in a study. Another option is using the patient as their own control, looking for a change from baseline. In some issues, such as growth, which are highly variable over time, establishing a meaningful change from baseline may be difficult. And you may have noticed that somehow we've skipped from one slide to the next, but I decided not to go back because of the problems I'm having with this particular clicker.

So when using placebo controls in pediatrics, we return to the concept of component analysis to evaluate the risk. There

are two types of risk with placebos, the risk of a placebo itself, which is usually minimal unless the placebo needs to be given by injection, in which case the injection weighs into the risk. The second risk is risk of harm from not receiving proven or effective treatment. Both must be no more than a minor increase over minimal risk since patients in the placebo arm do not benefit from study participation. This approach is consistent with ICH-E10 and the Declaration of Helsinki.

Here are some final thoughts on considerations for trials in achondroplasia. Since we are discussing treatment protocols with therapeutic agents, children must benefit from participation in the study. Age may be an important factor in whether the patient benefits from participation.

There should be data to support that the dose used in the study is expected to be effective.

The duration of the study must be sufficiently long to support a prospect of direct benefit.

For studies that include a placebo, the risk associated with a placebo, including placebo injections, must be considered when assessing the risk-benefit of participation in the study.

This concludes my presentation, and thanks for your attention.

DR. HUDAK: All right, thank you, Dr. Abraham and Dr. Snyder.

So we have some time for questions from the Committee for either Dr. Abraham or Dr. Snyder or any other FDA officer who has presented on this matter in general this morning.

Okay, Dr. Havens.

DR. HAVENS: So thank you for these interesting presentations. I had a few questions for Dr. Abraham. On clinical characteristics of growth and how that impacts the potential clinical complications of achondroplasia, you suggest that the pulmonary and cardiac complications are a function of chest size; is that -- do I interpret that appropriately?

DR. ABRAHAM: I have to say the answer is yes.

DR. HAVENS: So then the question becomes what proportion of the total adult chest size has occurred by age 5? Likewise, you suggest the mortality from achondroplasia is greatest, the mortality risk is greatest under age 5 related to sudden death, related to the size of the foramen magnum. So what percentage of the adult foramen magnum size has occurred by age 5? You'll see where this is going, obviously, to suggest that if we're thinking about studies in children with achondroplasia, the greatest benefit would seem to be in changing the early growth parameters which seem to have the greatest effect on early mortality and later cardiac and pulmonary complications.

DR. ABRAHAM: So to answer the first part of your question, I will say I don't have exact percentages about the size of chest circumference by the age of 5, nor do I have a

response for you regarding the craniocervical size. However, I would completely agree with you that in our understanding of the achondroplasia literature and what we know about the complications associated with achondroplasia, in that this condition, it results from a genetic mutation that is inherent at birth, that presumably if we could potentially find a way to give therapy starting from a young age to potentially prevent complications in infant and toddlerhood and then potentially ideally into adulthood.

DR. HAVENS: Thank you. So then the follow-up question, of course, is to the FDA ethicist. The standard for trials in children where there might be benefit, and this would be a mortality benefit we're talking about if it's going to change the size of the foramen magnum by age 4, because I think the bulk of the growth in the foramen magnum occurs before age 5, so this -- and the bulk of the deaths are in younger children, I believe.

So the question would be the standard for the FDA is to do a study in adults, find a PK parameter that is associated with a pharmacodynamic change of interest to then model a PK so you can bring the dose down into younger age groups and match the PK parameter of greatest PD significance to get the change you're after and then study that. So the question partly for the FDA is what would be required of a drug company that wanted to skip to the population where you would expect to find the

most impressive difference in, for example, mortality or chest size? Could the FDA give guidance to a company about the dataset that would be required short of clinical trials in older children, which would not be able to show these mortality benefits, in order to start these trials in younger children where the mortality benefits might be most expected?

DR. SNYDER: So typically we might allow nonclinical data to support some of that proof of concept, but I think the issue with this particular -- well, with any development program is that we need to think about how we would measure that change in, you know -- in that particular patient population, what specific change in the endpoint would we be looking at to look at that in the patient population and whether or not that study would be feasible.

DR. HAVENS: Well, foramen magnum diameter, for example.

DR. SNYDER: So if that's a measure that can be done easily within a reasonable number of patients, then I think that would potentially be an acceptable pathway forward.

DR. HUDAK: Okay, Dr. Pahys.

DR. PAHYS: I think if I may comment, one -- so as far as the chest expansion growth, as far as that, to my knowledge, around the age of 8 is when you've obtained most of your alveoli, so certainly before the age of 5 you'd see a significant benefit. As far as cranial -- or foramen magnum diameter or space available for the cord, generally by the age

of 5 you achieve the majority of your necessary space available for the cord, so I would agree with you there.

As far as follow-up, there are some challenges with measuring foramen magnum in infants. The best way to measure it is with an MRI or a CT scan. CT scans have a much faster -- and do not need to be obtained with sedation typically but have a prohibitive amount of radiation, whereas an MRI does not, but then the length of the study would require sedation, and that has its own risks inherent to it as well.

DR. HAVENS: Thank you. And just a follow-up, then, on the issue of spinal stenosis, so we were talking about foramen magnum, but one of the later complications is changes in the spine, so would that have the same kind of time frame of development?

DR. PAHYS: Yes. I think -- yes. And to touch on that again, we do typically follow achondroplasia kids with serial MRIs early on where you're less able to rely on their clinical examination, clinical complaints, because they're infants, so obtaining serial MRIs can almost be routine as part of your screening process.

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

DR. HUDAK: Dr. Wilson.

DR. WILSON: Thank you. So looking back for where the FDA has been involved with other growth disorders affecting children, the question is related to placebo use versus

non-placebo open label and also related to whether it's growth velocity or achieved adult growth. What has been the experience, and what were the guidelines? Could you help us? For instance, what the FDA applied for things like Turner syndrome and others were open label. Was that accepted and was the -- was it growth velocity or the achieved height at the end of the game, so to speak, or at the end of the treatment, because that might affect what would happen with treatments for achondroplasia moving forward and would affect the age groups which might achieve the greater emphasis for investigation, also moving forward, as well as prioritization. Is my question clear?

DR. ZEMSKOVA: This is Marina Zemskova.

So a majority of -- if you look into the label for growth hormone, this information is publicly available, and the majority of studies for Turner syndrome, for Noonan, other known growth hormone deficient states, used placebo-controlled studies and evaluated these patients up to final adult height.

DR. WILSON: At the early stages, was the growth speed or the growth velocity, was that a consideration, or was it only really the final adult growth?

DR. ZEMSKOVA: No, both.

DR. WILSON: Both were considered?

DR. ZEMSKOVA: Both were related as well.

DR. WILSON: Is it fair to say both are important?

DR. ZEMSKOVA: Um-hum

DR. WILSON: But what you perhaps were -- put greater emphasis on the final adult growth?

DR. ZEMSKOVA: All right.

DR. WILSON: Adult height, is that correct?

DR. ZEMSKOVA: Correct.

DR. WILSON: All right, thank you.

DR. HUDAK: Okay, Dr. Cunningham.

DR. CUNNINGHAM: My question is for Dr. Pahys, if I'm pronouncing it correctly. So I know that there are some protocols for much reduced radiation depending on what you're trying to look for in a CT. If we're trying to look at the size of a foramen magnum, can that be done with a much reduced CT protocol?

DR. PAHYS: Yes. Looking at specific aspects of the spine can be done with a fast spin MRI scanner that could potentially be done without sedation. Even localized CAT scans can be done just to a focal portion of the spine or the craniocervical junction, can be performed. But you would sometimes run the risk of missing everything, and if you're only going to focus on one spot, you may be missing other pathology that may be developing in other aspects of the spine. So just focusing on the craniocervical junction, you would then miss the potential evolution of spinal stenosis in the distal aspect of the spine.

DR. HUDAK: Dr. Cooke.

DR. COOKE: So I'll start with a comment and then a question or two. One thing to maybe distinguish the evaluation of efficacy of growth hormone in non-growth hormone and deficient indications like Turner syndrome and so on compared to studies of the growth effect on treatment in achondroplasia, I think it's important to recognize that in most of those other studies, substantially speaking, the growth velocity of those individuals is normal. So girls with Turner syndrome, girls with -- children with Noonan syndrome, generally the growth velocity is in the normal range, and so the impact on growth velocity has also been less -- has not been sustained, and so that final height outcome almost certainly was a necessary aspect of those studies. With achondroplasia, I think, although there is variability, the overall growth velocity is more distinctly subnormal within that population where that difference in growth velocity may be more important to study, although admittedly any attenuation of effect over time is still an important issue.

So the question I wanted to make sure it was clear for me was the issue of mortality in achondroplasia. One question is related to the fact that there's an increased mortality in adults from cardiovascular disease, and I'm curious, since that doesn't intuitively follow from what I understand about FGFR3 signaling or growth-related issues, what's understood about why there's this increased cardiovascular mortality in

achondroplasia and just to make sure it's very clear to me, this issue of increased early mortality from the foramen magnum stenosis and the sudden death, I think I understand that although that's a substantially increased risk, the bulk of the mortality is in adults from either cardiovascular or potentially neurologic problems in adulthood. So that simple question, is that correct? And then what is known about that cardiovascular disease in adulthood?

DR. ABRAHAM: Thank you. Yes, I think your impression is correct, that although there is increased mortality in infancy from, you know, the cervicomedullary compression, but it's still small, the number is still small. I will say that in the literature regarding cardiovascular mortality, I would have to say that I don't think it's well understood, and so these are sort of general numbers, general ideas that there is some increased mortality in the belief that it's from cardiovascular mortality, and I would ask the question to any of the panel members who perhaps have more information on that as well, but I don't think it's well understood.

DR. HUDAK: Okay, thank you. So we have a few other questions, but I think we'll wait on them until the session resumes after the Open Public Hearing because we have 33 speakers, and I want to make sure that everybody gets their -- up to their full 3 minutes.

So to introduce the Open Public Hearing session, a few

comments:

Both the FDA and the public believe in a transparent process for information gathering and decision making in the Agency, so to ensure such transparency at this open session hearing, FDA believes that it is important to understand the context of an individual's presentation. So for this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise us, the Committee, of any financial relationships that you may have with the Sponsor, its product, and if known, its direct competitors. So, for example, this financial information may include the Sponsor's payment of your travel, your lodging, or other expenses in connection with your attending this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, however, it will not preclude you from speaking.

The FDA and this Committee place great importance in this open hearing process. The insights and comments provided can help the FDA and this Committee in the consideration of the issues. That having been said, in many instances and for many topics, there will obviously be a variety of opinions, and I'm sure we'll hear some today. One of our goals in this hearing is to conduct it in an open and fair way where we respect what

every participant says and treat them fairly, with dignity, courtesy, and respect. Therefore, speak only when recognized by the Chairperson, and I thank you in advance of your cooperation.

So the mechanics here are that we have 33 speakers; I will call you sequentially from 1 to 33. As I call Number 1, if Speaker Number 2 can line up behind Speaker Number 1 and so forth and so on, so there's no delay in between presentations. There is a 3-minute limit. There is a box on the podium that has green, yellow, and red buttons, and it will count down, so by the time it flashes yellow there are --

MS. BRILL: Thirty seconds.

DR. HUDAK: -- 30 seconds, and when it hits red, it ends.

(Laughter.)

DR. HUDAK: So you have 30 seconds when it hits yellow, and then the hook will come out. All right, so to stay on time, I really do ask that people keep within 3 minutes because at that rate, 3 minutes, that's 99 minutes, and we have 90 minutes allotted for the session. So we'll get started. So Speaker Number 1, if you can please come forward and identify yourselves to the Committee and good luck.

MS. FREEDMAN: My name is Karen, and my son Judah was diagnosed with achondroplasia at 5 months old. Judah is now 4, and he's a force to be reckoned with. He's silly, funny, smart, curious, and carefree, but he doesn't know the extent of

the challenges he will face with achondroplasia.

For several months, doctors told us they had no concern about Judah's short limbs. They first told us this when I was 34 weeks pregnant, then again at his birth because he was average weight and length, and then again at a genetic evaluation. But after a second genetic evaluation, I received a call that began with telling me that my son has achondroplasia and continued by telling me the very many developmental and medical issues he would face, including potential serious surgeries. The telephone call ended with a terse "there are no treatment options." I was devastated. Thinking that I would not be able to protect my child from the physical and emotional pains of achondroplasia was not a fate I was willing to accept.

And so the search for answers and treatment began. I read about bone lengthening and was heartbroken that my child's only treatment option involved excruciating pain. This would be a painful price to pay for the hope of a small amount of autonomy, for my son to be able to reach a door handle or see over a counter or get up on a chair without struggle or assistance or to be able to wipe himself without a special device, basic tasks that average size people never give a second thought to.

Then came a sign of hope. A company was developing a treatment for achondroplasia. We enrolled in the measurement

phase of the trial and remained hopeful for enrollment in the drug phase of the trial. You see, this is not a vanity issue. This is for my son's physical and psychological health and well-being. Even a few inches of added length in his arms and legs could make a big difference for people with achondroplasia like my son. My son is only 4 and has a long list of pains and procedures. Between the ages of 1 and 2, Judah had seven ear infections, which caused a speech delay, and he still receives speech therapy. He's had sleep apnea, two sets of ear tubes, an adenoidectomy, and a tonsillectomy. My son gets frustrated every day watching friends walk and climb stairs easier and faster than him. Judah was extremely upset when a classmate recently asked him, if you're 4, why do you look like a baby? He couldn't ride his friend's bike because it didn't have pedal extenders, and he was too short to ride the school carnival rides with his friends. His small hands and short trident-shaped fingers make it difficult to hold tightly on to things.

Every single day I think about what this treatment has the power to do for my son's quality of life and what will happen without treatment. The window for effective treatment is finite, and every day that goes by without treatment is a day lost for us. I strongly support the clinical trials and treatments for achondroplasia developed by BioMarin, and I'm so grateful for their efforts.

Thank you.

DR. HUDAK: Thank you. Could Speakers Number 2 and 3 come up to the podium?

DR. BLAUSTEIN: Good afternoon. I'm David Blaustein. My travel was provided by Global Genes.

After Jacob, our son, was diagnosed with achondroplasia, we weren't sure how he was going to be affected. Being a doctor, I researched and spoke to everyone we could find. I spoke to the doctor who discovered the gene, Clanford Conemaugh (ph.), and worked with the Israeli group ProChon and numerous other scientists and physicians. There wasn't much available, and the science seemed to be evolving. We went to some finding from some Israeli group and tried to get an antibody to a growth plate; that wasn't successful. We reached out to a Japanese group a couple times based on publications that we saw on CNP peptides and mice. I was unsuccessful in reaching them.

Jacob, during this time, was doing very well, however. His development was on track, he had friends, he had interests, and he had a wonderful sense of humor. He had multiple ear infections which required numerous trips to the ENT for which he had periodic tube placements.

When Jacob was 10, he underwent limb lengthening for his lower extremities. We did this to correct bowing of his tibias and hopefully to prevent some down-the-road issues like back pain that many achondroplasia patients have. The doctors broke

all four of Jacob's tibias and femurs and put pins and rods in his thighs and shins. It was very painful, and Jacob would scream out for oxycodone every time his pain medication wore off. Every day we would have to clean these pins and pull them and turn the cranks, which pulled his bones apart so that more bone could fill in. We did this four times a day. Jacob could barely walk and couldn't go to school for 3 months, and it was a very tough experience. The end result was that his legs were straight and he gained 3 inches of height. However, in retrospect, I'm not sure I'd recommend that any child go through this.

We were hopeful that other treatments would come along. Through my work in the biotech industry, I heard about BioMarin. I learned that they had licensed the CNP drug from the Japanese group and later published their early findings of the tests. The results were striking. From that time on, Jill and my goal was to get Jacob in that clinical trial, if it became available.

Jacob has been on the active drug portion of the trial since September 2014 with Dr. Hoover-Fong and her team at Johns Hopkins. His growth has increased. Some notable other improvements like joint mobility, reduced snoring, and other areas that Jill will describe. He's able to do many more things that he would like to tell you. There haven't been really any serious side effects of the medicine. Once in a

while he has a small transient injection site reaction, but that usually goes away in about 30 minutes. That's rare. I can't say more in support of this treatment. I'm going to leave that to Jacob.

Thanks very much.

DR. HUDAK: Thank you.

DR. LUTTRELL: Hi, I'm Rosa Luttrell. This is my daughter, Kiana (ph.). She is 11 and was diagnosed with achondroplasia at birth. Global Genes provided our travel.

At 28 weeks gestation, during a routine ultrasound, Kiana's measurements were not on a normal growth rate. After numerous ultrasounds and an amniocentesis, we had more questions than answers. Kiana was delivered by emergency C-section at 34 weeks and was in an ICU for 3½ weeks. Based on x-rays, head circumference and long bone measurements, she was diagnosed with achondroplasia.

In our desperate search for information and treatments, our pediatrician connected us with Parents of Children with Achondroplasia. We had a better understanding that this was not just a social stigma of short stature but involved serious medical problems. Kiana had three surgeries for tubes to correct recurrent ear infections. Because kids with achondroplasia have smaller airways, her doctor had these minor surgeries scheduled at a hospital with advanced life support. The reality of potential for serious complications was

frightening. She also had her adenoids removed and is monitored for spinal canal stenosis, kyphosis, and bowing of her limbs.

Because her legs are shorter than her body, Kiana falls frequently, especially if she's moving fast. It is impossible to find age-appropriate clothes that fit her criteria as suitable to wear. The issues we have with clothes required her to be in counseling for almost a year. She would cry, get frustrated, pinch herself, and tell me she's fat. She has a lot of self-image issues. Although she's not in counseling now, we check in periodically with her counselor in case any other issues come up, especially since she is starting middle school this year.

Achondroplasia may not be an epidemic like diabetes or hypertension. As a pharmacist I know that drugs are approved to correct diseases that can simply be cured by lifestyle changes. As a parent I have to accept that no amount of diet, exercise, or lifestyle modifications will cure or improve her condition. I want for Kiana what every parent wants for her child, a chance to be whatever she wants. My hope for her future is that she can be focused on her education, have normal life experiences. This treatment is about correcting social stigma but to hopefully reduce serious complications. My biggest fear are the surgeries. What is important to me is that this study helps her grow, and her bones have to stay

straight to avoid surgeries; she has to grow. This treatment gives children with achondroplasia a hope of better quality of life, and BioMarin has my complete confidence and my support with clinical trial and treatment.

Thank you.

DR. HUDAK: Thank you very much. Speakers 4 and 5, come up to the podium.

MR. HAIDER: Hello, my name is Amer Haider, and my travel was supported by Global Genes. I'm here with my wife, Munira, she's also going to speak, and my son Ahmin, who is 9 years old. I'm here to share a deeply personal story.

For the first few years of Ahmin's life, there was a whirlwind of visits to the doctors, and you heard from many. At Stanford Children's Hospital, his neurosurgeon kept an eye on his brain with CT scans and MRIs to make sure his brain was not getting -- was not -- his brain was not getting compressed. His neurosurgeon also watched Ahmin's neck to make sure he was not at a risk of dying suddenly from respiratory arrest or brain stem compression. His orthopedist took x-rays to keep an eye on his spine, making sure that it did not compress the spinal nerves, and at age 4 he had ear tubes installed surgically so that he would stop having these chronic ear infections. Despite all the time Ahmin has spent in clinics and all the extra tens and thousands of extra medical cost, Ahmin is doing great. All right, good job. We're very

grateful for all the blessings we have, but we want more for Ahmin. As a dad, like all parents, I want to give my child the best I can provide, and one day in prayer and meditation, I asked myself, as a dad, how can I help Ahmin? And the answer I got was to make the world a better place and that will help Ahmin. This is why we collaborated with the LPA and families to start Growing Stronger, and we're excited that LPA and the community of support is supportive of all the diverse views.

We're happy to report that Growing Stronger, as a foundation, has raised over $500,000 from families to give grants to researchers to help discover potential therapies. We're also very happy to report that our grants are helping further research, notably the growth biomarker research from Dr. Horton, a renowned scientist, was seed funded by Growing Stronger. And it's an example of how families can make a difference.

In the end here, I want to make a plea to all of you. We need treatment options, and through our foundation we have used our own personal money and money from our friends to bring researchers into this arena. As a dad I hope your decision today will continue to encourage researchers and companies to invest in therapies so Ahmin and others will have options and choices.

Thank you very much.

DR. HUDAK: Thank you so much. Speaker Number 5.

(No response.)

DR. HUDAK: Speaker Number 6.

(Pause.)

DR. HUDAK: Okay, you're on.

MR. MOSCATO: Hello, I am Anthony Moscato III. I am 12 years old, and I have achondroplasia. I have five reasons why I think drug development is a good idea.

Number 1: I might be taller, stronger, and more independent. For example, I could reach things easier, like kitchen cabinets and the microwave, instead of having to use a stepstool or climbing on the counter or asking for help. Also, I could pour a gallon of milk more easily.

Number 2: I might have fewer surgeries. So far, I've had my tonsils and adenoids taken out. I've also had ear tube surgery three or four times to stop ear infections. I have trouble at home and school when I get ear infections because I can't hear well and I get dizzy. In the future I hope I don't need surgery on my bowed legs or spine.

Number 3: I might get to worry less about watching my weight. I can't get overweight because I have loose joints and I get knee pain. Sometimes I can't eat as much ice cream or French fries as my younger brother.

Number 4: I might be treated with more respect. I'll never forget the kindergarten aide at recess time who wouldn't let me play outside on the playground for unknown reasons. A

few weeks ago some kids on my school bus were poking me like I was a statue in my stomach and forehead.

Number 5: I might have fewer doctor appointments and medical equipment. I hate sleep studies. I see an orthopedist; geneticist; pulmonologist; ear, nose, and throat specialist; and audiologist just for my dwarfism. I use a CPAP at night for my obstructive sleep apnea. I also have to use ear plugs when I go swimming because I can't get water in my ears.

Those are my five reasons why I think the drug is a good idea. Thank you.

(Applause.)

DR. HUDAK: Thank you. I'm sorry, we're going to go to Speaker Number 5, Dr. Cohen, who apparently has a video that someone --

(Video starts.)

DR. COHEN: -- "the Dean of the Leonard Davis School of Gerontology at the University of Southern California. But I spent most of the last 30 years" --

"My name is Pinchas Cohen. I'm the Dean of the Leonard Davis School of Gerontology at the University of Southern California. But I spent most of the last 30 years studying growth disorders and overseeing clinical trials with growth-promoting therapies. And let me share with you some of the experience" --

"My name is Pinchas Cohen. I'm the Dean of the Leonard Davis School of Gerontology at the University of Southern California. But I spent most of the last 30 years studying growth disorders and overseeing clinical trials with growth-promoting therapies. And let me share with you some of the experience that me and my colleagues have had in this area.

"The field has been looking at new treatments for a variety of conditions from growth hormone deficiency to Prader-Willi syndrome to Laron's syndrome, and we've used numerous agents that we had been testing, from pituitary growth hormone to recombinant growth hormone, to various growth hormone-related agents like GHRH and IGF-1, and even in the extreme case of achondroplasia, limb-lengthening surgeries.

"The key question that we have to address is how to measure the success of any particular therapy, and there are a number of potential outcomes that have been evaluated, including adult height, the change in the height SDS or the relative height to the general population. But the most popular and the most valuable has been the annualized growth velocity, which is essentially the difference between the height in the beginning of one year and the height at the end of one year of treatment. This measure is noninvasive and accurate, it accommodates patients and physicians, it's clinically accepted as useful, practical, and reproducible, and importantly, it's comparable across genders, ages, and disease

severity. It's known to be predictive of multi-year growth and is used in most of the previously FDA-approved trials of various growth-promoting agents.

"We also have to ask how long such trials should be conducted for. And the majority of studies that have been conducted in the field were 1-year randomized clinical trials. These are accurate and predictive when they're properly powered. They're compatible with ethical and practical limitations associated with placebo or randomization to no treatment. They allow correction for bone age and for adult height predictions. They're sufficiently long to assess adverse events and overall safety. And most of them included informative extension studies to evaluate the long-term growth. And thus they lead to patient benefit and allow for assessment of patient and family satisfaction."

"My name is Pinchas Cohen. I'm the Dean of the Leonard Davis" --

DR. HUDAK: Okay, stop.

DR. COHEN: -- "School of Gerontology at the University of Southern California."

(Video stops.)

DR. HUDAK: All right. He got overtime. Our next speaker is coming to us by phone with some slides. No?

MS. BRILL: He's here.

DR. HUDAK: He's here. Oh, I'm sorry, there you are.

Good. You've got slides, though?

DR. SAVARIRAYAN: One slide.

DR. HUDAK: Okay, go for it.

DR. SAVARIRAYAN: Good afternoon. My name is Dr. Ravi Savarirayan, and I'm a clinical geneticist and pediatrician from Australia. I am a principal investigator for the BioMarin company, and I'm also in active discussion with several other companies that may have potential therapies for achondroplasia.

I've been caring for children with achondroplasia and their families for the past 22 years. I became a doctor so that I can help children with genetic conditions such as achondroplasia live the healthiest lives possible by preventing or treating the complications of their condition. When I first meet parents and families of new children, as you've heard today, diagnosed with achondroplasia, I do reassure them that their child can lead a normal and healthy life, but as you've heard today, I am impelled to outline to them that there are a variety of medical issues that can occur and that their child might have to face throughout their lives. These include medical issues such as the increasing likelihood of limb and spinal surgery, the increased risk of sudden death in early childhood, ear infections, and sleep disordered breathing, architectural issues such as living and functioning in a world designed for average people, and important psychosocial challenges consequent on looking different and being shorter

than average, such as teasing and problems with self-esteem.

Until very recently, there have been no specific precision therapies targeting down the line basis of achondroplasia. As a medical community, we have been left to manage complications after they have arisen with variable results. The mainstay of management has been surgical, which is risky and often leaves patients with achondroplasia in a worse situation than prior to their surgery. That's why I've been so cautiously optimistic about the promise of new targeted therapies provided by companies such as BioMarin and other companies as well.

It is my hope that these therapies that are precision therapies can specifically target and block the abnormal signals that cause achondroplasia and, subsequently, these medications will decrease the need for surgery and other interventions in this group of children, and indeed, they will have less time spending time with people like me and more time being children. I also hope this will translate into better function, self-esteem, independence, and access to the environment, such as public transport.

Medicine has always sought to relieve or prevent the symptoms of disease, and these medications could present a new and powerful option for children and their families living with achondroplasia, should they choose to employ it. It is my hope that these medications will be successful and increase the likelihood of a future with fewer doctor visits and hospital

stays, allowing more children, like the child that you see in the slide, to reach their potential.

Thank you.

DR. HUDAK: Thank you. Speaker Number 8.

MR. FRITTS: Good afternoon, my name is Seth Fritts, and I work for Global Genes. Global Genes submits and receives educational grants, support from industry, including BioMarin. Global Genes is a leading rare disease patient advocacy organization whose mission is to connect, empower, and inspire the rare disease community. We envision a globally connected community equipped to eliminate the challenges of rare disease. With international scope, Global Genes develops educational resources, programs, and events that unite patients, advocates, and industry experts.

As someone living with a rare disease, I have a unique perspective and passion for my work at Global Genes. There are more than 7,000 rare diseases affecting 30 million people here in the United States and 350 million globally. That's more than cancer and AIDS combined. Eighty percent of rare diseases are caused by faulty genes, and only 5% of rare diseases have an FDA-approved drug.

At Global Genes we encourage industry and regulators to develop treatments for rare disorders such as achondroplasia and appreciate the Agency's flexibility in regard to rare disease regulation. Options and choice, things that are as

rare as the disorders that many people face.

Thank you to the FDA, the Committee members, and most importantly the patients and caregivers for your time today.

DR. HUDAK: Thank you. Speaker Number 9. Maybe there are some slide -- a slide or slides?

DR. KAISERMANN: Yes, please.

(Pause.)

DR. KAISERMANN: I thank FDA for allowing me to speak here today. I am Morrys Kaisermann. I'm an employee of GSK, but I don't speak on behalf of GSK here. I am paying for my travel. I'm a Brazilian physician with 30 years of clinical experience. Like most of us, I had little exposure to rare disorders in my practice. That changed 10 years ago when my daughter Julia was diagnosed with achondroplasia. I won't be going into details about genetics and clinical features of achondroplasia, as they have been already revealed here and also described in many reviews and guidelines published.

So what I want to emphasize is that all those medical complications, they do really happen in real life with real people, as you can see here in this collection of posts coming from the social media describing the kind of issues people, both children and adults, endure because of achondroplasia.

So does achondroplasia need to be treated? I think so. This genetic disorder represents a clear unmet medical need. Effective treatments for achondroplasia will help reduce

medical complications in healthcare related to the skeletal dysplasia and will certainly improve the quality of life of affected children.

When I think in clinical development, I see three R's that are needed. The right design. New clinical trials exploring new potential therapies for achondroplasia have the right design. Is it correct and ethical to use standard trial designs, including the use of placebo in this special population? Are we using the right endpoints, as has already been emphasized here, to measure efficacy and safety? And are we exploring these trials and these new drugs in the right population? Should they be looking for younger children? I would like to remind the Committee that growth has an expiry date.

I want to introduce you to Julia, my daughter, just a few months after starting the Phase 2 study 3 years ago. As the father of Julia, it's my responsibility to allow her to have the best opportunities in her future. I believe this is what any parent wants for their children. For her, I traveled several times to the United States and several other countries across the world, including Japan. For her, we moved the family from Rio de Janeiro to the U.S. so she could join the Phase 2 study 3 years ago. I'm doing the best I can for Julia.

We parents hope the FDA will take the appropriate steps that will help move forward the clinical development of

treatments for achondroplasia.

Thank you.

DR. HUDAK: Thank you. Speaker Number 10.

MR. BLAUSTEIN: Hi, my name is Jacob Blaustein, and I am 14 years old. I have achondroplasia, and I have been taking BioMarin's drug for around 3 years. I have seen significant growth and am very pleased with the results. The medicine is very easy to take; it is a quick injection in my arms or legs and is a very small but powerful dose of medicine. Compared to limb lengthening and straightening, which I have personal experience with, the shot every day is way less painful than the harsh surgery where they insert pins into your legs.

Now I can reach many things that I could never reach before. It makes moving easier so I can participate in any activity that I want to do, and it makes me faster. I can do pull-ups, which I could never do before; I can do rock climbing and go running. I can pursue my passions with the height advantage it has given me. For example, I would not be able to metal sculpture and weld. I would also not be able to do glass blowing because I could not lift the pipe or reach the furnace. I can also reach our stove and cook, which I love to do.

I am as tall as some of my classmates now and nearly as tall as my mom. It makes me feel more part of a group and makes people less likely to identify me just because of my height. I am very happy that I am taking the medicine, and I

hope that the FDA approves the medicine and that other kids can have the opportunity to take it.

Thank you. Oh, and these are also like -- that's a vase that I made glass blowing, and the picture before was me holding a tool.

(Applause.)

DR. HUDAK: Very nicely done. Speaker 11.

DR. RAGGIO: My name is Cathleen Raggio, and I'm an orthopedic surgeon who over the last 30 years has cared for children and adults with achondroplasia. I also serve as a consultant for BioMarin, Ascendis, and Alexion. I come here today as a voice for the adults who are too disabled to travel and suffer from the consequences of being an aging person with achondroplasia. People with achondroplasia become patients with achondroplasia as they age. It may be in their late teens or in their forties when the effects of a small spinal canal causes symptomatic spinal stenosis. Pain, decreased ability to walk, if left untreated, progress to spasticity, loss of walking, and bowel and bladder changes.

A women I care for told me: "I wasn't always like this. I had a full-time job. I drove a car. I owned my own home. Now I am dependent on a caretaker for my activities of daily living. I am unable to work. I am wheelchair-bound." She is not rare. Many adults suffer, and I use that word not lightly, from the same outcome.

But let us look at metrics, the SF-36, the Guide to Patient Quality of Life. In a sample of adult achondroplasia patients, functional score is 56, population is 71; mental health is 38 compared to 70.

Clearly, the effects of achondroplasia do matter in adults. The availability of a treatment that could lessen the impact of disease burden in this population would be paradigm-shifting. If the growing skeleton developed in an average fashion, then the spinal stenosis should be lessened or eliminated. This means that the person would not have an extensive spinal decompression; it would make me obsolete, perhaps with instrumentation, screws. This would eliminate the risk of death, paralysis, infection, and nerve damage. This would maintain their quality of life. People deserve an option for care. If some people choose not to participate, that's their choice, but others also deserve a choice. Length of arms and legs can be important for hygiene and activities of daily living. Today, if a person would choose to increase their height, again, they face the surgeon's knife. Six to eight surgeries over 2 to 4 years, all with the involved risks and costs mentally, physically, and financially. Options are needed now. I come here to advocate for my patients and their families. Please give them options, please give them respect, please give them the hope for a better quality of life.

I thank you.

DR. HUDAK: Thank you. Speaker Number 12.

MS. OZAN: I'm Samantha Ozan, and my daughter Megan, age 10, has achondroplasia. My travel was provided by Global Genes.

Megan was diagnosed with achondroplasia after birth, although ultrasounds during my pregnancy showed short limbs. During her early years, she was on CPAP for apnea, had her tonsils and adenoids removed, and had surgery to open up her throat and nasal passages to help her breathe. She received physical and speech therapy, walked at 22 months, and said her first word at 26 months. Megan has oral issues with her teeth and tongue and has had braces for 2 years. She has challenges with personal hygiene because of her short arms. We've lowered light switches in our home, have stools everywhere, and switched to a van because she can't open and close regular car doors.

Megan is a wonderful child -- kind, caring, sweet, smart, and beautiful. Although she is not defined by her diagnosis, she has times of sadness that she is different. While I can explain achondroplasia and what it does to her bones, it doesn't take away the heartache her stature has on her quality of life. She just wants to fit in with her friends, which is hard when her peers leave her behind, like at Halloween when the other kids are running ahead to trick or treat. Plus the challenges that playgrounds and swimming pools present. She

tires easily when she walks and raises her arms and is too proud to use a stroller. She falls because her feet catch on things and it's hard for her to look down.

We are very grateful to participate in the BioMarin drug study. Megan began the Phase 2 study at age 7. We moved from Texas to Tennessee so that we could easily get to the appointments. She is not only taller, but her arms and feet grew, and her sleep apnea has improved. She now reaches sinks, sees over the counters, is more self-sufficient, and has more independence. She now makes her bed, fixes her hair, and ties her shoes. She loves the freedom of being taller and independent.

We want our daughter to have the best possible chances for a happy and fulfilling life. If her life has challenges and we can change it, of course we want to do that. Megan wants to take the medicine. She wants to be taller and more independent. She can see the difference that height makes. Megan, her dad, and I appreciate having this opportunity to change her life for the better, to grow and have this medicine from BioMarin available to help her reach her goals. This medicine is improving her life. It makes the world a better and more accommodating place for Megan and all the other children who have achondroplasia.

Thank you.

DR. HUDAK: Thank you. All right, Speaker 13.

MS. MAROHNIC: Hello, my name is Olga Marohnic, and I am the mother of a 15-year-old with achondroplasia whose name is Matthew. I am also the chairperson of the Hispanic Affairs Committee for Little People of America, and in that position I have helped hundreds of families in the 12 years that I've held that position.

My travel here has not been paid by anybody; I have paid my own way and my son's way. We are here because we want to be here, and we want to express our opinion.

Most of my most valued friends have various types of dwarfism. We have a supportive and diverse community of people with short stature who make up a segment of the population that these pharmaceuticals are targeting and trying to eradicate, in my view. My son is a typical freshman in high school. He has great friends, he does well in class, is quite popular in a positive way, and he doesn't like homework or shaving, as you can see. And he would like to have his classes start at 10:00 a.m. every morning, so yeah, very normal. In his own words, "I have a great life, so don't be sorry for me."

My son is not sick; he doesn't need medicine. My son is not broken; he doesn't need fixing. My son, what he needs is inclusion and acceptance, which come with education, not the type that is learned in schools but the kind that is earned by living in a society that can celebrate the uniqueness in all of us and take advantage of all our differences. He may have many

medical complications throughout his life, but there are solutions to all those medical complications. I may not like the solutions and he may not like the solutions, but there are solutions such as the decompression surgery.

In my opinion, these pharmaceutical companies are taking advantage of the fear that many parents are faced with, with having to raise a child with dwarfism. I know that; I have been there. I have talked to hundreds of parents that have been in the same boat. Many of those fears are what will his or her life be like? Will he or she be accepted or rejected? Will he or she be able to have a job? Will they be happy? How will they relate in this world, or what will people say? I know all these questions and many others, but naturally the answer is if my child were normal, then they will be happy, those fears go away.

I don't feel like children should be treated as guinea pigs just because somebody is in fear of what will happen. You love your child no matter what, and they will have a great life. Many of my friends are here right now. They have lives, they have children, they have medical complications, but so do many of us here that are average size, including myself.

That is our opinion. Thank you for your time.

DR. HUDAK: Thank you. Speaker Number 14. And there may be slides. There we go.

MS. CREWS: I'm Sarah Crews. My daughter Chandler is 24

and was diagnosed with achondroplasia at birth. Global Genes provided my travel.

Achondroplasia, the medical issues and the financial strain it causes, has impacted not just my daughter's quality of life but our entire family. Growing up with achondroplasia means you must have regular access to a good pediatrician who has likely never, ever seen a patient with achondroplasia; a neurosurgeon; an orthopedic surgeon; an ENT; and an anesthesiologist who has hopefully read the literature about anesthesia for achondroplasia. That list of specialists is at a minimum.

Although we have several major hospitals in Arkansas, specialty physicians don't practice there for more than a few years before moving on. To see the necessary specialists, we travel to three different states at least once a year. Chandler will be traveling for medical care for the rest of her life.

When my daughter was 16, she was unable to walk a city block. She was becoming less physically able, her 14-inch legs were severely bowed, and spinal stenosis was complicated by her lower lordosis. She wanted a more normal life and knew that limb lengthening was her only option. Even given the risks, the pain, and the time involvement, she was willing to do anything to get a better life. She had her legs lengthened twice and her arms lengthened. Each procedure was 4 months of

lengthening, 5 months of healing, and many months of physical therapy. It was very hard; however, all she changed were her proportions and alignment. If she had had the option of a drug like vosoritide, her other health complications possibly could've been lessened. Maybe it would have eliminated the need for pain and the many, many surgeries she has endured.

Unfortunately, when a baby is diagnosed with achondroplasia, there's no way to know what complications they will suffer, if any, as they grow. I personally know four families whose child with achondroplasia has died because of undiagnosed foramen magnum compression. Imagine having a child who is dependent on a trach and unable to get around without a motorized wheelchair. The extremely short arms make using a wheelchair even more challenging. If a treatment was available when Chandler was born, I would have put her on it immediately, knowing we could possibly prevent these severely disabling complications with a simple daily shot.

Thank you.

DR. HUDAK: Thank you. Speaker Number 15.

MR. COCKRELL: Hello, my name is Aiden Cockrell. My travel was provided by Global Genes.

I'm 11 years old, and I was diagnosed with achondroplasia as an infant. I have had multiple surgeries. I had a shunt put in when I was 7 months old and had it revised when I was 5. I have also had several ear surgeries. Some of my friends have

had spinal decompression surgery, but I've been fortunate enough not to have it, have that one.

I'm a participant in the clinical trial for vosoritide. I've been taking this medicine for 4 years. My geneticist, Dr. Phillips, told me when I started the trial that the medicine might not help me as much as it would if I had started taking it as a baby. I think if I had started taking that as a baby, it would've helped me a lot more.

This drug has been a lifesaver to me. I used to cry every night because of pain. I used to not be able to play sports because of pain. But now I can do anything I want. I can run miles, I can play sports, I can go on school field trips with a lot of walking. I've also grown a lot. Now I can go on amusement park rides, ride a 12-inch bike, and ride a scooter. I don't have as much neck or back pain. Neck, back, or leg pain. And it's all because of the drug. I thank God for vosoritide.

Participating in this trial has not been easy. I have to take a shot every day. I used to cry, but now it really doesn't hurt me anymore. The clinic visits are hard, too. They have to put an IV in my arm, and they almost always have to stick me more than once, and it really hurts. The tests like CT scans don't hurt but are very uncomfortable. I didn't really have a choice in being in the trial; my mom signed me up for it. When I got a little older, the nurses and the doctor

talked to me, and I did have a choice. Even though the IVs hurt and the tests are not fun, I want to help other people who want to treat their achondroplasia so that they can have a better life.

Thank you for giving me the opportunity to speak today.

(Applause.)

DR. HUDAK: Thank you, Aiden. Speaker Number 16 participating --

MS. DIGERONIMO: Hello?

DR. HUDAK: -- by phone. Yes, welcome.

MS. DIGERONIMO: Hi. Yes. Can everyone hear me? I'm sorry, there's a little bit of static on my end but --

DR. HUDAK: You're fine.

MS. DIGERONIMO: Okay. So I'll just starting reading my statement, but my name is Kristine Digeronimo, and I'm here today to speak on behalf of my son Darren Robert Jr.

During my pregnancy we found out DJ was a boy, and we were overjoyed. At around 37 weeks during a follow-up sono, we were told that DJ's long bones were weeks behind and he would likely have a form of skeletal dysplasia. We felt broken down as many forms are not compatible -- and we prayed for his health every day from that point on, and we haven't stopped.

When DJ was born, we were blessed to welcome him into a beautiful family, and weeks later it was confirmed that DJ had achondroplasia. Since DJ was born, he is so well determined

and I'm so happy -- he has overcome so much already. The day after his first birthday, he had decompression surgery and tubes put in his ears. He has had countless MRIs, and we make one trip every few months from New York to Baltimore to have his care followed by specialists. At just 19 months old, DJ is the strongest man I know and my hero. It breaks my heart to see him constantly struggle and work through his frustration. Mentally, he's an active, eager, curious 19-month-old, but physically he is stuck in a 6-month-old body. He is unable to express himself as he wants to or move the way his brain is telling him to. He's looked at as a baby, not a toddler, by society, and at such a young age, his lack of control and independence is already starting to not only affect his physical development but also his mental development as he is constantly treated like a baby. It makes me so sad to see his small legs beginning to bow and his back bending. As he starts to grow, the affects of achondroplasia begin to become more and more apparent.

I am here as a mother to advocate for my child because he deserves the best quality of life. In this day and age when there is medicine available to improve his overall quality of life, he should have the option to use it, as he deserves it. Time is such an essential part of achondroplasia, and each day that passes that he is denied any type of medication that is available, you are taking much of his opportunity for

effectiveness, and so much of his quality of life is being tarnished.

It is 2018; these children deserve to have this opportunity. They are not defined by a community or -- they are individuals. They have -- families and they deserve the ability to function in society without constant modification and pain and suffering throughout their life because of limb bowing or inability to complete simple human tasks such as wiping themselves after they use the bathroom. These are basic human needs, and they deserve this medication, and they deserve this opportunity to be able to function in society and strive to be the best people they can be.

Thank you.

DR. HUDAK: Thank you. That came through very clearly. Speaker Number 17.

MS. MUNIR-ISRAR: Global Genes provided my travel. My son Ibrahim is 9 years old and was diagnosed with achondroplasia at birth. My husband and I were in a shock, and we prayed that the doctor was wrong. Ibrahim was in intensive care for 4 days after he was born. Because of his narrow airway, he could not breathe on his own. That was his first medical complication from achondroplasia. Those 4 days changed our lives, and we slowly started understanding dwarfism. We had many questions. Why? How did this happen? What did we do wrong? How do we treat it? Is there a cure? I spend a lot of my free time

looking up information on dwarfism and a treatment. We soon realized that diseases can be cured but genetic disorders cannot.

Just because Ibrahim's condition is not life-threatening does not mean that there are no medical complications. He's had his share of medical problems. I had to quit my job for a few years to be with him and keep up with his doctor appointments. His first few years were spent in and out of hospitals. Surgery at age 1 for spinal decompression of the foramen magnum, multiple sleep studies for sleep apnea, four sets of ear tubes for continuous ear infection. He just lost his fourth pair of ear tubes, and he's hoping that he won't need another one, another surgery. He hasn't learned how to swim yet because he's fearful of going in water and increasing the risk of ear infection.

Ibrahim loves sports, just like his dad and older brother. He loves to play baseball, soccer, football, but unfortunately, he can't keep up with his friends, who have moved up in local sports leagues, because of low muscle tone in his legs. And plus he tends to fall a lot. Reluctantly, he has decided to explore karate for now. We know Ibrahim will face more challenges in the future as he gets older, social and medical challenges. And maybe all this could've been avoided if there were treatment options. He is who he is, and I'm grateful to God for bringing Ibrahim in our lives, but I feel like the

least we can do is make it less challenging for him and others like him.

When we heard about the BioMarin study, we were overjoyed and enrolled Ibrahim in the measurement study at UCSF. He wanted to be here in person, but he couldn't because of not wanting to miss school. I'm here to show Ibrahim's and my support for the clinical trials and treatment for achondroplasia.

Thank you.

DR. HUDAK: Thank you. Speaker Number 18.

DR. FUCHS: Good afternoon, everyone. My name is Hank Fuchs, and I'm President of Research and Development at BioMarin Pharmaceutical, Inc. It's a privilege to address you all today, having worked on vosoritide for people with achondroplasia for over 6 years.

Today's discussion represents a watershed of sorts in the journey to find improved health outcomes for another rare condition. We appreciate FDA Commissioner Gottlieb's recent efforts highlighting that drug development for rare conditions includes additional challenges. We are encouraged by Dr. Gottlieb's recently announced initiatives to facilitate efficient drug development in rare conditions and are optimistic that this meeting will support the efforts to foster innovation.

The achondroplasia community is inclusive and supportive,

and we recognize the pride in their identity, and we respect and support this. We also respect and work for families who want something different, namely, options for enhanced skeletal growth and better health outcomes.

Stature might be what some notice on the outside, but individuals diagnosed with achondroplasia have, as we have heard today, a higher mortality rate than all age groups examined. Sadly, this finding remains, even with the most recent developments in medicine. Individuals with achondroplasia also experience a high frequency of spinal complications, sleep disorder breathing, ear and auditory problems, among other common sequelae. At present there are no medical options to offer other than symptom-based management and supportive care for affected families.

At BioMarin, we hope to leverage genetic insights into the biology of achondroplasia and its underlying cause to enable fundamental changes in the tools available for families. Today we are discussing the roadmap to first registrations of medical options, such as vosoritide, though surely this will be the only -- will only be the first stop on the road to medical breakthroughs. BioMarin's program benefits from a solid understanding of the natural positive and negative regulators of bone structure and function. Ultimately, the aim is to reduce early and overall mortality, reduce severe complications in infancy resulting from frame and compression, improve spinal

and other sequelae, improve upper limb length and functionality, improve well-being and self-perception where desired. We've developed a program that begins to address this diversity of opportunity which is practical and methodical. Our program prudently investigates the biology in older children before proceeding to study infants. We recognize the importance of psychosocial support and will provide -- ensure the patients participating receive that.

BioMarin is proud of the collaboration we've undertaken over several years with dozens of academic experts and families to construct our program. One of those academic experts was the late Dr. David Rimoin, known for having the foresight in the early '70s to start the world's largest registry of skeletal dysplasia. Dr. Rimoin was also chair of the LPA's medical advisory board. We're grateful to Dr. Rimoin not only for the registry but also for the work that he did to help us develop vosoritide. If he were here today, he would tell us that vosoritide addresses the molecular mutation associated with achondroplasia and is meant to fundamentally transform and improve the lives of children with the condition. We're therefore grateful to hear this Committee's opinion and response to FDA's briefing documents and questions.

We look forward to your feedback and thank you.

DR. HUDAK: Thank you. Speaker Number 19, I believe, is Aiden's mother.

MS. COCKRELL: I won't introduce myself. I'm Alecia Cockrell; you've met my son, Aiden. He's 11, and he was diagnosed with achondroplasia when he was 6 weeks old. He is participating in the clinical trial for vosoritide, and our travel was provided by Global Genes. I'm not going to repeat the social -- I mean, the medical implications; you've heard them all. I'd like to focus on the functional and social issues.

Aiden used to want to hide; he didn't want to go places. He wanted to dress up in costumes so people wouldn't see him because he didn't want to be made fun of in public. A shopping trip is frequently ruined by staring, finger-pointing, people sneaking pictures. Occasionally, people will actually walk up and ask if they can have a picture. Kids have asked Aiden why his head is so big, why he looks like a baby. They picked him up at school, tried to carry him, drug him around by his feet. Just recently, about 2 months ago, he was lying on the floor in the church gym and a child his same age but much larger than him picked him up by his feet and started swinging him around. When Aiden yelled for help, the child dropped him on his head. This was not only painful to Aiden, but it was embarrassing and hurtful. This is his life; this is what he deals with, with achondroplasia.

Adults are frequently just as inconsiderate. Aiden was walking across his classroom to put something into the garbage

can, and the teacher asked him why he was up. He explained, and she said you're lying, you can't even reach the garbage can. All right, this is his life.

Aiden didn't start drug administration until he was 7 years old, so we knew we would not experience 100% of the drug's effects. Even so, we are pleased with the results. Typically, pain, leg bowing, spinal stenosis, these things get worse with age. For Aiden, all three of these have gotten better. Recent imaging has confirmed that there have been no changes in his neck or spinal condition in 3 years. Surgery 3 years ago was being talked about by his doctors; at this point surgery is not even on the table. Any amount of growth in the spinal column means growth all the way around. Length growth also means width growth, which helps relieve pressure on the nerves. Something that was once a huge risk for Aiden is now really just a consideration. This could be coincidental, but it could also be the effects of the drugs. If it wasn't for vosoritide, Aiden would most likely have had foramen magnum compression surgery, decompression surgery by now. He would most likely not have the range of motion that he has in his hands and legs and arms; he would not be able to play the sports that he plays. Aiden started the treatment way too late in life to get the best results, but it's not too late for other children with achondroplasia whose parents want them to have the most fulfilling childhood and to have a wonderful

life.

Thank you.

DR. HUDAK: Thank you. Speaker Number 20.

DR. BRONNIKOV: Hello, I'm Denis Bronnikov. I have a Ph.D. in human genetics, and I'm an executive at Roche. Global Genes provided for my travel.

Out there is my 2-year-old son Matthew. He's a smart and feisty kid with achondroplasia. My educational and professional background helped me be Matthew's health advocate, navigating through the maze of medical options and potential interventions that can benefit my son.

Matthew's diagnosis was as surprising as it was swift. Similar to the majority of parents with archon kids, the condition is not in either of our families. Minutes after stabilizing Matthew after his birth, the newborn pediatrician notified us that Matthew might have dwarfism. A week later Matthew's diagnosis was confirmed.

The costs of Matthew's medical care, including days of traveling to see doctors, have been significant. Costs for his birth alone were over $300,000. Tens of thousands of dollars are spent annually on regular check-ins with specialists to check Matthew's sleep patterns, conduct MRIs to monitor his foramen magnum compression, treat his frequent ear infections, and check changes in his profound kyphosis. Matthew has been a terrible sleeper and screamed a lot the first 18 months of his

life. Was he in pain? Was it fatigue? Countless hours have been spent by us, relatives, nannies to calm Matthew to sleep. The toll of sleep deprivation we encountered reduced our productivity and has been profound. We are fortunate that the foramen magnum compression that Matthew had earlier no longer needs an immediate surgical intervention. To help manage his kyphosis, however, Matthew is about to receive an uncomfortable and movement-limiting corset that he will have to wear most of the day for many months. No parent would want this device on his child. No parent would want his baby to go through the kyphosis-corrective surgery, enduring the risks and trade-offs associated with this procedure. Unfortunately, it's likely that Matthew will need one soon to prevent an injury of his spinal cord.

Next slide.

Existing means I'm not sufficient to alleviate the burden my younger son's condition makes on his health. Importantly, the key unmet needs of people with the condition are not limited to their use by the height and shorter limbs. If not treated with targeted therapy, Matthew is facing nearly certain surgeries, infections, complications from respiratory disorders, societal and psychological unrest, and also other hurdles as you see with achondroplasia. We can't wait for the moment when Matthew will be able to receive targeted, well-studied therapy to help him get healthier, reach his

potential, grow, and enjoy independence of living life to the fullest.

Thank you for your attention.

DR. HUDAK: Thank you. Speaker 21.

MR. JENA: My name is Satya Jena. I'm here to talk about my son Jeevan (ph.) Jena. Jeevan is a 10-year-old happy boy, diagnosed with achondroplasia immediately after his birth. My travel was provided by Global Genes.

Like every kid with achondroplasia, Jeevan had many challenges growing up. As an infant, he suffered from perpetual respiratory congestion issues and had his tonsils and adenoids removed. He had many ear infections with multiple antibody doses and three sets of ear tubes, including two tubes in both ears. His study showed sleep apnea. He's now on CPAP. His dental issues include overcrowding, and a jaw expander is being considered. Jeevan had low muscle tone, so we had to take him to a countless number of physical therapy sessions in addition to occupational and speech therapy. He managed to walk at the age of about 24 months but still has problems holding things tight because of loose joints in his wrist.

Jeevan's exposure to the real world came with its own set of challenges ranging from not being able to perform everyday mundane activities, like being able to climb up the stairs, using the restroom, or not being able to eat by himself. There have been issues with not being able to play with similar-aged

kids because of being either bullied or frequently stared at. I've gone to his school for 3 years and talked to his teachers multiple times to explain what to watch out for. If Jeevan is someplace else, this happens all over again.

Like any parent, we are looking for options to either treat or address some of these issues. We invested a significant amount of time researching and talking to various parents who are in a similar situation. Through this process we found out about BioMarin and swiftly enrolled Jeevan for the clinical research.

Increased height is the most important thing, not because of the height itself, but he can live like an average height person, do what everyone else can do, and not feel inferior because of his appearance.

From my standpoint, the treatment has helped him immensely, relative to expediting his growth process. He is more confident and is able to perform many of the things we take for granted that he could barely do when he was young, like putting on his clothes, reaching for the faucet, opening the door, or walking up the stairs. We are committed to continue Jeevan in this program for as long as we possibly can. If you ask me, as a parent, if I support the clinical research and treatment, then my answer is going to be 100% yes. Yes, just enroll your kid as early as possible; that way he or she can take full advantage of the treatment.

Thank you.

DR. HUDAK: Thank you. Speaker Number 22.

MS. KRAUS: Good afternoon. My name is Michelle Kraus, and I'm the Advocacy Director for Little People of America. Thank you for allowing us the opportunity to give our perspective on these potentially impactful drug programs.

I speak today knowing very well that with achondroplasia comes medical complications that challenge the quality of life we strive to achieve. Spinal stenosis, compression of the brain stem due to a tight foramen magnum, sleep apnea, hearing loss, and limb misalignment are some of the issues associated with this condition that can affect our members. These are the symptoms of achondroplasia we are focused on alleviating.

LPA is the largest and oldest support organization for people of short stature in the world. With over 7,000 members, many of whom have achondroplasia, we feel uniquely qualified to weigh in on these treatments. From LPA's beginnings over 60 years ago, we have been deeply committed to the value of diversity within the human species. Our founder, Billy Barty, celebrated dwarfism as part of the diversity of the human condition, and that tradition remains strong today. The community we have built has developed into a culture that is unique, vibrant, and filled with pride.

LPA realizes the potential value in the extension of clinical trials for achondroplasia. We feel that only with

more subjects and more time will we be able to determine if and how this drug impacts the morbidities associated with achondroplasia. It is of interest to us to see if these treatments result in benefits more valuable than an increase in physical stature. To this end, we hope that the FDA will push the pharmaceutical companies to pursue additional endpoints that will demonstrate this drug's effectiveness in reducing the common complications.

We want to stress that providing long-term psychological support will be critical to the participants and families of the trials. It will be important to (1) help address the impact of any side effects; (2) respond to any confusion about the trial's effect on the participants' appearance, and if and where they will find acceptance as to who they are; and (3) educate parents about their own expectations and responses to the trial and how it will relate to and affect their child's psychological well-being.

More than anything, we seek transparency. We need information. What are the side effects? What are the risks? Is it just height we are gaining, or are we solving the important issues that limit our quality of life?

Thank you for your time, and LPA looks forward to being an active participant in all the decisions that directly affect our community.

DR. HUDAK: Thank you. Speaker Number 23.

(No response.)

DR. HUDAK: All right, we'll go to Speaker Number 24.

MS. HARVEY: Hello, my name is Jamie Harvey. I'm cofounder of the MAGIC Foundation for Children's Growth and CEO of ICOSEP, the International Coalition of Organizations Supporting Endocrine Patients. I have no personal financial relationship with the Sponsor, but MAGIC does receive contributions via unrestricted grants from a number of companies for educational conferences in support of children impacted by these conditions, including BioMarin. I represent thousands of families affected by a variety of medical conditions, including achondroplasia.

As you know, one of the most difficult areas of healthcare is the conundrum of determining when medical treatments are deemed valuable. This is particularly true when dealing with complex and unknown treatments, and with each new advancement come more questions. I stand before you as a person who has personally experienced a lack of medical treatment options in my youth. I then faced similar problems for both of my children. Thanks to research and advancements, treatments were available for one of my children. The other child, with McCune-Albright syndrome, had no options.

Life-changing reality in those situations can be very dramatic. I can tell you, from our personal perspective as patients, this discovery process is an endless cycle, but I can

tell you with unequivocal certainty that it's an important opportunity because it's one of the rare times in our lives that we have hope. Every step in the discovery process is crucial for much more than we realize both today and tomorrow.

Achondroplasia is finally on the discovery path. In April 2016 the article entitled "Advances in Treatments of Achondroplasia and Osteoarthritis" concluded, "At first glance, achondroplasia and OA only seemed connected by the anatomical proximity of their affected tissue, but from that proximity stems a common developmental origin. Studying the pathways of development in the context of achondroplasia and OA holds the potential to inform efforts in regenerative medicine that seek to reverse these disease processes." This correlation was amazing and proved once again that each and every step in the discovery process is crucial for much more than we realize.

So as you consider this important scientific discovery of pharmacological treatment option for achondroplasia, please know we do support you. We realize that as a patient community we will never totally agree and not everyone will choose treatments, but I know from personal experience the option of treatment is essential and life changing. All we're asking for is a fair chance.

Thank you.

DR. HUDAK: Thank you. Speaker Number 25.

MS. BLAUSTEIN: Good afternoon. My name is Jill

Blaustein; I'm the mother of Jacob, who you met before, an intelligent, creative, funny, outgoing 14-year-old. He also happens to have achondroplasia. Global Genes provided our travel. Excuse me.

When I was 7 months pregnant, we learned by ultrasound and MRI that Jacob could have achondroplasia. He was definitively diagnosed at 11 months. He was not growing like other babies. I had no idea what achondroplasia entailed or what it meant. Jacob underwent x-rays and an MRI, which showed he had a compressed foramen magnum, and we were told that unless this changed, he would probably require brain surgery. We were so fortunate that the small passageway opened so he did not have to undergo that frightening surgery. Jacob has had numerous ear infections with numerous surgeries for ear tubes. He's had his tonsils removed twice, his adenoids out, and his turbinates reduced. He also developed sleep apnea. We've spent countless hours shuttling back and forth between doctors' offices and the hospital.

When Jacob was 7, my husband and I made the very difficult decision that he would undergo limb lengthening and straightening. My husband spoke about this gruesome surgery a little earlier.

And now to the good news. Jacob has been on vosoritide for about 3 years, and each year he grows 50% more than before he started vosoritide. He is now close to 5 feet tall. This

growth has made life easier and richer. He can reach sinks, toilets, light switches, and dishes all without assistance. He can cook on our stove, which is one of his many passions. He is now a healthier, more active person. He likes lacrosse, rock climbing, fencing. He loves to ski. And most recently, he learned how to surf. But his true passions are glass blowing and metal sculpting, which he can do now because he has increased strength.

Because his head and nasal passages have grown, his sleep apnea is no longer an issue. He breathes better, sleeps more fully, and has better stamina at school. Jacob does not need an adaptive device to use the toilet, and being more proportionate has made dressing himself easier. Jacob will be able to drive a car, ultimately, without any adaptation. He can ride the New York City bus by himself to and from school because he's much larger, and I'm not afraid that he's going to be bullied. Finally, Jacob's growth allows him to feel more like his peers. He is no longer the "only person" wherever he goes, and he has several peers at school who are his height.

I want to thank BioMarin for giving Jacob this incredible medicine. It has helped him physically, emotionally, and socially. It has made a tremendous difference in our family's life and in Jacob's ability to get along in the world. We thank you.

DR. HUDAK: Thank you. Speaker 26.

MS. CREWS: I'm Chandler Crews. Global Genes provided my travel.

Achondroplasia has impacted my life both physically and emotionally for 24 years. I have a 50% chance of passing on achondroplasia to any future children I may have. New parents are often told your child will be small; that's all. This is just false hope. Physical limitations with achondroplasia are more than just being short. With our age, bodies take a toll from daily life. I know many who are wheelchair-bound for life due to spinal stenosis and fusions, who need hearing aids and tracheotomies from complications of achondroplasia.

Growing up, it was hard explaining to my friends that I couldn't do something just because I was short. It was because of my spine, my neck, or because my arms and legs were not proportionate to my body. As a woman, dealing with feminine hygiene is not -- it's not easy, and if a spinal fusion is needed, it becomes more challenging. I couldn't wash my hair without assistance because my arms were too short to reach the top of my head. Driving was only an option with special equipment and sitting with the air bags dangerously close to my neck and chest. I couldn't get into the grocery store by myself because at 3'10" the automatic doors didn't sense I was there. Public restrooms are not only difficult because of getting on and off the toilet with 14-inch legs and short arms, but sometimes it's impossible to pull the door open to get out.

It has always been a constant struggle to be taken seriously as an adult. I would sense social discomfort from everyone I would meet, and this made meetings like job interviews difficult.

I became so frustrated with my height and lack of independence that I had limb lengthening. Each lengthening took about 7 to 8 months. I had three separate lengthening procedures to achieve my proportion and height. I would much rather have spent years taking a daily injection than to turn metal pins in my legs for months.

Although some of my peers with dwarfism embrace their physical novelty, I don't want any potential children I may have to be at risk of severe complications and disability. I don't want them to have to deal with all of the social struggles that can come with having dwarfism. Having achondroplasia isn't just being small or short; it's a lifetime of challenges, both physically and emotionally. If vosoritide has the ability to lessen complications and risks and eventually prevent them from happening at all, I think it is something that should be on the market.

Thank you.

(Applause.)

DR. HUDAK: Thank you. Speaker 27 is scheduled to participate by phone.

MS. BAILEY: Hello, my name is Rebekah Bailey, and I'm

here today from Minnesota. I'm here, like you all are, to talk about achondroplasia. I was born with achondroplasia dwarfism to two parents who also had it, and I have a younger sister living with it as well. I'm a college graduate with accomplishments in stage management and communications studies. Growing up, my dreams were limitless. I have an extremely supportive mother who surrounded her daughters with supportive people.

After the passing of my father in 1999, Little People of America granted my sister and I with a lifetime membership, and I have been an active member since. Little People of America is more than just a collective group of people with dwarfism. It's a tightly knit group of supporters, medical professionals, advocates, and families who care deeply about the health and well-being of one another. I'm an advocate; I fiercely believe in this organization and what it stands for.

Achondroplasia is the most common form of dwarfism, occurring anywhere between 1 in every 15- to 40,000 births. Eighty percent of achondroplasia births are to parents who are average height and have no history of the genetic disorder in their family. Achondroplasia can look like many things. Throughout my childhood I was what I'll say is lucky because I didn't have many of the common medical problems that can arise with achondroplasia. I've had five sets of tubes in my ears and sleep apnea in my early childhood, but that's about it.

Most of my friends and peers with achondroplasia cannot say the same.

For us, a medical breakthrough lies in health issues such as sleep apnea, spinal stenosis, and other corrective medical assessments. Please note the important difference when I say corrective versus elective. Limb lengthening is not a corrective surgery. It's an elective -- it's an elective choice, but in large, my community does not pursue, desire, or support. For us, a medical breakthrough is not in adding a handful of inches to make us better fit the mold of what society is built for. I am not deeply concerned with how different my life would be if I were 4'7" rather than 4 foot.

In the community, I think, we are here asking for clarity, transparency, and respect when it comes to corrective surgery. New families with no history of achondroplasia deserve crystal clear answers and options for the safety of their children. It is not on our list to spend thousands of dollars and the mental energy it would require having daily injections just to gain several inches. At the top of our list is equal treatment and be provided with transparent information for all corrective surgeries that will improve our quality of life.

Thank you.

DR. HUDAK: Thank you. Speaker Number 28.

MS. GONZALEZ: I'm Estefania Gonzalez. Global Genes supported our travel. I represent ALPE Achondroplasia, a

charity organization devoted to helping persons with achondroplasia and their families from all the world since year 2000. Three thousand people have consulted us, and hundreds have visit us to be assessed by our multidisciplinary team of specialists.

Achondroplasia is not just a question of height; it's internationally classified as a motor disability. There are many complications associated to achondroplasia. Children need special adaptations at school. Adults can't jump on a bus. They have problems for their personal hygiene. They can't reach countertops. Dwarfism is the only disability that seems to exist just for persons to be mocked, denigrated, and excluded. Social image of persons with dwarfism has not changed much in centuries. We dedicate great efforts to fight this psychosocial burden.

The first clinical trial on humans for drug for achondroplasia is taking place. It is scientific, subjected to the strictest controls by organizations such as the FDA. Parents are not so naive as sometimes thought of. We don't need to trust or distrust science; we get informed. We hope and expect.

Given the worsening of associated risks of achondroplasia as time goes by, did you know that a person with achondroplasia will undergo at least four surgeries in their lives? We want our children to benefit from any possible drug as soon as

possible. We are afraid when trials go on forever. Time pressures. We need to take difficult decisions, and leg lengthening, for example, is the only option nowadays to gain height. Who wants to enter a trial without a finish date? How long will they last, how long will it last, how long might I be taking a placebo? Isn't that unfair? My friend's son, Yago (ph.), who has achondroplasia, once said, "I can't wait to look people I talk to in the eye."

And what about younger children? This is a race against time. The sooner we start, the greater the benefits. Any drug targeting the root of the alteration, the FGFR3, will -- or malfunction and -- will improve all associated complications, not just height. Hearing problems, breathing problems, stenosis, and so on. Nevertheless, if only an objective criteria will prove or not the drug effect, specifically life quality, must be skeletal growth. It's the most clear and measurable.

We are in your hands. Thank you.

DR. HUDAK: Thank you. Speaker Number 29.

MS. MOSCATO: Good afternoon. I'm Sharon Moscato, and I have no financial relationship with anyone involved in today's meeting. I'm the average height mom of a 12-year-old son named Anthony Moscato, whose comments you heard earlier this afternoon, and I'd like to share five reasons why I believe drug development could be life changing for children with

achondroplasia and their families.

Reason Number 1: Every child should be free to maximize their human potential without juggling chronic medical complications. My son Anthony is a Big Brother, Lego master, honor roll student, two-time student of the month, published author in *LPA Today*, middle school speaker at a Dwarfism Awareness Month assembly, and peer mentor for autistic school mates. How much more might my son accomplish without also juggling obstructive sleep apnea, knee pain, multiple specialists, and chronic surgeries?

Reason Number 2: Achondroplasia brings with it a financial cost. The more obvious costs include multiple specialists such as orthopedists; geneticists; pulmonologists; ear, nose, and throat specialists; and audiologists; the related tests such as sleep studies, x-rays, and hearing tests; associated travel costs and medical and adaptive equipment, such as a CPAP, earplugs, and stepstools. The less obvious costs include pedal extenders for driving, tailoring clothing not designed to fit your body, and participating in social support groups such as Little People of America.

Reason Number 3: Achondroplasia also brings a steep emotional cost. As Anthony's mom, I am a care coordinator and tireless advocate when coordinating specialists, schooling, after-school activities, and summer camps. It is time-consuming, grueling, and utterly necessary. Procuring school

and summer camp accommodations are a minefield, especially with a condition as rare as Anthony's. Most perplexing to me and to others is how to balance my insistence that people treat my son like everyone else, except for one -- he is not like everyone else because of his orthopedic differences -- and hoping that people will understand the difference.

Number 4: Achondroplasia does not exist in a vacuum. It can and does exist with other chronic medical conditions. Besides achondroplasia, my son also manages a severe peanut allergy requiring him to constantly carry a talking EpiPen and Benadryl. And, by the way, our family does also include another child, Anthony's 10-year-old brother Matthew, who has his own dreams, needs, and special talents.

Lastly, the drug should be available for those who choose to use it. While he didn't choose to have achondroplasia, he should have the choice in how he treats it. For our family, it's not about adding a few inches of height to his frame for cosmetic reasons; it's about alleviating chronic medical conditions. He's a gift from God the way he is, but we respectfully request you consider the life-changing chance that this would give to kids like Anthony.

Thank you.

DR. HUDAK: Thank you. Speaker Number 30.

DR. ROSENFELD: My name is Ron Rosenfeld. I'm a consultant for BioMarin. I'm a pediatrician, and I've worked

in the field of pediatric endocrinology and growth disorders for 40 years. I'd like to share with you what I've learned over those 40 years about trial design and growth disorders.

Improvement in height is important for all conditions. It's not just final height, by the way, that we should be considering. I'm a pediatrician, and so normalization of growth in childhood is just as important to me. Start treatment early. The earlier, the better. The importance of sustained action, the importance of careful evaluation of skeletal maturation. Long-term controlled studies in children are difficult, and in fact, placebo-controlled trials to adult height are not only impractical, they're not feasible. And because of that, we've learned to appreciate the value of short-term controlled studies.

And I'd like to take a minute just to clarify that the FDA approval for conditions such as SHOX deficiency, Noonan syndrome, Prader-Willi syndrome involved short-term, observational, non-placebo-controlled trials and did not mandate final adult height data for all subjects.

There's value to carefully controlled historical data, especially if it's contemporaneous, because it allows you to evaluate the efficacy of treatment for your patients in parallel with contemporaneous historical database. Extension studies and registries are also important for both safety and unexpected benefits.

And, finally, let me tell you what I've learned about clinical trials specifically for achondroplasia. Number 1, it's a condition for which there is no effective medical treatment. All of the modalities that you've heard about are management modalities, and none address the underlying pathology.

Annualized growth velocity is, in fact, the only practical endpoint that we can evaluate.

Comorbidities will require years of evaluation and, in some cases, lifetimes of evaluation.

The goal of treatment in childhood should be to bring children with achondroplasia to the height velocity channel of average stature children.

The potential for the biggest impact is in the youngest children, but children of all ages may benefit.

And, finally, individuals with achondroplasia want options, and they want our respect for their ability to choose among those options.

Thank you.

DR. HUDAK: Thank you. Speaker Number 31.

MS. HARVEY: My name is Jamie Harvey once again, and I'm speaking on behalf of Amanda Tumbiolo.

"My 9-year-old daughter, Peyton, has achondroplasia. She struggles daily trying to make it in this average-height world. Life can be hard. It's painful to watch my daughter, at such a

young age, struggling to keep up with friends. Her 5-year-old brother, who is taller, runs and plays like the other children. He can go on amusement park rides and she cannot, which makes family trips challenging and very heartbreaking. She complains of leg and back pains, leaving her exhausted at the end of every day. We know the day will come when she will require a mobility chair, and it breaks my heart.

"Peyton struggles every day. Her short stature requires her to be in a five-point seat harness which she cannot unhook. So, daily, we hold up the drop-off line at school as I unhook her. She struggles with opening the heavy doors at school as the push bar is too high for her. She's not allowed to go on campus without a friend in case she gets stuck somewhere. At age 9, she requires her best friend's help in the school restroom. Her friend helps pull up my daughter's pants, button or zip them, and she has zero fine motor skills or strength. I'm forever grateful to her best friend but know the day is coming when she won't want to help her anymore. School is her bubble where she is respected, popular, and has great friends. She's very active on campus and earned a trophy in cross-country running a mile. She came in last, but she persevered with everyone cheering her on. Unity is what Peyton brings. She is different, not less.

"Outside that safe bubble is a very cruel world where she's stared at, spoken to as a 3- or 4-year-old, and called

many names. It's heartbreaking. She already is frightened at how she will accomplish tasks in life. She's terrified how she's going to get gas in a car. She's 9 and shouldn't have to be thinking about these things.

"We support the BioMarin clinical trial and treatments and hope she can be a part of it so she can have a fighting chance in life. I want to be very clear that we, as parents, are not trying to change Peyton. We want her to have a successful life in an average-height world. Please hear our cries as all kids with achondroplasia deserve this treatment option to grow. If this drug can make it happen, then let's make it happen. My little girl will always be different, but she is never less."

On behalf of Amanda and Peyton, thank you.

DR. HUDAK: Thank you. Speaker Number 32.

MS. SHAMIM: I'm Munira Shamim. Global Genes provided for my travel. Ahmin is my bright-eyed, full of life, 9-year-old son, and I'm here to advocate for his fair chance of living life with dignity, opportunity, health, and happiness. I want to tell you about functional challenges that Ahmin faces on a daily basis.

As a result of his short arms and legs, Ahmin is unable to reach the faucet of a sink, both height-wise and reach-wise. He cannot reach the top shelves in the refrigerator. He cannot reach the higher shelves in his closet. He cannot reach the higher shelves in the grocery store. He gets tired when he

sits in a chair for long because his feet do not reach the floor and dangle instead. He cannot seat himself on the toilet without having to grab the seat to mount himself. He cannot reach parts of his body for hygiene and care. The monkey bars in the park are beyond his reach. And in any case, his arms don't have the strength to hold him up. He's unable to keep up with family and friends while running, hiking, and camping. It is as though his body is too small to follow and keep up with the thoughts and wishes of his 9-year-old mind.

We adjusted light switches and the bathroom sink for his height, and there's stools around the house. However, in the outside world it is impractical for Ahmin to carry a stool and a grabber to reach and grip. The fact is the world is designed for people of average height, and the designers of this world did not keep Ahmin in mind. This experience can be isolating; it reduces self-esteem, sense of control, and a sense of having a meaningful existence.

I want to bring your attention to the pain that no doctor can see or treat. Being physically different at Ahmin's age is an invitation for bullying and social isolation. Sometimes a kid just wants to be a kid and to blend in and to not always be on the lookout for bullies. My worst fear is what happens when I'm not with him? I worry when he crosses the street, he will be too short to be noticed. In a situation of imminent danger, he will be too slow to exit quickly and will get crushed. I

fear that late one night in college, some drunk folks might fancy him for an inhumane game of dwarf tossing. In a world that tends to be superficial and judgmental, Ahmin will be judged by his short stature before being judged for his kind heart, good brains, or hard work. His appearance will always deny him a level playing field for opportunities in work and school, in making friends, and finding love.

Thank you.

DR. HUDAK: Thank you. And our last speaker, Number 33.

MS. EGGERTON: Last but not least, I hope.

DR. HUDAK: Absolutely.

MS. EGGERTON: Good afternoon, I wanted to thank all of you for allowing me to speak today. My name is Laci Eggerton, and I'm here to advocate for my son Jacob, who is 2 years old and was born with achondroplasia dwarfism.

Our son Jacob, in so many ways, is a normal happy little boy. He is full of laughter and love, but his diagnosis has already had an impact on him. He has endured chronic ear infections, pain in his legs, sensory issues due to delayed mobility, and difficulties in swallowing and breathing. The worst part for us so far is living with the knowledge that these medical issues will only continue to progress. We know his condition will render him to a life with bowed legs, unable to run with his friends, and will come to deny him the normal energy and curiosity of a child because of sleep apnea-induced

fatigue. We know that his condition will limit his range of movement and cause him debilitating pain with kyphosis and spinal stenosis. Above all, if he overcomes the normal social, physical, and psychological life issues, the medical complications that are associated will eventually shorten his life expectancy.

After our son was born, we were fortunate enough to take part in BioMarin's infant/toddler growth study at Vanderbilt, which we began October 2016. We are so honored to be a part of this study, and we are so thankful to the nurses and study staff who have become like family to us.

While our son's participation in the non-interventional growth study is helping advance knowledge of growth rates, it also means we have had to watch from the sidelines as the rest of the BioMarin study program progresses with success. The progress children have made in the interventional trials are very encouraging, and to see such pronounced impact on growth rates with such a reasonable safety profile gives us even more hope for our son.

While an infant/toddler study is planned to start soon, there is no guarantee we will take part. While we are confident that it is only a matter of time before this program successfully passes all the regulatory requirements to gain FDA approval, our son does not have the luxury of time. Our window of opportunity to impact his growth is limited. This Committee

could guide what hundreds of thousands of parents will tell their kids when they get older. This Committee could decide which two potential realities I get to tell my son. Will I get to tell him that his mom came to Washington, spoke with this Committee, pleaded with them to consider early access to a medication, and because of their compassion they found a way for him and others like him to grow much more than they would have otherwise and helped reduce some of the other risk? Or will I have to tell my son that unfortunately the rules governing the development of medications superseded an opportunity to impact his growth and that we missed the chance because his growth plates closed before we were able to gain access to this potentially life-altering medication?

I am asking you to please take my comments and those of other parents and advocates and of the scientists you have heard from and help find a path where the scientific development pathway is preserved, but at the same time where you find a path that allows me the opportunity to tell my son a story of success and not of failure.

Thank you.

DR. HUDAK: Thank you.

(Applause.)

DR. HUDAK: Let me just check to make sure that Speaker 23 hasn't slipped into the room unseen. Okay, well, that brings to close the public session, I think. On behalf of the FDA and

the Committee, we really thank the 31 speakers who talked about 32 perspectives. It was important, I think, that you told your stories, and it's very important that the FDA and the Committee hear those. Such amazing stories. Very heartfelt, very passionate, very thoughtful. I think that everybody gets an A for composition, public speaking, and poise, and our younger speakers get an A-plus. So let's give them a round of applause.

(Applause.)

DR. HUDAK: And just on a purely personal note, you know, obviously there is a lot of pain associated with this in many ways, but it is very uplifting to have heard the kindness, the love, and the advocacy that was talked about in this room, and we thank the families, the friends, the communities that supported your coming here and in your daily lives.

So, with that, we will turn to the more formal part of the program, and I think we have some questions that the FDA wants us to consider. So I'll remind the public that these are questions for the Committee here to consider, and only if you're recognized specifically can you contribute to the conversation.

So I think we have the first slide to show, the first question. Who's got the AV? Our AV person is on break. Do you have one I can maybe read? While we're waiting for the questions -- okay, I can read them. All right. So I will read

the question, and hopefully they'll flash up on the screen for you to see. So I'll read the question, and then I'll ask for anyone who has any questions about what the question means. Here we go, okay. Excellent.

Okay, so the first question is: Considering the various manifestations of complications of abnormal bone growth in achondroplasia, discuss potentially clinically meaningful study endpoints in the development of drug product(s) for achondroplasia.

So we've heard a lot of discussion about a variety of endpoints, we've heard a lot of perspectives from the community and some differences in those perspectives, so this is now open for discussion.

Yes, Dr. Neaton.

DR. NEATON: Would it be possible to put up the FDA's -- Dr. Abraham's Slide 10? I think it's the tenth slide. I didn't see a number on it. Maybe not.

DR. HUDAK: Slide 10 for Dr. Abraham?

DR. NEATON: It's the slide that's labeled growth velocity. So listening to the public hearing as well as thinking about this slide that was showed to -- that we saw earlier, it struck me that just, first of all, speaking about this slide, in different age groups, if you compare the second column with the third, the difference varies a lot, and so it suggests to me that in a relatively short-term study, if growth

velocity after a year was the primary endpoint, that it would be very important -- it could vary by age. Am I interpreting this correctly? I mean, just take the -- just taking the last three, the differences are like 24, 4, you know, 3 or 4 and then 3 or 4 again, and so that the choice of age that you would study, the expected difference to get to the -- what's referred to as average stature is different. And so on the one hand, that might help you kind of target an age group to study, but then if you target an age group to study, the finding may not be relevant to another age group. And so if you're going to study a broader age group, that might mean that even for this endpoint you might have to have a fairly sizable study in order to kind of take into account this variation.

If you move to kind of a clinical outcome, we saw a list -- I think Dr. Burman raised the question earlier about a list of outcomes and their feasibility, potentially, for even studying that kind of -- in kind of a trial like this, and we heard some of that. It struck me that in the public session that the types of clinical outcomes that might be relevant would be very different by age here as well. And so ear infections, for example, the types of surgery that people were experiencing, re-hospitalizations for various causes.

And so I just wonder, has the FDA thought about this? This is not an area that I'm an expert in, this particular field, but it strikes me that there's some data potentially

which exists and that we've heard that could guide you about both the appropriate kind of short-term outcome in terms of growth velocity but then, depending upon the age groups that you're studying, also the appropriate clinical outcomes. So it's more of a question than a comment, I guess.

DR. HUDAK: Anybody in the FDA want to respond?

DR. ABRAHAM: Thank you for your comment. And I think those are challenges that we've certainly entertained in our discussions, and you know, every drug development program is different, and what is possible or potential, although it might seem hard to do but may be necessary to do is to do more than one trial and look at perhaps different endpoints or the same endpoint in different groups. For example, if you have to do a study in infants to 3-year-olds versus 5- to 8-year-olds versus 10- to 14-year-olds, that is, perhaps, one path forward in understanding how any drug therapy might affect patients with achondroplasia, is to not just have one study with a large group but to break it down.

DR. HUDAK: Dr. Portman.

DR. PORTMAN: So to sort of address your question, because of the differences in the age, you really can't rely, I don't think, on the absolute changes in growth velocity but rather a standard based on age. So an SDS score for velocity would be the way you want to go. We face this in renal disease in short-statured kids on growth hormone, and that's the way we

solved it.

DR. NEATON: I understood these to be rates per year, what the numbers were here, but maybe I'm --

DR. ABRAHAM: They're annualized growth velocity rates; they're not SDS scores.

DR. HUDAK: Dr. Low Wang.

DR. LOW WANG: Thank you. Yes, so going back to the question of what clinical endpoints, I wanted to bring up this growth velocity slide as well, but I think that if we targeted a younger population, then I think annualized growth velocity in a shorter-term study might be a good design.

And at the same time, what I didn't have a great sense of is what's the quality of the natural history data that we have? And so one of the definitions or one of the criteria that the FDA brought up was the -- in terms of an open-label study versus a placebo-controlled study, if you had adequate natural history data, then you wouldn't need to use a placebo control. And so I guess I don't understand how good the data are in terms of survival, so we know that there's increased mortality in infants and toddlers with achondroplasia, but how much? What's the absolute incidence? And is that enough to be able to do an open-label study? So I think that if we targeted a younger population, so infants and toddlers or below age 2, we could potentially use the annualized growth velocity and survival even, depending on what that absolute instance is.

And then I think it's really important to look at some of the other clinical outcomes, so looking at some of the clinical effects of -- or complications of achondroplasia. I don't really know when some of these ages these manifest, but you know, of course, in kids we're trying to look for assessments that are less invasive, and so complications such as sleep apnea, disordered respiration, conductive hearing loss, those are potentially assessments that are less invasive, and if they occur early enough, those could be studied as well in a younger age group.

And lastly functional endpoints, of course. So that's another important thing. If there's some way to be able to measure that in that same group, or I guess that might end up being an older group, up to age 5 would be important to look at. So I guess the question is like do you think the natural history data are adequate, what we have?

DR. THANH HAI: This is Mary Thanh Hai from the FDA.

So what you're raising here is actually the challenge, and this is the reason why we want to bring this to an Advisory Committee to get advice on development programs in achondroplasia. As you have heard from the presentations, you've heard from the Open Public Hearing, it's a very variable presentation, and there are different impacts on patients at different stages of their lives.

So in this question here, Dr. Neaton asked to look at

Slide 10, but there are other endpoints that we have heard as well. And I think the question to the Panel here is that depending on the endpoint that you believe is clinically important, and again, you can call into the -- what you've heard in the Open Pubic Hearing, what stage in the patient's life would that be an appropriate time to actually evaluate? So, for example, if otitis media is important but that's something that only occurs before age 5 with respect to the consequences of multiple otitis media, then it doesn't make sense to do a program where patients are being enrolled in adolescence and above. So that's what we're trying to struggle with here is that there is a diverse number of clinical endpoints to evaluate, and we'd like to hear from the Panel what you think should be considered, and it doesn't have to be one trial. In fact, that leads to the substantial evidence that we often ask for. You just have one trial looking at one endpoint, and at the end of the day, we don't know how to interpret it, versus multiple trials, even looking at varied endpoints that have clinically meaningful impact on patients' lives that may be actually very important as well.

And, I'm sorry, with respect to natural history studies, that's -- yes, that is also a struggle. You heard a little bit earlier about the natural history studies that Dr. Abraham alluded to. Are they capturing all the different endpoints that you've heard today as well? And that's what we would need

if we're going to do a study where we can't have a concurrent control, and so that's something to think about with respect to whether or not one can have a placebo control, rely on a natural history as a concurrent control.

DR. HUDAK: Okay, I'll start down here.

Dr. Everett.

DR. EVERETT: Brendan Everett.

So with respect to Question 1 here where we consider the various manifestations and complications and what endpoints might be appropriate for a trial, so I think there's a number of different issues that are wrapped up here, and I'll start with the idea that potentially the size or the dimensions of the foramen magnum seems like something that, at least to the frankly lay observer, these sort of skeletal developments might be a reasonable endpoint with the caveat that I think it has time dependency, just as Dr. Neaton mentioned, and is clearly an issue in pediatrics. I found an abstract here published in 1989 that suggests that the bulk of the growth happens before 1 year of age. And that's not an appropriate endpoint if you're going to study children who are 60 months and older, for example, or 5 years and older. But it might be an appropriate endpoint, and it might deal with some of the other key complications that we heard about earlier, such as sleep apnea, for example.

I think the annual growth velocity actually strikes me as

an appropriate endpoint for a couple reasons. First of all, there's clearly -- if the medication being tested, any of the medications being tested works, there's an opportunity cost to waiting too long until allowing that drug to be available to other children. The opportunity cost is the children who don't have access to that. So if you wait for 20 years to get the perfect study to get the answers to whether or not achieved adult height is actually different in the active versus the placebo, you've missed the opportunity to provide that agent to many, many children who now have -- their epiphyses have fused and the game is out, right?

That said, I think growth velocity is a difficult one, particularly in an open unblinded trial. In cardiovascular medicine, when we do a blood pressure trial, patients often have their blood pressure checked by an automatic machine that doesn't present any numbers, that goes directly into the study database to prevent the investigators, and this is in a double-blind randomized trial, to prevent the investigators from interpreting or altering those data.

I would really worry about the reliability of the data of something about height, which is presumably something -- growth velocity comes from height, when the investigators know what medication the patients are getting and may have some assumptions about which direction the effect is going to be. You can perhaps attenuate that effect a little bit with the

placebo-controlled trial, but nonetheless, the measurement and the measurement error and the potential for bias, I think, is an important thing to consider as you construct an endpoint.

DR. HUDAK: Dr. Burman.

DR. BURMAN: Thank you. I agree with the comments that were made, and I'd just like to expand on them or discuss them briefly for just a second. Obviously, the key issue is what's the primary and what's the secondary outcomes based on this question, and I agree, it should be annualized growth rate seems to be the most quantitative, and I think we're going to be talking later about placebo versus non-placebo, and that's obviously relevant as well.

But then the other secondary outcomes, which are all potential complications of the disease, have to be stratified based on age, as was mentioned. Otitis, sleep apnea, hearing loss, motor functions all have to be stratified, and therefore, I agree with what the FDA said before, that there's probably going to be two studies looking at the various outcomes, foramen magnum being measured earlier than later. But I think the main outcome is annualized growth rate.

DR. HUDAK: Dr. Bhatia.

DR. BHATIA: I agree with the comments, but one of the common themes that we've heard this afternoon and this morning among the meaningful clinical complications has been sleep apnea, which is a potentially dangerous complication. So what

if that is a secondary endpoint -- there's a couple because even though I'm not -- I was trying to figure out, I was going to look at my orthopedic surgeon to explain to me how a tube growing north would create a growing sideways as well, which is what we're talking about.

But anyway, nonetheless, clinically that would be one of the most significant clinical complications that we can ameliorate if you go just back to -- average growth velocity, end height, everything else we talked about with small proportion was a meaningful outcome, but the secondary outcomes also gain a lot of importance.

Thank you.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: So one of the things that struck me in the public comment was the improvement in quality of life, which, you know, we've been talking about all of the clinical manifestations, but I think health-related quality of life is sufficiently rigorous. That, of course, would not be a primary endpoint but I think an essential endpoint that other parameters may not quantify. You know, I was struck by -- it seemed like quality of life may have not been directly related to quantity of growth height or end height, and so I wouldn't want to miss the overall improvement that isn't captured by the clinical manifestations.

DR. HUDAK: Dr. White.

DR. WHITE: I had a bunch of comments, and I'm not sure where to go. It seems to me that we're missing a big opportunity if we don't start early with this disease. Risk of sudden death in the first year of life is pretty high. Risk of ear infections and loss of hearing later and speech problems, you have to intervene early. Progression of the foramen magnum, other skeletal abnormalities. Some of this stuff is even manifest in utero. I mean, maternal fetal medicine frequently makes the diagnosis of probable achondroplasia, and you can do genetic testing and know whether the child has the gene by amniocentesis, if one chooses. So we can make this diagnosis pretty early with genetics.

It seems to me if we're going to intervene and if we're going to study this, we should study it in the period of time where it's most likely to do the most good, and that would be in the first year, 2, 3 years of life. That's where growth is greatest; changes can lead to need for surgery very early on. Ear infections, we could maybe have some intervention with. So it becomes a matter of what is the best thing to look at? Well, I think we need to evaluate the foramen ovale -- and I'm sorry, that's cardiac.

(Laughter.)

UNIDENTIFIED SPEAKER: Magnum.

DR. WHITE: This happens to me on a regular basis.

(Laughter.)

DR. WHITE: This foramen, not the other one. And so how do we do that? An MRI is probably the best measure that -- except you have to put the kids to sleep. But in the discussions, it sounds as if part of the general management of patients that have this problem is to evaluate with an MRI. So if that's considered at least a reasonable standard of care, then it doesn't become an ethical problem to put the child to sleep to do these studies in the first year of life as part of your protocol. Ear infections, we can easily keep track of those.

So it seems to me growth velocity is great, but you can always stretch a baby out. I mean, I don't know how many of you tried -- well, probably all of you have tried to measure babies for growth, and it's -- you know, my growth curves in my clinic look like this because it depends on how much the nurse stretches the baby out on that little table when you're doing the measurement. So I'm not sure that I believe growth velocity in first year of life is a particularly easily measurable process. My neonatologist here is making faces at me.

But it seems like a plan to evaluate growth velocity and skeletal abnormalities early on with MRI maybe once -- and you'd have to get someone to tell me what standard of care would be, but every 6 months or so for the first year and do interventions early would be -- those would be good endpoints

and should be evaluated early, not when you're 12, 13, or 14.

Thank you for your indulgence.

DR. HUDAK: So I'm going to try to alternate --

DR. WHITE: And we can close the foramen ovale very easily.

DR. HUDAK: You don't want to do that to the magnum, right. Okay. So I'm going to alternate, but just to comment on measurement. Yes, with the right instruments and the right training, it can be done accurately. That's very different than stretching a baby on the table and putting two pencil marks on the paper so --

(Laughter.)

DR. HUDAK: All right. Dr. Budnitz, I think you were next.

DR. BUDNITZ: So I'd just like to second comments made by a couple folks on the Committee that seems like there are -- there would be, and not being an endocrinologist or a pediatrician, I don't know for sure, but kind of growth disorder-specific activities of daily living instruments that would be validated and would just encourage those to be included also, not just in the -- as a secondary endpoint in the studies of the drug, but also in prospective natural history studies as well. And even if there are not those activities of daily living, are there other functional measurements that are standardized, like ability to touch one's

knees, to be very simplistic, but ones that can translate into, you know, the benefit is defined by the FDA framework of, you know, impacting how a patient functions or survives? So I think those might be important to include as outcomes as well.

DR. HUDAK: Dr. Wilson.

DR. WILSON: So to build on what the others have said -- Peter Wilson.

One is questionnaires plus potentially objective measurements. Questionnaires could be done for sleep, for going to the parents, and then potentially, if above a certain threshold, do sleep studies, and those can be done at home, not necessarily in sleep labs. This is how we approach sleep apnea in adults in a population setting.

Another one, because we heard about airways, I've wondered whether FEV1 or any some sort of simple spirometry, there are emergency rooms, very simple -- whether that's of use in children, but some of these are really easy, and there are simple devices available; we just don't have data. My colleague here has found a quality of life instrument in achondroplastic children in Germany; isn't that right --

DR. WEBER: Yes.

DR. WILSON: -- Tom? So that ought to be translated and tested somewhere here also in the States. And then the final one is strength, so elements adapting to the smaller size hands and arms, some sort of grip strength for these children with

small hands and upper arm, and lower extremity kick strength or biceps/triceps strength. Those could be some other measures that could be used as secondary measures to complement, in addition to growth measures.

DR. HUDAK: Dr. Cataletto.

DR. CATALETTO: I just wanted to answer some of the points that Peter brought up based on pediatrics. We're usually not able to get office spirometry until you're about 5 or 6. Very, very effort-dependent. I have to get you on the right day at the right time of the day. And then also about sleep, we don't do home sleep studies in general, and for the most part, because kids are little wiggly worms, we tend to do them in a supervised setting so if they dislodge the wires or the -- you know, the leads, they're able to be done again.

DR. WILSON: So, to follow up, for those who end up with a diagnosis of sleep apnea who did get an active molecule, though, you could see whether they improve.

DR. CATALETTO: Absolutely.

DR. WILSON: So that would -- you know, you can go as far as the -- in a lot of chronic disease medicine in adults, we do a questionnaire, objective measurements, and then treatments, and then you can also back out of it as well, but try to use as best as possible objective data rather than self-reported data.

DR. CATALETTO: One of the things that was interesting in the data that they presented was the fact that they chose to do

a composite of tonsillectomies and sleep apnea. The primary treatment for kids who are surgical candidates is an adenotonsillectomy. And so it would be very interesting if we could separate out those ages into the peak of when the tonsils and adenoids are at their greatest size because we know that just from the craniofacial configuration of someone with achondroplasia, even what looks like a relatively small obstruction may actually be more of an obstruction given the limited space. So it's really a matter of following it and watching it. And the last point is that we tend to look at the sleep studies more frequently than the adult people do because a child is growing and their facial configuration is growing as well.

DR. HUDAK: Dr. Pahys.

DR. PAHYS: So thank you. I would agree with the majority of the comments that have already been stated. In my opinion, there's a litany of data points that need to be addressed, and that certainly -- they're all very relevant. But as far as concerning endpoints, looking at the most objective measures that are available and reproducible is what's most important to evaluate, and certainly, I think height respectfully is probably one of the most reproducible and objective measurements that you can get from infancy, from newborn to teenagers, as well as the diameter of the foramen magnum, neural canal width. They can be obtained objectively with good

reproducibility, inter- and intra-observer reliability, with routine studies that we're getting on these patients, regardless if they're in the study or not. Typically, we get MRIs on a patient at the time of diagnosis for hydrocephalus, also foramen magnum dimensions, and then annually unless there are any changes in their exam.

But the other examples that we've been discussing, quality of life, even neurologic changes, otitis media, all of them definitely have a subjective component to them. While it's all certainly relevant to have those data points included as far as endpoints, what is the easiest and most objective points to follow and monitor objectively? I think it's important to focus on those measurements, neural canal width, foramen magnum diameter, and height. I know height isn't the primary -- isn't the only goal of any intervention, but again, it's the most likely reproducible and objective measurement of success or failure.

And I certainly agree with the rest of the Panel in their discussions of earlier evaluation, and most of your canal width is obtained between the age of 2 and 5, so earlier intervention, earlier monitoring is certainly, I think, warranted and important to start in infancy, but definitely before age 5.

Thank you.

DR. HUDAK: Dr. Cooke.

DR. COOKE: So while the ideal therapy would clearly correct all of the abnormalities, the height deficit, the neurologic abnormalities, I'm very comfortable saying that if you had a therapy that just impacted final height, there would be a benefit to that as long as that improvement was significant and significant in a clinical way, not just a statistical way.

So if, you know, final -- if improvement in final height -- and I think we heard from the open panel discussion this afternoon that there were substantial morbidities just related to size issues that I think really supports that benefit of final height as an important outcome. Now, the challenge there is final height outcome takes a long time, and so I'm not sure that a trial to final height is absolutely necessary to get evidence for that. And so I think as we've discussed, growth velocity change in a well-designed, placebo-controlled trial that's controlled for age of the patient, pubertal status, and all those other issues that we know are going to affect growth velocity could be sufficient to provide enough evidence of a final height benefit to justify it.

Now, I would add, beyond what I think has been said already, that I think that data would have to be more than a single year trial of growth velocity just because of the question about attenuation of the effect over time. One thing

I would add is that it's not surprising to see a decrease in growth velocity even with effective therapy since the normal growth rate in children declines over time. So seeing, for instance, that with therapy, even with completely effective therapy, the growth velocity is lower in the second year of therapy than the first year of therapy, that wouldn't concern me about a true attenuation of effect, but I think being able to evaluate if there was a concerning attenuation of that effect would be necessary. How much beyond 1 year, whether it's 2 years or longer, I think depends on that second year data, but if there's a marked attenuation in that growth velocity with that second year of therapy, I would have questions about using growth velocity as a surrogate for final height, which is what you would end up doing.

Now, I think combining what others have said, I think the other key area of investigation for achondroplasia is this issue of early growth of the foramen magnum and other issues related to the neurologic, and I think that is another important investigation that should be done early. I think the challenge is this issue of initiating a therapy at birth in a child without sufficient confidence of safety to justify that, and where that level of confidence comes, I think, varies with the early data. So I think a subsequent study, you know, and how subsequent to initial evaluation of growth that would be, I'm not sure, but I would ask for investigations in that early

age as soon as is feasible from a safety standpoint.

DR. HUDAK: Dr. Havens.

DR. HAVENS: Thank you very much. First of all, I wanted to say thank you to the people who presented today. I think those were powerful statements from the community that really helped me focus a lot on what we're trying to do.

And so what we heard about and saw pictures of is not just what we've been talking about in terms of stature, but also shunted hydrocephalus, which may be more a function of changes in the jugular foramen size, not just the foramen magnum. So there's other base-of-the-brain endpoints that you could look at. Clinical endpoints would include not just abnormal polysomnography or size of -- or hydrocephalus seen on MRI, but also the number of times that you needed to have shunted hydrocephalus or hydrocephalus shunted in a treatment versus a control group. I think the presentations today broadened out many of the potential clinical endpoints that you could look at in a study, but again, to me, argue for earlier treatment studies when these things are the most important to deal with.

DR. HUDAK: Dr. Snyder.

DR. SNYDER: So I just want to make a comment about non-therapeutic procedural sedation in pediatric studies. So you heard me talk about minor increase over minimal risk, and the Pediatric Ethics Subcommittee met in 2015 and discussed non-procedural -- non-therapeutic procedural sedation, and they

weren't able to determine whether or not it met that criteria, but they did issue a number of different recommendations that we generally ask when we're consulted to be placed in FDA protocol so that IRBs can follow those recommendations and consider them when they're looking at protocols.

And my understanding is that even for patients in a placebo arm who might require an MRI and require some type of procedural sedation, that might be approved as a minor increase over a minimal risk by an IRB. So I don't think that -- although it's ideal for those procedures to be done as part of clinical care, and we would look at the number of procedures that needed to be done in a protocol in terms of making that determination, I don't think we should preclude those procedures in a placebo-controlled trial if we think that they might be scientifically relevant.

DR. HUDAK: Dr. White.

DR. WHITE: I just wanted to add to what you said. I would have difficulty approving -- I was on that committee, and we met. I would have trouble committing to non-procedural or non-beneficial sedation to do MRIs unless it's standard of care for the treatment of those patients who are in the placebo group or those participants who are in the placebo group. And from what you're saying, it's pretty much standard of care that these children are going to get MRIs, and it's really just a matter of determining how often they're going to get the MRIs

early in life to evaluate the head and the foramen -- I did it again -- foramen magnum.

DR. SNYDER: Well, so if the MRIs are only done typically, you know, annually but you might --

DR. WHITE: Then you would have to kind of stay with that.

DR. SNYDER: You know, I don't know that that necessarily is what's happening, but you know -- because we see a number of protocols where non-procedural sedation is used as part of a protocol in placebo arms.

DR. PAHYS: Surveillance studies on achondroplasia can vary based on the patient and the practitioner, so I think there, to my knowledge, is no set defined criteria that needs to be performed on this, you know, basis. It's similar to like the Downs patients; how often are you monitoring their cervical spine? It varies based on the practitioner and which way the wind is blowing. Certainly, it is established that regular screening studies, especially in the early ages, is appropriate for monitoring purposes.

DR. SNYDER: So it sounds like you have enough variability within the population that that would be covered within the protocol anyway, you know, so --

DR. PAHYS: I think it's within the standard clinical care.

DR. SNYDER: -- it may not be an issue with this particular study design.

DR. WHITE: I think it would become a moot point as long as we did some sort of survey to find out if we're in the general range of practice for the general care of these patients.

DR. SNYDER: And you have to look at the type of sedation, too. I mean, there's a wide range. Sometimes you're just giving something to make them relax so that they can sit through the MRI, and other times, you know, if you're looking at something that's more intensive, then that may not be acceptable depending on the patient population and their comorbidities.

DR. PAHYS: I think it varies based on the institution. The higher volume pediatric institutions are able to do -- when you know there's no other pathology that you're looking for, you don't have to do, you know, innumerous axial scans. You can do a sagittal scout T2 image that will give you all -- basically nearly all the information you need with one series. As opposed to, you know, a 3-hour scan, you can do it in 5 to 10 minutes. But, again, that's not always available at every center, so in the major centers it's performed quite commonly, but there's also -- at those centers they have the ability or patients, if you will, to try alternatives to general anesthesia as far as other measures they might do, you know, sugar water or anything, wrap the kid up, that can get them still enough for a short enough period of time to obtain an

adequate study to evaluate for hydrocephalus, neural canal width, and foramen magnum diameter.

DR. SNYDER: And if you look at the recommendations that the Pediatric Ethics Subcommittee has posted online, there are a number of recommendations, one that includes, you know, having a pediatric anesthesiologist doing it at a center that is comfortable doing the procedures, limiting the amount of time, that type of thing, so that you reduce the risks to the patient when you have to do those procedures.

DR. HUDAK: Dr. Zemskova.

DR. ZEMSKOVA: Yes, I have just a question, just want to make sure I understand clarification from those who said that annual growth velocity might be sufficient for 1 year in this population. Did you consider that this will be related in that patient with disproportional growth, because my impression -- assumption is made based on other improvement in other states where you see proportional growth. Here you have kids with disproportional growth where their annual growth velocity will be of the same evaluation as in kids with proportional growth.

DR. COOKE: I may not be understanding your question, but I don't think the fact that disproportionate short stature in achondroplasia would alter how I would evaluate for a growth response. So, yeah, I think I would be comfortable with still doing it in a similar way.

Maybe I'll take advantage of this to just kind of respond

to an earlier question about the ability to evaluate the growth response in a neonate or in an infant. There certainly is more measurement error in an infant than in an older child, even in an endocrine practice where we do that all the time and are very careful. On the other hand, you know, we're looking at differences of growth rate of 44 versus 20 cm in the normal versus achondroplasia. So I think the measurement error should easily be, you know, washed out by a treatment benefit, and if it's not, then I would be very concerned about that, so I'm not concerned about the ability of following growth in an infant.

But I think I'd be very interested in looking at the effect on disproportion of a therapy for achondroplasia, and certainly, if there was evidence that you could eliminate or correct the disproportion with therapy, I would weigh that into my interpretation of a beneficial effect that would be above a change in growth velocity, just more evidence that this really is impacting the growth plate abnormality, but I'm not sure that I would require that since I think just getting improved outcomes in terms of statural height and arm length which, you know, clearly is a disability that's been described in the open session and other places, that would be sufficient even if the disproportion wasn't corrected.

DR. PAHYS: I would also argue that measurement of, you know, limbs versus complete stature height is very challenging and would be -- the inter- and intra-observer reliability would

be all over the place when trying to measure arm length, leg length without radiographs, and that would obviously add, you know, additional radiation exposures that would be prohibitive. So I think overall stature is probably the most feasible for measurement purposes as opposed to looking at limb length changes as well.

DR. COOKE: Maybe just to state it more specifically, I would absolutely agree that, you know, actual height velocity or height change would be the primary measure, but certainly the disproportion should be a very important secondary outcome measure.

DR. HUDAK: Okay, we will do three more questions and then come to a consensus. So Dr. White.

(Off microphone response.)

DR. HUDAK: Oh, is that down? You're done, all right.

DR. WHITE: I'm done.

DR. HUDAK: Dr. Cataletto.

DR. CATALETTO: Oh, sorry.

(Audio cuts out.)

DR. CATALETTO: -- the chest because there are so many pulmonary complications, because your chest changes as you grow, the whole configuration of your chest will change as you age, and because as you increase your growth, there is fairly frequently the complication of scoliosis which will affect even how we look at pulmonary function. So I would love to see that

as a secondary outcome.

DR. HUDAK: Okay, Dr. Neville and then Dr. Abraham, and then we'll summarize.

DR. NEVILLE: So one of the comments I was going to make was you were talking about potentially different studies, so depending on the age that you studied, for me, that would dictate the length of the study. And I think we're going to get to this later, but one of the things I'm sitting here grappling with -- maybe especially, maybe not in the earliest age group, is I don't know what a clinically meaningful safety endpoint is because it seems like growth and quality of life and complications are good endpoints for efficacy, but in a previously unstudied population of our youngest patients, I think safety may be challenging.

DR. HUDAK: Dr. Abraham.

DR. ABRAHAM: Thank you. I just wanted to ask a question to Dr. Pahys regarding the foramen magnum diameter, just for more information for ourselves. Do you have a sense of like what percentage increase in diameter would, I guess, be clinically significant or could potentially reduce, you know, the risk of sudden infant death or prevent other complications, just to get an idea of like, you know, what are we looking for over a 12-month period of time?

DR. PAHYS: I think anything beyond, you know -- I don't know that I would say percentage increase is that significant

that you could say that they're now at a markedly less chance of catastrophic injury. I know we look for neural canal width of greater than basically 10 mm and above. Usually, you have -- the cord has enough room to breathe, so anything kind of above that, you're in good shape. Anything below that is usually constrictive and will likely require intervention. So I don't know that, you know, I'd say a percentile increase is one, but usually more, it's just the cord needs, you know, so much space to breathe, so usually anything about 10 mm you're in reasonable shape, if that helps.

DR. ABRAHAM: Yeah, that's helpful.

DR. HAVENS: And there are papers that were provided in some of the references, by Hecht 1989, paper showing that growth of the foramen magnum in this population compared to normal or to average growth populations, so some of those normative data already exist for this group.

DR. ABRAHAM: Thank you.

DR. HUDAK: Okay, let's try to bring this to consensus, but before I do that, I want to ask a couple informational questions. So the first one I have, which I think is really important, is what is the incidence of death in this group due to CNS issues? Considering that there are -- if the incidence of this is 1 in 20,000 in this country, that is 200 children with achondroplasia from age 0 to 4, so within that 800 patients, how many of those patients per year succumb to

complication related to a narrow foramen magnum or sleep apnea or something like that? Do we know?

DR. HAVENS: Again, the Hecht series of papers are very old, though, from the '80s, show a change in SMR up to age 34, but the change is greatest in the youngest populations in terms of --

DR. HUDAK: I'm not asking for the anatomy. I'm asking for the incidence of death.

DR. HAVENS: No, no, no. This is the mortality ratio.

DR. HUDAK: Okay.

DR. HAVENS: The mortality ratio is different in achondroplasia compared to the normal population with the greatest differences being in the youngest age groups and being different than average size up to age 34 but then -- but these are very old studies, which is why you would have to take into account current interventions that would prevent death that might have otherwise occurred, like shunting hydrocephalus and CPAP and other surgeries.

DR. LOW WANG: So just in terms of overall sudden death, I mean, this is not only related to cord compression but also to a few other things. It looks like I found in the background information 5 to 10% of achondroplastic children, so that's pretty high incidence, and so if that's 50 times normal --

DR. HUDAK: By what age of --

DR. LOW WANG: And I don't know how -- this is from a 2014

reference. I don't know if that's from a more older population.

DR. HUDAK: Five to ten percent in the first year, that's pretty significant.

DR. ABRAHAM: I don't know that that's in the first year. This is from an article by Ireland et al., one of the references that's provided, and I think, you know, those authors basically say, you know, the risk of sudden infant death is approximately 5 to 10%, but I don't know that we have more, you know, in exactly what age group or any other information than just literally that statement.

DR. NEATON: One year?

DR. ABRAHAM: No, that's what I'm saying; I don't think we have that information.

DR. HUDAK: The incidence of sudden unexpected infant death is about 1 to 2 per 1,000, so --

DR. COOKE: And just to be clear, sudden infant death, by definition, is in the first year of life, so that would be the first year.

DR. HUDAK: Right. Infants, infants, the first year. Correct. Okay, well, that's an important number to know. I think that is an important, potentially, I think, efficacy variable. So let me just ask if there is anybody on the Committee, around the table, that would pick a primary efficacy outcome other than growth velocity?

(Off microphone comment.)

DR. HUDAK: Okay, so comment.

DR. WHITE: I think that there are other -- I think it was clear from the public comments that not everybody's worried about being taller, and it's the morbidity associated with the disease process that really has more effect on their life than whether they're tall or short. And I think that the parameters that we could get from damage to the central nervous system and abnormalities of the bone growth, not necessarily length, might be more important.

DR. HUDAK: Mary, you had your hand -- you had your hand up.

(Off microphone comment.)

DR. HUDAK: Oh, okay. All right, so everybody else thinks that growth velocity in some way is the -- Melody.

DR. CUNNINGHAM: Melody Cunningham.

I really think in the -- you know, I sort of see these as two different patient groups, and I know that we -- there's a substantial difference in patients with achondroplasia and normal stature patients in infancy in terms of the growth velocity, but I think the really -- it's sort of concurrent with that, and maybe even more meaningful from the standpoint of mortality and outcomes is looking at the diameter of the foramen magnum. So as I think of the infants, that's what I think.

DR. HUDAK: Dr. Havens.

DR. HAVENS: And I, too, would put this into the context of two separate studies. One might be in the group of people who have -- age 2 to 10 where we saw that growth was essentially flat, you might be able to look reliably for growth velocity changes in that group, which would be a more accurate representation of -- what we want to do is get a study that's going to make it so you can study in younger kids, and Dr. Baiten (ph.) is concerned about sample size, everybody's concerned about the duration and the variability in the outcome, so it's harder to do it in younger kids. You could do growth velocity in older kids, but in the adolescent age group you have to be careful because there are changes in growth over time, and so you'd need to be careful.

So in an older population, growth velocity might be okay, which would allow you to move towards studying younger people, but the opening comments from Dr. Baiten suggested growth velocity might be hard to look at in that age group, if I understood it right.

DR. HUDAK: Okay, so I think we get into some of the other questions, get into some of these other issues about age of studies, how to design your study, whether it should it be randomized, controlled, placebo, you know, other things. We'll get to those. We discussed some of that in this -- so considering this question narrowly, clinically meaningful

endpoints in the development of the product, I think that you've probably heard a consensus, not unanimity maybe, but a consensus that growth velocity is an important measure and is objective, but as importantly, there are these other issues that have to be developed, not as primary but as secondary outcomes that are critical.

Some new things came up with the session today that did get to specific issues related to functionality, quality of life; these are things that have been talked about, but I think they're very important, you know, looking at -- I don't think we could talk about this here, we'll defer that until after the break, but I think a lot of these issues need to be in the matrix, you know, if only to demonstrate that you're not having any signal that these things are worse. I'm not sure you're going to get power to study on any of these things that will give you a primary efficacy endpoint that will be significant, but I think if you see -- consensus appears to be that if you see, you know, good growth velocity parity or getting toward what a normal person does and a reduction of some of these other morbidities, that that would be a very appropriate way to sort of think about this.

DR. BHATIA: I think you got, I think, something like a structure function claim. Growth velocity is one thing, and then with the caveat that we can't measure 0 to 1, but that's beside the point. So what clinical outcome is going to be

beneficial to the child? And that's one thing, whatever we choose, foramen magnum, foramen ovale, whatever -- we got to choose a clinical outcome.

DR. HUDAK: All right. Yes. One last comment, and we'll break.

DR. NEATON: I'll see if I can say this clearly. So it seems like one of the concerns about the younger age group, appropriately so, is safety and understanding the safety of any treatment that you're going to use in an older age group before you go to the very young. On the other hand, I thought what we heard during the public comment, and I think what was supported here is that potentially there are kind of efficacy kind of outcomes that are probably going to be more commonly observed in the younger age group that you could measure.

And so I just want to say that in many trials, I mean, I'm involved with one right now with a vaccine, it's very common to begin the trial in older people and progressively go to younger people in the same trial once you've established the safety of the product to a certain degree in the older -- in this case, the older children. And so there may be -- some thought should be given to kind of a more broadly inclusive trial for across the age range that we're looking at here that allows you to kind of move to a younger age group once you've established the safety in the older kids for the treatment, and that would potentially allow you to not only look at growth velocity but

potentially get at more comorbidities which are more common in the younger kids.

DR. HUDAK: So I'll just make a comment, and then we can break, but I think that that's certainly one philosophy, but as several people here have said, I think that you lose an opportunity in those first 2 years. I mean, you are 1 cm different in your height at birth, and by 2 years, you're way behind. And given that, given the fact that no one has anything more than theoretical concerns about toxicity at this point and the opportunity for reducing morbidity in the 0- to 2-year-old is so high that it would, as a neonatologist, I would embrace a study that concurrently enrolled children in the first year and two of life, as we have with -- there are design considerations and so forth, but I wouldn't say that we need to show safety in, you know, 2 to 18 before we do 0 to 2. I would say let's be efficient and let's do everybody. But we can talk about that after the break.

DR. NEVILLE: Can I just add to that that there is precedent in other rare diseases of doing what you just said? So I think that (a) the safety is theoretical, (b) it may be long term, and (c) there is precedent already in the rare disease space.

DR. HUDAK: And with that we'll take -- Dr. Abraham desperately wants to say something.

DR. ABRAHAM: So fast.

DR. HUDAK: Okay.

DR. ABRAHAM: I want to make a correction so that we don't leave with the wrong information. I want to read you what was in the Ireland article about the reduction or about the frequency. They write, "While serious complications such as sudden death due to severe compression of the spinal cord at the foramen magnum impact on only 5 to 10% of children," etc., so early monitoring is important. So I want to say that what I had said before or what we thought before, which is 5 to 10% in the first year of life, is not correct. It's in children, and it encompasses multiple complications.

DR. HUDAK: Okay, thank you --

DR. ABRAHAM: Thank you.

DR. HUDAK: -- for finding that. Okay, we are on break for 10 minutes.

(Off the record at 3:41 p.m.)

(On the record at 4:03 p.m.)

DR. HUDAK: Okay, so we are going to resume. We have Questions 2, 3, and 4 to discuss, but we have touched, in some part, on each of these questions in our discussion on Question Number 1.

So let me read Question Number 2 and then ask if there are any clarifications the FDA should make on this question. So Question Number 2 reads: For the potential clinical study endpoints proposed under Question 1, discuss whether there is a

specific age for which treatment initiation should be considered to most effectively increase height, reduce disproportional growth and/or decrease the incidence and/or severity of achondroplasia complications. Specifically, comment on whether there is a pediatric age-specific subpopulation that should receive priority for investigation of drug treatment.

Anyone have any clarifications on that question?

Dr. Neville.

DR. NEVILLE: I just have a clarification on the length of study and the differences between the infant group --

DR. HUDAK: That's in Number 4.

DR. NEVILLE: Okay. It was a clarification, Dr. Hudak.

DR. HUDAK: Like I said, we've covered this to some extent. Does anyone want to make a stab at integrating their views on this? Dr. White is always --

DR. WHITE: No, no.

DR. HUDAK: No? No, you're itching for that button, go ahead.

DR. WHITE: I'm not going to.

DR. HUDAK: Please.

DR. WHITE: This is Michael White, New Orleans.

I mean, the obvious intervention should take place in utero, but you can't treat the mother because they don't have the gene, unless they're already achondroplastic, and that's a

problem because you would really like to start treatment before you start seeing all the manifestations of the abnormality of the genetic disorder that they've inherited and we see it easily, I mean, at 20 weeks gestation. Actually, the maternal fetal people will probably see it about 16, 12 to 16 weeks, they can see it. So the ideal time point would be as soon as you identify the abnormality, go for it, but we can't do that, so move on.

DR. HUDAK: Dr. Wilson.

DR. WILSON: So where is the slide with the different groups? So it was the FDA's slide number -- with the growth velocity, and we have infants -- we have birth, infancy, 1 year, 2 to 10, pubertal years. So starting with that sort -- for the secondary endpoints is where I was going, it might be the 2- to 10-year window but that's probably too wide a window to especially get secondary endpoints, and it would also have to have a structure. But you could imagine potentially a cut halfway between, like 2 to 5 or 6 and then 6 to 10.

And then when you get into puberty, it starts to become more complicated. As Dr. Cooke said, you probably would need to start adjusting for other -- many other things related to puberty because some people are going through puberty at a different -- and then you get -- puberty can go from age 10 to 11 all the way up to 16, for sure, and then stretch a little bit. It becomes more problematic. So I think the window I

like, especially for secondary endpoints, would be 2 to 10 and maybe an early group and a later group within that window, for instance, if secondary endpoints got enough purchase for interest.

DR. HUDAK: Dr. White.

DR. WHITE: We are limited by the population of subjects that we have as potential participants because, you know, we got 200 kids a year approximately, in the United States that are born with this disorder, and we would like to be able to get an effective treatment for them as soon as possible. And we're not going to be able to enroll all those, so in order to get statistically meaningful data, it's going to be -- you can speak to this better than I can. How many potential subjects do you think we would need to participate to get a reasonable answer within a reasonable period of time, and can we enroll those?

And then the other question we're going to have is if we want to have a control group or a placebo group or however you wish, then we cut the treatment group in half, and it's going to be really hard to get enough people to stay in the trial, particularly the ones that are in the placebo group, to get a meaningful endpoint, I think.

DR. NEATON: The short answer to your question is I don't know because that's going to depend upon the variability in this measurement, which I'm not an expert in this particular

field. My point earlier, if this reflects appropriately kind of the natural history and the average stature for other children, is that if you were studying -- if you're doing a fixed-term study, say a year or 2 years, the sample size required to detect kind of a given difference is going to be much bigger kind of for the older children compared to the very young children, and it's going to depend upon age because the expected difference is if you think of interventions that are going to move a person with the genetic disorder to the average stature, that difference varies by age.

And so, you know, I thought the discussion earlier, whether you do something along the lines that I suggested, if you're concerned about safety or just going full blast into it, considering from the get-go a broader age ranges makes sense because it may very well be you do a study and you establish that it has a pronounced effect on growth velocity and you have a decent secondary outcome, as Peter is talking about, and as well as safety, it may preclude the ability to do a second trial. A properly controlled randomized trial is what I think you need to do.

DR. HUDAK: You're getting into Question 3, so that's good. That's all right.

Dr. Neville.

DR. HAVENS: Can I follow up on Dr. Neaton's --

DR. HUDAK: Oh. Dr. Neville, is your thing up?

(Off microphone response.)

DR. HUDAK: Okay, Dr. Havens.

DR. HAVENS: Well, just to make the point again, on that table of growth velocity, if our goal here is to put together the strongest possible dataset that would lead to potential FDA approval of a drug, you would want to find the group where the potential change would be the largest so that you could show that in the smallest group of patients over the shortest period of time. Do I paraphrase you --

DR. NEATON: That would be one approach. I guess, to me, if this drug or any drug that was being considered was going to be used across a broader age group, I'd want to study the broader age group so that I understood -- I mean, if you studied it in the infancy, as was being suggested earlier, that based upon this table might be the easiest to show benefit in terms of growth velocity, but that may not address the benefit of the drug totally in older age groups. And so I think I would want some data across the board among potential -- you know, the age distribution where this drug would be considered and perhaps not limited.

DR. HAVENS: Thank you.

DR. NEATON: But then you would have to appropriately power your study on data like this, taking into account that for any fixed duration study, those differences by age are going to vary.

DR. HUDAK: Dr. White, again.

DR. WHITE: The down side to all this is that we won't have any long-term safety data. I mean, we're not -- we would like to provide an effective therapy as quickly as possible, but the downside to that is if we treat infants, we're not going to know the long-term safety until those subjects are through puberty or 20 or 25 or 30 because some of the possible side effects of using this CNP analogue that may have effects on other tissues that may not show up early in life, and it's going to be a small population of people who take this, and it may be years before we see a significant side effect profile because of the small numbers we're going to have to use. So we're kind of balancing safety against effectiveness in trying to get something out for people that will allow some of these families to have their -- either it's going to work for their children and let's get it to them and take some risks and I think -- I don't know how to assess that.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: So I have a comment/question to that. My understanding is the Agency can require postmarketing data, because in the space that I do clinically, we often do that, not knowing long-term data. So I mean, I agree with you, and I think the endpoint that you -- is what would that be? But I think because a lot of these -- you know, we're pushing for a first in human to be first in children for some of these

disorders, and I think it's going to be a question we face over and over, so I think you just build in postmarketing surveillance.

DR. THANH HAI: Mary Thanh Hai, FDA.

So I think what you're referring to are postmarketing required studies that we're authorized to require companies under FDAAA. That's when we have a safety signal that we feel that there's benefit that's already been established with the drug, but we feel that it needs to be better characterized in the postmarketing setting. So, yes, we do have those authorities to do that. You know, this is really more on a conceptual level because we're not talking about any particular product here. I think one thing to think about, though, is that if you go -- when we go that route of a PMR, it really should also consider the feasibility of collecting good data to evaluate that safety signal.

So if you have a premarket program that is limited in getting that information and there's also efficacy or the promise of really, really strong efficacy that is going to be used more widely than you had approved the product for, how the product is used postmarketing may actually limit the ability to do a well, adequate design trial to look at safety, and again, that's the issue of people dropping in on a drug or not wanting to be enrolled in a postmarketing trial for safety.

DR. HUDAK: Okay, Dr. Burman.

DR. BURMAN: Thank you. I just wanted to raise the issue, and this was mentioned in the documents, of not using age but using maybe age between 0 and age 2, but a broader range. And I agree with what Dr. Everett and Dr. Neaton just said, from age 2 to 16 or 15, but maybe it should be related to Tanner stage rather than age because the bone growth will stop at the end of puberty, and that could be variable.

DR. HUDAK: Dr. Portman.

DR. PORTMAN: So this is a rare disease, and one of the questions we have to ask is how many patients can we enroll? How long can the study run? It's a feasibility issue. By doing some of the things that have been said here, using the younger population, not only is their need great, but their response may be greater; it's sort of an enhancement type of design that could allow you to do the study and prove efficacy with less patients. Then you get to the issue of the secondary endpoints, which are, in large part, complications of the disease, and you may not see those in a relatively small study. So in order to really get to safety, we need to have a rigorous registry or a long-term study that can help us identify and report these beyond just reporting to the FDA what, you know, side effects but an actual registry. Put the money and the resources there, and use a more expeditious study design to prove your efficacy.

DR. HUDAK: Dr. Cunningham.

DR. CUNNINGHAM: Melody Cunningham.

I mean, it almost seems like we're working towards talking about either two different studies or a longer duration study getting the safety data but with a planned subanalysis of our infant -- you know, our infant group in 0 to 2, which is -- and 0 to 1 is where the deaths, the sudden deaths in achondroplasia occur. So it feels like it's either two studies or one study with a subset analysis intended from the beginning in that infant population.

DR. HUDAK: Any other thoughts? So let me -- okay.

DR. WILSON: Yeah. So Dr. White was reminding me that there are 200 births a year, and to start to even get safety data in, you know, Year 0 to 1 or 2, given even what fraction can be recruited, this is going take 2 to 4 years, at least, to even get safety data in infants. And it's not a 1-year study in infants because of getting the access to 200 all around the states versus you might get safety data quicker with a 1- to 2-year study with a larger denominator to draw from in the 2 to 5 or the 6 to 9 group where you're especially quicker to identify and have a lot of support groups as well, who would be very interested in helping to support registries and next generation secondary outcome assessments and stuff.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: So I have a question to that and in general because my guess, at least -- so I'm applying what I know in

the oncology space to this, which may not be at all relevant, but it would seem to me that we're talking about, in general, a framework of a year or a 2-year study. But I'm left with thinking -- because we run into this with novel chemotherapy agents. Okay, so you do a year or a 2-year study, but then in clinical practice, how long would a drug be given, right? So some of the agents I work with, it's cumulative toxicity and cumulative efficacy. So I just think that's something for us to bear in mind and ponder.

DR. HUDAK: Good point. All right, we have two more, Dr. Low Wang and then Dr. Cooke.

DR. LOW WANG: Thanks. So I think looking at specifically like Question 2, which is, you know, whether there's a specific age where we think that we would most effectively increase height and reduce that disproportional growth and decrease the incidence and severity of complications, I agree that I think that infants of less than a 2-year age group is really the age group to focus on. But I think that in terms of being able to prove that you're reducing the severity of the complications, I think you really need to extend the study a bit longer. So a short-term 1-year study is probably not going to be enough. I think, for a primary endpoint of annualized growth velocity, maybe 2 years would be ideal. But I think that once you start to get into some of these other endpoints, even 2 years may not be long enough, but I think 2 years would be reasonable.

DR. COOKE: With regard to studying safety in the different populations, I agree that the numbers make studying infants much more problematic than older populations of children. But I want to highlight and remind people that there's a lot different between an infant and a 5-year-old in terms of potential toxicity effects, so there's a lot of nephron growth, there's a lot of brain growth, there's a lot of organ growth in general that could be impacted in that age group in a way that's not detected in older children. So, yes, you know, studying the older children for safety, for what it can -- before maybe broadly studying in infants, but that safety issue needs to be studied very specifically in that population in a different way than older children.

DR. HUDAK: So you're right. I mean, I think that on the other hand -- so the developmental sensitivity to drugs in terms of complications is going to be very important, but on the other hand, verifying -- just the fact that you verify safety in a 5 and older population isn't going to guarantee that you've got safety in a 0 to 2.

So let me call the question, and let me phrase it this way. So we're asked to decide whether or not there is a priority age-specific subpopulation, so I'll throw out two options. The first is to design the study where all children at any age who are having lower growth velocity than normal should be studied -- that ignores a lot of the fine points of

how you do that, but just in principle -- versus picking one age range and then doing a study there and then moving to a different age range, which the priority would be, in that case, doing the study in the population you choose first then moving to the second population.

If I were to ask for a show of hands just to get some sense -- this is not a vote; this is just an attempt to figure out whether there's consensus. Anyone in favor of doing all babies, infants through pubertal children, as opposed to doing just some age first and then another age second? Who subscribes to the first view? I can't vote; it's not a vote.

(Off microphone comment.)

DR. HUDAK: So everybody who would prefer to do one age range and then get an answer there and then move to another age range, raise your hand.

(Show of hands.)

DR. HUDAK: Okay, all right. Well, there's a consensus. All right. We'll move to Question Number 3. And this gets into some other things we've talked about but -- so the consensus for Question 2 was that there was -- there were more votes -- there's more opinions that you should do this sequentially rather than doing it in totality from the beginning across the population.

Okay, the third question.

DR. BLAHA: I just want to make one point. Another

possibility is parallel studies. That you didn't mention, I guess. There could be one big study, there could be two sequential studies, or there could be parallel studies that have different features to them. I just wanted to point that out.

DR. HUDAK: Well, I think that -- so the nuance I didn't mention specifically is if you studied everybody, you know, you're really doing different parallel studies because you're looking at different, you know, outcomes and you maybe have a different way to analyze your population groups. But the fact is you're doing it all contemporaneously rather than doing one and then waiting and then doing another population. So if there is some confusion about that, that wasn't meant to be confusing, but that's what was meant.

Okay, Question Number 3: Discuss the design(s) of clinical trial(s) that will generate a robust evaluation --

DR. NEVILLE: Sorry, but that changes my opinion.

DR. HUDAK: Okay.

UNIDENTIFIED SPEAKER: Mine, too.

DR. HUDAK: All right. Well, let me go back and redo the question.

DR. NEVILLE: Sorry.

DR. HUDAK: All right. That's all right.

DR. NEVILLE: I'm not the only one, though.

DR. HUDAK: Okay. So let me re-pose the question. The

question is would one study all age groups with the appropriate study design within each particular subpopulation, or would one rather study one population and then next in time study another population? Because I think we're being asked to look at priority populations, and in my mind, a priority population is a population you study first. Okay, so let's redo the show of -- Dr. Cunningham, are you still confused? Go ahead.

DR. CUNNINGHAM: Melody Cunningham.

So I think if we're asking the question, say drug limited, say study personnel limited, and we're looking at a priority population, that for me is 0 to 2. If we're not limited by that and we're asking, you know, how are we going to get the best data on safety and efficacy, I would say enrolling most ages, if not all ages, and then looking at the subgroup populations, so sort of a parallel design.

DR. COOKE: Can I add just one -- just a hypothetical? If one were to study a group from 4 to 7 and saw no change in growth velocity, then I think it would be wrong to be studying it in the 1-month-old baby at the same time. So taking this from a totally "we don't know any data" about an agent, I'd say we need to demonstrate a clear impact on growth velocity because that's the one invariant aspect of this disease that should be impacted by a therapy, and if it doesn't have a clear impact on that, I can't justify treating a 1-month-old baby.

DR. HUDAK: You've entered interesting territory because

you're talking hypotheticals, and there's more to it than that, right? So maybe our views are colored by that.

DR. WILSON: Peter Wilson.

To build a little bit on -- I think, David, is I don't think we've seen Phase 2 data for infants, have we? Yeah. Or anywhere. There's nothing in the literature, I'll just say that as a comment. So we have had all of these, but there wasn't anybody who said I got this when I was an infant, for the public hearing. So I think whoever's studying any growth agent for ACH, I'd like to see at least a Phase 2 study in infants before seeing a trial or whatever moving forward. I think that may be the biggest win, but we need to see safety for that. That could also be a boomerang, and the safety profiling for infants is probably a lot more metabolic, in addition to MRI concerns and sudden infant death syndrome, but their kidney health, liver health, etc., etc.

DR. HUDAK: All right. Well, that's clear as mud. Let's come back to that after Question 3 because Question 3 may shed some additional light on it. So this is a question on the designs that generate a robust evaluation of the efficacy and safety of the study drugs in the intended population(s). And then the question is whether or not this trial needs to be a randomized, placebo-controlled trial or not, depending upon the population or subpopulation of the study, and then discuss the strengths and limitations of the proposed trial designs which,

in the simplest form, would be the strength and limitations of doing an RCT versus doing an open-label Phase 2 with self controls or historical controls.

All right, Dr. Low Wang, you lead it off.

DR. LOW WANG: Cecilia Low Wang.

So what I heard earlier is that we don't have adequate contemporary data in terms of natural history for achondroplasia. So what we're relying on is pretty old, maybe decades old data. So that, to me, tells me that, you know, we need a placebo-controlled trial. Randomized would probably be better to try to reduce bias. And I think if we don't have the safety data in that population that we're talking about, 0 to 2, I mean, it really does need to be Phase 2. So Phase 2 randomized controlled, placebo-controlled safety and efficacy study.

DR. HUDAK: Dr. Portman.

DR. PORTMAN: So, again, this is along the lines of what you just mentioned. I don't know the data that's available. This is a rare disease, and if we have good historical data of the growth rates -- we've seen growth curves -- if we have good rates of these secondary very concerning outcomes, then we have historical data potentially, and the current drug could be tested in a single-arm study. There are new techniques for looking at synthetic control groups where you can use your historical controls to actually put together a group of -- if

the data is contemporary, to put together a group of controls from historical data that can give you a very effective way of determining efficacy.

DR. HUDAK: Dr. Blaha.

DR. BLAHA: Yeah, Mike Blaha.

I'll just keep my comments brief. I feel very strongly that a randomized, placebo-controlled, and blinded study would be required and would take care of many of the other issues we've talked about, and I would feel more comfort about the outcome discussion in the setting of a randomized controlled, placebo-controlled trial. I think that's mandatory here to really understand from what I've gathered. I'm not trustworthy of using historical controls.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: I'm going to respectfully disagree and agree with Dr. Portman in that. Again, in my field, my experience is that -- you have not even shown benefit but a potentially beneficial agent in a rare disease. You'll never be able to accrue to the trial; people will just wait until they get the drug.

DR. HUDAK: So I missed that last part.

DR. NEVILLE: From a practical standpoint, it's been my experience that in rare diseases with potentially beneficial drugs, people don't want to randomize to the control arm, so you actually have quite a bit of difficulty accruing to those

studies. And so I would argue along the lines of what Dr. Portman said, that I think if someone went back and more meticulously looked at recent historic controls, that you could make an argument for a Phase 2 if you pick something like growth velocity versus historic controls. And I would argue against a randomized controlled trial.

DR. HUDAK: All right, we'll start with Dr. Everett.

DR. EVERETT: Brendan Everett.

So I think I hear you, and I note in the cardiology literature there's a study of Marfan's that had difficulty enrolling for exactly the reason you've described. The difficulty is that if you want an accurate assessment of the risks, you need a placebo comparison group. So you cannot get that with historical controls; you must have people who are actively randomized to placebo to compare to. Now, there may be other study designs where you can entice people to enroll because, for example, it's a crossover design where people get placebo for the first year and then they get active drug for the next year, and you don't know which group you're going to be assigned to first, and so you can then compare the growth velocities for the year when you're getting -- before you cross over and then after you cross over.

My concern is that you cannot measure something -- you have to demonstrate efficacy. Honestly, it's out of respect to the population who wants and needs the drug. You don't want to

give them something that doesn't work, so you have to be able to demonstrate the efficacy, and you also have to know whether or not that efficacy is paired with potentially significant and substantial side effects and toxicities, and the only way to do that is with a placebo arm.

DR. BLAHA: And accurate assessments of the effect size.

DR. HUDAK: Dr. Weber.

DR. WEBER: You know, one way to approach this, and I think we've been talking about targeted groups, but if you -- and this will, to some extent, allay some of the concerns of folks who are enrolling into the placebo arm, is a younger group aged 5 to 8 and then, you know, you have a year, if it's a year dedicated trial, to show the annualized velocity change, and you've got that, and at least that's some reassurance. It's not going to be a long-term trial, and if it's proven to be effective, they would have a chance, then, to get into the trial. And I would echo the other gentleman's complaints -- or comments as well.

DR. HUDAK: Dr. Burman.

DR. BURMAN: Thank you. I strongly agree as well -- Ken Burman -- that we need a placebo control, and I think you just mentioned that it could be for a year or 2, and then the group that was in the control could get the medication, realizing that alters the long-term outcome but does give them the drug for that period of time. And I think it would be inappropriate

and probably unethical to approve a drug without the best study possible for the hundreds or thousands of patients, for the future years, who will get the drug and we really wouldn't know definitely that it was effective.

DR. WEBER: Just if I could add something. There's an opportunity cost. If you approve the drug without truly knowing that it's efficacious, that shuts down development of alternative agents that might actually be efficacious. So you have to be careful that while there's a desperate need, and we heard that very clearly, that you establish that the drug actually works before you start administering it to people.

DR. HUDAK: Dr. Neaton.

DR. NEATON: Actually, I don't have a lot more than I said earlier. I have seen no data or heard any discussion today that we have any contemporaneous or even historical data that would allow you to kind of do a non-randomized study here with either a contemporaneous or a historical control, particularly when you consider growth velocity possibly as well as safety outcomes. And so I think you need to do it right, and a randomized trial is going to be the way you do it.

DR. HUDAK: Dr. Portman, did you have something else?

(Off microphone response.)

DR. HUDAK: Dr. Havens.

DR. HAVENS: Well, out of respect to the people who spoke today, some of the things that I think we heard from them is

that, number one, there's many strong-willed people in that group who will demand shared decision making with whatever physician is offering them this drug, and if you want to be able to say to a family, this drug works, then you have to have data. It's the only respectful thing you can do for your patients, is to develop data that everybody can believe in, which is a randomized controlled trial of excellent benefit. We heard today from people who moved from different countries to this country to get this drug. If we don't do a study that's adequate to prove that drugs work, then we aren't doing the right thing.

DR. HUDAK: Okay. Dr. White.

DR. WHITE: I wanted to agree with you that we're going to have trouble accruing if there's a placebo arm. But beyond that, we have to consider the fact that the placebo arm, if it's a blinded placebo study, we're going to have to get approval to do daily injections in a pediatric population, which most IRBs are going to frown upon, and I think we're going to have to go to Health and Human Services to convene an ethics conference and get the families to come back and tell us how strongly they feel about participating in the trial. So it's more than just whether we can do the trial and get subjects; it's also going to be whether we can do it as a blinded, placebo-controlled trial that we're going to have to think about.

DR. HUDAK: Dr. Thanh Hai.

DR. THANH HAI: Mary Thanh Hai from FDA.

As I'm listening to the conversation, I'm reminded about the growth hormone programs for the non-growth hormone deficient short statural conditions, and I can't remember which one it was, but I think there was one program where it was an untreated control for 1 year, so -- or maybe it was placebo control; I can't remember. But then the second year they were switched, and there were two doses that were studied, and so this may get to the question of the difficulty of conducting a long 2-year placebo-controlled trial. And so I'm curious just hearing if your experiences with respect to dose control, different dose control, because if you can see a dose response -- and that's actually also evidence of effectiveness, and you can also evaluate for safety as well. So that speaks to the importance of adequate dose finding in any of these programs.

DR. HUDAK: Dr. Low Wang.

DR. LOW WANG: Thanks. Cecilia Low Wang.

So I think the alternative to a placebo-controlled trial is to have good natural history data, and if we don't have good natural history data, then we have to collect it, and that takes years, and so I think that's the other problem. And so if we're trying to make things as expedient as possible, I think we're between a rock and a hard place here.

DR. WHITE: The muscular dystrophy trial that we -- Michael White, sorry.

The muscular dystrophy exon-skipping trial where we did have an HHS meeting for ethics, it did use the incentive of at the end of the control period everyone would be enrolled to receive the medication if it was proven to be reasonable while they were analyzing the data, and that might be, as you said, the way that we could get around to make sure people will enroll, is that everybody gets enrolled, there's a randomization, but at the end of whatever period is agreed upon, everyone then has access until the data comes in, might be a way around that.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: I would also echo -- I think you bring up a good point for any promising agent -- that another way around it -- because I think, again, talking about a lot of these agents have novel mechanisms that things can't necessarily be easily extrapolated from adults, and so that multiple dose study may be an additional way around that, and it's a lot more palatable to patients.

DR. HUDAK: Dr. Neaton.

DR. NEATON: So just a couple comments. One that, you know, I think in my mind if you're going to do a placebo-controlled trial, whether it's 1 year or 2 years, it's really important to build into the protocol that if the drug is found

to be efficacious, that the participants in the control arm be given access to the drug as well as the people still on the drug during the period of time before licensure.

Secondly, the comments here, kind of going back to one of your earlier questions, I think, reflect the difficulty that was in my mind of doing sequential studies, because if you establish kind of in the first study that safety and efficacy and you think that's going to be a hard study to do with a placebo-controlled trial, it will be harder to do in the second study.

DR. HUDAK: I agree with you. Just practically that's a very important issue.

Dr. Wilson.

DR. WILSON: So what about the possibility of a standard placebo control and then a stronger agreement than usual for no cost or very low cost for those who had been in the placebo control at the end, if it was a positive trial, that everybody, everybody's going to get this medication for a certain interval at extremely low cost because you were in the key trial that did this and you volunteered to do this, because in my experience with injectables, biologics, there become barriers immediately, the costs are high, and if I had a child there and it's just -- I'd say to my spouse and my child, it's just one more year and you're going to be part of a key thing; it's not 3 years, it's not 5 years, it's 1 year, because I like to think

to design a trial that could have that result for 12 months of data with primary and/or secondaries.

And then it's likely some things are going to be very positive first and then maybe different things that are positive, which is going to make interpretation even more complex, I understand. But then everybody -- is that unfavorable in terms of moving forward, if everybody gets a guarantee from sponsors that you're going to get -- because you were in the key trial, and there's going to be maybe 50 or 100 in each arm, so there are 200 affecteds in the nation who get this. It's not thousands and thousands. And wait one more year and participate and then you'll be good to go, so to speak.

DR. HUDAK: Dr. Snyder.

DR. SNYDER: So I was just going to make the comment that the decision in terms of the placebo length, and that being a minor increase over minimal risk, would be independent of whether or not the patient were to receive treatment towards the end of the trial. And that obviously, I think, would be IRB determinant in terms of, you know, getting injections daily for 2 years. You know, I know that we have some precedent for 2-year trials with placebos, but I can't think of one that's daily. I know some of the growth hormone ones were three times a week, and we've had infusions for 2 years in some of the MS trials. So you know --

DR. HUDAK: We recommended that they were able to use central lines in the exon skipping. I don't know --

DR. SNYDER: Yeah, but that wasn't related to the fact that there was an extension trial. That was related to the fact that we determined under 50.54 that it was ethical to include that port in the placebo arm because --

DR. HUDAK: Correct.

DR. SNYDER: -- of the burden of getting those continued infusions in the placebo arm.

DR. HUDAK: I'm sorry if I may have obfuscated what I was saying, but --

DR. SNYDER: Yeah, I'm sorry.

DR. HUDAK: -- my intent was that it's going to be hard to get daily injections into a placebo arm for infants, independent of everything else, and that we probably would have to convene at the HHS level.

DR. SNYDER: We'd have to look more at precedent to see what's been done in the past.

DR. HAVENS: So can you clarify that issue? Are daily injections in a placebo arm likely to meet the ethical decisions that you're talking about?

DR. SNYDER: Potentially, yeah. So I think, you know, in Europe the study is approved now for daily injections for a year with a placebo arm.

DR. COOKE: Some of the growth hormone trials had daily

injections as a placebo arm for it. So it has precedent in FDA trials.

DR. SNYDER: Right, I'm sorry. So in FDA trials --

DR. HUDAK: Thank you, that clarifies it.

DR. SNYDER: Yeah, we obviously go under different regulations.

UNIDENTIFIED SPEAKER: So if I can go back to the placebo issue, yes, if -- certainly, I think most companies, if you were going to have a placebo arm and a treatment arm, that you're going to offer the therapy, you know, as part of an extension study to those who are not. I mean, I think that's pretty standard. The real question is, is the patient the same? Have you lost growth potential, you know, in that year that they were on that placebo? And then, you know, is it the same situation? Is it the same benefit for them to be on the drug after they've been on the placebo?

DR. WILSON: If I could insert?

DR. HUDAK: Dr. Wilson.

DR. WILSON: I'm an adult endocrinologist, but I have taken care of children with Type 1 diabetes, and we don't have that choice. We have to give them insulin every day. And Dr. Cooke is doing this every day. So it's not like an insulin decision for a Type 1. This is something else.

DR. HUDAK: Mary. Dr. Cataletto.

DR. CATALETTO: I just had a comment about the placebo

effect. We're dealing with very small numbers and if what you're saying to people is if you get the placebo, then I will give you the drug, you know, in the extension study with the implication that the drug is effective, we don't know that. So if the placebo effect is higher than it might otherwise have been, it's our fault.

DR. HUDAK: Dr. Low Wang, did you have a question?

(Off microphone response.)

DR. HUDAK: No? Dr. Portman, did you have another question? I was just looking at whose thing is up.

(Off microphone response.)

DR. HUDAK: All right, let us just put Question Number 4 up because we can discuss Question Number 4, and then we can sort of see if we can integrate some sort of consensus.

So Question Number 4. This is 3. Four was there; it disappeared. There we go.

So this is comment on the required duration of a clinical trial or trials that will allow for an adequate assessment of long-term efficacy and safety of the drug. Consider durations for the core, extension and postmarketing phases of the trial.

So to the extent that we haven't talked about this, anybody want to make any more comments?

(No response.)

DR. HUDAK: All right, so hearing none, let me just make a couple comments and sort of see if we can bring this to some

sort of a consensus, then.

So I think most people have spoken in support of a study design that is a randomized controlled, blinded, placebo trial, placebo-controlled trial, for reasons that relate to let's make sure we -- if there is efficacy, let's prove it beyond a shadow of a doubt. Let's have an opportunity to look in that design at comparative safety as well, even though it may be a relatively short duration we're looking at. So I think I've heard that.

There is some discussion about whether or not we might alter that design if we've got really good contemporaneous control data in the population, but there's a lot of skepticism about that.

One of the other issues, of course, is the sustainability, durability of effect that we won't know until we actually do a study that extends the treatment for a long term. And there is concern that we would not be able to do that study as a randomized, placebo-controlled trial because patients and families wouldn't buy into that, especially if early 1-year efficacy results were clear.

There is also the concern that was raised legitimately about are there cumulative safety issues that might arise with longer cumulative exposures or exposures that are just more powerful at an earlier age of development? The last part of that question one could maybe get at by doing the randomized

controlled study in that population. The other question is really only something that would be known if one looked at registries and one looked at the precedents in every patient who's enrolled in the trial up to that age that they were enrolled and then try to construct a database over time to sort of see what, you know, sort of side effects that might have been apparent by that point and then sort of going forward with that. So there's a potential to look at that within the same patient group, if you will.

And the point then was brought about duration, that we thought that duration of some reasonable period of time to actually be able to tease out efficacy and get some initial safety in that period of time seems to be maybe between a year and maybe pushing it to 2 at the most.

And then there was the design of, you know, the extension, that at some point there will be an answer on -- or a signal, I think, on efficacy, yes or no, and do you build in a design where children can cross over, or all children, at some point after they start the trial, receive the actual treatment and then continue to accumulate data.

So those are some of the things I heard, and I'm not sure we can integrate that into one big coherent consensus, but anybody willing to give it a stab?

Dr. Dracker.

DR. DRACKER: I think you need at least 2 years to look at

clinical efficacy in these patients, and then if you do a crossover trial, you're going to need an additional year for the group that will cross over, so you're looking potentially at a 3-year trial. Long-term follow-up can be done as a separate adjunct to any trial you do.

DR. HUDAK: Dr. Cooke.

DR. COOKE: I'm not sure I understand the ability and limitations of and the difference between an extension and a postmarketing phase. Postmarketing studies are substantially for safety issues, correct? Are there any outcome issues that can be studied in those?

DR. HUDAK: I'll just clarify this. So the way I use extension was you've got your enrolled patients, you extend their treatment, you're still under a protocol, and you're still collecting data very carefully according to a script. You're looking at particular outcomes. Postmarketing is once the drug is approved and out there, it's willy-nilly and --

DR. COOKE: I understand that.

DR. HUDAK: -- people get the drug. You know, so it's very different --

DR. COOKE: No, I understand that aspect, but I guess the issue is, I think, again, in terms of the impact of therapies on size, I think, for the various reasons we've talked about, growth velocity is a reasonable marker for that, as an efficacy marker. I would agree that it should be at least 2 years on

therapy.

But, ultimately, I think it would be best if we had final height data. What I'm not clear about is whether that final height data could be done in an extension study and whether that extension study needs to have data before approval or whether there's an ability to get sufficient data in a postmarketing study, which, again, you know, is not controlled. Admitting that there's some uncertainty about the natural history, I think the final height outcome in achondroplasia is pretty solidly understood. So at final height, I don't think we have this uncertainty about whether there's a difference between a treated and untreated group. So I guess that's where I'm unsure about what to recommend because I do think some ultimate data about final height should be sought after and obtained.

DR. HUDAK: So I agree with you, and I think that, you know, one of the things that would be important would be for every patient in the study to continue to have data that comes in, looking at whether they got treatment or not, how long, what their final adult height was, what their complications were; that would be critical. So that would be the extension sort of registry component, I guess, of the study.

A postmarketing trial is different, and postmarketing information won't give you that information. So I think maybe FDA can comment on that, but that's -- to what extent does the

Agency have the ability in a trial to sort of say we need to follow up all these patients for side effects and for final adult height at some point?

DR. THANH HAI: Mary Thanh Hai, FDA.

So as I mentioned earlier, we have the authority to request -- require the postmarketing study for safety. Efficacy is a different conversation and a benefit. We're going in a realm of a different path of approval and not a traditional approval. We're talking about accelerated approval, but that's -- I think we really should stick with what we can do in a traditional pathway approval, and we're not talking about any particular product here. So if you're talking about a postmarketing trial that we can require information, it would have to be for safety. Of course, that doesn't preclude companies from doing studies, and we certainly have had that, where they're trying to understand better and get benefits or efficacy data for which they can always submit under a supplemental NDA.

DR. HUDAK: Dr. Zemskova.

DR. ZEMSKOVA: Yes, I just wanted, again, clarification. If you think that a 1-year study might be sufficient to validate efficacy, do you consider that, as was mentioned earlier, that it's just for endpoints, whatever it is, in your growth velocity or annualized growth velocity and complication, because my understanding is that to improve some complications,

this might take longer than 1 year, and as I heard earlier, that improvement in annualized growth velocity is as important as improvement in complication. So my question is whether we still need longer studies to demonstrate that growth improved and complications improved.

DR. COOKE: I think it would take a lot longer to study complications in even 2 years. So I just feel even the growth data would require 2 years on treatment to make sure that there isn't that attenuation after the first year, just based on growth trials in other indications and therapies.

DR. HUDAK: Dr. Wilson.

DR. WILSON: To build on what Dr. Cooke was saying, also in consideration, most trials we have 1:1 matching, and since there is a real reluctance perceived by this Advisory Committee in general for this condition, that patients would not want to go on placebo, is to consider other than 1:1 matching. And, for instance, it might be 3:1 or 4:1 matching, something like that, which would change the power calculations and the statistics.

And then you'd say I want to know more about those persons who are not on active treatment, so you would have those -- let's say it was 20% in the trial who are on placebo for 1 or 2 years, and then essentially almost the same protocol would be administered as the baseline registry to people not involved with this study at all, and they would be monitored on an

annual basis in what I would call a contemporary registry, which is a current history or a contemporary history of people not on, and it's a hybrid trial. And Dr. Neaton should weigh in for his thoughts on -- but this is one of the ways to embrace the concept of people who are going to be included in the study, have a much greater chance of being on active treatment than on placebo.

DR. NEATON: Well, I think that's not a bad idea, going to 4 to 5:1 allocation. Rather, I think a 2:1 allocation would be reasonable, and you could probably get by with a relatively modest increase in sample size. But I thought what we were talking about before was if you design, say, a 2-year study with growth velocity as well as collecting safety and some of the other complications that we've talked about, if that data is positive, then the control group as well as the treatment group would all be offered the treatment, and they would be kind of followed until final height for safety. But that wouldn't mean that there would be a delay until that follow-up was complete for drug approval. The drug approval could occur earlier following kind of meeting their criteria for the pivotal trial. That's what I thought we were talking about.

DR. HUDAK: Dr. Blaha.

DR. BLAHA: I would defer to my statistical colleagues, but could there not be a 1-year interim analysis looking for a large effect size, and if it's not met, we continue for 2

years? In other words, you don't have to say for sure 1 year, for sure 2 years, but building that statistical analysis plan.

DR. HUDAK: Any other thoughts?

(No response.)

DR. HUDAK: So going through, let's back up to Question Number 2, which is where we got off track and I confused everybody about the population, priority populations. So let me try to do this again. So does everybody agree that the population to treat where you might most effectively increase height, reduce disproportionate growth, and/or decrease the incidence or severity of complications in achondroplasia is the 0- to 2-year age group? Does anybody disagree? Raise your hand.

(Show of hands.)

DR. HUDAK: Okay, so we've identified a priority population per the actual instructions on the question. In terms of a study, would one do sequential or concurrent enrollment across the age ranges?

DR. BLAHA: Can I comment? Well, I mean, I don't mean to open up a whole new bag of worms here, but I would consider an older adult, older kids -- it doesn't have be a Phase 3 randomized controlled study, but it has the potential to be a Phase 2 safety and efficacy smaller study in infants that's a separate analysis but parallel, but they're ones -- if one's designing an efficacy study, one's actually testing safety.

DR. HUDAK: So would these both be randomized, placebo-controlled?

DR. BLAHA: Well, I think that the lateral -- does not have to be randomized, and that could be a separate discussion, but that's why I think they could be parallel but very different studies.

DR. HUDAK: Okay, so --

DR. BLAHA: And the outcome can be different.

DR. HUDAK: Right. No, I understand. So what I'm saying is do you want to do -- the trial designs may be different; they may be two versus three, randomized, not randomized, whatever, but in terms of providing access for this population.

DR. BLAHA: Well, I mean, I always prefer a randomized controlled trial, but I'm not a pediatrician, so I defer to the ethicists and the pediatric investigators because maybe that study in infants is not possible to be randomized and placebo controlled. If it's going to be, that would be great, but I would definitely think that the pivotal efficacy study absolutely has to be randomized and placebo controlled. Infants, I think, is a separate story that has a lot of other complexities to it, but it should be parallel.

DR. HUDAK: I think the infants need to be randomized controlled as well because we --

DR. BLAHA: It gets to the whole idea of the injections and --

DR. HUDAK: What's that?

DR. BLAHA: That gets to the idea of placebo injections in this age group, which I guess is an ethical issue but may be outside of the scientific question.

DR. WILSON: Can I ask a question? Do you really need a randomized study in infants? What you need is a safety study, and an open label would probably do it but perhaps not. But you need to be able to have confidence in your measurements at the beginning and at the end, and Dr. Cooke brings up that the measurements, if it really works, it's going to make a big difference. But you may want more than having a baby on a table and measuring it that way. You may want to do radiographic height, you know, body length measurements by scout films or some other truly objective measurement rather than, well, we put the baby on the examining table and we drew two pencil marks and this is the length. You may want something that could later actually have an image and it was read out is what I'm getting at, something objective.

DR. HUDAK: So I'm struggling with trying to have a frame and answer to this question, then. So let's do it this way. So let's go to the 0- to 2-year age, which everybody thinks is a priority in terms of Question 1, and then ask whether or not Question 3, a study in that group should be a randomized, placebo-controlled trial or not, because I've heard different opinions.

A show of hands. Who thinks it should be a randomized, placebo-controlled trial in the 0 to 2 group?

(Show of hands.)

DR. HUDAK: Okay, I think we've got consensus on that. And then the 2- to 18-year old group, however you subdivide that, the same question, randomized controlled versus -- randomized controlled?

(Show of hands.)

DR. HUDAK: All right, so I think we've got close to unanimity on the issue that the study should be randomized controlled across the age span.

Dr. Weber, you're shaking your head.

DR. WILSON: I think those of us who felt more of a Phase 2 design for the youngest children, we're not objecting to placebo controlled. Part of it is it might jumpstart the field even if we already had that in hand, is the Phase 2, and I think that can be obtained in a flash actually, and within a year you can know. As Dr. Cooke has mentioned, if it really works in the 0 to 2, you're going to know really fast, I think.

DR. HUDAK: Dr. Neville.

DR. NEVILLE: Going back to the previous point made, if we're talking about frameworks for a theoretical study, it can allow for additional dose finding in a Phase 2 versus a randomized Phase 3, right? So maybe we are pretty much or maybe for any given molecule, a Phase 2 would need to be done

first. And I agree it would accrue much more quickly with additional dose finding and safety.

DR. HUDAK: Good point. So, yes, I think that's probably what FDA would want you to do in that age group anyway, to do some Phase 2 PK studies and then sort of go from there. Those could be done quickly, as you know.

So okay. So I think we've answered the subpopulation of priority. I think we've answered Question 3. If you flip to Question 3, which talks about the type of design in terms of randomized, placebo controlled. And Question 4 was about the duration, and I think we've got a consensus of somewhere between 1 to 2 years.

Dr. Cooke.

DR. COOKE: I do just want to point out that if we think about just a 1-year trial, then if you look at the data on growth hormone treatment in achondroplasia, you would see a significant increase in growth velocity with growth hormone treatment in that first year, and I think everybody recognizes that growth hormone treatment for achondroplasia is not an effective therapy. And so I really want to emphasize the need to go beyond that first year.

DR. HUDAK: All right. Well, then, I'll ask the question. Who is of the opinion that we need to do 2 years or longer?

DR. COOKE: I'm going to add more detail.

DR. HUDAK: Who wants to respond?

Dr. White.

(Off microphone comment.)

DR. HUDAK: Yes.

DR. COOKE: Let me extend my comment, just to be sure. I think the problem with making these general comments is it's ignoring all of the preclinical data as well, and clearly preclinical data could be very different from one agent compared to my growth hormone example. So I think that does have to play into that decision and consideration, but just recognizing that 1-year growth velocity data can be very deceptive.

DR. HUDAK: Dr. Weber.

DR. WEBER: Sure, a comment about the growth hormone example. Again, this is not so much related to growth, although by extension in the osteoporosis, the bone density world, growth hormone actually paradoxically causes lower bone density before it increases the density. So there's difference in the biology of the two agents that has to be taken into account from certain drugs to growth hormone, so I just wanted to make that point. So a shorter trial may work in that regard for this.

DR. HUDAK: Dr. White.

DR. WHITE: Michael White.

I was just looking back at the data on Exondys because I think there is something to be learned from that. That drug

was approved, and I don't know what you called the approval provisionally. An ongoing study, it mandated that Sarepta will have to perform confirmatory studies to establish that Exondys can slow down disease progression, and it seems like we're sort of in that same point here, where 2 years will give you data that there is some effect, but what you want, I think, is ongoing data that it actually has an end effect or not.

DR. COOKE: That is the ideal. I think the problem there is that that would take longer than I think is appropriate to delay therapy for all of the other reasons.

DR. WHITE: They approved the drug. It's being used; it's just that the company has to continue to collect data to prove that it is indeed effective in the long run at changing the outcome of the disease.

DR. COOKE: I think that's a different approval process than we're discussing, if I understood the answer.

DR. ABRAHAM: Yes, you're talking about Sarepta. That was approved as an accelerated approval.

DR. HUDAK: Okay. And we're not trying to -- that's not one of our goals, is to have accelerated approval. So I think the consensus is that 2 years would be better than 1 year, maybe not sufficient completely, but you have to balance this issue of how long do you really have to demonstrate effect in a placebo-controlled trial versus -- and on the flip side of this, the worst-case scenario, of course, is okay, let's

suppose that you get an increase in growth velocity by, you know, 2 cm a year for 2 years, you know, but if you run that out, your effect would stop after 2 years and you'd get zero effect. So your effect on final adult height would be 4 cm, which is not clinically significant. There's no way I can think of to determine that ahead of time other than following these children out for a long period of time and see where they do wind up in terms of final adult height.

So I think there are some inherent, real, practical difficulties with designing, you know, the trial that you'd like to provide all of the information. The issue of final efficacy and the issue of cumulative safety are things that are going to have to be determined in very careful, prospectively designed registries and data, visit encounters that give you the appropriate data. So I think that's also the consensus that I've heard around the table.

All right, FDA, anything else that we haven't covered that you wanted us to cover?

(No response.)

DR. HUDAK: Are we good? Any final comments from Committee members or guests?

Dr. Burman.

DR. BURMAN: Just one quick comment. Two quick comments. Number one, any protocol that is approved that we're considering for children should, I think, have a radiation

exposure discussion and analysis to make sure they're not exposed too much, you know, when we're using CAT scans or radiology over standard of care. Number one.

And, number two, just to remind everyone that FGF is thought, in some instances, to be an oncogene, to proliferate cells and cause cancer, and that should be kept in mind in the longer-term studies.

DR. HUDAK: Good points. Thank you.

Dr. Neville.

DR. NEVILLE: If we're done talking about the topic, I just want to give a shout-out to you. You're one of the best chairs I've ever had the honor of working with, so thanks. But don't go like this, Mark.

DR. HUDAK: Thank you.

Anything else from FDA? All right.

Yes, Dr. Thanh Hai.

DR. THANH HAI: Just final comments. I'd like to thank the Committee. Some of you were actually here yesterday as well, so a 2-day commitment to FDA; to the staff, FDA reviewers who actually helped put this meeting together, and your presentations. And I very much thank the public, patients, and the families who came here to speak on this condition; it has been very, very helpful to the Agency. I'd like to personally shout out for one patient who also did the glass-blowing class. I'm a glass artist, so thumbs up to you. Thank you very much.

DR. HUDAK: And we are adjourned.

(Whereupon, at 5:15 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OPEN SESSION

OF THE

JOINT MEETING OF THE PEDIATRIC ADVISORY COMMITTEE (PAC) AND THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

May 11, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration.

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SHAYLAH LYNN BURRILL

Official Reporter