



**Minutes of a Joint Meeting of the Pediatric Advisory Committee and
the Endocrinologic and Metabolic Drugs Advisory Committee
*Open Session***

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

May 11, 2018

Advisory Committee Members Present

Mark Hudak, M.D. - Chair
Danielle Boyce, M.P.H.
Mary Cataletto, M.D., FAAP
Melody Cunningham, M.D.
Robert Dracker, M.D., M.H.A., M.B.A., CPI
Peter Havens, M.D., M.S.
Michael White, M.D., PH.D., FACC, FAAP
Michael Blaha, M.D., M.P.H.
Daniel Budnitz, M.D., M.P.H.
Kenneth D. Burman, M.D.
Brendan M. Everett, M.D., M.P.H.
Cecilia C. Low Wang, M.D., FACP
James D. Neaton, PH.D.
Thomas J. Weber, M.D.
Peter W.F. Wilson, M.D.
Jatinder Bhatia, M.D., FAAP
David Cooke, M.D.
Kathleen Neville, M.D., M.S., FAAP, FCCP
Joshua Pahys, M.D.
Han Phan, M.D.

Non-Voting Member

Ronald Portman, M.D., FAAP – Industry Rep

Designated Federal Officer

Marieann R. Brill, M.B.A., RAC, MT(ASCP)

FDA Participants

Smita B. Abraham, M.D.
Mary Thanh Hai, M.D.
Donna L. Snyder, M.D., FAAP
Marina Zemsanova, M.D.
Susan McCune, M.D.

Open Public Hearing Speakers

Karen Freedman
Dr. David Blaustein
Rosa Luttrell
Amer Haider
Anthony Moscato III
Pinchas Cohen, M.D.
Ravi Savarirayan, M.D.
Seth Fritts
Morrys Kaisermann, M.D., PH.D.
Jacob Blaustein
Cathleen Raggio, M.D.
Samantha Ozan
Olga Marohnic
Sarah Catherine Crews
Aiden Cockrell
Kristine Digeronimo
Shahzadi Munir-Israr
Hank Fuchs, M.D.
Alecia Cockrell
Denis Bronnikov, PH.D.
Satyabrata Jena
Michelle Kraus
Jamie Harvey
Jill Blaustein
Chandler Crews
Rebekah Bailey
Estefania Gonzalez
Sharon Moscato
Ron Rosenfeld, M.D.
Amanda Tumbiolo
Munira Shamim
Laci Eggerton

Agenda

12:05 p.m.	Welcome and Introductions	Mark Hudak, MD Chair, Pediatric Advisory Committee (PAC)
12:10 p.m.	Opening Statement	Marieann R. Brill, MBA, RAC, MT(ASCP) Designated Federal Officer, PAC Office of Pediatric Therapeutics (OPT) Office of the Commissioner (OC), United States Food and Drug Administration (FDA)
12:15 p.m.	Recognition of Service	Susan McCune, MD Director, OPT OC, FDA
12:20 p.m.	FDA Presentation	Smita Abraham, MD Medical Officer, Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation II (ODE-II), CDER, FDA
12:34 p.m.	FDA Ethics Presentation	Donna L. Snyder, MD, FAAP Pediatric Ethicist/Team Lead OPT, OC, FDA
12:47 p.m.	Clarifying Questions to FDA	Committee members
1:00 p.m.	Open Public Hearing	
2:42 p.m.	Questions to the Committee/Committee Discussion	
3:40 p.m.	Break	
4:03 p.m.	Questions to the Committee/Committee Discussion	
5:15 p.m.	Adjourn for day	Mark Hudak, MD Chair, Pediatric Advisory Committee (PAC)

Introduction

The Pediatric Advisory Committee (PAC) and the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) met jointly on May 11, 2018 to identify and discuss important elements of drug development programs for products intended for the treatment of achondroplasia (ACH). The meeting was divided into two sessions, one closed to the public and the other open for public participation. In the closed session, the committees discussed the clinical development program for a specific investigational new drug. In the open session, the committees discussed general considerations for ACH drug development programs, including clinically meaningful outcome measures, age of patients who might benefit most, study designs, and duration of pivotal trials. The open session included an open public hearing.

ACH is an inherited, autosomal dominant, short-stature skeletal dysplasia caused by a gain of function mutation in the fibroblast growth factor-3 (FGFR3) gene, a negative regulator of endochondral bone formation. ACH patients are at risk for multiple complications because of their abnormal bone growth. Complications are most prominently observed in neurological, musculoskeletal, cardiorespiratory and ear, nose and throat systems. The most severe complications are usually neurologic in nature and often result from the decreased diameter of the craniocervical junction and spinal canal (e.g., central sleep apnea and neurogenic claudication due to spinal cord compression). Musculoskeletal complications include deformities of thoracolumbar vertebrae, tibial bowing, flexion contractures of the hip, and joint hypermobility. Musculoskeletal and neurogenic impairments also contribute to complications such as

obstructive sleep apnea, recurrent ear infections, conductive hearing loss, speech delay, and developmental motor delays. There is no cure or specific treatment for ACH. The available supportive treatments aim to prevent or mitigate complications of the disease.

Open Public Hearing

The comments provided during the open public hearing were largely supportive of drug development in the field of ACH and included testimony from 32 speakers, including 16 parents of children with ACH, 5 children with ACH, a representative from BioMarin Pharmaceutical, Inc., and representatives from organizations such as Growing Stronger, Global Genes, and Little People of America (LPA).

Parents and children with ACH described factors impacting their desire for drug development for ACH. The medical complications associated with ACH, such as sleep apnea and recurrent ear infections, and the associated need for recurrent surgeries and doctor appointments were noted to be particularly burdensome by nearly all parents and children. Families also frequently cited a desire for autonomy, particularly related to hygiene and self-care. Independence in other aspects of daily life was also described (e.g., being able to trigger automatic door sensors). Several parents described significant fatigue, poor durability/stamina, pain and poor strength as factors affecting daily life. Psychosocial aspects of ACH were illustrated, such as social stigma, teasing, and issues with self-image. The financial impact of the diagnosis was described by several parents, including the cost of home modifications (e.g., lowering light switches), adaptive equipment, travel for doctor appointments, tailoring clothing, and support group participation and travel. Parents also remarked on the time spent arranging medical appointments, school/camp accommodations, travel, and so forth.

Some parents expressed concern that younger children with ACH are not given the opportunity to enroll in clinical trials of new drugs and worried these children would not gain access until after substantial bone growth was complete. For similar reasons, some expressed dissatisfaction with the possibility of receiving placebo in a clinical trial. An orthopedic surgeon and consultant for BioMarin reminded the committee that children with ACH become patients with ACH in adulthood, with significant loss in ability to perform activities of daily living.

One parent of a child with ACH and the chairperson of the Hispanic Affairs Committee of the LPA expressed concerns that the pharmaceutical industry is taking advantage of parents' fears and cautioned not to use children as "guinea pigs." The Advocacy Director from LPA emphasized that the impact of morbidities is more important than increasing height and asked that FDA promote endpoints that impact morbidity, stating "is it just height we are gaining, or are we solving the important issues that limit our quality of life?"

Committee Discussion

Listed below are the four discussion points presented to the committee, followed by a description of the discussion:

1. Hallmark clinical features of ACH are short stature and disproportional growth. Attenuated growth velocity manifests early in life. In addition, ACH complications can occur at an early age (e.g., infants and toddlers are at high risk for severe neurologic complications) or later in life (e.g., cardiovascular complications). Considering the various manifestations and complications of abnormal bone growth in ACH, discuss potential clinically meaningful study endpoints in the development of drug product(s) for ACH.

The committee agreed that annualized growth velocity (AGV) is a reasonable primary endpoint for clinical trials in ACH, but that data on final adult height should be obtained to validate long-term clinical

efficacy. An increase in final adult height was considered clinically meaningful, though if marked attenuation in growth velocity is seen with treatment over time, the committee would have concerns for using AGV as a surrogate for final adult height. The committee recognized that waiting for final adult height measures from a clinical trial would prevent the opportunity to treat many children with ACH. Strategies for obtaining these data were discussed, such as implementing a post-marketing study requirement or a registry. The importance of proportional growth was discussed and the committee agreed proportionality should be assessed as a secondary objective.

Emphasis was placed on using an objective, reproducible, non-invasive measurement and the committee agreed that height is the simplest and most reliable measure. Additional clinically meaningful endpoints that could be objectively measured were discussed, including polysomnography for sleep apnea, frequency of otitis media, neurologic assessments, and measurement of the size of the foramen magnum via MRI. Additionally, two committee members cited use of validated instruments to assess improvements in quality of life and activities of daily living as important outcome measures to include. The committee noted that powering a study on any of these endpoints may be challenging and agreed these would be important to include as secondary endpoints. The committee noted that the frequency of these ACH complications vary by age, so these secondary endpoints would need to be stratified by age or that trials conducted in different age groups may need age-specific secondary endpoints.

2. For the potential clinical study endpoints proposed under Question 1, please 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 ACH complications. In your discussion, comment on whether there is a pediatric age-specific sub-population that should receive priority for investigation of drug treatment. If no, provide rationale.

The committee agreed that the sub-population of children less than 2 years of age with ACH should be the priority for study. The committee suggested that the greatest benefit for patients with ACH may be through improvement in early growth parameters. The committee noted that, for example, the cardiorespiratory and neurologic complications of ACH are a function of the size of the chest and foramen magnum, respectively, and these may be mitigated through early treatment. The committee emphasized that conducting trials in younger children during a critical period of growth may be the most informative and impactful. Furthermore, the committee noted that if AGV is targeted, the duration of study may be shorter and sample sizes smaller, given that growth occurs rapidly in this age group.

The committee acknowledged that initiating studies at an earlier age might limit collection and analysis of long-term safety data unless the protocol included specific requirements for follow-up assessments. However, the committee recognized that evaluating older patients first may not always capture important safety issues that may be encountered in younger patients with immature organ development. The importance of acquiring comprehensive and consistent post-marketing data to assess long-term safety was stressed, particularly given that products for ACH will be used for many years in clinical practice.

Consensus was reached on conducting parallel studies, rather than sequentially studying each age group. The committee suggested, for example, conducting a phase 2 study in younger children simultaneously with a phase 3 study in older children. The committee agreed that a randomized, controlled trial would ultimately be necessary for children less than 2 years of age.

3. Discuss the design(s) of clinical trial(s) that will generate a robust evaluation of the efficacy and safety of study drug(s) in the intended population(s). Consider whether a randomized placebo-controlled trial is required to allow for such evaluation(s). Discuss the strengths and limitations of the proposed trial design(s).

The committee reached consensus that a randomized, blinded, placebo-control trial design is critical for the evaluation of efficacy and safety for products intended to treat ACH. Although the possibility of using natural history data to support an open-label study was proposed and supported by one committee member, several committee members expressed skepticism about the use of natural history data, even if reliable contemporaneous data on the natural history of ACH is available. The potential for bias in an open-label study may limit the reliability of height data obtained in a study. Several committee members firmly emphasized that approving a product without a placebo-controlled, blinded trial that categorically establishes efficacy would be unethical and would be a disservice to the ACH population.

The committee recognized the potential feasibility concerns for a placebo-controlled trial, particularly of 2-year or longer duration, because patients may be unwilling to remain on a study given the possibility of placebo. Committee members suggested using specific design elements, such as 2:1 randomization or cross-over after an appropriate (but unspecified) interval to help mitigate patients' concerns regarding prolonged placebo.

4. Considering the discussions above (in particular, selection of efficacy endpoint(s) and trial design), comment on the required duration of a clinical trial(s) that will allow for an adequate assessment of long-term efficacy and safety of the drug. In your discussion, consider durations for core, extension and post-marketing phases of the trial(s).

The committee agreed the duration of study should be at least 2 years to obtain adequate growth data. Some committee members questioned whether an even longer duration may be necessary, but did not commit to a specific timeframe.

Please see transcript for details.

I certify that I attended the May 11, 2018 meeting of the Pediatric Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired during the open session.

/s/
Marieann Brill, MBA, RAC, MT, ASCP
Designated Federal Officer

/s/
Mark Hudak, MD
Chairperson, PAC