UNDERSTANDING THE PATIENT PERSPECTIVE ON AGE-APPROPRIATE MEASURES OF GROWTH IN RARE DISEASE DRUG DEVELOPMENT

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DISCLOSURE

- Dr. Mohamadi is an employee of and holds shares in BioMarin Pharmaceutical, Inc.
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MEANINGFUL ENGAGEMENT OF PATIENTS

- Time is critical to patients with rare diseases, and drug developers strive for efficiency in developing important therapies for them.
- Integrating the patient voice starting at research and development and continuing even after a medicine is approved is important to best serve the unique needs of each community.
- For very young patients, the perspectives of their parents or primary caregivers provides important insight into burden of disease, burden of available treatment, if any, and unmet need.

INCLUSION OF THE PATIENT PERSPECTIVE IN DRUG DEVELOPMENT

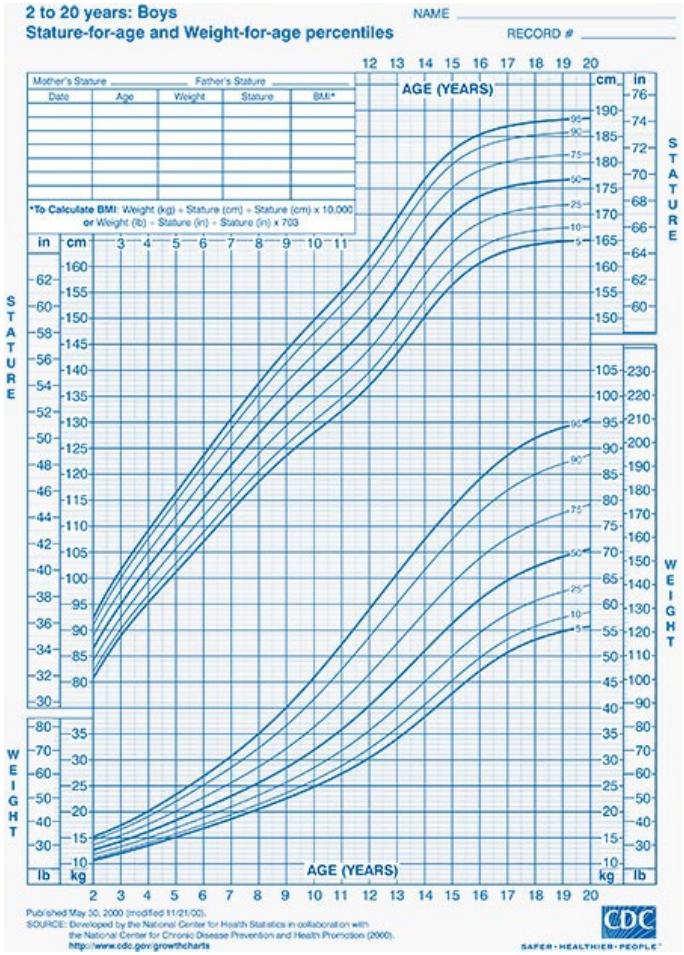
Inclusion of pediatric patients in endpoint development and data collection has historically involved leveraging the parent/caregiver voice

- Understand unmet need through early engagement
- Obtain input on key study design elements
- Co-create study materials
- Share the science of programs throughout clinical development

Recent initiatives have sought to establish models and best practices for involving and engaging children and young adults in the drug development process

- Engage with pediatric condition-specific Patient Advocacy Groups
- International Children's Advisory Network (iCAN)
- European Young Person's Advisory Group Network (eYPAGnet)

CONSIDERATIONS: DRUG DEVELOPMENT FOR PEDIATRIC GROWTH DISORDERS



- Underlying cause of linear growth attenuation
- Heterogeneity of short stature syndromes
- Finite timeframe for intervention
- Impact of growth/stature on an individual's feeling and function

All of which impact the selection of clinically meaningful endpoints

PRIMARY ENDPOINTS USED TO SUPPORT APPROVAL OF SHORT STATURE INDICATIONS

Indication	Endpoint
Growth Hormone Deficiency	Height Velocity*
Idiopathic Short Stature	Height Velocity
	Final Height
	Final Height SDS
Insulin-like Growth Factor Deficiency	Height Velocity
Noonan Syndrome	Height Velocity
Short for Gestational Age	Height Velocity SDS
	Final Height
	Height SDS
Turner Syndrome	Near Final Height/Final Height
	Height velocity

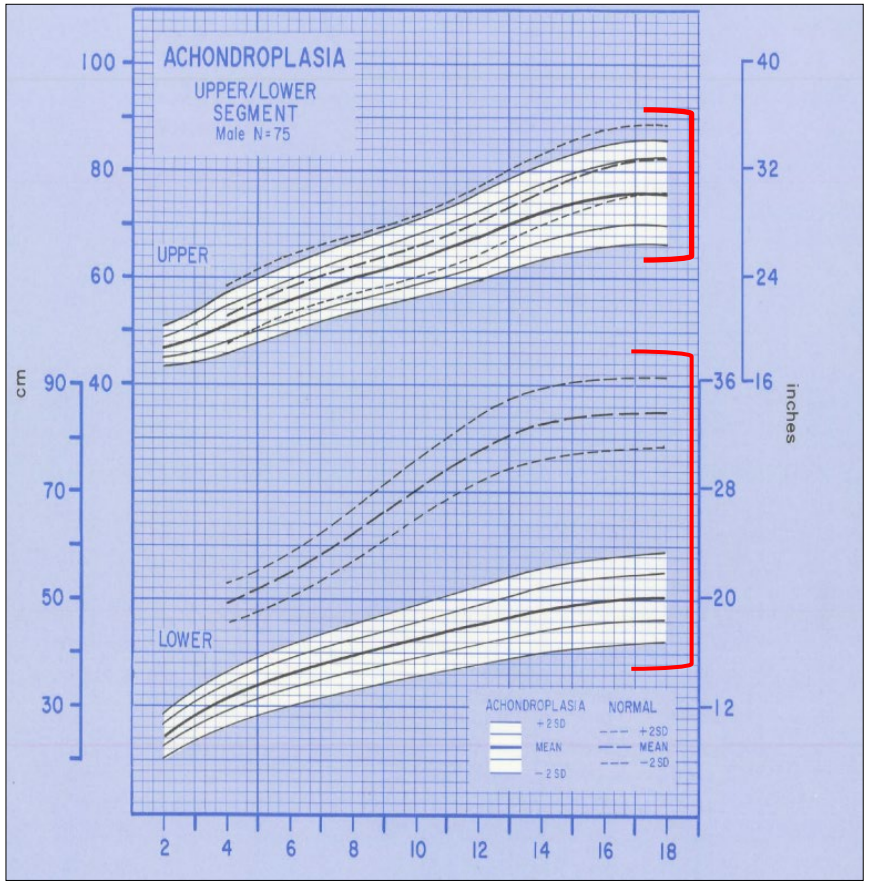
*Height Velocity includes: Average Height Velocity, Annualized Height Velocity, Growth Velocity, Average Growth Velocity, Annualized Growth Velocity, Growth Rate, Average Growth Rate, Annualized Growth Rate

SUMMARY OF KEY ADVANTAGES OF GROWTH VELOCITY AS AN ENDPOINT FOR PEDIATRIC GROWTH DISORDERS

- The endpoint is objective and leverages measurements that are routine in pediatric clinical care
- It is non-invasive
- It has utility in a range of drug development scenarios – from growth hormone therapies to treatments that target the underlying pathophysiology of the pediatric growth disorder

CASE EXAMPLE: AGE-SPECIFIC CONSIDERATIONS IN MEASURING GROWTH IN PEOPLE WITH ACHONDROPLASIA

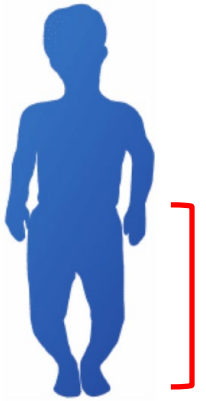
- Most common skeletal dysplasia[1]
  - 1/25,000 births[2]
  - Affecting over 250,000 world wide[3]
- Disorder results in a failure of normal cartilage conversion into bone and significantly shortened bones[1]
  - Complications arise secondary to bone compression of nervous tissues or other tissues
- Disproportionate short stature due to proximal shortening of the lower limbs[1,4]



Adapted from Horton, et al[5]

Sitting height for the achondroplasia population (solid lines, white area), overlaps with normal population (indicated by dash lines).

Lower segment for the achondroplasia population (solid lines, white area), is below normal population (indicated by dash lines), with no overlap.



Lower segment

[1]Shirley ED, et al. *J Am Acad Orthop Surg*. 2009;17:231-241. [2]Wynn J, et al. *Am J Med Genet A*. 2007;143A:2502-2511. [3]Ireland PJ, et al. *Appl Clin Genet*. 2014;7:117-125. [4]Horton WA, et al. *Lancet*. 2007;370:162-172. [5]Horton WA, et al. *J Pediatr*. 1978;93:435-438.

THE CHALLENGE OF HETEROGENEITY

- Heterogeneity exists in the condition itself *and* in the perspectives of patients.
- The work of the FDA and other stakeholders to address representativeness when obtaining the patient perspective is valuable and appreciated.
- Further, discussions about the representativeness of the available data and plans to improve the representativeness of data that will be considered in cases where heterogeneity (in condition, perspective, or both) is an issue should be encouraged.

THE CHALLENGE OF FINITE OPPORTUNITIES FOR INTERVENTION

- Despite being slowly progressive and heterogeneous conditions, pediatric growth disorders share the challenge of limited windows of opportunity for meaningful treatment intervention.
- Finite opportunity to impact skeletal growth in childhood.

"Every single day, I think about…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."

- Parent of 4 y.o. male with ACH[1]

"Time is such an essential part of achondroplasia, and each year that passes that he is denied any type of medication that is available, you are taking away much of his opportunity for effectiveness and so much of his quality of life is being tarnished"

- Parent of 19 month old male with ACH[1]

[1]FDA Joint Meeting of the Pediatric Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee, May 11, 2018.

PATIENT PERSPECTIVE: RELEVANCE OF HEIGHT TO FEELING AND FUNCTION

- Height as a barrier to independence – e.g., having sufficient height to trigger automatic door sensors, reaching bathroom door locks without assistance
- Height as a driver of need for adaptive aids – e.g., desk size at school
- Implications of height on mobility

> "Because her legs are shorter than her body, Kiana falls frequently , especially if she is moving fast." – Mother of 11 y.o. girl with ACH[1]

- Patient perspectives on height and importance of height as a treatment goal are heterogeneous with many factors, including cultural identity, impacting one's perspective on height

[1]FDA Meeting of the Pediatric and Endocrinologic and Metabolic Drugs Advisory Committee Meeting, May 11, 2018. Transcript available here.

PATIENT PERSPECTIVE AND REGULATORY IMPLICATIONS

- For growth disorders where treatment options are inadequate or lacking and unmet need persists, timeliness is a crucial consideration in selection of appropriate endpoints.
  - Improvement in height has been mentioned as a goal of treatment of people (or parents of children) with ACH who desire treatment for short stature.[1]
  - Assessment of improvement in final height may be assessed using objective, but more timely, measures, such as growth velocity.
- Prolonged exposure to placebo, and loss of opportunity for treatment benefit, is a key concern of patients and should be considered in evaluating the appropriateness of an endpoint.

"Even a few inches of added length in his arms and legs could make a big difference for people with ACH like my son." – Mother of 4 y.o. boy with ACH[1]

[1]Of 32 people with ACH (or parents or advocates of children with ACH) who testified at an FDA public hearing, 30 were supportive of treatment for ACH. Of those supportive of treatment for ACH, the importance of height was mentioned in their testimony. May 11, 2018. Transcript available here.

FDA ADVISORY COMMITTEE PERSPECTIVE: CLINICALLY MEANINGFUL STUDY ENDPOINTS

- FDA meeting of the Pediatric and Endocrinologic and Metabolic Drugs Advisory Committee on May 11, 2018 sought to address the following:

  "*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*"

- Panelists supported AGV as an acceptable endpoint across all pediatric age ranges -- easy to measure and reproducible
- Panelists acknowledged improvement in the complications of the condition should be evaluated as key secondary endpoints
  - Developmental, functional, and QoL measures, among others

CLOSING REMARKS

- The patient perspective is valuable in drug development, and industry should seek to incorporate it as early as possible in the R&D continuum.
- Patient experience data provide evidence that growth velocity is meaningful to patients and presents a viable path forward for the development of drugs for patients in need.
- QoL endpoints are important as secondary outcome measures for longer-term follow-up and post-approval evidence generation.
- Drug developers welcome opportunities to continue to collaborate with the FDA and the patient community to understand the patient perspective and incorporate the patient perspective in a meaningful way in drug development and regulatory review.