FDA U.S. FOOD & DRUG ADMINISTRATION

Joint Meeting of the Pediatric Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee

Open Session

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U.S. Food and Drug Administration

Overview

- Achondroplasia Background
- Regulatory Background
  - Drug Development

Achondroplasia

Achondroplasia (ACH)

- most common form of dwarfism
- inherited, autosomal dominant, short-stature skeletal dysplasia
- cause: gain of function mutation in the fibroblast growth factor-3 (FGFR3) gene, a negative regulator of endochondral bone formation

Achondroplasia – clinical features

- Short stature
  - Reported final adult height in women and men of approximately four feet
- Disproportional growth
  - Long narrow trunks and shortened extremities, especially in the upper arm and thighs
- Large head, out of proportion to body size, with prominent forehead
- Hands are short and broad with fingers exhibiting a three-pronged appearance (trident) at birth

Achondroplasia – clinical complications

Neurologic

- Foramen magnum stenosis → cervico-medullary cord compression
  - Sleep apnea
  - Disordered respiration
  - Myelopathy
  - Sudden infant death
- Internal hydrocephalus
- Intracranial hypertension
- Spinal stenosis

Achondroplasia – clinical complications

Musculoskeletal

- Thoracolumbar gibbus
- Tibial bowing
- Joint hyperextensibility and hip flexion contractures
  - Development of spinal stenosis in child- and adulthood

Musculoskeletal and Neurologic

- Reduced chest circumference with altered function, upper airway obstruction and cervico-medullary compression can result in obstructive sleep apnea or chronic respiratory insufficiency

Achondroplasia – clinical complications

Less severe, more common

- Recurrent ear infections
- Conductive hearing loss
- Speech delay
- Developmental motor delays
- Dental abnormalities

Achondroplasia – mortality

- Age-specific mortality increased in ACH individuals of all ages
- Increased mortality in infants and toddlers due to sudden death
- Increased mortality in adults related to increased incidence of cardiovascular and neurologic disease

Achondroplasia – social challenges

- Combination of impairment in body structure and function presents challenges in performance of activities of daily living
- ACH children
  - Mobility
  - Self-care
  - Hearing
  - Availability of adaptive aids at school,
    - e.g. heavy doors, high doorknobs, desk size
  - Socialization

Performance at school and education

Growth velocity in ACH

Stage of Growth	Achondroplasia	Average Stature
Birth (length)	47.4 cm	48.5 cm
Infancy	20 cm/year	44 cm/year
1 year	10 cm/year	14.4 cm/year
2 – 10 years	5 cm/year	5.5 cm - 7 cm/year
Pubertal years	5 cm/year	8.3 – 9.3 cm/year

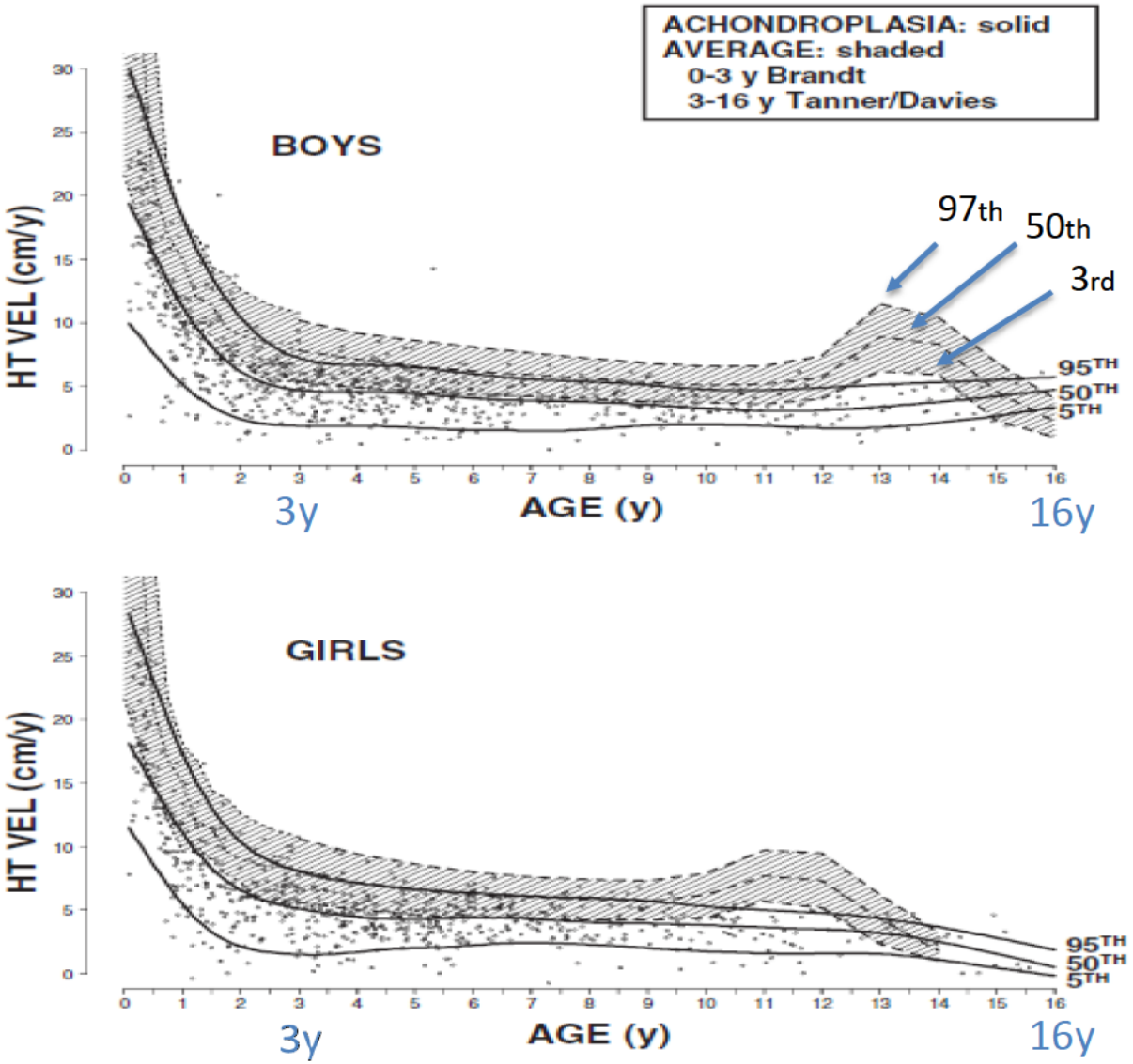
- Pubertal growth spurt in ACH individuals is controversial

Source: Hoover-Fong J, Shulz KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index In children with achondroplasia: interpretation in relation to indexes in height. Am J Clin Nutr 2008; 88:364-71

Growth velocity in ACH

- Reduced final adult height
  - Height gain in ACH particularly limited during infancy and puberty, two periods of rapid linear growth
  - Decrease in growth rate fluctuation during ACH childhood also contributes to reduced final height

Height velocity



Source: Hoover-Fong J, Shulz KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index In children with achondroplasia: interpretation in relation to indexes in height. Am J Clin Nutr 2008; 88:364-71

Current pediatric practice

- No cure or specific treatment for ACH
- Available supportive treatments aim to prevent or treat complications of ACH

Therapies for short stature in ACH

- Growth hormone, no clear long-term treatment benefit established
- Surgical limb lengthening reported to add 15-30 cm to standing height
  - Repeat procedures
  - Wound complications
  - Complications related to stretching of non-skeletal tissues including nerves and blood vessels
  - Cosmetic effect of long legs and short arms might not appeal to some individuals

REGULATORY BACKGROUND
DRUG DEVELOPMENT

Regulatory Framework

- To be approved for marketing, a drug must be safe and effective for its intended use

- Effective: Must demonstrate substantial evidence
  - "…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." (21 CFR 314.126 (b)(5))

- Safety is considered in the context of whether the benefits outweigh the risks (benefit-risk assessment)

Regulatory Framework: Benefit-Risk

- For product approval, data must support that the benefits of the product outweigh its risks

- Benefit: 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

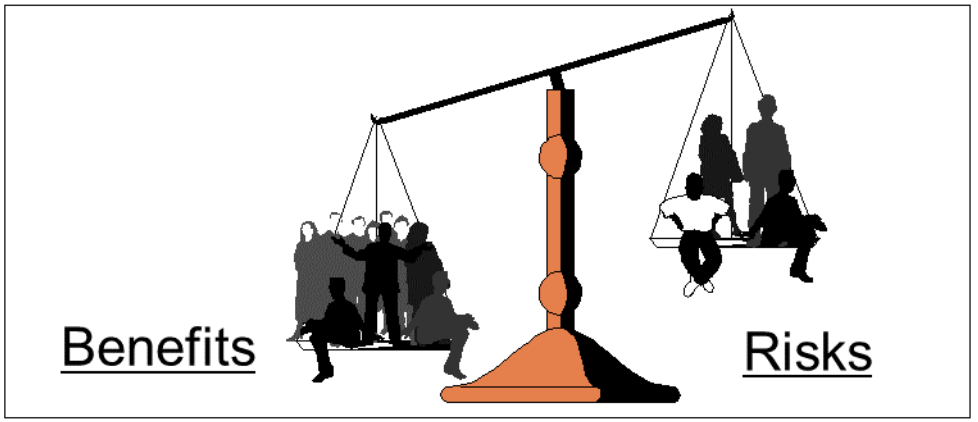
Trial Design

Adequate and Well-Controlled Investigations

- Trials that adhere to the principles of Good Clinical Practices
- Robust trial designs
  - Control group, randomized
  - Choice of an appropriate population
  - Choice of an appropriate primary efficacy endpoint
    - Primary efficacy endpoint – direct measure of how the patient feels, functions or survives

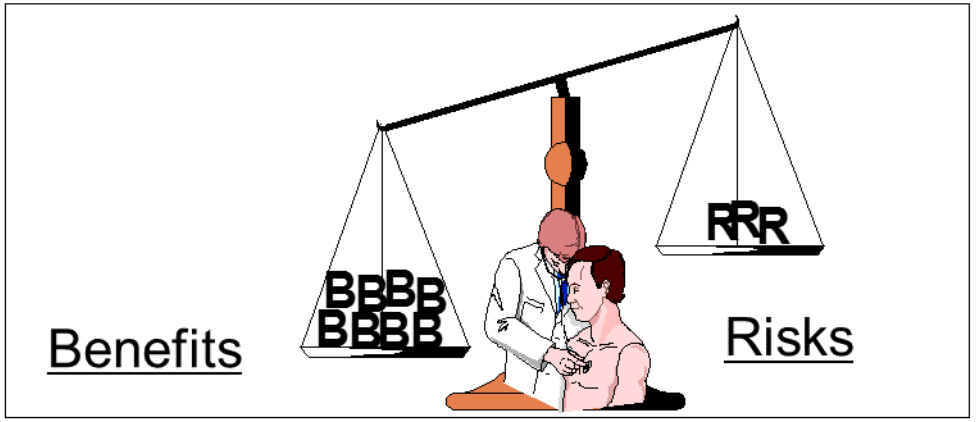
FDA

evaluates
benefits/risks
for the population



Provider

evaluates
benefits/risks
for a patient



Patient

evaluates
benefits/risks
in terms of
personal values

Questions to the Committee

1. Considering the various manifestations of complications of abnormal bone growth in ACH, discuss potentially clinically meaningful study endpoints in the development of drug product(s) for ACH.

Questions to the Committee

2. 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 ACH complications.
    a. Comment on whether there is a pediatric age-specific sub-population that should receive priority for investigation of drug treatment.

Questions to the Committee

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).
    a. Consider whether a randomized, placebo-controlled trial is required to allow for such evaluation(s)
    b. Discuss the strengths and limitations of the proposed trial design(s).

Questions to the Committee

4. 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.
    a. Consider durations for core, extension and post-marketing phases of the trial

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