

**Joint Meeting of the Pediatric Advisory Committee and  
Endocrinologic and Metabolic Drugs Advisory Committee  
March 22, 2018**

**Background Document for Open Session.**

**Introduction**

Achondroplasia is the most common form of dwarfism and is estimated to occur in between one in 10,000 to 30,000 livebirths.<sup>1</sup> Achondroplasia 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.

Within the last several years, scientific research has allowed for greater understanding of the molecular pathways involved in the pathogenesis of achondroplasia (ACH). With this understanding has come the ability to identify potential therapeutic targets for the treatment of ACH. An opportunity also exists to engage the scientific community with expertise in the care of patients with ACH, clinical trial conduct, and drug development early to advise FDA as the Agency considers multiple development programs for ACH. Key topics of discussion include clinically meaningful outcomes of drug therapy, age of patients who might benefit most by drug therapy, study design and duration of pivotal trials.

To best identify therapeutic goals of the ACH community and subsequently design a robust clinical drug development program, we ask the committee to consider the following.

**Draft Points to Consider**

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.

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.

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).
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).

## **Background**

### *Description of Disease*

ACH is the most common form of dwarfism and is estimated to occur in between one in 10,000 to 30,000 livebirths.<sup>1</sup> 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. The most obvious clinical features of ACH are short stature, with reported final adult heights in women and men of approximately four feet; and, disproportional growth manifested as long narrow trunks and shortened extremities, especially in the upper arms and thighs.

ACH patients are at risk for multiple complications because of their abnormal bone growth. Complications occur in multiple organ systems; however, they are most prominently observed in neurological, musculoskeletal, cardiorespiratory and ear, nose and throat systems. As might be expected, many of the co-morbidities are inter-dependent.

The most severe physical complications are usually neurologic in nature and often result from the decreased size/diameter of the cranio-cervical junction and spinal canal. Patients are at risk for internal hydrocephalus, intracranial hypertension, cervico-medullary cord compression, foramen magnum stenosis and spinal stenosis among others.

Cervico-medullary cord compression can result in hypotonia, respiratory insufficiency, central sleep apnea, and myelopathy (injury to spinal cord). Sudden death has also been linked to these complications albeit in approximately 5-10% of ACH children.<sup>2</sup>

The major secondary complications are musculoskeletal in nature. ACH children may suffer from a thoracolumbar gibbus (wedge deformity in the lower back vertebrae) and tibial (lower

leg) bowing in the early childhood years. These conditions in combination with other musculoskeletal conditions including hip flexion contractures and joint hypermobility can lead to the development of spinal stenosis both in child- and adulthood.<sup>2</sup> The most common complication of ACH in adults is lumbar spinal stenosis with compression of the spinal cord and associated neurogenic claudication (pain in lower back, buttocks or legs due to spinal cord compression).<sup>2,3</sup>

Musculoskeletal and neurogenic impairments contribute to cardiorespiratory complications.<sup>2</sup> Reduced chest circumference with altered mechanical function, upper airway obstruction and cervico-medullary compression or a combination of these factors can result in obstructive sleep apnea and chronic respiratory insufficiency. Less severe, but more common complications can include: recurrent ear infections, conductive hearing loss, speech delay, developmental motor delays, and dental abnormalities.

Age-specific mortality is reported to be increased at all ages in ACH. Increased mortality in infants and toddlers is primarily due to sudden death, most often a result of central apnea, a complication of foramen magnum and cervico-spinal stenosis.<sup>4,5,6</sup> In adult ACH patients, increased mortality rates were related to cardiovascular disease, neurologic disease, and accidents; however, cardiovascular disease was the leading cause of death. The exact mechanisms behind the increased risk of cardiovascular death have not been fully elucidated.<sup>1,4,5</sup>

Individuals with achondroplasia also experience multiple social challenges throughout their lives. The combination of impairments in body structure and function can present significant challenges in performance of activities of daily living. Major areas of participation that are affected for ACH children are mobility, self-care, education and performance at school.<sup>2</sup> Furthermore, these challenges along with their altered body schema can result in psychosocial stress for the patients and their families.

### *Growth Velocity in Achondroplasia*

There are only a few natural history studies that describe the longitudinal growth of achondroplasia patients.<sup>7,8,9</sup> An overview of this growth rate data from birth through puberty is provided. Infants with ACH have shorter birth lengths on the average of -1.6 standard deviations (SD) below the mean for an average stature infant. Earlier data showed that in the first few months of life, the growth rate appeared relatively normal.<sup>8,9</sup>

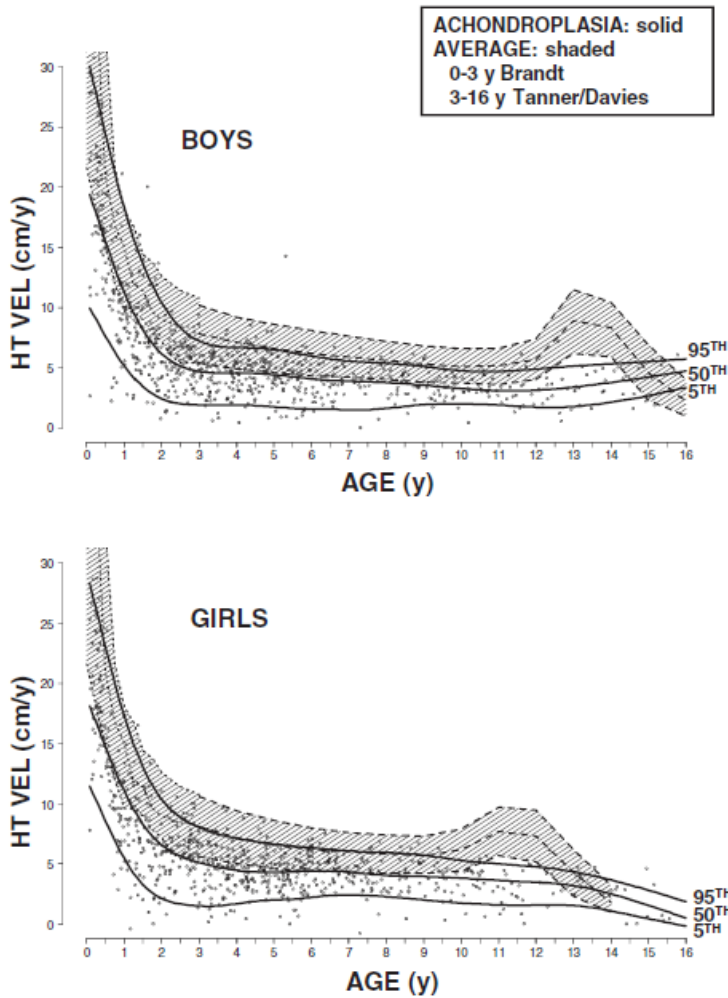
However, more recent data show a significant difference in growth rates during this stage, approximately 20 cm/year in ACH versus 44 cm/year in average stature infants, such that toddlers with ACH are at a height approximately -5 SD below the mean for average stature children by two years of age.<sup>7,8</sup>

Although toddlers with ACH are well below average stature height by age two years, the difference in growth rates between ACH and average stature children between the ages of 2-10 years is not as significant.<sup>7,8,9</sup> During this period, growth rates are reported as stable in ACH children at rates of approximately 4-5 cm/year and in average stature children ages 4-10 years are approximately 5-7 cm/year (Figure 1).<sup>7,8,10</sup>

Over the age of 10 years, growth rates in average stature children range from 5.5 cm to just under 7 cm/year in children whereas the velocity remains at 4-5 cm/year for ACH subjects over the age of 10 years. Controversy exists as to whether a pubertal growth spurt occurs in ACH patients.<sup>7,9</sup> Median height velocities throughout the pubertal years in ACH remain at approximately 5 cm/year in boys and girls through age 16 years. In contrast, median height velocity in average stature boys is 9.3 cm/year in boys aged 13.5 years and 8.3 cm/year in girls aged 12 years.<sup>7,10</sup> Not unexpectedly, final adult height (16-18 years) was reported as 6.5 standard deviations below the mean for ACH subjects.<sup>8</sup>

The difference in patterns of growth between ACH (as a result of the genetic mutation) and average stature children appears to be driven by the lower rates of growth in ACH, particularly during infancy and puberty, which are periods of rapid linear growth.<sup>7</sup> In addition, as stated in one study, growth rates do not fluctuate above and below the mean in ACH children nearly as much as is observed in average stature children and this also is a source of decreased growth velocity and final height.<sup>9</sup>

**Figure 1. Height velocity curves in achondroplasia and average stature children**



Source: Hoover-Fong et al. 2008 (Reference #7)

\*0-3 years, 10<sup>th</sup>, 50<sup>th</sup>, 90<sup>th</sup> percentiles represented; 3-16 years, 3<sup>rd</sup>, 50<sup>th</sup>, 97<sup>th</sup> percentiles represented

### *Current pediatric practice*

There is no cure or specific treatment for ACH. The available supportive treatments aim to prevent or treat complications of the disease. Many of the complications appear at predicted ages including during adulthood and can often be minimized or potentially even prevented if detected and treated early. Best practices and achondroplasia management guidelines have been developed in many countries with these efforts in mind.<sup>1,2,3,11,12</sup>

To address short stature in ACH patients, trials with human growth hormone have been completed. Although some increase in growth rate was observed, no clear long-term benefit has been established and most experts do not recommend growth hormone treatment for ACH.<sup>1</sup>

Surgical limb lengthening is another approach that has been used to increase stature. Although up to 15-30 cm has been added to standing height, use of this procedure is controversial as it often requires repeat procedures, long-term use of orthopedic appliances, wound complications and complications related to stretching of non-skeletal tissues including nerves and blood vessels.<sup>1</sup> Furthermore, the growth rate of the growth plate can be disturbed by these procedures; and, last, but, not least the cosmetic effect of long legs and short arms may not be suitable for some patients.<sup>13</sup>

## **Regulatory Background for Drug Development**

To be approved for marketing, a drug must be safe and effective for its intended use. For a drug to be effective, substantial evidence consisting of adequate and well-controlled investigations must show that the drug product will have the effect it is represented to have under the conditions of use prescribed or recommended (21 CFR 314.126(b)(5)). Safety is not explicitly defined in the regulations and is considered in the context of whether the benefits outweigh the risks. For a product to be FDA approved, data must support 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. Similarly, ensuring a strong clinical trial design from which reliable efficacy and safety data can be collected is critical to the drug development process. Among other things, a robust trial design generally entails use of a control group and a randomization procedure, which reduces bias of immeasurable confounders and provides greater confidence that a positive drug effect is, in fact, due to the drug; choice of an appropriate population for whom the drug is intended; and choice of an appropriate primary endpoint. The primary endpoint should be clinically meaningful, i.e. a direct measure of how the patient feels, functions or survives.

### *Ethical Considerations*

The Additional Safeguards for Children (21 CFR 50 subpart D) must be considered when pediatric patients are enrolled in a clinical trial. Unless the risks of an investigational agent are no more than a minor increase over minimal risk (21 CFR 50.53), the administration of an investigational agent in children must offer a prospect of direct clinical benefit to individually enrolled patients, the risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52). Additionally, adequate provisions must be made to obtain the permission on the parents and the assent of the child as per 21 CFR 50.55.

Prospect of direct clinical benefit is based on the structure of the intervention within the context of the clinical trial. Consequently, for a patient to directly benefit from participation in a study, the investigational agent must be provided at an appropriate dose and duration to result in a potential effect. Additionally, all components in a protocol must be evaluated individually as well as collectively, a concept known as “component analysis.”<sup>a</sup> Patients who receive placebo in a study do not directly benefit from participation in a study. The risk of these patients’ participating in the trial must not exceed a “minor increase over minimal risk” (21 CFR 50.53). This risk includes the risk of withholding known effective therapy where a therapy exists. The criteria for approval under 21 CFR 50.53 includes that participation in the trial contributes to generalizable knowledge for understanding or ameliorating the disease.

Subpart D provides protections to all pediatric patients below the age of majority and does not specify that one age cohort or subgroup is more vulnerable than another. However, prospect of direct benefit and the risk-benefit profile may vary within the pediatric population. For example, pediatric patients who have fused epiphyses and are no longer growing may not benefit from enrollment in trials for ACH evaluating drug effect on linear growth and enrollment of these patients in a study would not justify the risk. However, pediatric patients that are growing have a prospect of direct benefit. Prospect of direct benefit will also be impacted by the specific goals of the therapy and the ages at which that therapy might be most effective.

The current standard for establishing effectiveness of an investigational agent is the completion of two adequate and well-controlled clinical trials. However, FDA may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.<sup>b</sup> This flexibility has been used to approve drugs for rare diseases. Given that ACH is an orphan population, the sponsor will have limited opportunities to enroll patients in efficacy trials.

The use of an external or historical control group raises concerns about the ability of such trials “to ensure comparability of test and control groups and their ability to minimize important biases.”

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<sup>a</sup> Food and Drug Administration. (2013). 21 CFR Parts 50 and 56 - Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products. *Federal Register*, 78(38), 12937-12951.

<sup>b</sup> Food and Drug Administration. (1998). Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Retrieved from <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072008.pdf>

“The placebo control design, by allowing blinding and randomization and including a group that receives an inert treatment, controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug. These influences include spontaneous change (natural history of the disease and regression to the mean), subject or investigator expectations, the effect of being in a trial, use of other therapy, and subjective elements of diagnosis or assessment.”<sup>c</sup>

One of the main considerations in developing clinical trials for ACH is determining the appropriate duration of the trial. Consideration must be given to the duration of the placebo-controlled phase of the study as well as the total duration of the trial to establish overall clinical benefit, which includes durability of response and long-term safety. If a blinded study is conducted, and sham injections are required, the risk determination for the trial must incorporate the risk of the sham injections. To be acceptable, since there is no direct clinical benefit to receiving sham injections, both the placebo and the injection must be approvable under 21 CFR 50.53 as no more than a minor increase over minimal risk unless referred to a federal panel for review under 21 CFR 50.54. Weekly injections up to 2 years have been conducted in pediatric patients undergoing studies for Multiple Sclerosis

(<https://clinicaltrials.gov/ct2/show/NCT01892722?term=Fingolimod&cond=Multiple+Sclerosis&age=0&rank=1>).

Even if found to be ethically permissible, a study with a placebo-controlled component is only feasible if parents are willing to enroll their child in the study. Among other things, parents may be reluctant to enroll their child into a placebo-controlled trial because of the possibility that injections may be given without prospect of benefit, or because of the duration of the study.<sup>14</sup> On the other hand, consideration must be given to the fact that children might be administered a study drug from which they do not experience any clinical benefit, yet are at risk for possible adverse reactions to the study drug.

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<sup>c</sup> Food and Drug Administration. (2000). Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials. Retrieved from <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073139.pdf>



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