Bone age in children with achondroplasia: findings from a cohort of children participating in the PROPEL studies

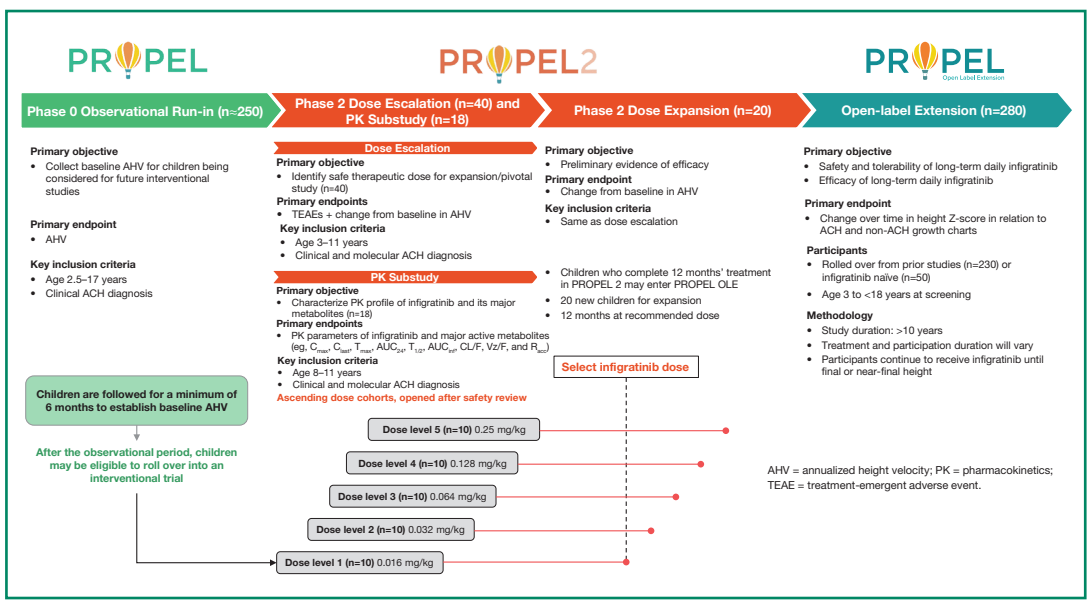
Ravi Savarirayan,[1] Josep Maria De Bergua,[2] Paul Arundel,[3] Jean Pierre Salles,[4] Antonio Leiva-Gea,[5] Melita Irving,[6] Vrinda Saraff,[7] Helen McDevitt,[8] Maria Salcedo Montejo,[9] Marc Nicolino,[10] Valerie Cormier-Daire,[11] Peter Kannu,[12] Mars Skae,[13] Michael B. Bober,[14] John Phillips III,[15] Toby Candler,[16] Paul Harmatz,[17] Howard Saal,[18] Julie Hoover-Fong,[19] Elena Muslimova,[20] Terry Cho,[20] Richard Weng,[20] Daniela Rogoff[20]

[1]Murdoch Children's Research Institute, Melbourne, Australia; [2]Hospital Vithas San José, Vitoria-Gasteiz, Spain; [3]Sheffield Children's NHS Foundation Trust, Sheffield, UK; [4]Hôpital des Enfants – Toulouse, Toulouse, France; [5]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [6]Guy's and St Thomas' NHS Foundation Trust, London, UK; [7]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [8]NHS Greater Glasgow and Clyde, Glasgow, UK; [9]Hôpital Femme Mère Enfant, Bron, France; [10]Hôpital Necker-Enfants Malades, Paris, France; [11]University of Alberta – Stollery Children's Hospital, Edmonton, AB, Canada; [12]Manchester University NHS Foundation Trust, Manchester, UK; [13]Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA; [14]Vanderbilt University Medical Center Nashville, TN, USA; [15]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, USA; [16]Benioff Children's Hospital Oakland, Oakland, CA, USA; [17]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [18]Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [19]QED Therapeutics, San Francisco, CA, USA

Background

- **Bone age (BA)** is commonly used in pediatrics to define skeletal maturity for medical and non-medical purposes. Its assessment is based on predictable changes of ossification centers over time. Typically, it is calculated based on radiographs of the left hand and wrist or knee.[1,2]
- A child's bone age may or may not approximate his/her chronological age (CA). Factors influencing the progression of skeletal maturation include sex and nutrition, as well as metabolic, genetic, and social factors and acute or chronic diseases, including endocrine dysfunction.
- Normal BA range is represented by two standard deviations (SDs) above and below the mean.[3]
- **Achondroplasia (ACH)** is the most common short-limbed skeletal dysplasia, affecting between 1 in 15,000 to 1 in 30,000 live births in the US, with an estimated global prevalence of 250,000.[4,5]
- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene,[6,7] which is a negative regulator of endochondral bone formation.
- Characteristic clinical features of ACH include: disproportionately short stature; smaller than average chest; macrocephaly with frontal bossing; midface hypoplasia; curvature of the spine; hypermobile joints; leg bowing; and shortening of the fingers and toes.[8]
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges throughout their lifetime.[9]
- **BA in achondroplasia (ACH)** has not been fully characterized. Calculation is challenging given difficulties in comparing X-rays with standard radiographs if using the Greulich–Pyle (GP) method;[10] using the alternative Tanner–Whitehouse (TW) method is complex and requires experience.
- Few publications have described delays in BA in children with ACH. One study showed a delay of 1.4 years for males and 1.2 years for females, with a mean±SD difference between CA and RUS (radius, ulna, and short bones) BA of 0.9±1.1 years for children <10 years and 1.6±0.9 years for those >10 years.[11] Another study described a mean delay in BA of 11.6 months for boys and 8.2 months for girls during early childhood; although still evident in adolescent boys, the delay was almost absent in girls by the age of 16 years.[12]
- The **PROPEL** (NCT04035811) and **PROPEL2** (NCT04265651) studies (Figure 1) were designed to provide preliminary evidence of the safety and efficacy of infigratinib as precision treatment of children with ACH.[13]
- Infigratinib is an orally bioavailable and selective FGFR1/2/3 tyrosine kinase inhibitor in development for ACH. Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.[8] The long-term efficacy and safety of daily use of oral infigratinib is being assessed in the **PROPEL OLE** study.

Figure 1. PROPEL, PROPEL2, and PROPEL open-label extension study designs



Objective

- Here we describe BA at baseline in a group of in children participating in the Phase 2 dose-finding PROPEL2 study evaluating the preliminary safety and efficacy of infigratinib in children with ACH.

Methods

Study design

- PROPEL2 is a prospective, Phase 2, open-label study designed to provide preliminary evidence of the safety and efficacy of oral infigratinib in children with ACH, and to identify the dose of infigratinib to be explored in future studies.
- Children 3–11 years of age with ACH who completed ≥6 months of observation in the non-interventional PROPEL study are eligible to participate in PROPEL2. The study design and eligibility criteria for PROPEL and PROPEL2 have been described in detail elsewhere.[13]

Assessments

- Left-hand radiographs of children with ACH enrolled in the PROPEL2 study who had imaging data available at the time of the analysis were evaluated at baseline for BA using the RUS method (TW2) by a single reader blinded to the children's age and sex.
- The relationship of BA to CA was expressed as BA:CA ratio (BA/CA) and BA–CA overall and by sex. SD score was calculated using SD data from the GP atlas.[10]

Results

- In total, 56 children with available BL imaging data were evaluated in this analysis. Their baseline demographic characteristics are summarized in Table 1.

Table 1. Baseline characteristics

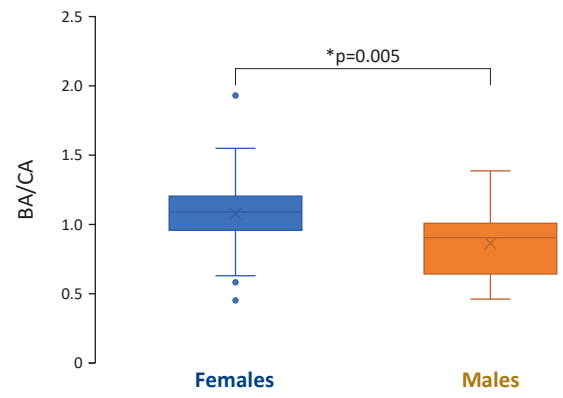
Characteristic	Total (n=56)
Sex, n (%)	
Female	34 (60.7)
Male	22 (39.3)
Age, years[a]	
Median	8.0
Mean ± SD	7.6 ± 2.2
Age of female participants, years[a]	
Median	8.0
Mean ± SD	7.5 ± 2.2
Age of male participants, years[a]	
Median	8.1
Mean ± SD	7.9 ± 2.2

[a]Chronological age.

Table 2. Bone age

Characteristic	BA, years	BA/CA
All participants		
Median	8.2	1.0
Mean ± SD	7.6 ± 2.9	1.0 ± 0.3
Female participants		
Median	8.7	1.1
Mean ± SD	8.0 ± 2.9	1.1 ± 0.3
Male participants		
Median	6.9	0.9
Mean ± SD	7.0 ± 2.7	0.9 ± 0.2

Figure 2. BA/CA in female and male participants

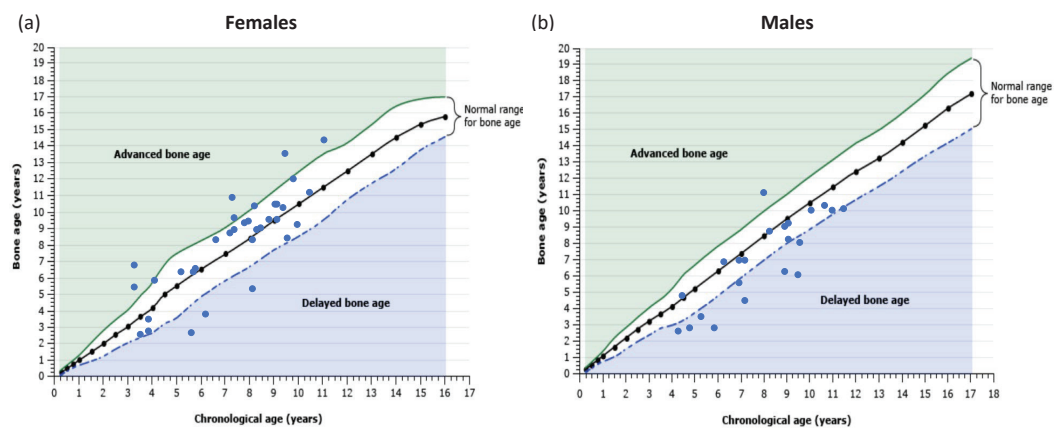


The lower and upper bounds of the rectangles represent the first and third quartiles, the horizontal line represents the median, the whiskers extend to the highest and lowest values within 1.5 × the interquartile range and data beyond the end of the whiskers are outliers and are plotted as points. The X represents the mean

Bone age of PROPEL2 participants compared with standard charts

- Nine children (16.1%; 6 females, 1 male) had a BA that was more than +2 SDs for age and sex, indicating an advanced BA compared with CA.
- Thirteen children (23.2%; 3 females, 10 males) had a BA that was delayed compared with CA, i.e. less than –2 SDs for age and sex (Figures 3a and 3b).

Figure 3. Distribution of BA vs CA in female and male participants



The normal range is represented by 2 SDs above and below the mean (white area on this chart).
BA is delayed if it is below this threshold (blue area), and advanced if it is above this threshold (green area).

Conclusions

- This analysis of data from children enrolled in the PROPEL2 study did not confirm previous findings suggesting a delay in BA in pre-pubertal children with ACH.
- BA was more advanced in females than in males in this study, but within the expected variability for the age group.
- This work suggests that BA estimation in children with ACH can be employed for the same purposes as in children without skeletal dysplasia.

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