Evaluation of body mass index and metabolic parameters in children with achondroplasia participating in the PROPEL study

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] Fernando Santos-Simarro,[9] Marc Nicolino,[10] Valerie Cormier-Daire,[11] Peter Kannu,[12] Mars Skae,[13] Michael B. Bober,[14] John Phillips III,[15] Christine Burren,[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]Hospital Universitario La Paz, Madrid, Spain; [10]Hôpital Femme Mère Enfant, Bron, France; [11]Hôpital Necker-Enfants Malades, Paris, France; [12]University of Alberta – Stollery Children's Hospital, Edmonton, AB, Canada; [13]Manchester University NHS Foundation Trust, Manchester, UK; [14]Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA; [15]Vanderbilt University Medical Center Nashville, TN, USA; [16]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, USA; [17]Benioff Children's Hospital Oakland, Oakland, CA, USA; [18]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [19]Johns Hopkins University, Baltimore, MD, USA; [20]QED Therapeutics, San Francisco, CA, USA

#PSAT105

Background

- 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 USA, with an estimated global prevalence of 250,000.[1,2]
- Children and adults with ACH have disproportionate short stature[3] and are at risk for several significant comorbidities, including obstructive sleep apnea, chronic otitis media with conductive hearing loss, and spinal stenosis.[4]
- Obesity is a major health problem in ACH and aggravates breathing difficulties (i.e. sleep apnea), back and joint pain, and reduced mobility.[5]
- Individuals with ACH are predisposed to abdominal obesity, although the reason for this is not completely understood.[5,6]
- Nevertheless, the metabolic effect of visceral obesity does not suggest an association with the development of a diabetic profile.[5]
- The PROPEL study (NCT04035811) is a prospective, non-interventional study designed to examine baseline growth parameters and health status in children being assessed for potential enrollment into interventional studies with infigratinib, an oral fibroblast growth factor receptor (FGFR)1–3 inhibitor in development for ACH (Tables 1, 2).
- Details on the study design are presented elsewhere.

Table 1. PROPEL study key inclusion criteria

Key inclusion criteria
• Signed informed consent by study participant or parent(s) or legally authorized representative (LAR) and signed informed assent by the study participant (when applicable)
• Age 2.5 to 10 years (inclusive) at study entry
• Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist)
• Ambulatory and able to stand without assistance
• Study participants and parent(s) or LAR(s) are willing and able to comply with study visits and study procedures

Table 2. PROPEL study key exclusion criteria

Key exclusion criteria
• Hypochondroplasia or short stature condition other than ACH
• Females who have had their menarche
• Height <–2 or >+2 standard deviations for age and sex based on reference tables on growth in children with ACH
• AHV ≤1.5 cm/year over a period ≥6 months prior to screening
• Concurrent disease or condition that, in the view of the Investigator and/or Study Sponsor, may impact growth or where the treatment is known to impact growth
• Significant abnormality in screening laboratory results
• Treatment with growth hormone, insulin-like growth factor-1, or anabolic steroids in the previous 6 months or long-term treatment (>3 months) at any time
• Treatment with a C-type natriuretic peptide analog or treatment targeting FGFR inhibition at any time
• Regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable)
• Use of any other investigational product or investigational medical device for the treatment of ACH or short stature
• Previous limb-lengthening surgery

Objective

- To evaluate body mass index (BMI) and metabolic parameters in a subgroup of children with ACH participating in the PROPEL study.

Methods

Assessments

- BMI was calculated at the time of enrollment and compared with USA sex- and age-specific BMI curves for children with ACH.[7]
- Blood samples (not fasting) for clinical laboratory tests were collected at baseline in a subset of children who started screening for the Phase 2 study PROPEL 2 (described elsewhere).[8,9]
- Cholesterol, triglycerides, and glycated hemoglobin (HbA_{1c}) levels were measured centrally, and results compared with laboratory reference ranges for the pediatric population.

Results

- Data from 86 children were analyzed (mean±SD age 6.1±2.5 years; female n=52; Table 3).
- The mean±SD BMI was 20.5±1.6 kg/m^2 (range 17.9–24.6 kg/m^2) in boys (Figure 1A) and 21.2±2.2 kg/m^2 (range 16.8–26.2 kg/m^2) in girls (Figure 1B):
  - Eight of 52 girls (15.4%) and one of 34 boys (2.9%) had a BMI above the 95th percentile for sex and age based on BMI curves for ACH.
- The mean±SD cholesterol level, measured in a subset of 43 children, was 4.2±0.7 mmol/L (normal range [NR] 2.59–4.66 mmol/L; Figure 2). The mean±SD triglyceride level in this subset was 0.9±0.5 mmol/L (NR 0.56–1.36 mmol/L; Figure 3):
  - Cholesterol was elevated in nine of the 43 children (20.9%); triglycerides were elevated in eight of the 43 children (18.6%).
- HbA_{1c} was measured in 28 children. The mean±SD HbA_{1c} fraction of total hemoglobin was 0.052±0.002 (NR 0.04–0.06; Figure 4):
  - Although all values were within NRs, 19 of 28 children (67.9%) had values above the mean for laboratory reference values.
- No correlations between BMI and cholesterol, TG, or HbA_{1c} levels were observed.

Table 3. Baseline patient characteristics

Characteristic	Total (n=86)
Age, years	
Median (range)	6.2 (2.5–10.8)
Mean (SD)	6.1 (2.5)
Age group, n (%)	
<3 years	12 (14.0)
3 to <5 years	22 (25.6)
5 to <8 years	26 (30.2)
≥8 years	26 (30.2)
Sex, n (%)	
Male	34 (39.5)
Female	52 (60.5)
Race, n (%)	
White	54 (62.8)
Asian	8 (9.3)
Black or African American	4 (4.7)
Other	7 (8.1)
Not reported	13 (15.1)

Figure 1. BMI in children enrolled in PROPEL: (A) boys and (B) girls

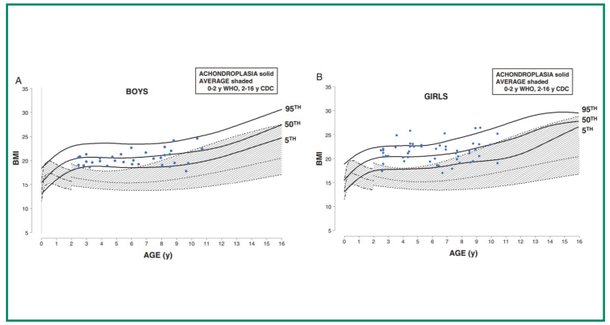
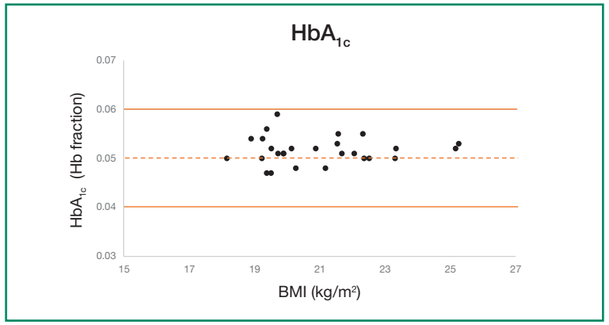


Figure 2. Cholesterol levels in children enrolled in PROPEL

Figure 3. Triglyceride levels in children enrolled in PROPEL

Figure 4. HbA_{1c} levels in children enrolled in PROPEL



Study limitations

- Family history of lipid disorders or dietary patterns in these children were not taken into consideration for this analysis.
- Most samples were not collected in fasting condition, which could influence the findings. Nonetheless, sample collection is in line with current recommendations for lipid testing, as serum lipid levels show minor variation after eating.

Conclusions

- This analysis of data from children enrolled in the PROPEL study illustrates the importance of using BMI tables developed for children with ACH when providing guidance on weight management.
- Average cholesterol and HbA_{1c} levels in this cohort, although normal, were above the mean for the reference population. This highlights the importance of a healthy diet, weight management, and regular physical activity starting at a young age.
- Additional studies are needed to understand the relationship between BMI and body composition in individuals with short stature and to further investigate the clinical relevance of these findings given that no association between increased BMI and metabolic syndrome has been described in adults with ACH.

Acknowledgements

- The authors would like to acknowledge all study participants, parent(s) or LARs, together with participating sites, investigators, and study staff involved in PROPEL.
- Editorial/writing support for this poster was provided by Miller Medical Communications Ltd. This work was funded by the study sponsor (QED Therapeutics Inc.).

References

1. Horton WA, et al. Lancet 2007;370:162–72.
2. Waller DK, et al. Am J Med Genet A 2008;146A:2385–9.
3. Hoover-Fong J, et al. Am J Med Genet A 2017;173:1226–30.
4. Unger S, et al. Curr Osteoporos Rep 2017;15:53–60.
5. Saint-Laurent C, et al. Orphanet J Rare Dis 2019;14:253.
6. Saint-Laurent C, et al. PLoS One 2018;13:e0195876.
7. Hoover-Fong JE, et al. Am J Clin Nutr 2008;88:364–71.
8. Savarirayan R, et al. Ther Adv Musculoskel Dis 2022;14:1759720X221084848.
9. Savarirayan R, et al. ENDO 2022 PROPEL studies poster (#PSAT106).

Presented at ENDO 2022, June 11–14, Atlanta, GA, USA