Comparison of quantitative computed tomography bone mineral density measurements of vosoritide-treated children with achondroplasia to an untreated achondroplasia reference population

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Introduction

- Achondroplasia is a skeletal dysplasia caused by pathogenic variants of the fibroblast growth factor receptor 3 *(FGFR3)* gene,[1,2] leading to impaired endochondral ossification, skeletal changes, and multisystem complications[2,3]
- Vosoritide is a C-type natriuretic peptide analog that promotes endochondral bone growth in children with achondroplasia by activating natriuretic peptide receptor B (NPR-B) signaling,[4] which counteracts FGFR3-mediated inhibition of chondrocyte proliferation and differentiation, thereby improving bone growth[4,5]
- In the ongoing open-label CANOPY ACH-EXT (111-205) clinical trial, vosoritide provided sustained improvements in bone growth in children with achondroplasia for up to 10 years, including increasing annualized growth velocity[6]
- Previously, we found that children with achondroplasia treated with vosoritide in CANOPY ACH-EXT (111-205) had increased radial and tibial trabecular and cortical volumetric bone mineral density (BMD) using peripheral quantitative computed tomography (pQCT)[7]
  - However, the absence of a control group limited the ability to determine whether observed changes resulted from vosoritide treatment

Objectives

- To compare radial and tibial BMD of vosoritide-treated children with achondroplasia measured by pQCT using whole-body clinical CT scanners to published cross-sectional data obtained with high-resolution pQCT (HR-pQCT) in similarly aged children with untreated achondroplasia[8]

Methods

Clinical trial population

- Thirty children with achondroplasia began vosoritide in the open-label CANOPY ACH-2 study (111-202; NCT02055157) and transitioned to CANOPY ACH-EXT (111-205; NCT02724228), completing up to 10 years of vosoritide treatment
- pQCT scans were acquired at least annually using whole-body clinical CT scanners calibrated with a hydroxyapatite phantom
- At baseline, distal and proximal volumes of interest (VOIs) were positioned on the radius and tibia (**Figure 1**)
  - To account for growth during follow-up, affine registration was applied based on changes in bone length between the baseline and follow-up scans
- For each VOI, BMD assessments of integral, trabecular, and cortical bone compartments of the distal radius and tibia were determined using previously described methods[7] and included in this analysis

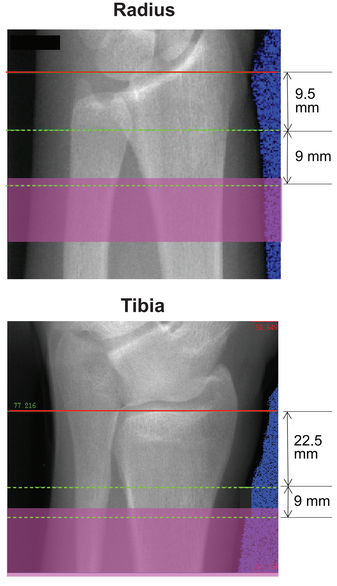
Untreated reference population

- The reference population consisted of 10 untreated individuals with achondroplasia aged 11.7–23.4 years and 21 age- and sex-matched individuals of average stature from a published cross-sectional study[8]
- Reference measurements were obtained using HR-pQCT, as previously described[8]

Comparison

- To compare with the published data, median BMD values of CANOPY ACH-EXT (111-205) trial participants aged 11–18 years were plotted, including all available assessments within the time frame for each child, against the reference population[8]
- Differences in technology, scan region location, age, and race precluded statistical comparisons

Figure 1. Placement of the distal VOI on the radius and tibia



The reference lines were used by the HR-pQCT analysis software to determine the relative positions of the HR-pQCT analysis VOIs, which are independent of a given participant. The pink band indicates the approximate positions and the pQCT analysis VOIs; however, the exact sizes and locations are participant-dependent.
BMD, bone mineral density; HR-pQCT, high-resolution peripheral quantitative computed tomography; VOI, volume of interest.

Results

Baseline demographics

- Participants in the open-label CANOPY ACH-EXT trial (n = 30) had mean ± standard deviation (SD) age at treatment initiation of 8.2 ± 1.6 years. A total of 43.3% were male, while 70.0% of participants were White and 20.0% were Asian (**Table 1**)
- Mean (SD) estimated time on treatment between the first and last available CT scans was 7.5 ± 2.0 years (median 7.0 years; n = 30), including the first 2 years of the CANOPY ACH-2 study
- In the 11- to 18-year age range, 29 of the 30 participants selected for this study contributed assessments across a total of 58 visits
  - Mean age across all 58 visits was 13.8 ± 1.9 years
- Individual participants contributed assessments from a minimum of 2 to a maximum of 8 visits
- Baseline characteristics in the reference populations were as follows (**Table 2**):
  - Untreated participants with achondroplasia had a median age (range) at evaluation of 15.0 years (11.7–23.4); 80.0% were male and 100% were Asian
  - The age- and sex-matched average-stature group (n = 21) had a median age (range) at evaluation of 15.7 years (12.1–38.7); 76.2% were male and 100% were Asian

Table 1. Baseline demographic and clinical characteristics at first dose in the CANOPY ACH-EXT population

Visit	Overall N = 30
Age at treatment initiation, years	
Mean ± SD	8.2 ± 1.6
Min, max	5.8, 11.1
Sex, n (%)	
Male	13 (43.3)
Female	17 (56.7)
Age at treatment initiation, n (%)	
≥5 to <8 years	15 (50.0)
≥8 to <11 years	14 (46.7)
≥11 to <15 years	1 (3.3)
Race, n (%)	
White	21 (70.0)
Asian	6 (20.0)
Not provided[a]	2 (6.7)
Other	1 (3.3)
Ethnicity, n (%)	
Not Hispanic or Latino	28 (93.3)
Hispanic or Latino	2 (6.7)

[a]Due to patient privacy rules.
max, maximum; min, minimum; SD, standard deviation.

Table 2. Baseline demographics for reference participants with untreated achondroplasia and average stature[8]

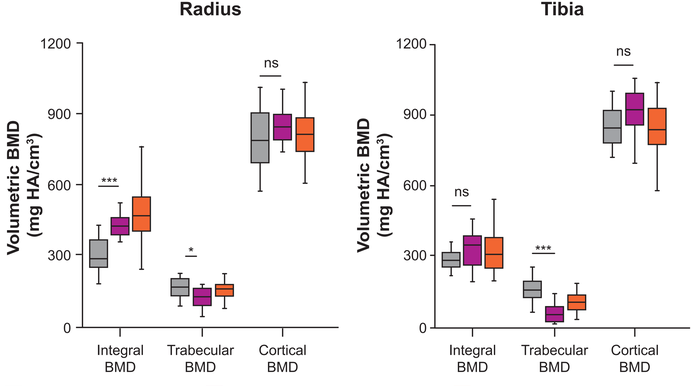
Visit	Average stature N = 21	Untreated achondroplasia N = 10
Age at pQCT assessment, median, years	15.7	15.0
Min, max	12.1, 38.7	11.7, 23.4
Sex, n (%)		
Male	16 (76.2)	8 (80.8)
Female	5 (23.8)	2 (20.0)
Race, n (%)		
Asian	21 (100.0)	10 (100.0)

Reference data for participants with average stature and untreated achondroplasia were acquired from Liang H, et al. *Calcif Tissue Int.* 2023;112(1):13–23.[7]
max, maximum; min, minimum; pQCT, peripheral quantitative computed tomography.

Bone mineral density

- For radius and tibia, trabecular, cortical, and integral BMD were numerically similar between vosoritide-treated children aged 11–18 years and children with untreated achondroplasia (**Figure 2**)
  - Absolute values for integral, trabecular, and cortical volumetric BMD appeared comparable between children with achondroplasia who did and did not receive vosoritide
  - In published HR-pQCT data, radial integral BMD was higher, while trabecular BMD was lower in the radius and tibia for children with achondroplasia compared with matched children of average stature[8]

Figure 2. BMD of children with average stature, children with untreated achondroplasia, and children with achondroplasia treated long-term with vosoritide



Solid lines are the median, boxes are interquartile ranges, and whiskers are minimum and maximum. Reference populations are measured using HR-pQCT (untreated achondroplasia cohort and average-stature cohort), and statistical testing was performed as reported by Liang H, et al. *Calcif Tissue Int.* 2023;112(1):13–23.[8] Asterisks indicate statistical significance: *P < .05; **P < .01; ***P < .001; ****P < .0001. Parameters for CANOPY ACH-EXT trial participants with vosoritide-treated achondroplasia were measured by pQCT; participants provided yearly scans and may be represented more than once in the calculated median values.
BMD, bone mineral density; HA, hydroxyapatite; HR-pQCT, high-resolution pQCT; ns, not significant; pQCT, peripheral quantitative computed tomography.

Conclusions

- While direct comparisons are limited due to differences in technology, scan region location, age, and race, children with achondroplasia who received long-term vosoritide had distal radius and tibial BMD comparable with individuals of average stature or untreated achondroplasia
- CANOPY ACH-EXT (111-205) participants appear representative of children with achondroplasia, supporting the interpretation and generalizability of the trial results

References

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Disclosures

KE and **TF** are employees of Clario Inc., which was contracted by BioMarin Pharmaceutical Inc. to perform this analysis. **CCT**, **AL**, and **JW** are employees and potential shareholders of BioMarin Pharmaceutical Inc.

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