Effect of long-term vosoritide treatment in pediatric participants with achondroplasia on bone mineral density and bone content: results from quantitative computed tomography analyses

Poster # Sat-572

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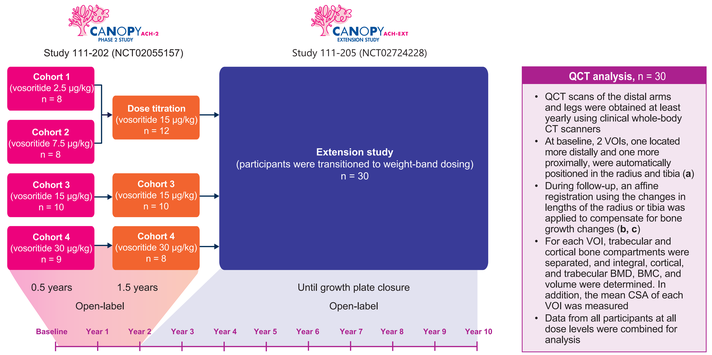
Introduction

- Achondroplasia (ACH) is a skeletal dysplasia that is caused by constitutive activation of the fibroblast growth factor receptor 3 (*FGFR3*) gene, leading to impaired endochondral bone growth[1]
  - Typically, C-type natriuretic peptide (CNP) downregulates FGRF3 signaling in chondrocytes by inhibiting the MAPK-ERK pathway, a downstream pathway of FGFR3[2]
  - Preclinical studies further suggest that CNP has anabolic effects on bone outside of the growth plate, including upregulation of genes involved in ossification, extracellular matrix organization, bone development, and mineralization (for further details, please visit Poster # Sun-133)[3,4]
- Vosoritide, a modified recombinant analogue of CNP, stimulates endochondral bone growth by activating natriuretic peptide receptor B (NPR-B), which inhibits the MAPK/ERK pathway in chondrocytes[5]
  - Vosoritide is the only approved precision therapy for children with ACH[6]
- The ongoing CANOPY ACH clinical program has more than a decade of longitudinal data demonstrating that vosoritide is well tolerated and provides significant, sustained improvements in annualized growth velocity for children with ACH[7]
- The effect of long-term vosoritide use on bone parameters related to growth measured using peripheral quantitative computed tomography (QCT) imaging has not been investigated extensively

Objective

- To assess bone growth parameters in children with ACH receiving vosoritide long-term using peripheral QCT imaging

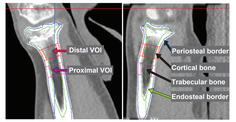
Study Design



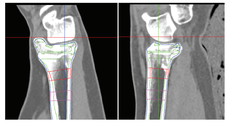
QCT analysis, n = 30

- QCT scans of the distal arms and legs were obtained at least yearly using clinical whole-body CT scanners
- At baseline, 2 VOIs, one located more distally and one more proximally, were automatically positioned in the radius and tibia (**a**)
- During follow-up, an affine registration using the changes in lengths of the radius or tibia was applied to compensate for bone growth changes (**b, c**)
- For each VOI, trabecular and cortical bone compartments were separated, and integral, cortical, and trabecular BMD, BMC, and volume were determined. In addition, the mean CSA of each VOI was measured
- Data from all participants at all dose levels were combined for analysis

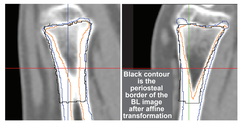
a. Tibia VOIs BL, bone length: 145 mm



b. Tibia VOIs year 10, bone length: 221 mm



c. Affine registration of year 10 to BL



All vosoritide doses were administered once daily at home as subcutaneous injections. Bone length measurements were taken by a technician using the CT scout scans representing a manual image-based central standardized assessment. All QCT analyses were performed with MIAF-Forearm (version 1.1.1R).
BL, baseline; BMC, bone mineral content; BMD, bone mineral density; CSA, cross-sectional area; CT, computed tomography; MIAF, Medical Image Analysis Framework; QCT, quantitative CT; VOI, volume of interest.

Results

Participants

- Thirty participants (17 females, 13 males) aged ≥5 to <15 years at initiation who received long-term vosoritide treatment in the phase 2 CANOPY ACH-2 dose titration study (111-202) and the CANOPY ACH-EXT extension study (111-205) were included in this analysis (**Table 1**)
- The mean duration of vosoritide treatment was 7.32 years (minimum, 2.8 years; maximum, 10.6 years), and the mean follow-up time was 7.95 years

Table 1. Baseline demographics at first dose of the CANOPY ACH-EXT population (all treatment arms combined)

Characteristic	Overall N = 30
Age at treatment initiation, years	
Mean (SD)	8.16 (1.57)
Min, max	5.8, 11.1
Sex, n (%)	
Male	13 (43.3)
Female	17 (56.7)
Age subgroups at treatment initiation, n (%)	
≥5 to <8 years	15 (50.0)
≥8 to <11 years	14 (46.7)
≥11 to <15 years[a]	1 (3.3)
Race, n (%)	
White	21 (70.0)
Asian	6 (20.0)
Not provided[b]	2 (6.7)
Other	1 (3.3)
Ethnicity, n (%)	
Not Hispanic or Latino	28 (93.3)
Hispanic or Latino	2 (6.7)

[a]Age subgroup was excluded from analysis, as additional participants are needed. [b]Due to patient privacy rules.
Max, maximum; min, minimum; SD, standard deviation.

Changes from baseline in distal tibia bone parameters

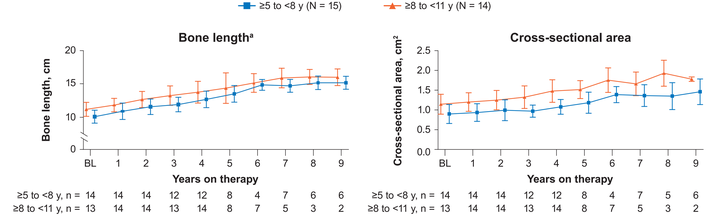
- Overall, QCT analyses of several bone parameters showed a general trend of improvement over time for all age groups. Detailed results for the distal tibia are shown in **Table 2**
  - Similar results were observed for the distal radius, proximal radius, and proximal tibia

Table 2. Changes from baseline in distal tibia bone parameters in all participants (N = 30)

Bone QCT parameters	Mean change from baseline to year								
	Year 1, n = 26	Year 2, n = 22	Year 3, n = 21	Year 4, n = 22	Year 5, n = 17	Year 6, n = 10	Year 7, n = 12	Year 8, n = 9	Year 9, n = 8
Bone length, cm[a]	1.2 (0.5)[b]	2.3 (1.0)	3.5 (0.9)	4.3 (1.1)	5.3 (1.7)	6.5 (1.7)	7.3 (1.4)	8.2 (1.7)	8.9 (1.7)
Average CSA, cm^2	0.4 (0.2)	0.6 (0.2)	0.9 (0.3)	1.2 (0.4)	1.3 (0.4)	1.6 (0.6)	1.7 (0.4)	1.9 (0.5)	1.8 (0.8)
Integral BMC, mg	114 (89)	207 (137)	270 (175)	408 (266)	522 (286)	650 (340)	801 (354)	837 (411)	923 (365)
Integral volume, cm^3	0.4 (0.2)	0.8 (0.3)	1.1 (0.4)	1.4 (0.5)	1.5 (0.4)	1.9 (0.7)	1.9 (0.4)	2.2 (0.7)	1.9 (0.8)
Integral BMD, mg/cm^3	−6 (22)	−7 (23)	−17 (38)	−7 (55)	7 (55)	3 (63)	27 (43)	21 (40)	56 (62)
Cortical BMC, mg	58 (83)	97 (104)[c]	104 (183)[d]	255 (258)[d]	323 (274)	449 (301)	558 (301)	568 (303)	633 (258)
Cortical volume, cm^3	0.08 (0.06)	0.1 (0.1)[c]	0.1 (0.1)[d]	0.3 (0.2)[d]	0.3 (0.2)	0.5 (0.2)	0.6 (0.2)	0.5 (0.3)	0.6 (0.2)
Cortical BMD, mg/cm^3	−8 (51)	−3 (47)[c]	−19 (65)[d]	22 (88)[d]	25 (86)	41 (91)	47 (104)	61 (64)	107 (75)
Trabecular BMC, mg	56 (70)	99 (90)[c]	150 (113)[d]	144 (60)[d]	174 (114)[f]	192 (106)[g]	250 (139)[h]	248 (135)[i]	272 (124)[i]
Trabecular volume, cm^3	0.3 (0.2)	0.6 (0.3)[c]	0.9 (0.5)[e]	1.1 (0.5)[e]	1.0 (0.4)[f]	1.5 (0.8)[g]	1.3 (0.4)[h]	1.6 (0.5)[i]	1.3 (0.8)[i]
Trabecular BMD, mg/cm^3	9 (19)	16 (21)[c]	23 (24)[e]	18 (19)[e]	26 (25)[f]	19 (28)[g]	44 (32)[h]	41 (30)[i]	49 (39)[i]

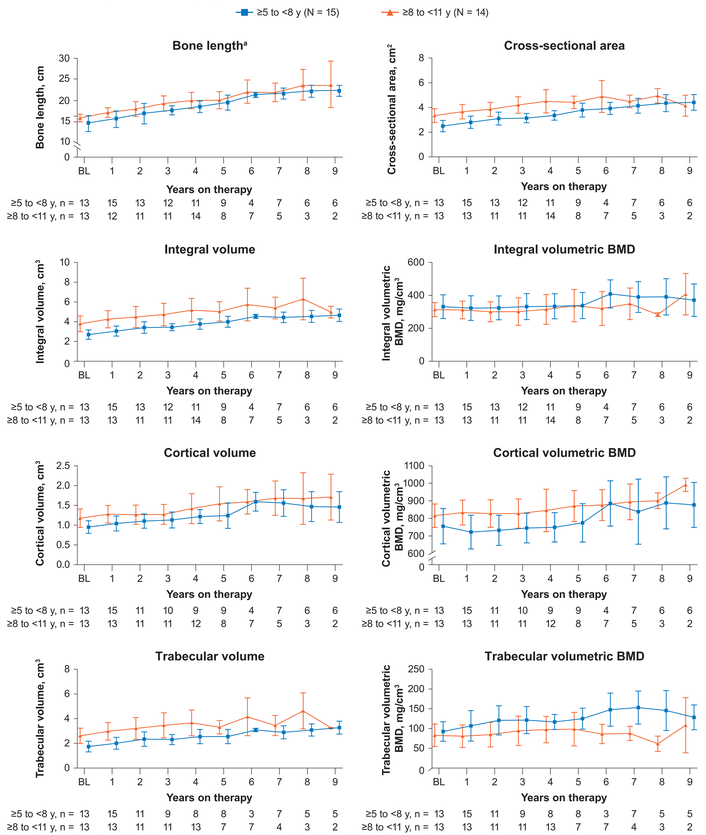
The change from baseline is based on the participants with available measurements at both time points, and the calculation accounts for missing data. All values are mean (SD). Year 10 analyses are ongoing. [a]Bone length measurements were taken by a technician using the CT scout scans representing a manual image-based central standardized assessment. [b]n = 25. [c]n = 20. [d]n = 19. [e]n = 18. [f]n = 15. [g]n = 9. [h]n= 11. [i]n = 8. [j]n = 7.
BMC, bone mineral content; BMD, bone mineral density; CSA, cross-sectional area; CT, computed tomography; QCT, quantitative CT; SD, standard deviation.

Distal radius bone parameters by age at vosoritide treatment initiation



Data presented are mean (SD). [a]Bone length measurements were taken by a technician using the CT scout scans representing a manual image-based central standardized assessment.
BL, baseline; CT, computed tomography; SD, standard deviation.

Distal tibia bone parameters by age at vosoritide treatment initiation



Data presented are mean (SD). [a]Bone length measurements were taken by a technician using the CT scout scans representing a manual image-based central standardized assessment.
BL, baseline; BMD, bone mineral density; CT, computed tomography; SD, standard deviation.

Conclusions

- CANOPY ACH-2/CANOPY ACH-EXT is the first study to use this novel QCT technology for assessment of bone growth in treated children with ACH
- Long-term vosoritide treatment in children with ACH was associated with increases in size (bone length and cross-sectional area) and bone mineral density (integral, cortical, and trabecular) at the distal and proximal tibia and radius. The combined changes are suggestive of improved bone strength[4,7]
  - These results complement the previously reported annual growth velocity and height increases in children with ACH receiving vosoritide[1,8]
- The lack of a control arm limits our ability to differentiate growth from treatment effects
- Additional research is needed to confirm results from this small, single-arm analysis suggesting that vosoritide improves bone strength for children with ACH

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Disclosures

KE and **TF** are employees of Clario, Inc., which was contracted by BioMarin Pharmaceutical Inc. to perform this analysis. **C-CT, AL**, and **JW** are employees of BioMarin Pharmaceutical Inc. and hold stock ownership.

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