Effect of vosoritide on spine morphology in young children with achondroplasia: 1-year results from a double-blind, randomized phase 2 study

Poster # Sun-555

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Introduction

- Achondroplasia is a rare skeletal dysplasia caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene that results in impaired endochondral bone growth[1-4]
- Spinal stenosis, a serious complication of impaired bone growth caused by narrowing of the spinal canal with potential cord compression, is associated with a variety of symptoms including pain, paresthesia or muscle weakness/numbness in the limbs, and in more severe cases, reduced mobility or incontinence[5,6]
- Persistent thoracolumbar kyphosis (≥20° angle) is associated with increased risk of symptomatic spinal stenosis requiring surgical intervention[7]
- The spinal canal reaches near final size before 5 years of age in average-stature children and even earlier in children with achondroplasia, making early intervention essential to prevent spinal deformities[6,8]
- Vosoritide is a C-type natriuretic peptide analogue that is a targeted, potent stimulator of endochondral bone growth approved for treatment of achondroplasia in children whose epiphyses are not closed[9]
  - An extensive clinical trial program spanning over a decade has demonstrated durable improvements in growth and body proportionality with vosoritide treatment compared with untreated children with achondroplasia[10-15]
  - To date, there are limited data available regarding the effect of vosoritide on spinal morphology

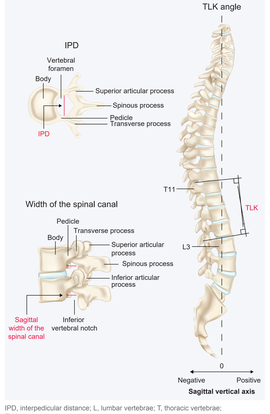
Objective

- To examine the key parameters of spinal morphology in children <5 years of age with achondroplasia who were treated with vosoritide or placebo for 1 year in the phase 2 CANOPY ACH-2I clinical study (111-206; NCT03583697)

Methods

- This secondary analysis included participants from CANOPY ACH-2I (111-206; NCT03583697), a placebo-controlled, randomized phase 2 trial evaluating the safety and efficacy of vosoritide in children with ACH aged 0 to <5 years
  - Participants were randomized to daily subcutaneous placebo or vosoritide (age-based dose of 15 [2 to <5 years] or 30 [0 to <2 years] µg/kg/day)
- Spinal morphology of participants was assessed at baseline and week 52 using lateral and anterior/posterior radiographs that were centrally read by independent radiologists
  - Interpedicular distance (IPD) was defined as the distance between the medial aspects of both pedicles (**Figure 1**)
  - The sagittal width of the spinal canal was measured at the inferior level of the pedicle
  - Thoracolumbar angles were measured from the proximal vertebrae at the top of thoracic vertebra 11 (T11) through the distal vertebrae at the top of lumbar vertebra 3 (L3) and encompassed T11 through L2
- The least squares mean (LSM) changes from baseline were calculated using an analysis of covariance model to account for differences in demographics and baseline characteristics

Figure 1. IPD, spinal canal width, and TLK angle assessment



IPD, interpedicular distance; L, lumbar vertebrae; T, thoracic vertebrae; TLK, thoracolumbar angle.

Results

Participants

- The placebo-controlled CANOPY ACH-2I trial enrolled 75 participants, of whom 67 had spinal morphology assessments at baseline and week 52 (**Table 1**)

Table 1. Participant demographics and baseline characteristics

	All (0 to <5 years)	
	Placebo (n = 27)	Vosoritide (n = 40)
Age at day 1, years		
Mean (SD)	2.15 (1.54)	2.05 (1.48)
Median (Q1, Q3)	1.93 (0.50, 3.31)	1.88 (0.49, 3.05)
Sex, n (%)		
Male	12 (37.5)	23 (53.5)
Female	15 (46.9)	17 (39.5)
Race, n (%)		
White	21 (65.6)	27 (62.8)
Asian	6 (18.8)	11 (25.6)
Multiple	0	2 (4.7)
Ethnicity, n (%)		
Not Hispanic or Latino	24 (75.0)	37 (86.0)
Hispanic or Latino	3 (9.4)	3 (7.0)
AGV, cm/year		
Mean (SD)	9.84 (8.18)	11.69 (7.72)
Median (Q1, Q3)	5.16 (4.00, 16.06)	8.00 (5.37, 18.30)
Height Z-score[a]		
Mean (SD)	−4.29 (1.52)	−3.87 (0.91)
Median (Q1, Q3)	−4.02 (−5.47, −3.09)	−3.88 (−4.39, −3.23)

Analysis includes participants with both baseline and week 52 spinal parameters.
[a]Z-Scores were derived using age-sex specific reference data for average-stature children per the US Center for Disease Control and Prevention.
AGV, annualized growth velocity; Q, quartile; SD, standard deviation.

IPD and width of lumbar spinal canal

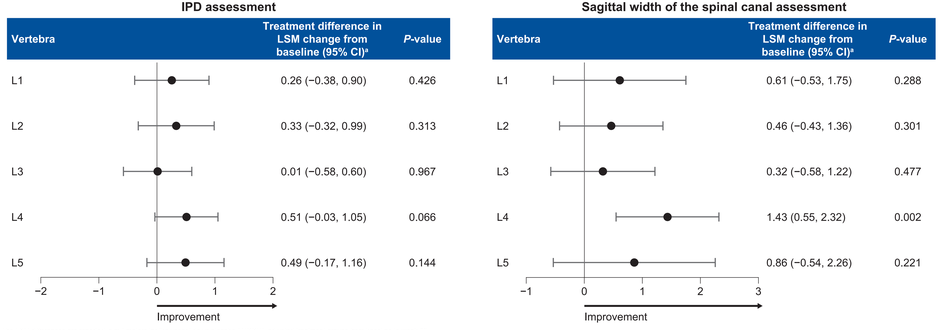
- The mean IPD and spinal canal width were generally comparable between groups at baseline and increased from baseline to week 52. Improvements in IPD and spinal canal width were greater with vosoritide across L1 through L5 compared with placebo after 1 year of treatment (**Table 2** and **Figure 2**)
  - Vosoritide treatment had the greatest impact on L4 both in terms of IPD and spinal canal width increase

Table 2. LSM change from baseline in IPD and sagittal width of spinal canal (mm) in the lumbar spine

	Placebo				Vosoritide			
	n	Baseline	Week 52	LSM change from baseline (95% CI)	n	Baseline	Week 52	LSM change from baseline (95% CI)
IPD (mm)								
L1	27	14.9 (2.3)	16.1 (1.6)	1.06 (0.58, 1.54)	40	15.4 (2.1)	16.6 (1.8)	1.31 (0.92, 1.70)
L2	27	14.4 (2.0)	15.3 (1.7)	0.85 (0.35, 1.34)	40	14.5 (1.8)	15.7 (1.5)	1.18 (0.78, 1.58)
L3	27	13.6 (2.0)	14.4 (1.6)	0.78 (0.34, 1.23)	40	14.0 (1.8)	14.7 (1.6)	0.80 (0.44, 1.16)
L4	27	12.6 (2.0)	13.1 (1.6)	0.47 (0.06, 0.88)	40	13.0 (1.9)	14.0 (1.8)	0.98 (0.65, 1.31)
L5	27	12.3 (2.2)	12.8 (1.6)	0.48 (−0.02, 0.98)	40	12.6 (2.0)	13.6 (2.0)	0.98 (0.57, 1.38)
Sagittal width (mm)								
L1	26	12.5 (2.5)	12.5 (2.3)	0.06 (−0.77, 0.88)	34	12.0 (2.8)	12.7 (2.2)	0.66 (−0.05, 1.37)
L2	26	11.9 (2.4)	12.0 (1.9)	0.05 (−0.59, 0.70)	34	11.5 (2.6)	12.0 (2.3)	0.52 (−0.04, 1.08)
L3	26	11.8 (2.6)	12.2 (2.0)	0.44 (−0.21, 1.09)	34	11.3 (2.8)	12.0 (2.2)	0.76 (0.20, 1.32)
L4	26	12.3 (2.9)	12.6 (2.3)	0.19 (−0.45, 0.83)	34	11.3 (3.1)	12.9 (2.5)	1.62 (1.07, 2.18)
L5	25	13.3 (3.7)	13.9 (3.0)	0.51 (−0.49, 1.51)	31	12.4 (4.2)	13.7 (3.4)	1.37 (0.48, 2.26)

Data shown as mean (SD) unless indicated otherwise.
CI, confidence interval; IPD, interpedicular distance; L1–L5, lumbar vertebrae 1–5; LSM, least squares mean; SD, standard deviation.

Figure 2. Effect of vosoritide on IPD and spinal canal width at week 52 compared with placebo

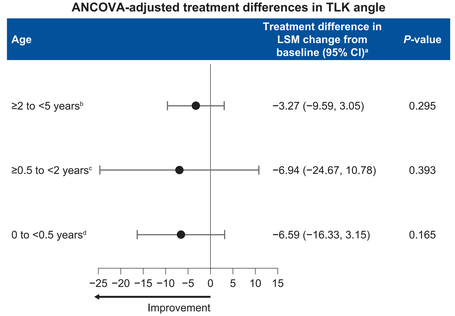


The LSM differences are reported in millimeters for the vosoritide vs placebo ANCOVA-adjusted treatment groups from baseline to week 52.
[a]Treatment difference in LSM change was calculated as vosoritide − placebo.
ANCOVA, analysis of covariance; CI, confidence interval; IPD, interpedicular distance; L1–L5, lumbar vertebrae 1–5; LSM, least squares mean.

TLK angle

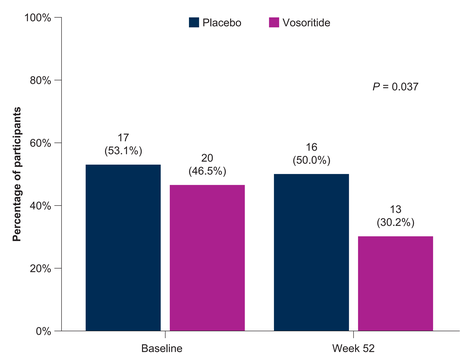
- The TLK angle can naturally increase (worsen) in sitting-age children with achondroplasia and tends to improve naturally when children begin to walk. Persistence of TLK in adolescents and adults increases the risk of neurological sequelae requiring surgical intervention[16,17]
- The worsening of TLK angle was reduced (improved) with vosoritide treatment in children 0 to <0.5 years (−3.27°), and greater improvements in TLK angle were observed in children ≥0.5 to <2 and ≥2 to <5 years (−6.94° and −6.59°, respectively; **Figure 3**)
  - The proportion of children with a pathological (≥20°) TLK angle was lower after 1 year of treatment with vosoritide (30.2%) compared with placebo (50.0%; $P = 0.037$; **Figure 4**)

Figure 3. Effect of vosoritide on TLK angle at week 52 compared with placebo



Age cohorts represent age at treatment initiation. The LSM differences are reported in degrees for the vosoritide vs placebo ANCOVA-adjusted treatment groups from baseline to week 52.
[a]Treatment difference in LSM change was calculated as vosoritide − placebo. [b]vosoritide, n = 11; placebo, n = 7. [c]vosoritide, n = 10; placebo, n = 7. [d]vosoritide, n = 18; placebo, n = 13.
ANCOVA, analysis of covariance; CI, confidence interval; LSM, least squares mean; TLK; thoracolumbar kyphosis.

Figure 4. Proportion of participants with ≥20° TLK angle



P-value is derived from Chi-square test.
TLK; thoracolumbar kyphosis.

Conclusions

- Vosoritide treatment increased the IPD and spinal canal width across all lumbar vertebrae and improved TLK angle in young children with ACH after 52 weeks of treatment compared with placebo
- Increased endochondral ossification driven by vosoritide treatment in young children (<5 years of age) may increase axial skeletal growth and suggests that early intervention before spinal maturity may positively impact spinal morphology
- Further analyses from the long-term extension study CANOPY ACH-EXT (111-208, NCT03989947) will confirm whether the improvements in spinal canal width and TLK angle translate to reduced rates of clinical complications or surgical correction

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Acknowledgments

We thank all trial participants, their families, study-site staff, and investigators. Medical writing support was provided by Rachel Corrigan, PhD, of Red Nucleus, and funded by BioMarin Pharmaceutical Inc. Project management support was provided by Justin Potuzak, PhD, of BioMarin Pharmaceutical Inc.

Disclosures

KKW has received grants from Ascendis, BioMarin Pharmaceutical Inc., QED Therapeutics/BridgeBio, and Ultragenyx; royalties from UpToDate.com; consulting fees from BioMarin Pharmaceutical Inc. and QED/Bridgebio Therapeutics/BridgeBio; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BioMarin Pharmaceutical Inc. **MI** has received consulting fees from Ascendis, BioMarin Pharmaceutical Inc., QED Therapeutics/BridgeBio, Sanofi, and Tyra; speaker fees from Ascendis, BioMarin Pharmaceutical Inc., Ipsen, QED Therapeutics/BridgeBio, and Sandoz; travel support from Ascendis, BioMarin Pharmaceutical Inc., and QED Therapeutics/BridgeBio; and has participated as a clinical trial investigator for Ascendis, BioMarin Pharmaceutical Inc., and QED Therapeutics/BridgeBio. **JEH-F** has participated in advisory boards and served as a consultant for Ascendis, AstraZeneca, BioMarin Pharmaceutical Inc., Children's Mercy Research Institute, Medscape, Pfizer, QED Therapeutics, and Therachon and has received research support from AstraZeneca, BioMarin Pharmaceutical Inc., and QED Therapeutics. **SM**, **CR**, and **IS** are employees and stockholders of BioMarin (UK) Ltd. **AD** is an employee of and stockholder of BioMarin Pharmaceutical Inc. **RS** has received consulting fees and travel support from Ascendis, BioMarin Pharmaceutical Inc., and QED Therapeutics and has participated as a clinical trial investigator for Ascendis, BioMarin Pharmaceutical Inc., QED Therapeutics, and Sanofi.

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Presented at American Society for Bone and Mineral Research (ASBMR) annual meeting; September 5–8, 2025; Seattle, WA, USA