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Long-term effects of vosoritide on bone density and body composition in children with hypochondroplasia: a 3-year prospective DXA study

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INTRODUCTION

Hypochondroplasia (HCH) is a fibroblast growth factor receptor 3 (FGFR3)-related skeletal dysplasia characterized by disproportionate short stature and altered body proportions[1]. Beyond growth impairment, individuals with HCH frequently display abnormal body composition and increased adiposity, which may contribute to adverse cardiometabolic outcomes. Vosoritide, a C-type natriuretic peptide (CNP) analog that promotes endochondral bone growth by antagonizing FGFR3 signaling, is approved by the FDA for achondroplasia[2]. It has recently shown efficacy in improving growth velocity in children with HCH[1].

However, its effects on body composition, particularly on lean and fat mass distribution, remain largely unexplored.

AIM

To evaluate longitudinal changes in bone mineral density (BMD), bone mineral content (BMC), and body composition during 36 months of vosoritide therapy in children with HCH.

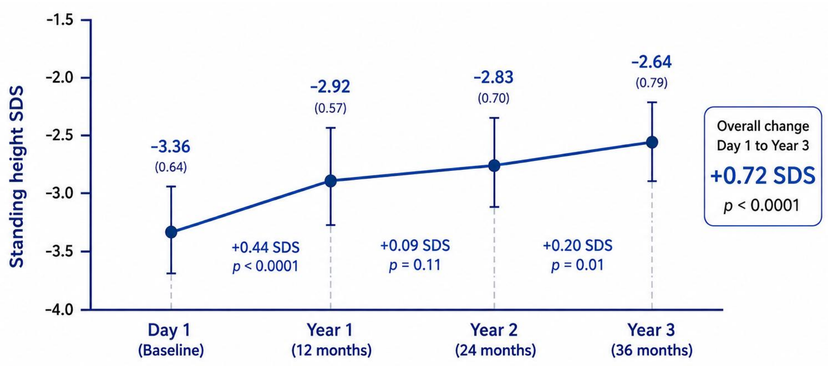
METHOD

- This prospective, single-arm phase 2 study (NCT04219007) included 24 children with genetically confirmed HCH treated with vosoritide (15 µg/kg/day), 13 of whom continued treatment beyond 1 year in an extension phase of the study.
- Anthropometric and dual-energy X-ray absorptiometry (DXA) assessments were performed at baseline, 12, and 36 months.
- Outcomes included total body less head (TBLH) and lumbar spine BMD and BMC, as well as body composition parameters (fat mass, lean mass, fat percentage, lean-to-fat ratio).
- Sex/age- and height/sex/age-adjusted DXA Z-scores were analyzed.
- Paired analyses were performed using Wilcoxon or t-tests as appropriate.

RESULTS

Linear growth:

Vosoritide treatment resulted in sustained improvement in linear growth over 3 years (height SDS +0.72, p < 0.0001). Mean standing height SDS improved from −3.36 ± 0.64 at baseline to −2.64 ± 0.79 at 36 months (Fig. 1).



Standing height SDS Mean (SD)	Day 1 (Baseline)	Year 1 (12 months)	Year 2 (24 months)	Year 3 (36 months)
	-3.36 (0.64)	-2.92 (0.57)	-2.83 (0.70)	-2.64 (0.79)

Fig. 1. Longitudinal changes in standing height SDS during 3 years of vosoritide treatment in children with hypochondroplasia.
**Values are presented as mean (SD); error bars represent SD. Changes between time points are presented as mean differences (95% CI).*

Body mass index:

- BMI SDS decreased modestly over time (Δ −0.41, p = 0.02), with no evidence of increasing relative adiposity.
- Baseline: 1.50 (1.20, 2.40) → Month 36: 1.24 (0.74, 1.73), p = 0.02

Body composition analysis:

- Total lean mass increased from 12.5 kg to 17.8 kg, p = 0.0005
- Total fat mass increased from 6.0 kg to 8.2 kg, p = 0.0005
- Fat percentage showed no significant change: −1.3% (p = 0.11)
- Lean-to-fat ratio showed a trend toward improvement (+0.17, p = 0.09)

BMI and body composition associations:

BMI correlated with:

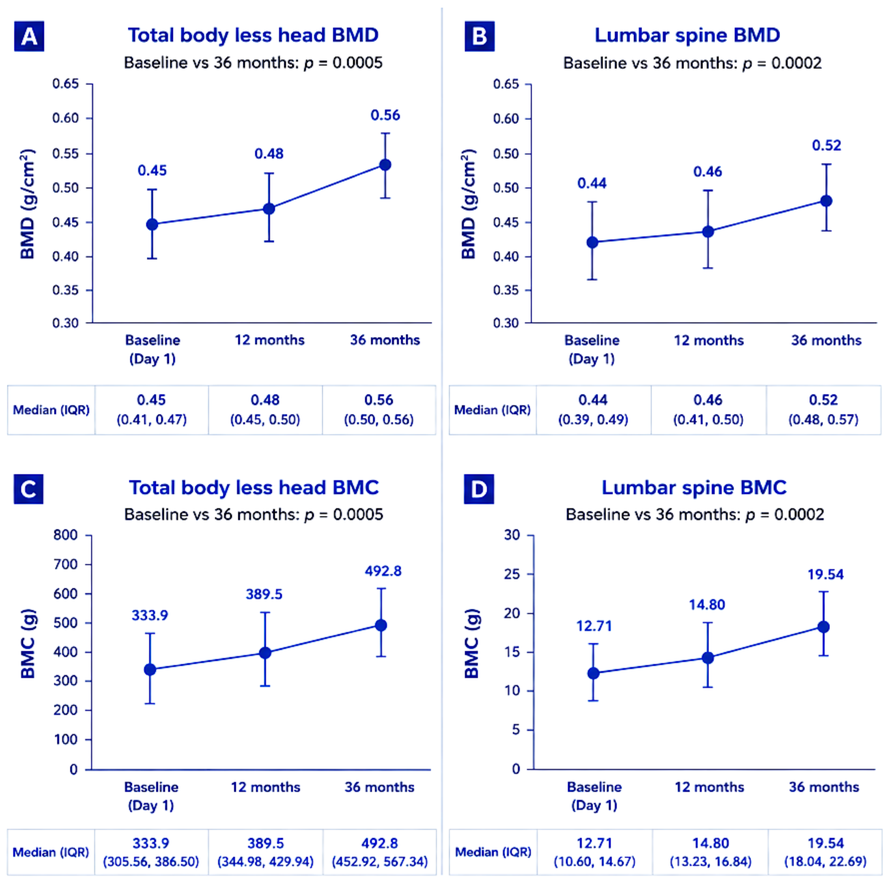
- Fat mass percentage: r = 0.83, p = 0.0005
- Lean mass percentage: r = -0.83, p = 0.0005
- Lean-to-fat ratio: r = -0.85, p = 0.0002

No significant correlation was observed with absolute fat mass (r = −0.05, p = 0.88).

These findings suggest increased lean mass without disproportionate fat accumulation. The parallel increase in lean mass and bone parameters supports a functional interaction between musculoskeletal development during therapy.

Bone health parameters:

Absolute bone parameters increased progressively over 36 months: TBLH BMD and BMC (both p = 0.0005), and lumbar spine BMD and BMC (both p = 0.0002) (Fig. 2).



	Baseline (Day 1)	12 months	36 months
Median (IQR)	0.45 (0.41, 0.47)	0.48 (0.45, 0.50)	0.56 (0.50, 0.56)

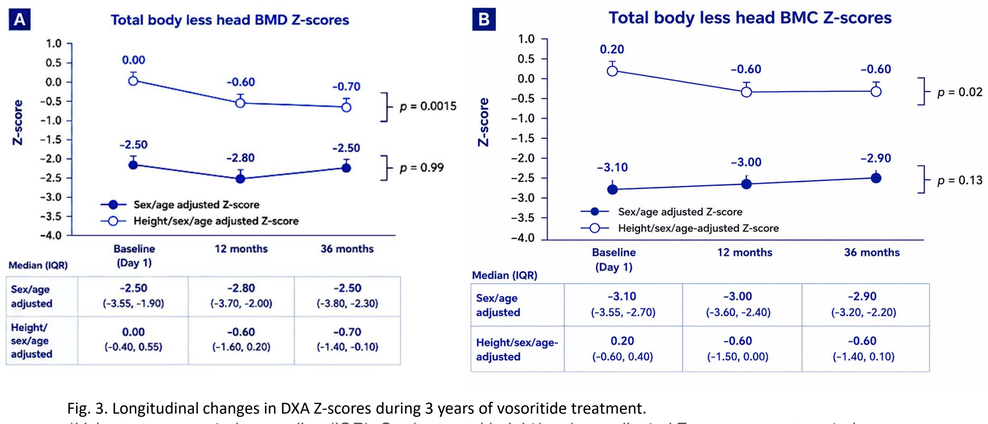
	Baseline (Day 1)	12 months	36 months
Median (IQR)	0.44 (0.39, 0.49)	0.46 (0.41, 0.50)	0.52 (0.48, 0.57)

	Baseline (Day 1)	12 months	36 months
Median (IQR)	333.9 (305.56, 386.50)	389.5 (344.98, 429.94)	492.8 (452.92, 567.34)

	Baseline (Day 1)	12 months	36 months
Median (IQR)	12.71 (10.60, 14.67)	14.80 (13.23, 16.84)	19.54 (18.04, 22.69)

Fig. 2. Longitudinal changes in bone mineral density and bone mineral content during 3 years of vosoritide treatment.
**Values are presented as median (IQR). P-values represent comparisons between baseline and 36 months. IQR, interquartile range; BMD, bone mineral density; BMC, bone mineral content; TBLH, total body less head.*

Sex- and age-adjusted BMD Z-scores remained largely stable, while height/sex/age-adjusted Z-scores showed a mild decline over time, suggesting that bone accrual partially parallels, but may not fully match, rapid linear growth (Fig. 3).



Median (IQR)

	Baseline (Day 1)	12 months	36 months
Sex/age adjusted	-2.50 (-3.55, -1.90)	-2.80 (-3.70, -2.00)	-2.50 (-3.80, -2.30)
Height/sex/age adjusted	0.00 (-0.40, 0.55)	-0.60 (-1.60, 0.20)	-0.70 (-1.40, -0.10)

Median (IQR)

	Baseline (Day 1)	12 months	36 months
Sex/age adjusted	-3.10 (-3.55, -2.70)	-3.00 (-3.60, -2.40)	-2.90 (-3.20, -2.20)
Height/sex/age-adjusted	0.20 (-0.60, 0.40)	-0.60 (-1.50, 0.00)	-0.60 (-1.40, 0.10)

Fig. 3. Longitudinal changes in DXA Z-scores during 3 years of vosoritide treatment.
**Values are presented as median (IQR). Sex/age- and height/sex/age-adjusted Z-scores are presented as indicated. P-values represent comparisons between baseline and 36 months. IQR, interquartile range; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; BMC, bone mineral content; TBLH, total body less head.*

CONCLUSIONS

Three years of vosoritide therapy in children with HCH was associated with sustained increases in absolute BMD, BMC, and lean mass, alongside significant growth improvement.

However, height-adjusted bone parameters did not improve proportionally with linear growth, highlighting the importance of careful DXA interpretation in skeletal dysplasia. Long-term follow-up is required to determine whether bone accrual fully normalizes with continued treatment.

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