Early and sustained vosoritide treatment is associated with favorable body composition trajectories in children with achondroplasia

Poster LB20

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Introduction

- Achondroplasia is a skeletal dysplasia characterized by diminished endochondral bone growth that is associated with multisystem alterations in physical development and body composition[1,2,3]
  - Children with achondroplasia are predisposed to developing excess fat mass and a higher body mass index (BMI) early in childhood, which becomes more prominent in adolescence compared to average-stature children[4,5]
- Vosoritide, a first-in-class recombinant C-type natriuretic peptide analog, stimulates endochondral bone growth and provides durable improvements in height gain and body proportionality in children with achondroplasia[6,7]
- Here, we present the impact of long-term vosoritide treatment on body composition in children and adolescents initiating treatment aged ≥5 to <15 years from the phase 3 CANOPY ACH-3 trial (111-301; NCT03197766) and its long-term extension study CANOPY ACH-EXT (111-302; NCT03424018)

Objective

To investigate the long-term effects of vosoritide treatment on body composition in children with achondroplasia

Methods

- The phase 3 CANOPY ACH-3 randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of vosoritide in children aged ≥5 to <18 years at treatment initiation compared with placebo for 52 weeks (**Figure 1**)[8]
  - The extension study CANOPY ACH-EXT continued to evaluate the long-term impact of vosoritide for over 7 years
- This analysis reports body composition (**Table 1**) using dual X-ray absorptiometry for participants aged ≥5 to <15 years at treatment initiation

Figure 1. CANOPY ACH-3 and CANOPY ACH-EXT study design

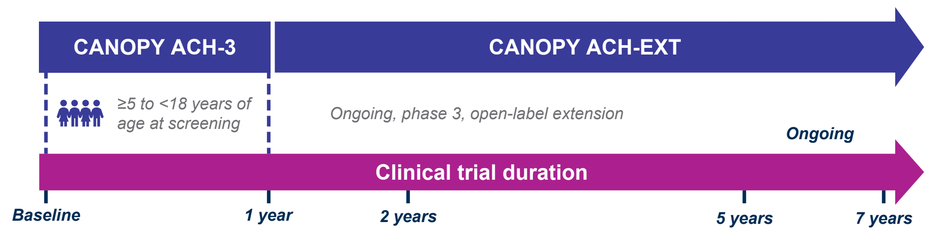


Table 1. CANOPY ACH-3 and CANOPY ACH-EXT body composition post hoc analyses

Endpoint	Time point	Statistical analysis[a]
Overall (≥5 to <15 years)		
Height Z-score (average stature-referenced)[9,b]	Baseline	Pearson's correlation with baseline BMI
Change from baseline in WBLH fat mass, lean mass, and fat-to-lean mass ratio	Year 1	ANCOVA model-tested LSM difference vs placebo
WBLH fat-to-lean mass ratio	Year 6	Pearson's correlation for change in BMI, BMI Z-score (average stature-referenced),[9,b] and height Z-score (average stature-referenced)[9,c]
BMI Z-score (achondroplasia-referenced)[10,b]	Over time	Change from baseline
Quality of life (PedsQL physical score)	Year 6	Pearson's correlation for change in BMI Z-score (average stature-referenced)[9,b]
Adolescents (≥11 to <15 years)		
Change from baseline in WBLH fat mass, lean mass, and fat-to-lean mass ratio	Year 1	ANCOVA model-tested LSM difference vs placebo
WBLH fat mass, lean mass, fat-to-lean mass ratio	Over time	Change from baseline

[a]Data are included for children ages ≥5 to <15 years at the time of treatment initiation, and analyses were descriptive.
[b]BMI Z-scores were referenced to age- and sex-matched reference data for average-stature children (CDC 2000 dataset)[9] or untreated children with achondroplasia (Merker 2018 dataset).[10]
[c]Height Z-scores were referenced to age- and sex-matched data for average-stature children (CDC 2000 dataset).[9]
ANCOVA, analysis of covariance; BMI, body mass index; CDC, US Centers for Disease Control and Prevention; LSM, least squares mean; PedsQL, Pediatric Quality of Life Inventory; WBLH, whole body less head.

Results

Participants and treatment exposure

- Of the 119 participants who enrolled in CANOPY ACH-EXT, 58 received vosoritide and 61 received placebo during CANOPY ACH-3
- Most participants were male (52.9%), and the mean age at the start of vosoritide treatment was 9.18 years (**Table 2**)

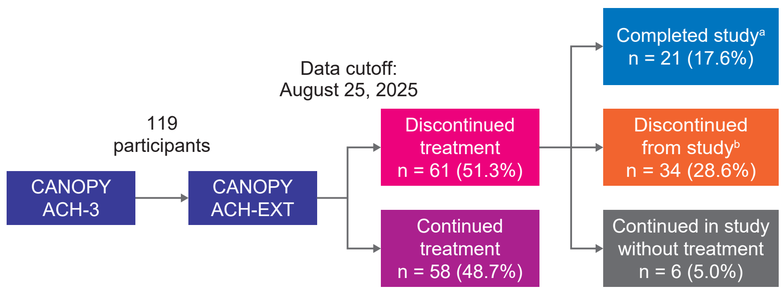
Table 2. Participant demographics and baseline characteristics

	Overall N = 119
Age on day 1 of study drug,[a] years, mean ± SD	9.18 ± 2.60
Sex, n (%)	
Male	63 (52.9)
Female	56 (47.1)
BMI, kg/m², mean ± SD	22.82 ± 4.84
BMI Z-score (achondroplasia-referenced),[10] mean ± SD	0.19 ± 1.16
BMI Z-score (average stature-referenced),[9] mean ± SD	1.75 ± 0.60
Height Z-score (achondroplasia-referenced),[11] mean ± SD	0.28 ± 0.99
Height Z-score (average stature-referenced),[9] mean ± SD	−5.12 ± 1.09

[a]Day 1 is the day of first dose of vosoritide in either 111-301 or 111-302.
BMI, body mass index; SD, standard deviation.

- At baseline, height deficit as measured by height Z-score (achondroplasia-referenced) was not correlated with BMI (R = 0.071, P = 0.4446)
- As of August 25, 2025, 48.7% (n = 58) of participants were continuing treatment (**Figure 2**)
- Median (minimum, maximum) treatment duration was 5.9 (1.7, 7.8) years

Figure 2. Participant disposition and treatment exposure



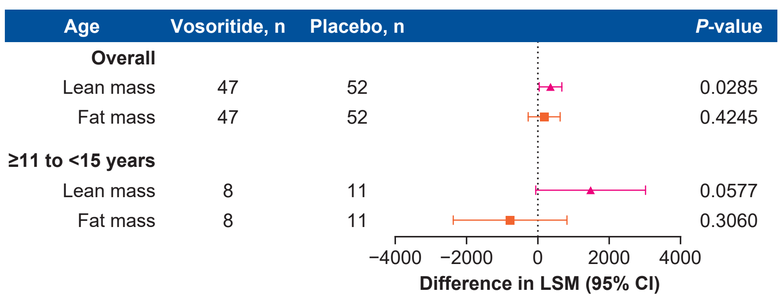
[a]Followed until closure of the epiphyses or reached 16 years of age for females and 18 years of age for males, whichever came later (protocol amendment 6 and onward).
[b]Reasons for early withdrawal from the study were withdrawal by participant (20 [16.8%]), lost to follow-up (5 [4.2%]), study termination by the sponsor (3 [2.5%]), physician decision (1 [0.8%]), and other (5 [4.2%]).

Body composition

Whole body less head (WBLH) dual X-ray absorptiometry

- In the overall population, WBLH lean mass significantly increased and differences in fat mass were similar in children treated with vosoritide compared with placebo after 52 weeks (**Figure 3**)
  - Adolescents treated with vosoritide trended toward increased lean mass and less fat mass increase

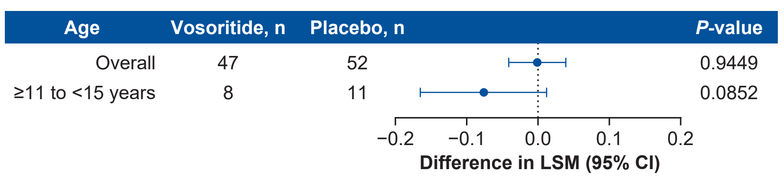
Figure 3. Change from baseline in WBLH lean mass (g) and fat mass (g) in children and the adolescents subgroup after 52 weeks of vosoritide treatment



Difference in LSM was calculated as vosoritide minus placebo.
CI, confidence interval; LSM, least squares mean; WBLH, whole body less head.

- Downward trends in the fat-to-lean mass ratio after 52 weeks of vosoritide treatment compared with placebo were primarily driven by adolescents (**Figure 4**)

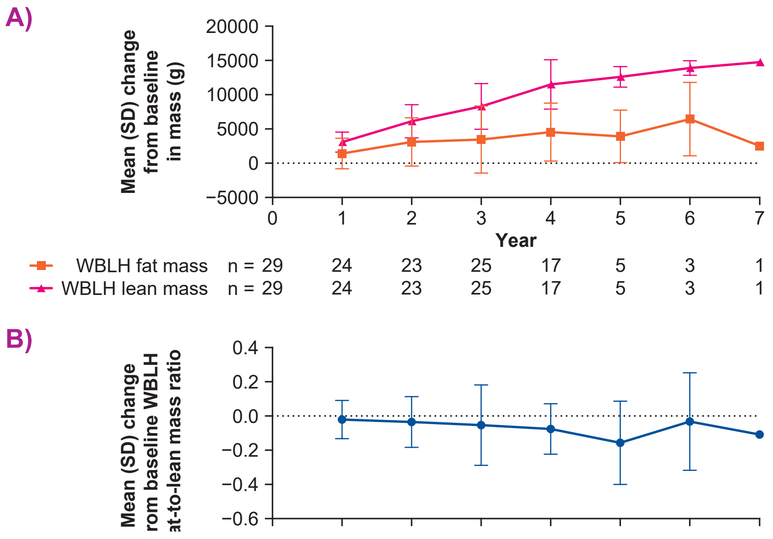
Figure 4. Change from baseline in WBLH fat-to-lean mass ratio in children and the adolescent subgroup after 52 weeks of vosoritide treatment



Difference in LSM was calculated as vosoritide minus placebo.
CI, confidence interval; LSM, least squares mean; WBLH, whole body less head.

- Before vosoritide initiation, mean (SD) fat-to-lean mass ratio was 0.556 (0.213), 0.590 (0.201), and 0.642 (0.232) in the ≥5 to <8, ≥8 to <11, and ≥11 to <15 years groups, respectively, indicating that fat-to-lean mass ratio tends to increase with age in this population without treatment
- Despite this trend, the treated adolescents had the largest decrease in WBLH fat mass and fat-to-lean mass ratio and increase in lean mass over time, with the most pronounced reduction at year 5 following initiation of vosoritide (**Figure 5**)

Figure 5. Change from baseline in WBLH A) fat mass or lean mass, and B) fat-to-lean mass ratio in adolescents over time



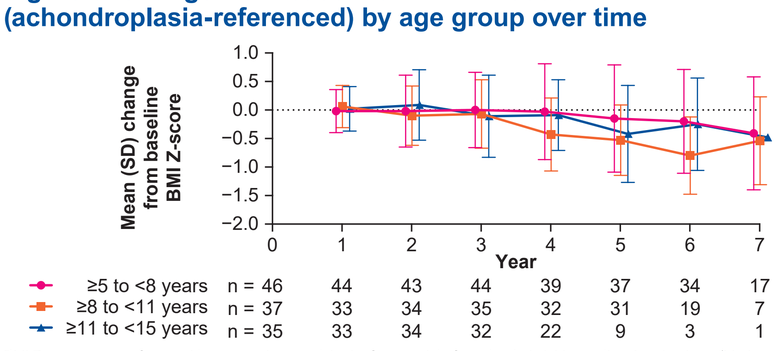
SD, standard deviation; WBLH, whole body less head.

- In all participants, android-to-gynoid fat mass ratio remained stable (data not shown)

BMI

- Over time, the BMI of children treated with vosoritide continued to decrease compared to untreated children with achondroplasia (**Figure 6**)

Figure 6. Change from baseline in BMI Z-score (achondroplasia-referenced) by age group over time



BMI Z-scores were referenced to age- and sex-matched reference data for untreated children with achondroplasia (Merker 2018 dataset).[10]
BMI, body mass index; SD, standard deviation.

- After 6 years of treatment with vosoritide, reduced WBLH fat-to-lean mass ratio positively correlated with a reduction in BMI and BMI Z-score but did not correlate with changes in height Z-score (**Table 3**)

Table 3. Correlation between change from baseline in WBLH fat-to-lean mass ratio and BMI, BMI Z-score, or height Z-score at year 6

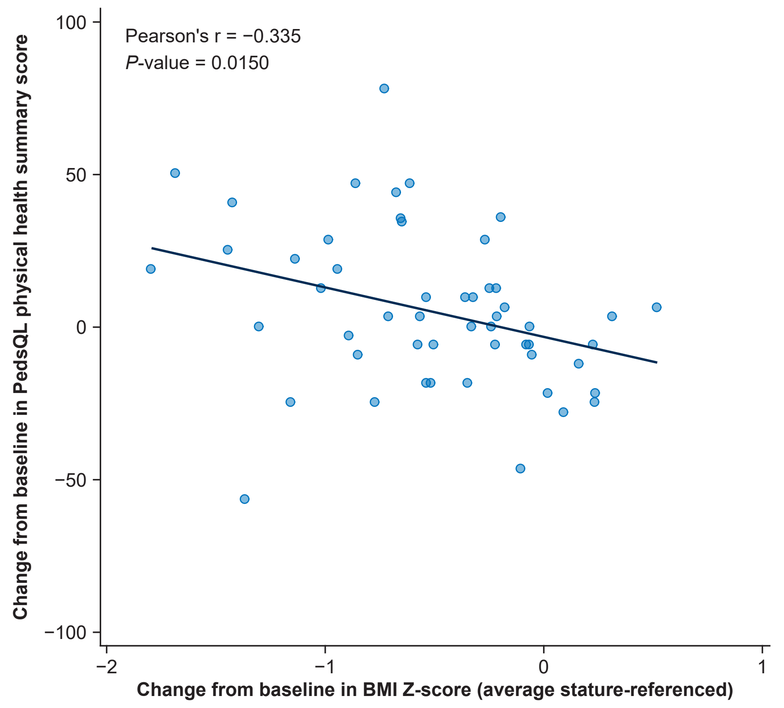
	Full analysis set (N = 119)
Correlation parameters for change from baseline in WBLH fat-to-lean mass ratio vs	
Change from baseline in BMI	n = 43
Pearson's r	0.489
P-value	0.0009
Change from baseline in BMI Z-score (average stature-referenced)	n = 43
Pearson's r	0.429
P-value	0.0041
Change from baseline in height Z-score (average stature-referenced)	n = 43
Pearson's r	−0.064
P-value	0.6858

Each correlation was based on participants with data available at year 6. BMI and height Z-scores were referenced to age- and sex-matched reference data for average-stature children (CDC 2000 dataset).[9]
BMI, body mass index; CDC, US Centers for Disease Control and Prevention; WBLH, whole body less head.

Quality of life

- After 6 years of treatment with vosoritide, improved caregiver-reported PedsQL physical health summary scores, a measure based on activities such as running and walking as well as fatigue, correlated with improvements in BMI Z-score (**Figure 7**)

Figure 7. Correlation between change from baseline in PedsQL physical health summary score and BMI Z-score (average stature-referenced) at year 6



PedsQL physical health summary scores were caregiver reported. BMI Z-scores were referenced to age- and sex-matched reference data for average-stature children (CDC 2000 dataset).[9]
BMI, body mass index; CDC, US Centers for Disease Control and Prevention; PedsQL, pediatric quality of life inventory.

Safety

- Long-term safety remained favorable and predictable

Conclusions

- These results suggest that vosoritide treatment in adolescents increased lean mass compared with untreated children with achondroplasia
- In untreated children with achondroplasia, fat-to-lean mass ratio and BMI increase with age[4,5]; however, consistent with previous reports in individuals of very short stature[12], improvements in fat-to-lean mass ratio and height Z-score were not correlated, suggesting that the body composition improvements in adolescents treated with vosoritide were not driven only by height gains
- Sustained, long-term vosoritide treatment may positively impact body composition and contribute to improved physical functioning
  - Due to small sample sizes, sex-specific effects could not be evaluated; therefore, more research is needed on the impact of these changes on achondroplasia-associated health outcomes

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