Early Start, Maximum Impact: Long-term Trial Data Supporting Cumulative Clinical Benefit in Children Who Initiated Vosoritide <2 Years Old

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Introduction

- Achondroplasia is a rare skeletal dysplasia caused by diminished endochondral bone ossification that hinders early growth and often results in multisystem complications[1,2]
- Vosoritide, a first-in-class recombinant C-type natriuretic peptide analog, targets impaired endochondral bone growth and is approved to treat achondroplasia from birth in the US[2]
  - To maximize clinical benefit, guidelines recommend early, continuous treatment with vosoritide[2]
- Here, we present 4-year outcomes from CANOPY ACH-EXT (111-208, NCT03989947) to assess durability and breadth of benefit in children who initiated treatment aged <2 years and estimated cumulative height gain for children treated from 0.5 years old until age 16 years for females and 18 years for males

Methods

- CANOPY ACH-EXT includes study 111-208, which is an ongoing open-label extension of the phase 2 CANOPY ACH-2I (111-206)[1] study, a randomized, double-blind, placebo-controlled trial
- Safety, adherence, and efficacy endpoints (**Table 1**) for CANOPY ACH-EXT are presented from participants who were aged <2 years at treatment initiation and with ≥4 years of treatment (111-208)

Table 1. CANOPY ACH-EXT study endpoints

Study	Endpoints	Statistical analyses	Statistical comparator datasets
111-208	Height	Baseline-adjusted cross-sectional comparative analysis	Hoover-Fong et al 2021 (CLARITY)[4]
	Height Z-score (CDC-referenced[4])	Baseline-adjusted cross-sectional comparative analysis	Hoover-Fong et al 2021 (CLARITY)[4]
	Height Z-score (achondroplasia-referenced[5])	Descriptive summary statistics	
	Upper-to-lower body ratio	Longitudinal analysis of covariance model tested paired differences	Del Pino et al 2018[6]
	Arm span	Descriptive summary statistics	
	Arm span-to-height ratio	Descriptive summary statistics	
	BMI	Baseline-adjusted cross-sectional analysis	Observational/placebo data (vosoritide clinical program) and CrescNet[7]
111-208 111-302[a]	Estimated cumulative height gain beyond natural history	• Difference between mean AGV in treated vs untreated children per annual interval by age and sex[4,8] • Sum of height gain at all age intervals • Bootstrapping for 95% CI	

Z-scores were normalized to age- and sex-matched children of average stature (CDC)[5] or untreated children with achondroplasia.[4]
All comparators were age- and sex-matched untreated children with achondroplasia.[4,6,7,8]
[a]Data from children aged 5 to <18 years at treatment initiation in study 111-302 were used for this analysis.
AGV, annualized growth velocity; BMI, body mass index; CDC, US Centers for Disease Control and Prevention; CI, confidence interval.

Results

Participants and treatment adherence

- Of the 33 participants who enrolled in 111-208 aged <2 years, 11 were <0.5 years of age and 22 were 0.5 to <2 years of age at treatment initiation (**Table 2**)
- As of August 2025, at least 4 years after treatment initiation, treatment adherence remained high (**Table 2**)

Table 2. Participant baseline characteristics, study disposition, and treatment adherence

	<0.5 years (n = 11)	0.5 to <2 years (n = 22)
Sex, n (%)		
Male	5 (45.5)	11 (50.0)
Female	6 (54.5)	11 (50.0)
Growth parameters		
BMI Z-score (ACH-referenced), mean ± SD	0.5 ± 0.9	0.1 ± 1.1
Height, cm, mean ± SD	56.8 ± 2.0	69.1 ± 4.2
AGV, cm/year, mean ± SD	22.0 ± 3.9	10.9 ± 3.6
Height Z-score (ACH-referenced), mean ± SD	−0.1 ± 0.5	0.5 ± 0.7
Discontinuations[a]	3 (27.3)	5 (22.7)
Treatment duration, years, mean ± SD	4.5 ± 0.8	4.8 ± 1.5
Adherence, %, mean ± SD	94.8 ± 7.6	97.3 ± 4.3

All data presented as n (%) unless otherwise specified.
[a]Reasons for treatment discontinuation were adverse event (1 [9.1%] in the <0.5 years group), lost to follow-up, participant's request, and other.
ACH, achondroplasia; AGV, annualized growth velocity; BMI, body mass index; SD, standard deviation.

Safety

- Long-term safety remained manageable and predictable (**Table 3**)

Table 3. Summary of AEs

	<0.5 years (n = 11)	0.5 to <2 years (n = 22)
Total treatment exposure, person-years	53.19	105.75
Number of AEs	479 (9.006)	777 (7.347)
AEs leading to study-drug or study discontinuation	2 (0.038)	0
AEs leading to study discontinuation	0	0
Number of SAEs	9 (0.169)	5 (0.047)
SAEs leading to study-drug or study discontinuation	1 (0.019)	0
AEs of special interest		
Injection-site reaction[a]	16 (0.301)	15 (0.142)
Fracture	0	0
Hypotension	2 (0.038)	0

The number of events and event rates per person-year are reported.
[a]Excluding bruising and lasting ≥24 hours.
AE, adverse event; SAE, serious AE.

Efficacy

- At year 4, gains in height and height Z-score (US Centers for Disease Control and Prevention-referenced)[5] continued to increase compared with untreated children with achondroplasia (**Table 4**)

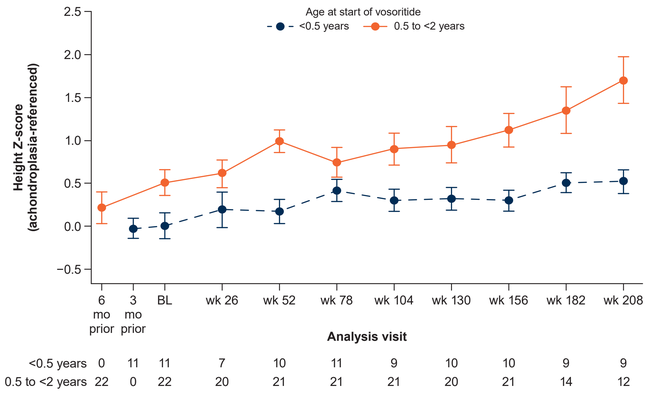
Table 4. Linear growth

	<0.5 years (n = 11)	0.5 to <2 years (n = 22)
Comparative cross-sectional analyses vs untreated at year 4	n = 9	n = 14
Height gain, cm, mean difference (95% CI)	2.8 (1.2, 4.5)	4.7 (2.8, 6.6)
P-value	0.004	0.0002
Height Z-score (CDC-referenced), mean difference (95% CI)	0.9 (0.3, 1.4)	0.8 (0.4, 1.2)
P-value	0.006	0.0008

CDC, US Centers for Disease Control and Prevention; CI, confidence interval; SD, standard deviation.

- Height Z-scores referenced to untreated children with achondroplasia continued to increase over time (**Figure 1**)

Figure 1. Height Z-scores (achondroplasia-referenced) over time



	6 mo prior	3 mo prior	BL	wk 26	wk 52	wk 78	wk 104	wk 130	wk 156	wk 182	wk 208
<0.5 years	0	11	11	7	10	11	9	10	10	9	9
0.5 to <2 years	22	0	22	20	21	21	21	20	21	14	12

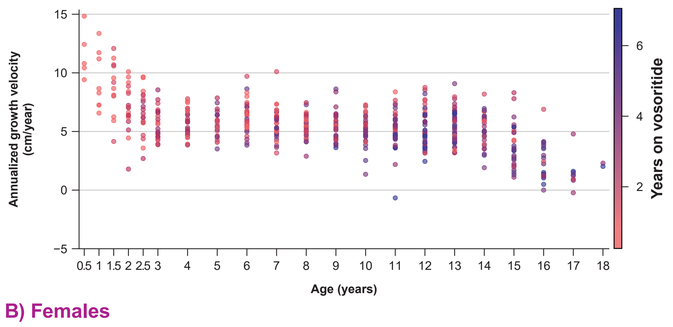
Achondroplasia-referenced height Z-scores (CLARITY 2021).[4]
BL, baseline.

Estimated additional height gain

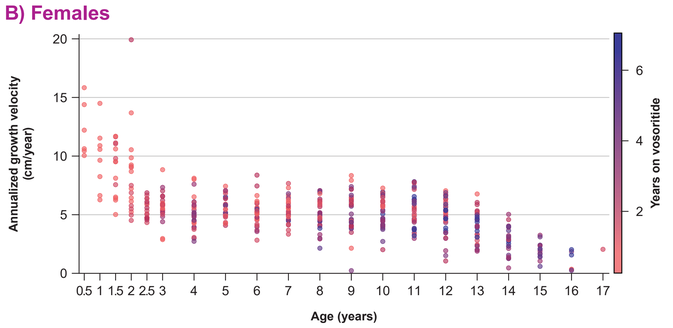
- The impact of vosoritide on AGV is consistent regardless of time on treatment across ages (**Figure 2**), allowing AGV to be pooled across CANOPY ACH-EXT studies[1,3]
- AGV approached that observed in an average stature population for the years after infancy (**Figure 3**)

Figure 2. AGV vs age and years on vosoritide treatment

A) Males



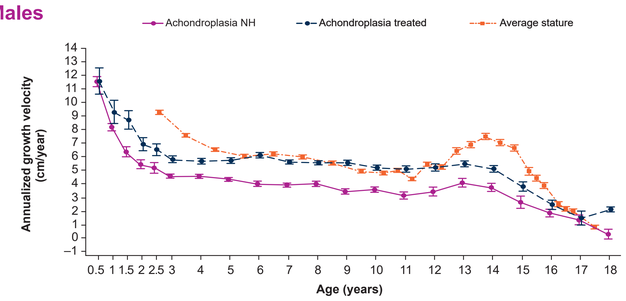
B) Females



Data pooled from 111-208 and 111-302. Colored dots represent years on treatment (darker dots represent longer treatment exposure).
AGV, annualized growth velocity.

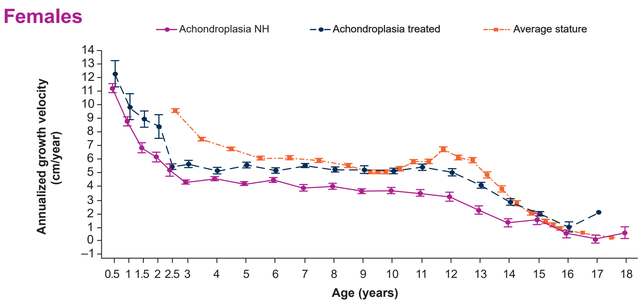
Figure 3. Mean 6- or 12-month interval AGV by age

A) Males



	0.5	1	1.5	2	2.5	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Achondroplasia treated	5	8	12	18	19	24	31	29	37	40	40	41	44	47	44	43	35	29	21	8	2
Achondroplasia NH	216	203	170	127	127	228	197	165	123	92	84	68	65	54	45	37	29	22	22	20	9

B) Females

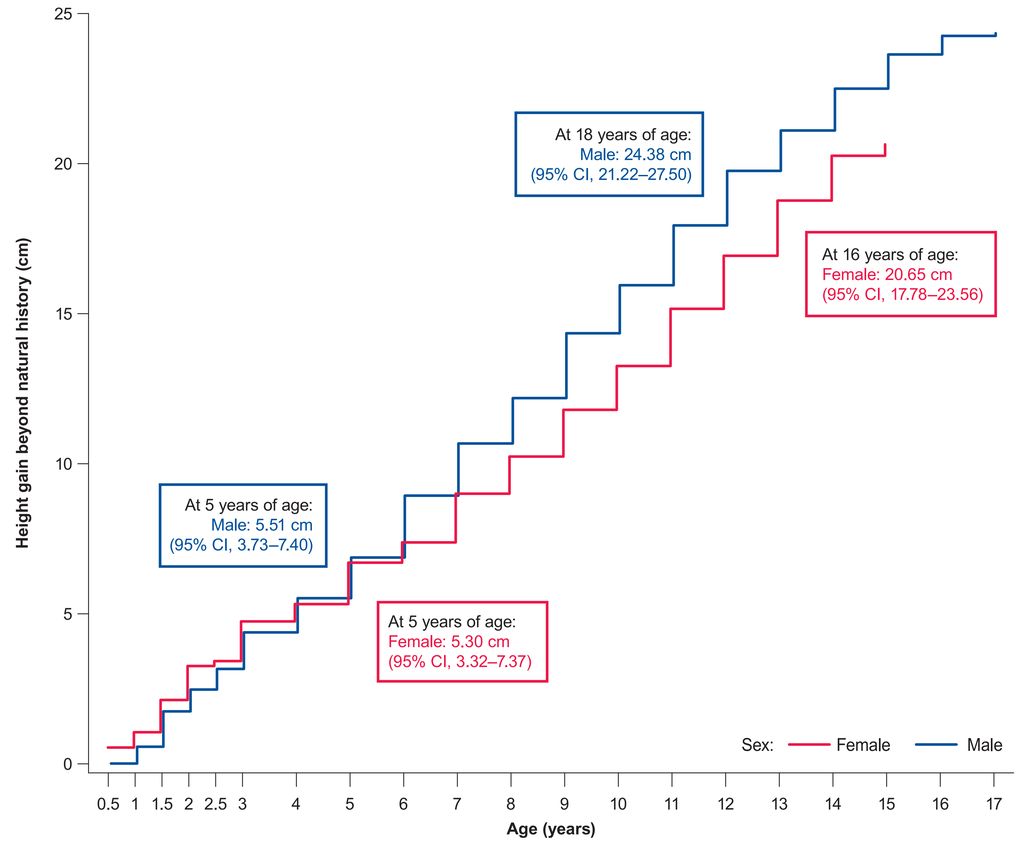


	0.5	1	1.5	2	2.5	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Achondroplasia treated	5	8	14	18	18	24	28	27	31	38	38	35	37	39	38	35	26	16	6	1	0
Achondroplasia NH	218	175	160	102	90	206	187	148	105	87	80	75	66	52	42	41	36	26	20	13	7

Data pooled from 111-208 and 111-302 for ACH treated population. Age represents growth from that age to the next age. ACH NH reference data are from Hoover-Fong et al,[4] and average-stature reference data are from Prader et al.[8]
ACH, achondroplasia; AGV, annualized growth velocity; NH, natural history.

- Additional cumulative height gain beyond natural history was estimated for treatment with vosoritide beginning at 0.5 years of age using pooled AGV results from CANOPY-EXT (**Figure 3**) as the sum of height gain at all age intervals (**Figure 4**)
  - The estimated cumulative height gain (95% confidence interval [CI]) compared with untreated children with achondroplasia if continuously treated from 6 months to 18 (males) or 16 (females) years of age was 24.38 (21.22, 27.50) cm and 20.65 (17.78, 23.56) cm, respectively

Figure 4. Estimated cumulative height gain beyond natural history if treatment begins at 0.5 years



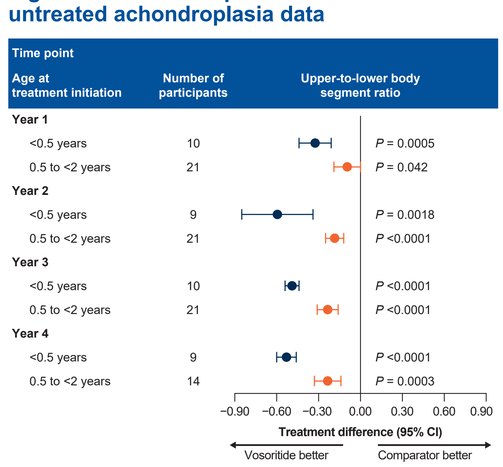
	0.5	1	1.5	2	2.5	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Female:	6	8	14	18	18	24	28	27	31	38	38	35	37	39	38	35	26	16	0	0
Male:	5	8	12	18	19	24	31	29	37	40	40	41	44	47	44	43	35	29	21	8

CI, confidence interval.

Body proportionality and body mass index (BMI)

- Vosoritide-treated children had improved upper-to-lower body ratio (ULBR) least squares mean (95% CI) of the paired difference vs modeled untreated achondroplasia data.[6] Paired difference is the ULBR change from baseline in treated participants minus ULBR change based on age- and sex-matched 50th percentile from the modeled del Pino data.[6] Those who initiated vosoritide treatment earlier had better ULBR over time (**Figure 5**)

Figure 5. ULBR LSM paired difference vs modeled untreated achondroplasia data



Untreated children with achondroplasia comparator data are from Del Pino 2018 modeled data.[6]
CI, confidence interval; LSM, least squares mean; ULBR, upper-to-lower body ratio.

- Over 4 years of follow-up, arm span continued to increase while arm span-to-height ratio remained stable across years of treatment (**Table 5**)
- Following 4 years of treatment, BMI significantly improved compared with untreated children with achondroplasia (**Table 5**)

Table 5. Arm span and BMI changes from baseline at year 4

	<0.5 years (n = 9)	0.5 to <2 years (n = 14)
Arm span, cm, change from baseline, mean ± SD	24.4 ± 2.7	22.2 ± 3.0
Arm span-to-height ratio, change from baseline, mean ± SD	−0.004 ± 0.031	0.003 ± 0.026
Comparative cross-sectional analysis vs untreated at year 4		
BMI, kg/m², mean difference (95% CI)	−1.3 (−2.6, −0.01)	−1.8 (−2.7, −0.9)
P-value	0.0492	0.0006

BMI, body mass index; CI, confidence interval; SD, standard deviation.

Conclusions

- Vosoritide continues to have a manageable safety profile and remains well tolerated with long-term treatment
- Efficacy of vosoritide based on AGV remains consistent, and all other endpoints continued to improve
- Estimated cumulative height gains beyond natural history increase with extended treatment duration
- Early treatment initiation has a positive impact on height and body proportionality and body composition, which may improve functional independence and lower surgical burden
- To maximize benefits, treatment with vosoritide should begin early and continue while growth potential exists
- Data presented here are a part of BioMarin's confirmatory evidence package intended to support conversion to full approval of vosoritide in the United States

References

1. Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024;8(1):40–50. **2.** Savarirayan R, et al. *Nat Rev Endocrinol*. 2025;21:314–24. **3.** Savarirayan R, et al. *Lancet*. 2020;396(10252):684–92. **4.** Hoover-Fong J, et al. *Genet Med*. 2021;23:1498–1505. **5.** US Centers for Disease Control and Prevention. CDC growth charts. National Center for Health Statistics. Accessed January 29, 2026. https://www.cdc.gov/growthcharts/clinical_charts.htm. **6.** Del Pino M, et al. *J Pediatr Endocrinol Metab*. 2018;31(4):421–28. **7.** Pesl M, et al. *Orphanet J Rare Dis*. 2022;17:229. **8.** Prader A, et al. *Helv Paediatr Acta Suppl*. 1989;52:1–125.

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Disclosures

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