Effect of long-term vosoritide treatment on growth in children with achondroplasia in open-label, multicenter clinical trials

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I have the following potential conflicts of interest to report:

I have received consulting fees from BioMarin Pharmaceutical Inc. and have participated as a clinical trial investigator for Ascendis, BioMarin Pharmaceutical Inc., and Roche

Learning objectives

At the end of the sessions, participants will be able to

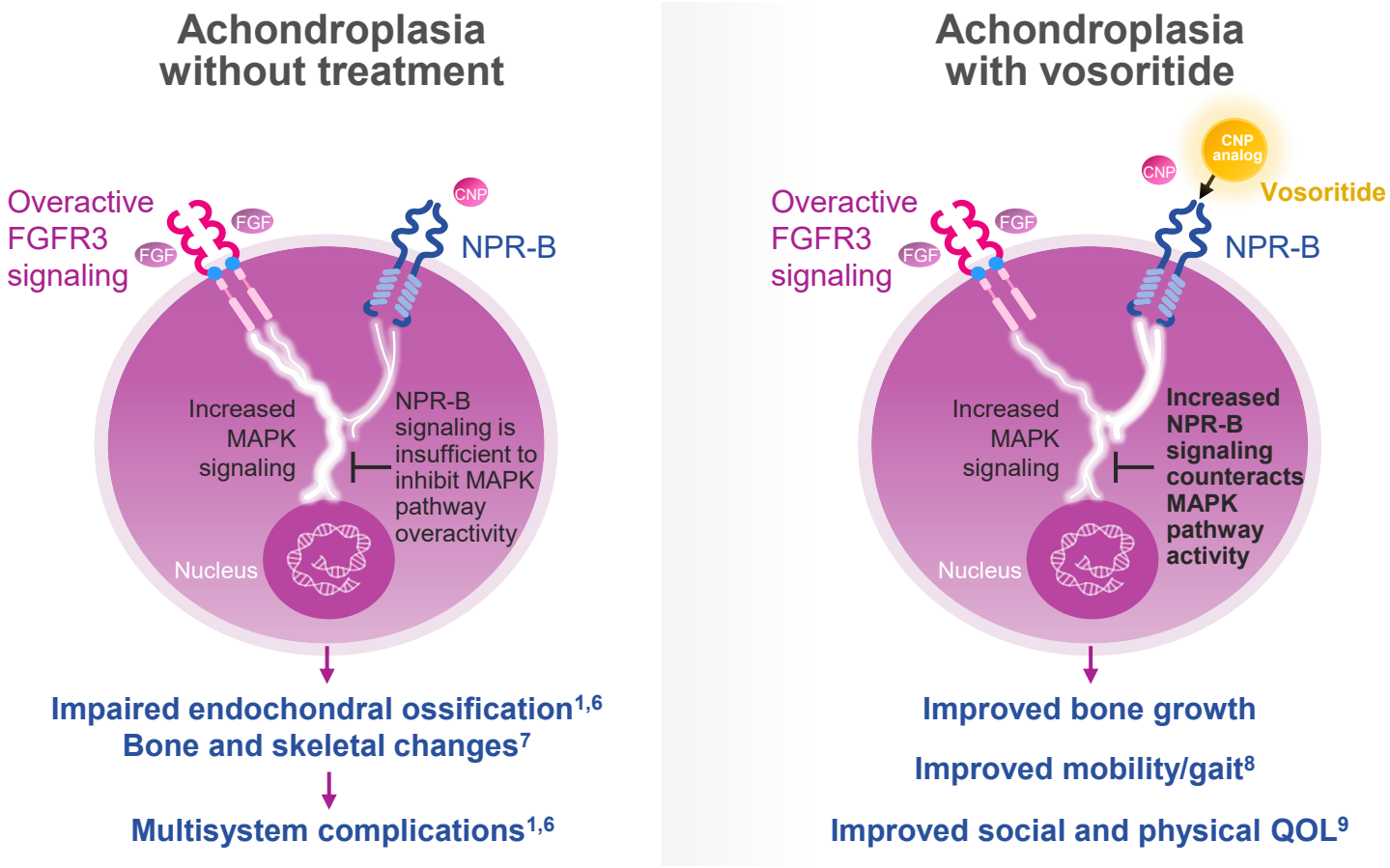
1. Explain the study design of the ongoing, open-label extension trial CANOPY ACH-EXT (111-208, 111-205, 111-302) that is evaluating the impact of long-term vosoritide treatment in children with achondroplasia;

2. Identify different measures of growth, including height, height Z-score, arm span Z-score, and arm span-to-height ratio; and

3. Describe the impact of long-term vosoritide treatment on growth vs natural history in children with achondroplasia who are enrolled in CANOPY ACH-EXT and have up to 8 years of follow-up

Vosoritide stimulates endochondral bone growth

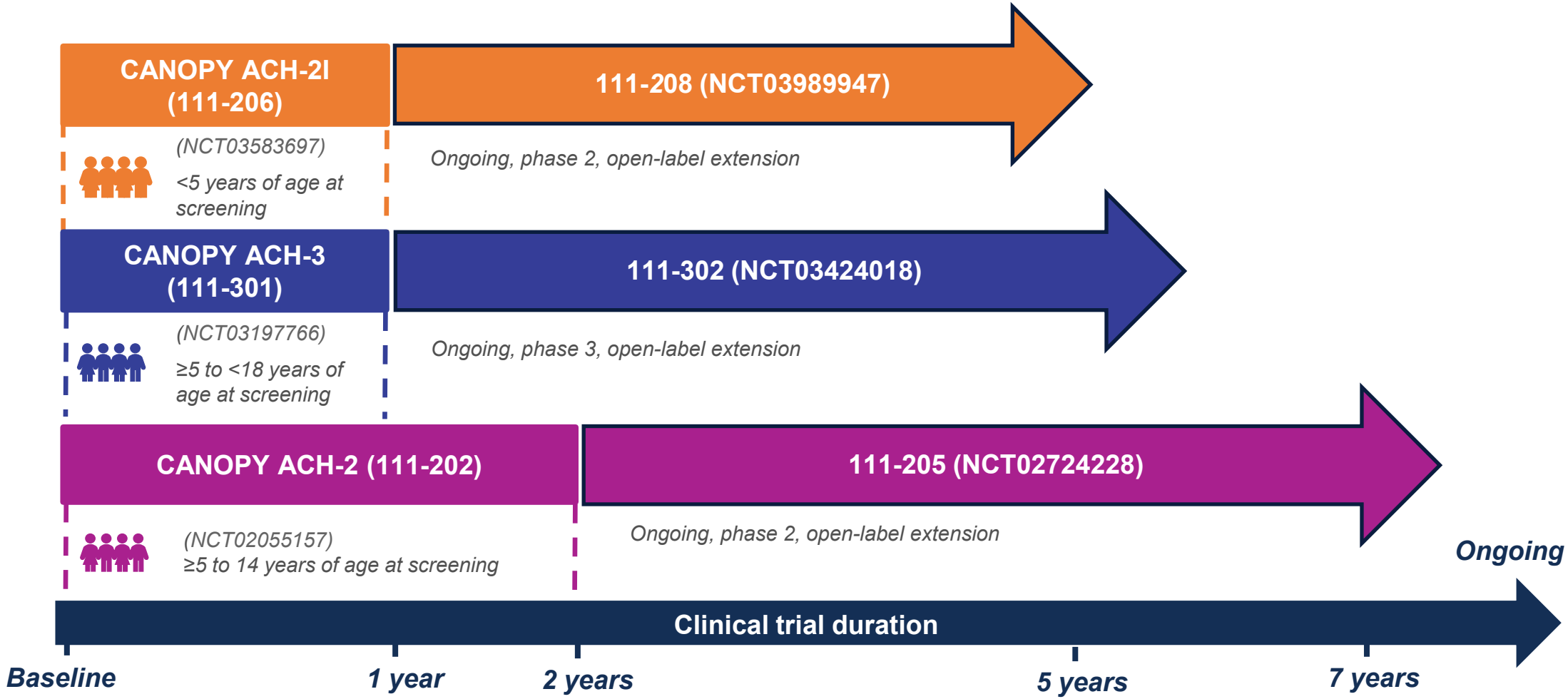
- Vosoritide, a CNP analog, is approved in 47 countries to treat achondroplasia until closure of the epiphyses[1,2]
- In phase 2 and 3 pivotal trials, vosoritide demonstrated statistically significant improvements in growth vs placebo across all pediatric age groups, with a favorable safety profile[3,4,5]



Here, we demonstrate the impact of long-term vosoritide treatment on growth vs natural history

1. VOXZOGO (vosoritide). Prescribing information. BioMarin Pharmaceutical Inc.; 2024. **2.** Savarirayan R, et al. *Nat Rev Endocrinol.* 2025;21:314–24. **3.** Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024;8(1):40–50. **4.** Savarirayan R, et al. *N Engl J Med.* 2019;381(1):25–35. **5.** Savarirayan R, et al. *Lancet.* 2020;396(10252):684–92. **6.** Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024;8(4):301–10. **7.** Stender M, et al. *Bone.* 2022;162:116472. **8**. Reincke S, et al. *J Endo Societ*. 2025. doi:10.1210. **9.** Savarirayan R, et al. *Genet Med*. 2024;26:101274.
CNP, C-type natriuretic peptide; FGF, fibroblast growth factor; FGFR3, FGF receptor 3; MAPK, mitogen-activated protein kinase; NPR-B, natriuretic peptide receptor B; QOL, quality of life.

Confirmatory data package: CANOPY ACH-EXT study design



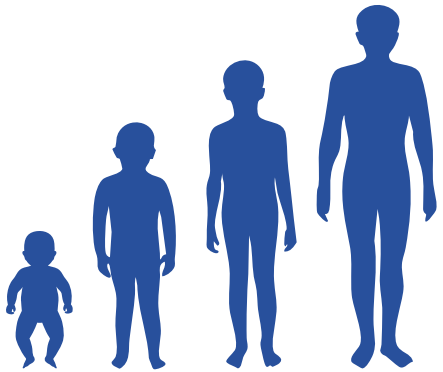
All analyses for CANOPY ACH-EXT studies included data from the first dose of vosoritide in the CANOPY ACH core studies.

Participant baseline characteristics

As of August 2025

222

children with achondroplasia enrolled in CANOPY ACH-EXT trials



Parameter	111-208 <5 years of age at screening	111-205 ≥5 to 14 years of age at screening	111-302 ≥5 to <18 years of age at screening
Enrolled, n	73	30	119
Age on day 1, years, mean ± SD	2.6 ± 1.7	8.2 ± 1.6	9.2 ± 2.6
Male sex, n (%)	37 (50.7)	13 (43.3)	63 (52.9)
Standing height, cm, mean ± SD	74.07 ± 10.60	100.16 ± 8.03	103.57 ± 11.91
Height Z-score (achondroplasia-referenced), mean ± SD	0.29 ± 0.78	0.39 ± 0.91	0.28 ± 0.99
Height Z-score (average stature-referenced), mean ± SD	−4.18 ± 1.11	−5.12 ± 1.00	−5.12 ± 1.09
Baseline arm span Z-score (achondroplasia-referenced), mean ± SD	−0.36 ± 1.19[a]	−0.12 ± 1.07	−0.32 ± 1.25
Treatment duration, years, mean ± SD	5.0 ± 1.5	7.4 ± 2.2	5.5 ± 1.6
Median (min, max)	5.4 (1.0, 7.2)	7.2 (6.1, 9.2)	5.9 (1.7, 7.8)

[a]n = 40.
max, maximum; min, minimum; SD, standard deviation.

Treatment adherence remained high across all 3 clinical studies

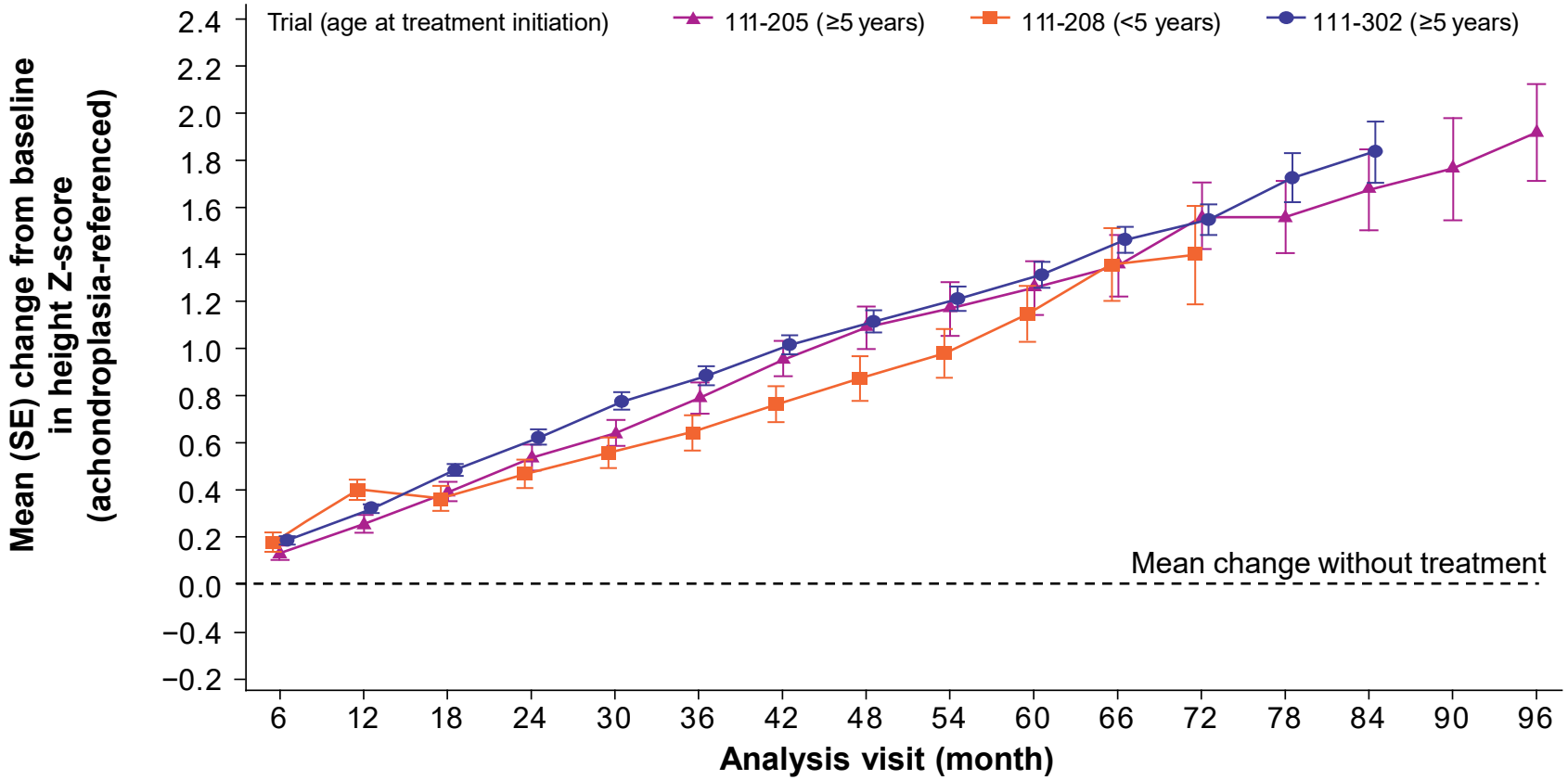


	111-208 <5 years of age at screening	111-205 ≥5 to 14 years of age at screening	111-302 ≥5 to <18 years of age at screening
Enrolled, n	73	30	119
Percent adherence (compliance with the study protocol), mean (SD)	97.7 (4.2)	96.3 (5.1)	97.1 (4.9)

- Some participants in 111-205 and 111-302 discontinued treatment after reaching predefined near-final adult height criteria, consistent with expected treatment completion

In studies 111-205 and 111-302, 43.3% (13/30) and 18.5% (22/119) of participants, respectively, reached near-final adult height (growth plate closure and annualized growth velocity <1.5 cm/year) and subsequently completed treatment.
AGV, annualized growth velocity; SD, standard deviation.

Height Z-score referenced to achondroplasia natural history increased over 8 years of follow-up across all age groups



111-205 (≥5 years)	30	30	30	29	30	29	29	29	24	24	19	19	17	15	12	12
111-208 (<5 years)	59	65	63	62	61	59	55	48	46	40	28	19				
111-302 (≥5 years)	111	111	109	112	109	111	103	91	86	77	69	56	38	24		

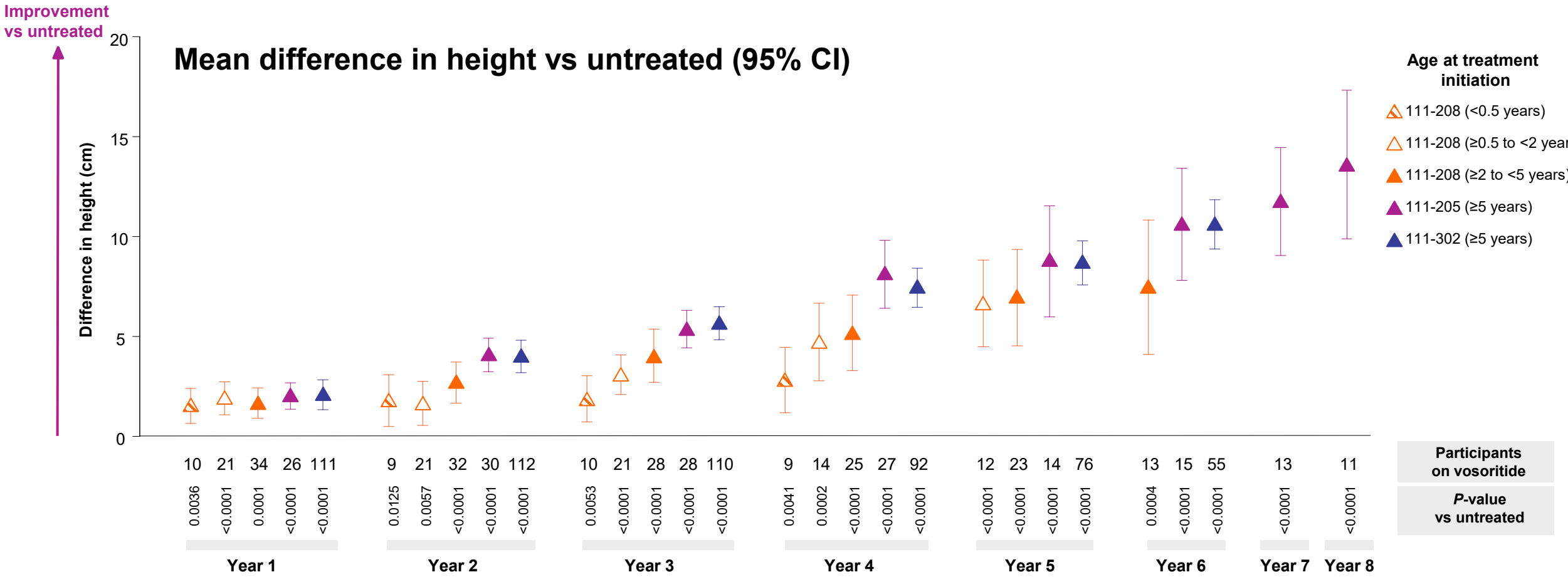
- Z-score measures deviation from the mean of a reference population
- Continuously increasing Z-scores demonstrate sustained improvement in height with vosoritide treatment compared to an untreated reference

Height Z-scores were referenced to age- and sex-matched untreated children with achondroplasia (CLARITY).[1]

1. Hoover-Fong J, et al. *Genet Med*. 2021;23:1498–505.

SE, standard error.

Height difference continues to increase compared to untreated children with achondroplasia with long-term vosoritide treatment

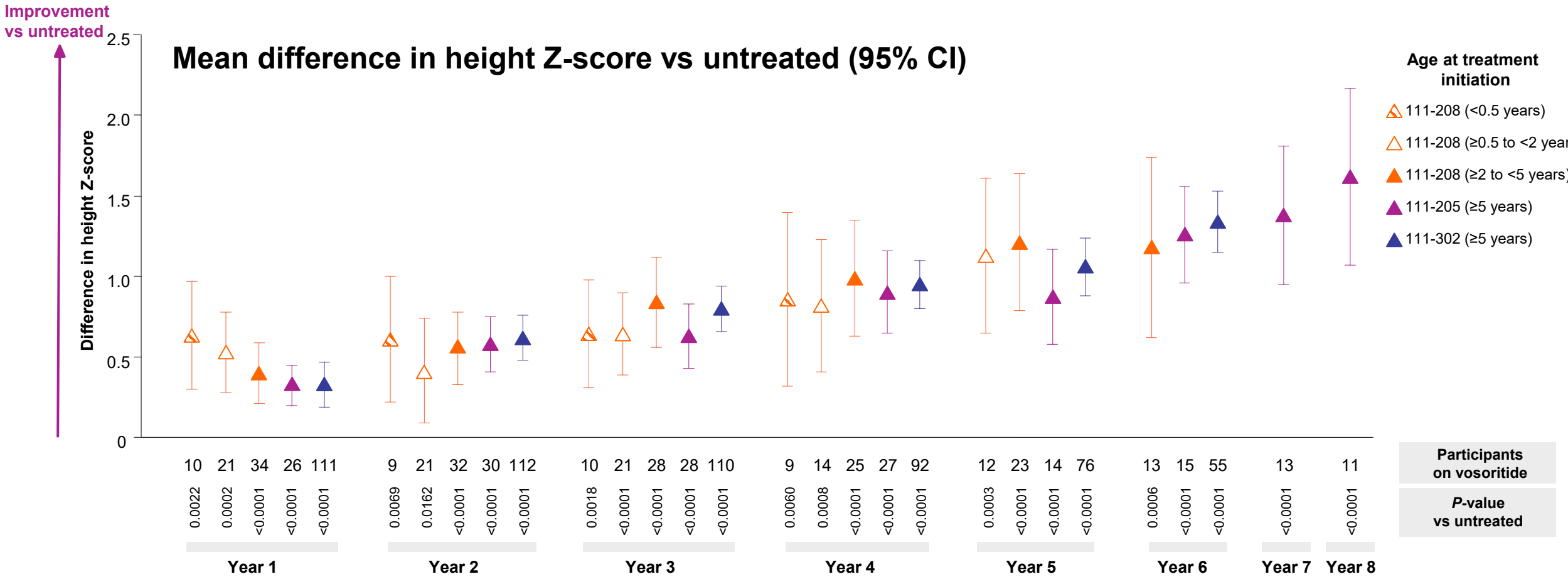


P-values are from baseline-adjusted cross-sectional analyses comparing vosoritide-treated participants with CLARITY achondroplasia natural-history data[1] as a comparator. Results from 111-205 were rebaselined, with day 1 being the day of the first dose of 15 or 30 µg/kg vosoritide in study 111-202.

1. Hoover-Fong J, et al. *Genet Med*. 2021;23:1498–505.

CI, confidence interval.

Difference in height Z-score referenced to average stature increased compared with untreated children with achondroplasia with long-term vosoritide treatment

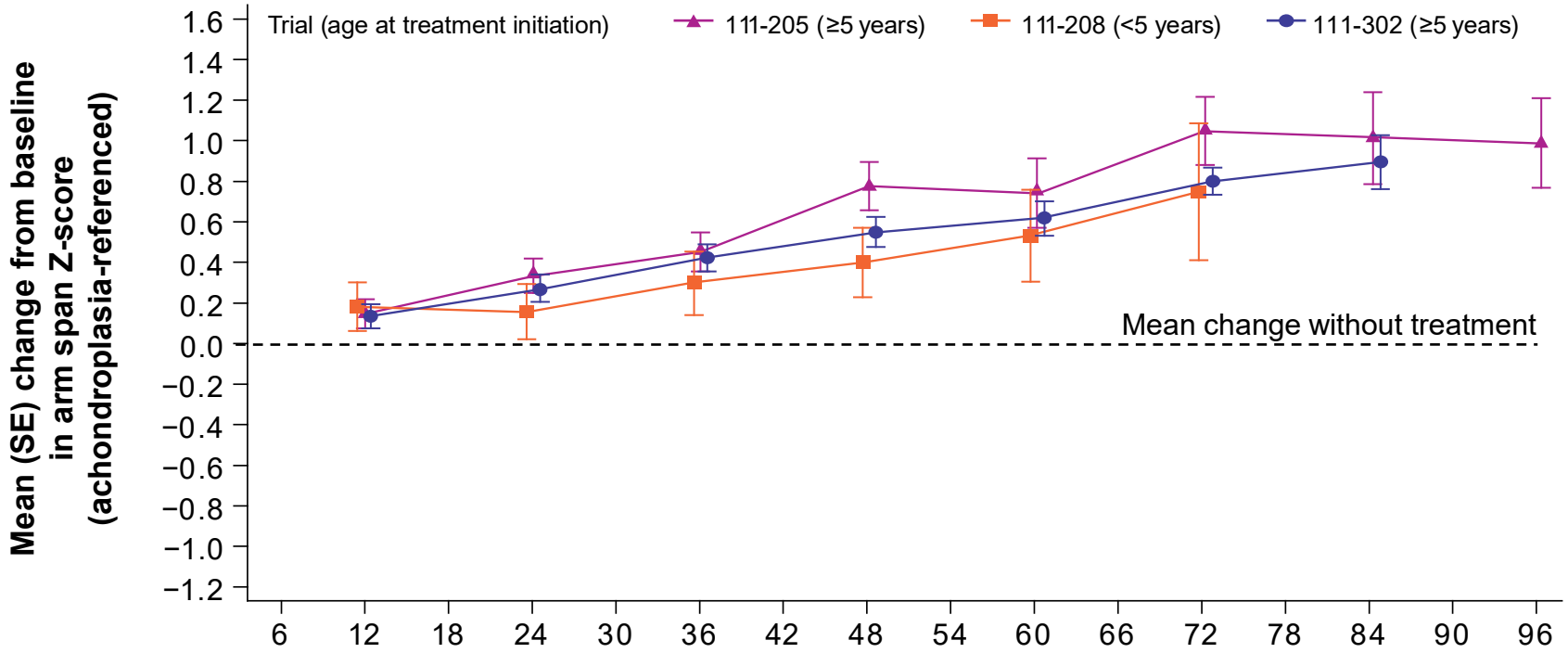


P-values are from baseline-adjusted cross-sectional analyses comparing vosoritide-treated participants with CLARITY achondroplasia natural-history data[1] as a comparator. Results from 111-205 were rebaselined, with day 1 being the day of the first dose of 15 or 30 µg/kg vosoritide in study 111-202. P-values

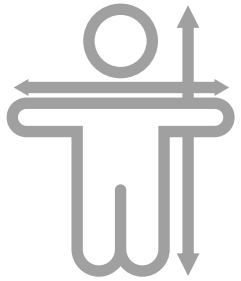
1. Hoover-Fong J, et al. *Genet Med*. 2021;23:1498–505.

CI, confidence interval.

Arm span Z-score referenced to achondroplasia natural history increased over 8 years of follow-up



111-205 (≥5 years)	20	21	20	20	15	11	11	10
111-208 (<5 years)	34	29	27	25	23	13		
111-302 (≥5 years)	104	103	105	92	77	56	24	



- Arm span-to-height ratio remained stable across all years of treatment (data not shown)

Arm span Z-scores were referenced to age- and sex-matched untreated children with achondroplasia[1] and are only available for children aged ≥2 years (111-205, 111-302) or >2 years (111-208).

1. Merker A, et al. *Am J Med Genet*. 2018;176A:1819–29.

SE, standard error.

Safety summary

Consistent, manageable long-term safety profile across

10,638

person-years of exposure

No slipped capital femoral epiphysis events observed across all 3 studies

	111-208 N = 73 369.94 PY		111-205 N = 30 241.46 PY		111-302 N = 119 686.59 PY	
	Incidence %	**Event rate/PY**	**Incidence %**	**Event rate/PY**	**Incidence %**	**Event rate/PY**
AEs	98.6	6.982	100	5.39	99.2	3.57
Adverse drug reactions[a]						
ISRs[b]	20.5	0.387	56.7	0.18	10.9	0.05
Hypotension[c]	2.7	0.008	46.7	0.14	14.3	0.03
Fatigue	2.7	0.005	13.3	0.03	7.6	0.015
Dizziness	6.8	0.032	23.3	0.05	12.6	0.033
Syncope	1.4	0.003	3.3	0.01	1.7	0.003
Pre-Syncope	1.4	0.003	13.3	0.02	6.7	0.013
Nausea	6.8	0.032	20.0	0.05	12.6	0.033
Hypertrichosis[d]	4.1	0.008	0	0	1.7	0.004
Femur fracture	2.7	0.005	6.7	0.01	4.2	0.007
Discontinuation due to AEs	1.4	0.005	3.3	0.004	0.8	0.001
SAEs	28.8	0.087	26.7	0.05	25.2	0.07
Related SAEs	1.4	0.003	0	0	1.7	0.01
Grade ≥3 AEs[e]	24.7	0.070	30.0	0.05	21.8	0.06

[a]Identified for vosoritide. Additionally, increased alkaline phosphatase was identified as an adverse drug reaction based on laboratory findings and occurred at a frequency of >10% in the pivotal phase 3 study CANOPY ACH-3 (111-301). [b]ISRs include grade ≥2 events or events lasting for >24 hours (excluding bruising).
[c]Includes both symptomatic and asymptomatic events. [d]Includes preferred terms of hypertrichosis and hair growth abnormal. [e]Severity based on CTCAE grade.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ISR, injection-site reaction; PY, person-years; SAE, serious AE.

Conclusions



Vosoritide provides durable and consistent improvements in growth for children with achondroplasia, with height and arm span Z-scores consistently increasing over time, compared to untreated children across all ages



Vosoritide offers a growth benefit across age groups regardless of age at treatment initiation



Vosoritide maintains a well-established safety profile with up to 8 years of follow-up and high treatment adherence, with over 9 years of treatment exposure in some children

Acknowledgments

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