OC7.4

Long-term height gain and maintenance of treatment effect in children with achondroplasia receiving vosoritide

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CONFLICT OF INTEREST

Ravi Savarirayan

☒ I have the following potential conflicts of interest to report:

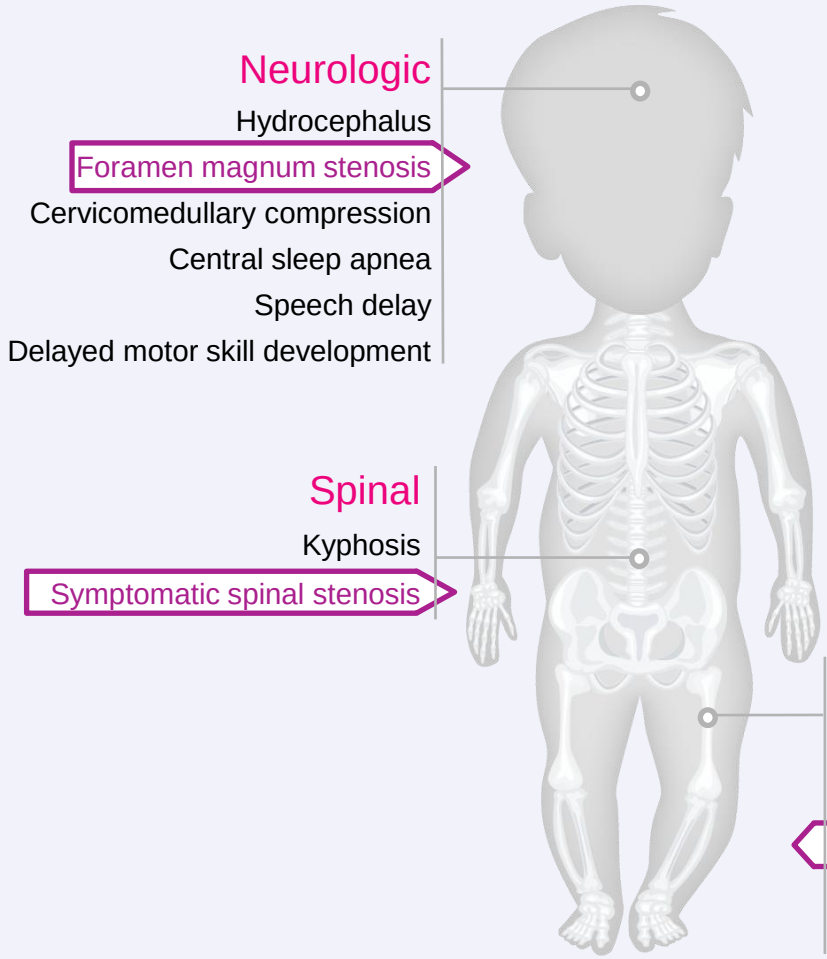
- ☒ Research grants from BioMarin Pharmaceutical Inc
- ☒ Consulting fees from Ascendis, BridgeBio Pharma, and BioMarin Pharmaceutical Inc
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ **I declare that I have no potential conflict of interest.**

Achondroplasia is a genetic condition of impaired endochondral bone growth

Disproportionate growth leads to multisystem medical complications and functional challenges that continue throughout life[1,2]

Medical complications[1]



Functional challenges[1]

- Impaired physical functioning
- Reduced mobility/gait
- Accessibility changes
- Social/emotional impact

1. Pauli RM, et al. *Orphanet J Rare Dis.* 2019;14(1):1. **2.** Savarirayan R, et al. *Nat Rev Endocrinol.* 2025. doi:10.1038/s41574-024-01074-9

Vosoritide efficacy and safety for achondroplasia is established with over a decade of data from clinical trials and the real world

Vosoritide, the first approved precision therapy for ACH, is a recombinant C-type natriuretic peptide that stimulates endochondral bone growth[1,2]

Vosoritide is currently approved in over 40 countries

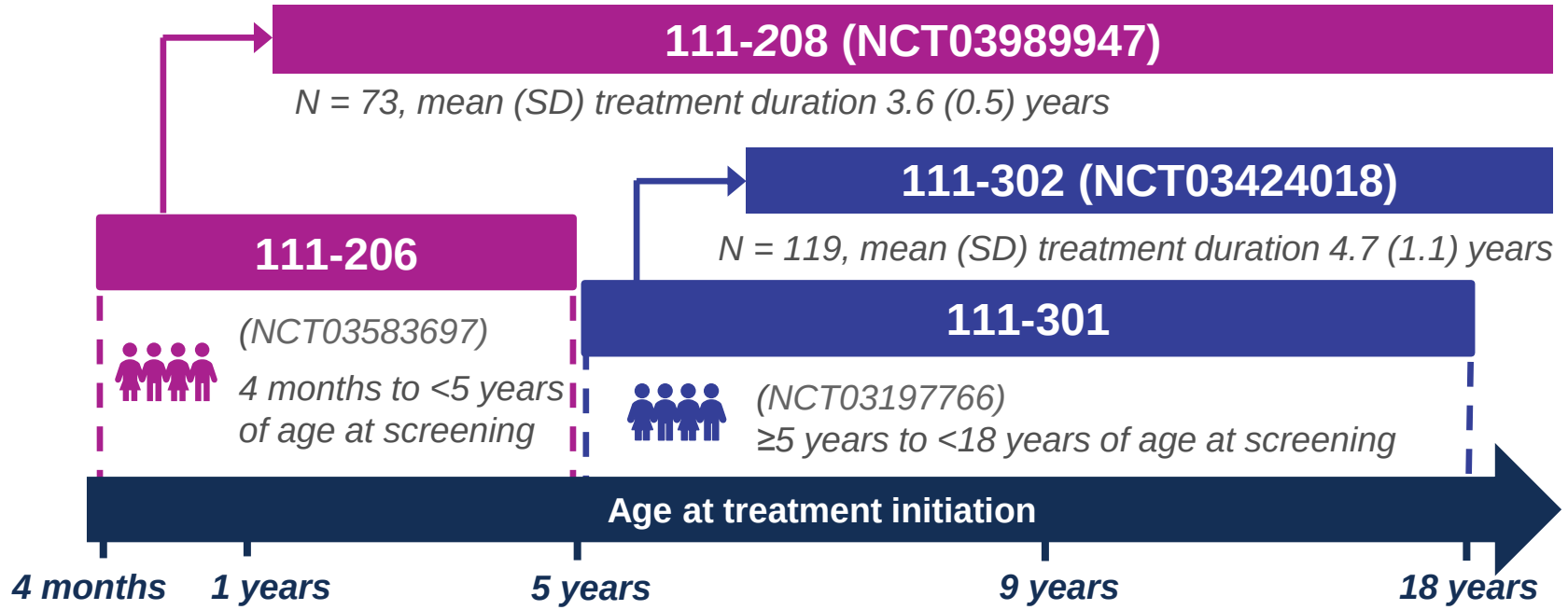
Over a decade of clinical trials and real-world experience with vosoritide has demonstrated that treated patients have significant and sustained improvements in growth and that treatment is well tolerated[3-6]

Vosoritide initiation is approved in infancy, and international guidelines recommend starting vosoritide treatment soon after diagnosis to provide children with maximal opportunity for clinical benefit[1,7,8]

1. Savarirayan R, et al. *Nat Rev Endocrinol.* 2025. doi:10.1038/s41574-024-01074-9. **2.** Lorget F, et al. *Am J Hum Genet Rep.* 2012;91:1108-14. **3.** Savarirayan R, et al. *Med*. 2024; doi:10.1016/j.medj.2024.11.019. **4.** Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024. doi:10.1016. **5.** Sawamura K, et al. *J Pediatr Orthop*. 2025. doi:10.1097/BPO.0000000000002980. **6.** Reincke S, et al. *J Endocr Soc*. 2025. doi:10.1210. **7.** U.S. Food and Drug Administration approved BioMarin's VOXZOGO (vosoritide) for children under 5 years with achondroplasia. Accessed March 6, 2025. https://investors.biomarin.com/news/news-details/2023/U.S.-Food-and-Drug-Administration-Approves-BioMarins-VOXZOGO-vosoritide-for-Children-Under-5-Years-with-Achondroplasia-10-20-2023/default.aspx. **8.** VOXOGO. Prescribing Information. EMA label. Accessed August 14,2024.
ACH, achondroplasia.

Clinical benefits of early and continuous treatment from infancy to final adult height are unknown

- No single clinical trial has followed an individual cohort for the entire growth period; however, overall growth benefit may be estimated with cross-sectional analyses of different studies that collectively span the full age range
- Treatment effect is maintained regardless of time on vosoritide, providing a rationale for pooling trial AGV data to estimate total growth benefit



Follow-up was continued until discontinuation or near-FAH for LTE studies 111-302 and 111-208. Data cut was on February 25, 2024. Study 111-208 converted to weight-band dosing. Near-FAH was defined as evidence of growth plate closure and <1.5 cm/year annualized growth velocity.
AGV, annualized growth velocity; SD, standard deviation.

Estimation of the cumulative additional clinical benefit

111-208 **111-302**

Mean AGV is similar from overlapping ages (5–9 years) across studies

Aim: Estimate <u>cumulative additional growth</u> vs natural history if treated from infancy until final adult height

Mean interval AGV

On-treatment, cross-sectional, paired height assessments:

- *6 ± 1.5 months (≥4 months to 3 years)*
- *12 ± 3.5 months (≥3 years to FAH)*

Additional growth

Age-specific additional growth:

- *Mean vosoritide interval AGV minus natural history ACH AGV (CLARITY[1])*

Cumulative additional growth

- *Estimates of cumulative additional growth if continuously treated with vosoritide (4 months to final adult height) were determined by summation of interval growth over time*
- *CIs (95%) were based on bootstrapping distribution with 10,000 samples*

Data cut was performed on February 25, 2024.

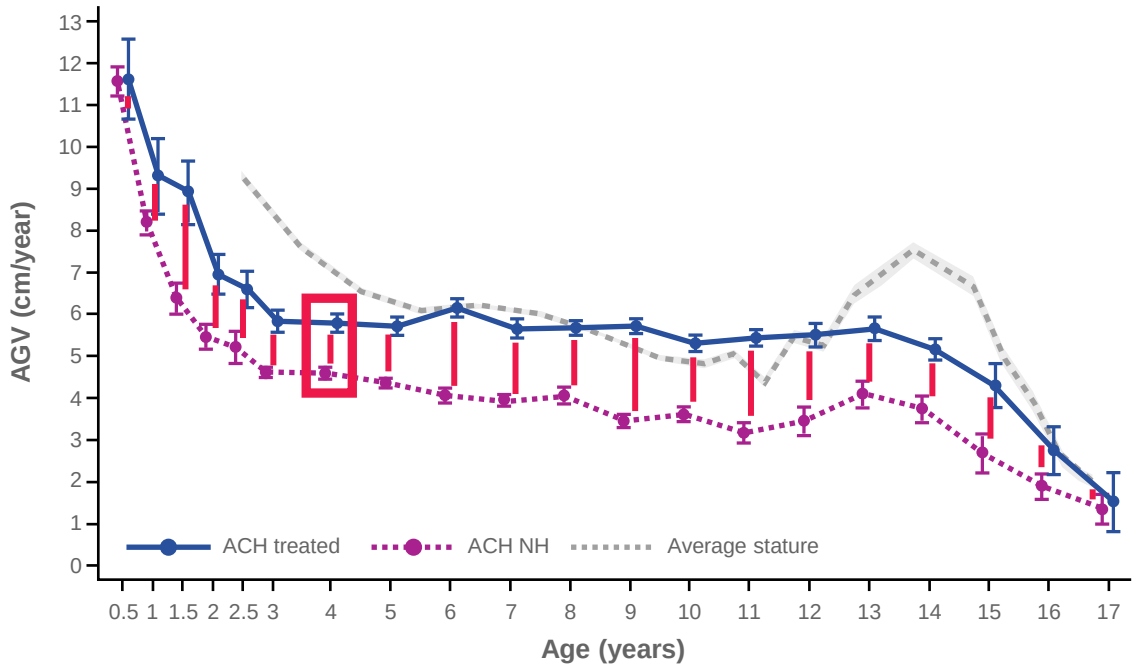
1. Hoover-Fong JE, et al. *Genet Med*. 2021;8:1498-1505.

ACH, achondroplasia; AGV, annualized growth velocity; CI, confidence interval.

Vosoritide improved AGV from 0.5 to 17 years of age

Vosoritide-treated children with ACH have increased AGV across all ages compared with untreated children with ACH

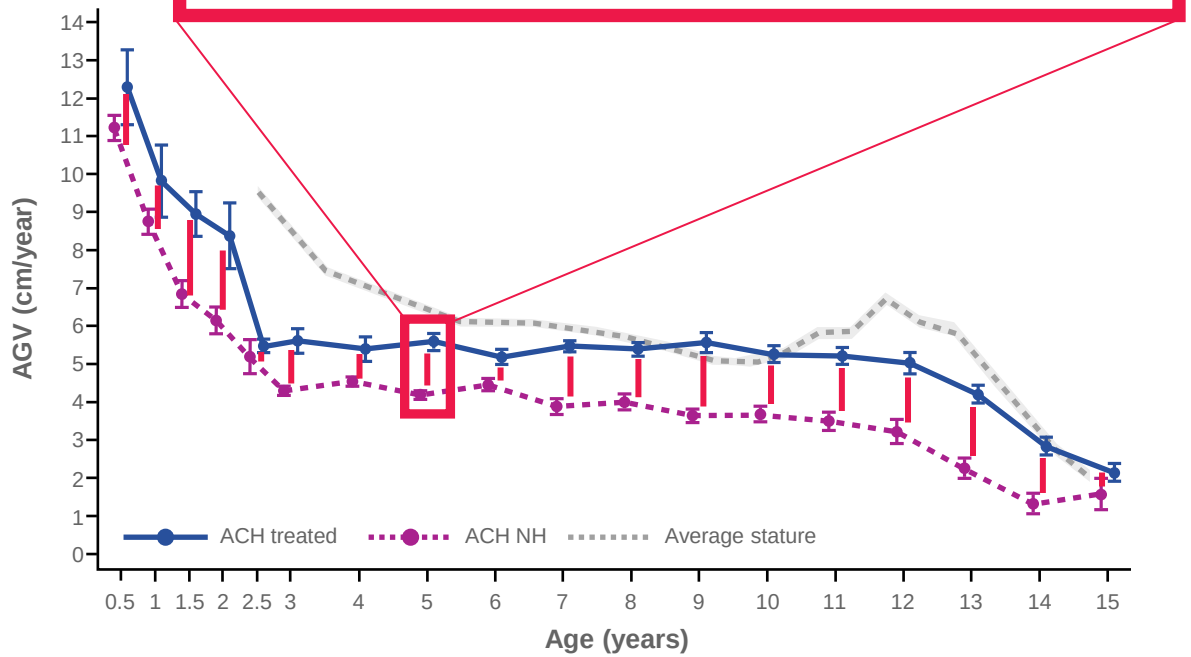
Males



ACH Treated	5	8	12	18	19	23	28	26	30	34	35	37	40	38	32	29	26	17	11	6
ACH NH	216	203	170	127	127	228	197	165	123	92	84	68	65	54	45	37	28	22	22	20

Females

Interval age additional growth = treated AGV – natural history AGV



ACH Treated	6	8	14	18	18	18	16	22	28	36	30	28	31	32	31	28	21	10		
ACH NH	218	175	160	102	90	206	187	148	105	87	80	75	66	52	41	41	36	26		

Data are presented as Mean ± SE.

1. Hoover-Fong JE, et al. *Genet Med*. 2021;8:1498-1505. **2.** Prader A, et al. *Helv Paediatr Acta Suppl*. 1989;52:1-125.

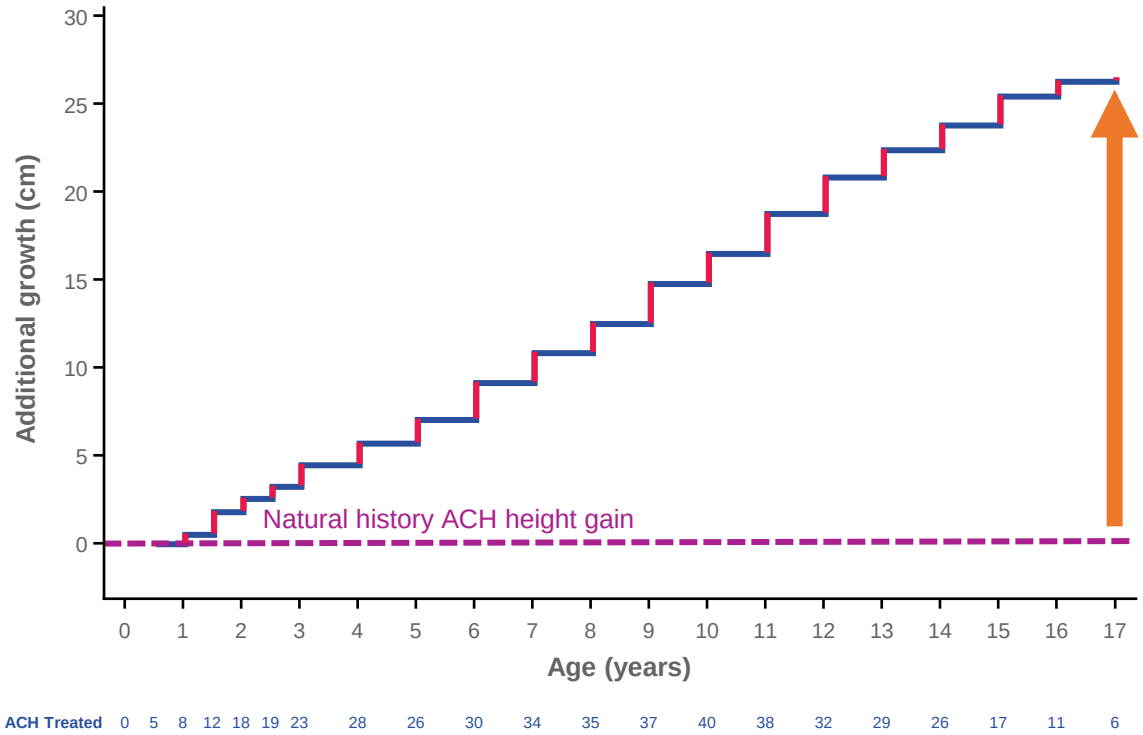
Untreated ACH population is referenced from CLARITY.[1] Average-stature population is referenced from Prader A et al, 1989.[2]

ACH, achondroplasia; ACH NH, achondroplasia natural history population; AGV, annualized growth velocity; SE, standard error

Vosoritide from infancy provides additional cumulative growth beyond natural history

26.4 cm (95% CI, 22.9–29.8) predicted additional growth at final adult height

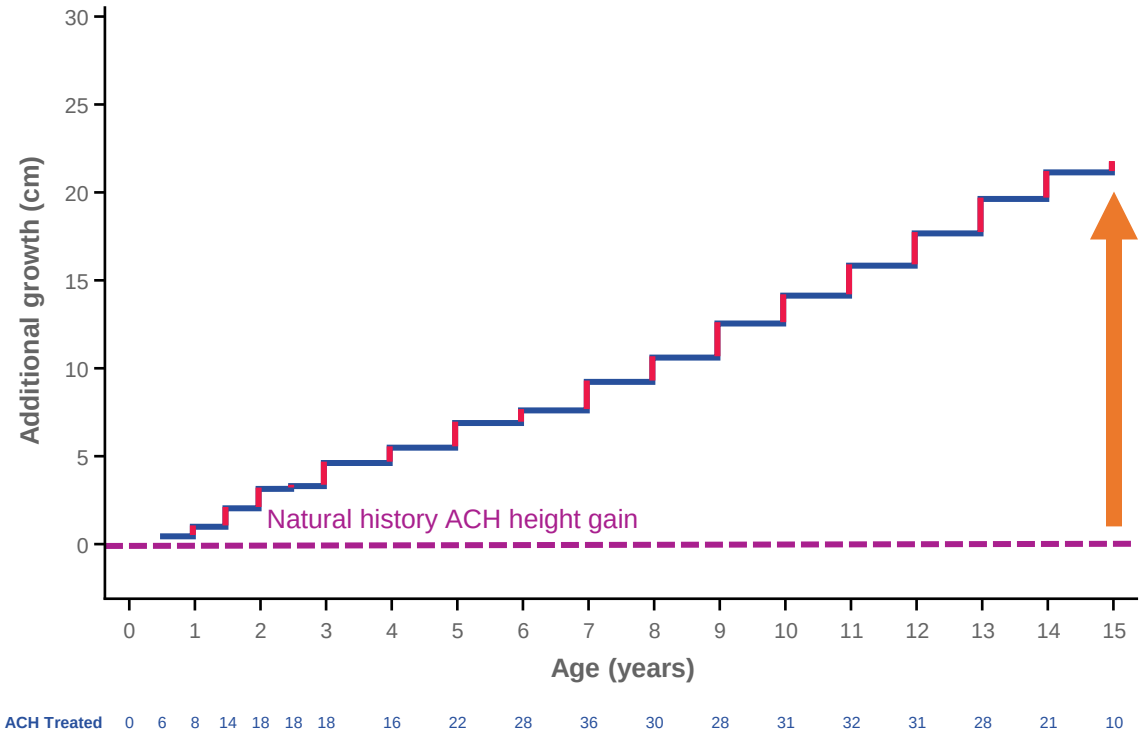
Males



ACH Treated	0	5	8	12	18	19	23	28	26	30	34	35	37	40	38	32	29	26	17	11	6

21.7 cm (95% CI, 18.7–24.6) predicted additional growth at final adult height

Females



ACH Treated	0	6	8	14	18	18	18	16	22	28	36	30	28	31	32	31	28	21	10

ACH, achondroplasia; CI, confidence interval.

Conclusion

Estimated long-term additional growth beyond natural history suggests early and continuous vosoritide treatment may maximize clinical benefits for children with ACH

Over a decade of clinical trials and real-world experience of vosoritide has demonstrated that treated children have significant and persistent improvements in growth[1-4]

Here, we show data estimating that early and continuous vosoritide treatment from 4 months to 17 years of age will sustain increased annual growth beyond natural history

Treatment with vosoritide soon after diagnosis, during infancy and until final adult height is reached may lead to additional growth that could lessen the severity or prevent complications of ACH

1. Savarirayan R, et al. *Med*. 2024. doi:10.1016/j.medj.2024.11.019. **2.** Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024. doi:10.1016. **3.** Sawamura K, et al. *J Pediatr Orthop*. 2025. doi:10.1097/BPO.0000000000002980. **4.** Reincke S, et al. *J Endocr Soc*. 2025. doi:10.1210

ACH, achondroplasia.

Cumulative growth with treatment from infancy is added evidence that early treatment initiation provides long-term benefits

Preventing complications

Neurological

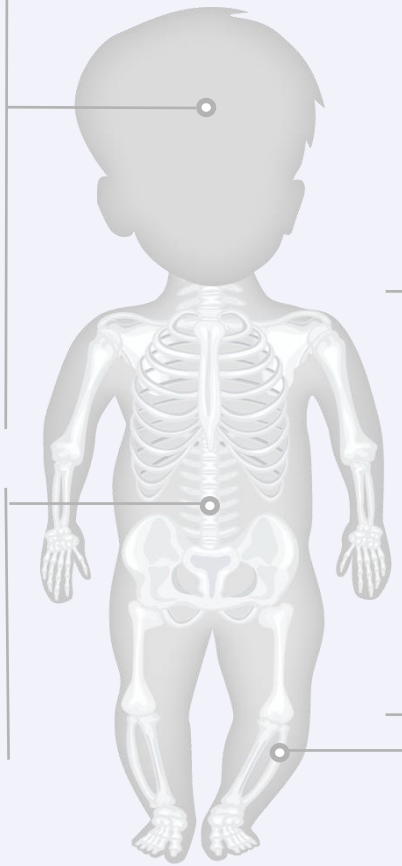
Foramen magnum stenosis & sleep testing

- In a retrospective study, no children who initiated vosoritide aged <2 years developed foramen magnum stenosis and vosoritide initiation in children aged <3 years improved sleep quality[1]

Spinal

Symptomatic spinal stenosis

- In a prospective observational study, vosoritide improved spinal alignment in young children with ACH after 1 year of treatment[2]



Musculoskeletal

Body proportionality

- In clinical trials, vosoritide improved upper-to-lower body segment ratio vs untreated children[3,4]

Genu varum

- In a prospective observational study, vosoritide improved genu varum in young children with ACH after 1 year of treatment[2]

Increased Functionality

Improved mobility/gait

- In an observational study, vosoritide provided clinically significant improvements in the 6-minute walking distance test from baseline after 1 year of treatment[5]

Improved QOL

- In a clinical trial, vosoritide positively impacted physical and social QOL after early treatment initiation in children with ACH after 3 years[6]

1. Lourenco C, et al. 2025. Abstract at ACMG. P156 March 18-22, 2025**. 2.** Sawamura K, et al. *J Pediatr Orthop*. 2025. doi:10.1097/BPO.0000000000002980. **3.** Savarirayan R, et al. *Med*. 2024. doi:10.1016/j.medj.2024.11.019. **4.** Savarirayan R, et al. *Lancet Child Adolesc Health*. 2024. doi:10.1016. **5.** Reincke S, et al. *J Endo Societ*. 2025. doi:10.1210. **6.** Savarirayan R, et al. *Genet Med*. 2024;26:101274.
ACH, achondroplasia; QOL, quality of life.

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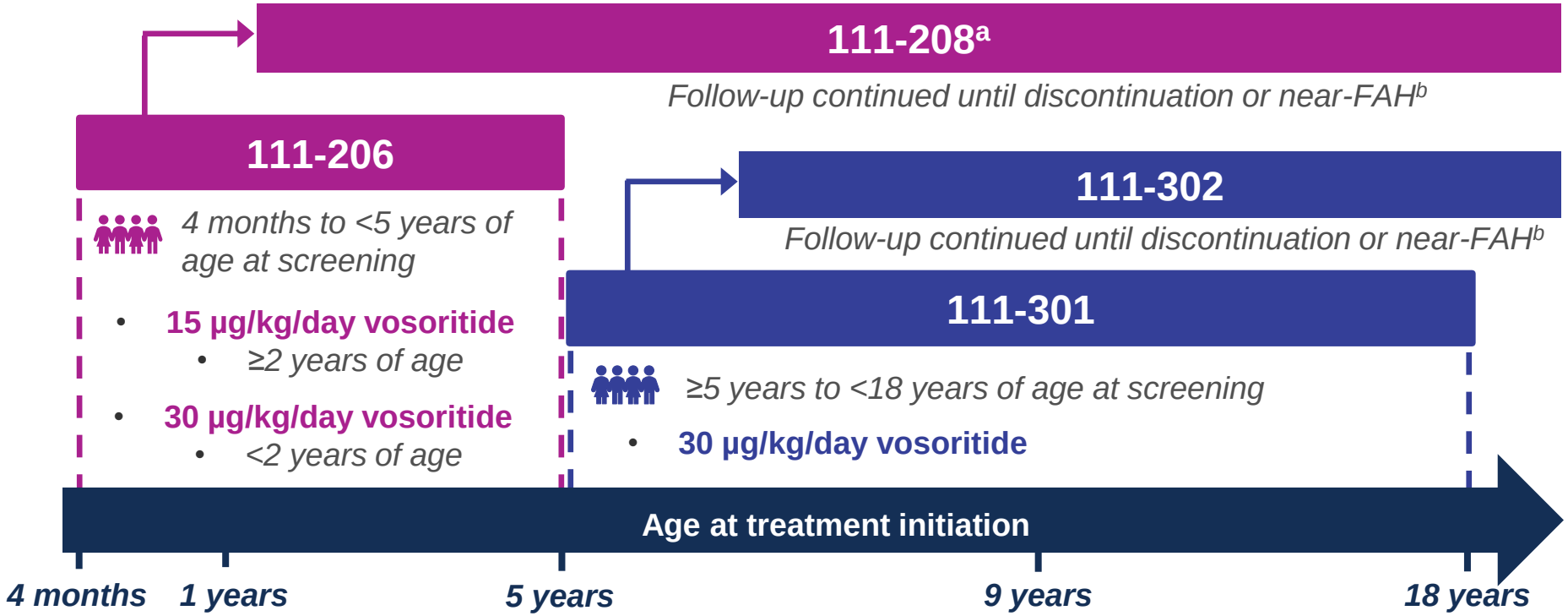
- Medical writing support was provided by Rachel Corrigan, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

Appendix

Pooled clinical results from infancy until FAH

- Participants were pooled from the phase 3 study 111-301 (NCT03197766) active arm and its ongoing LTE 111-302 (NCT03424018) and the phase 2 study 111-206 (NCT03583697) active arm and its ongoing LTE 111-208 (NCT03989947) Data cut Feb 2024
  - 119 children from 111-302 had a mean (SD) treatment duration of 4.7 (1.1) years
  - 73 children from 111-208 had a mean (SD) treatment duration of 3.6 (0.5) years



[a]Study 111-208 converted to weight-band dosing. [b]Near-FAH was defined as evidence of growth plate closure and <1.5 cm/year annualized growth velocity.
FAH; final adult height; LTE; long-term extension; SD, standard deviation.

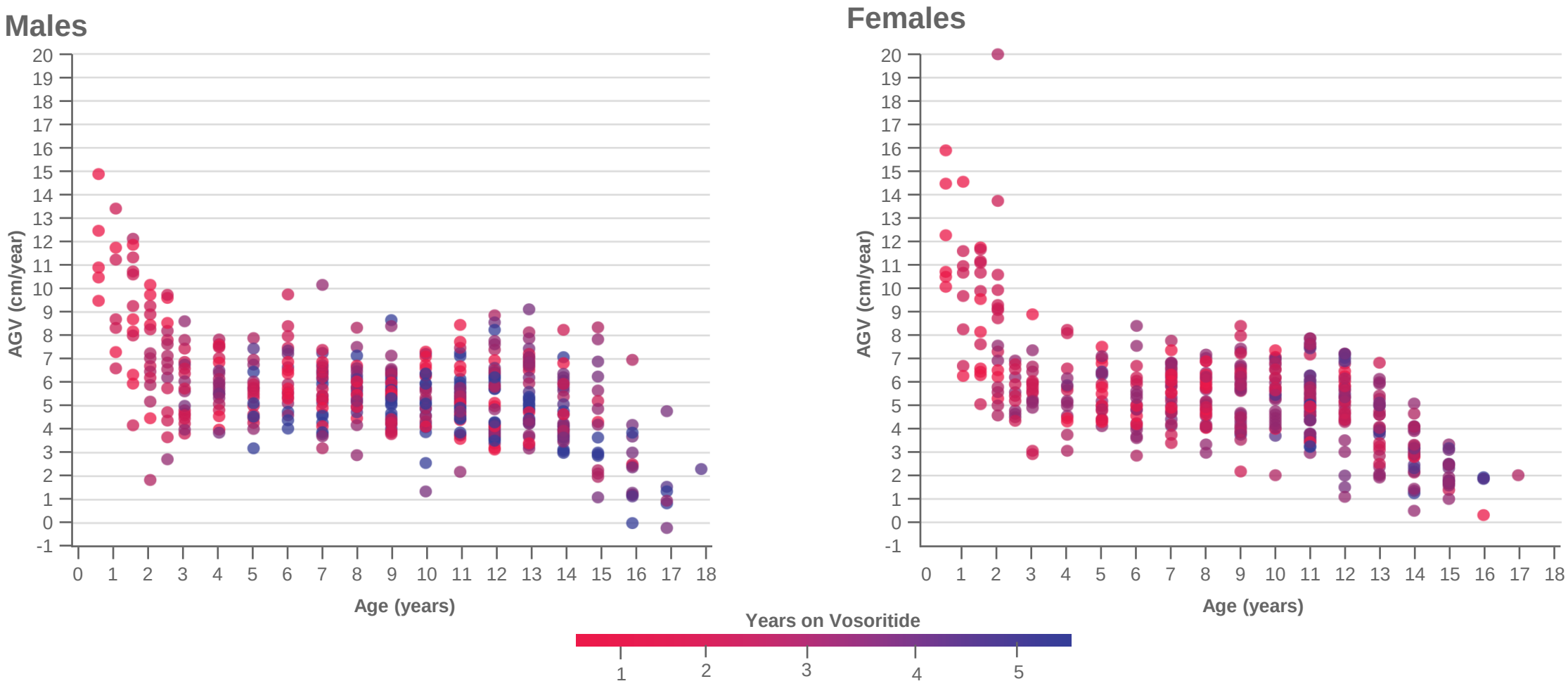
Participant characteristics at treatment initiation

	111-302 (N = 119)	111-208 (N = 73)
Mean (SD) age, years	9.18 (2.60)	2.63 (1.65)
Min, max	5.1, 15.9	0.38, 6.0
Mean (SD) duration of treatment, days	1705.6 (386.4)	1328.7 (189.2)
Min, max	618, 2565	1113, 1596
Male, n (%)	63 (52.9)	37 (50.7)

Max, maximum; min, minimum; SD, standard deviation.

AGV is at any age interval is independent of time on therapy

In vosoritide-treated children with ACH pooled from 111-302 and 111-208, AGV is similar regardless of treatment duration

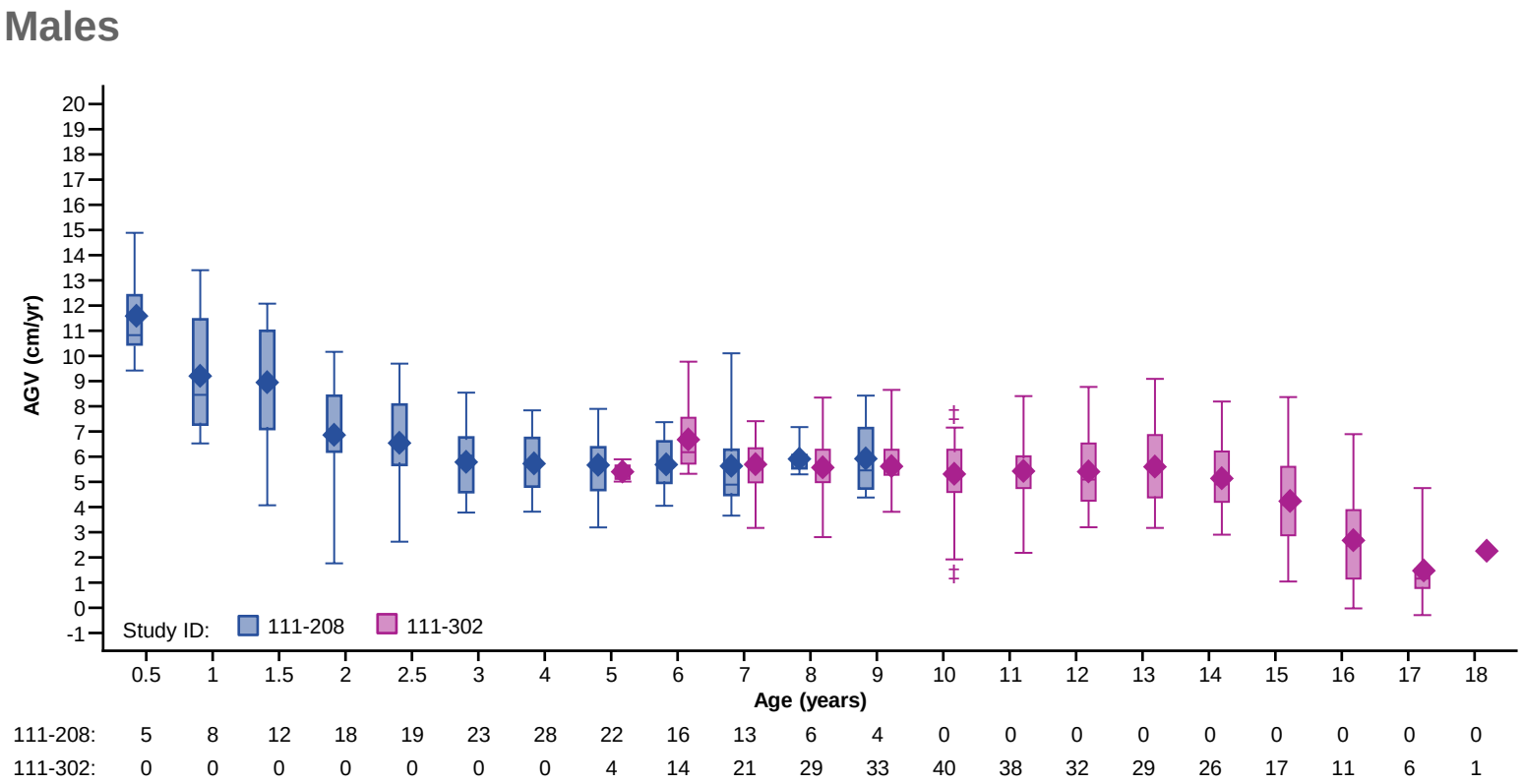


Time on vosoritide was derived as the time from first dose to the midpoint between the 2 height assessments used to derive AGV.
ACH, achondroplasia; AGV, annualized growth velocity.

Consistent AGV across 2 clinical studies

AGV was similar in overlapping age intervals (5–9 years) from studies 111-208 and 111-302

- To demonstrate the potential benefits of long-term vosoritide treatment from age 0.5 years to final adult height, we used pooled data from phase 2 and phase 3 studies to model AGV maintenance and additional cumulative growth across age and sex compared with untreated children with ACH



Interval age AGV are displayed as median (midline), mean (diamond), 25th and 75th percentiles (box edges) and 2.5th and 97.5th percentiles (whiskers). Asterisks represent outliers.
ACH, achondroplasia; AGV, annualized growth velocity.