PERSISTENCE OF GROWTH PROMOTING EFFECTS IN CHILDREN WITH ACHONDROPLASIA UP TO 7 YEARS: UPDATE FROM A PHASE 2 EXTENSION STUDY WITH VOSORITIDE

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演題発表内容に関連し，筆頭および共同発表者が開示すべきCOI関係にある企業などとして，

① 役員・顧問：BioMarin

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Persistence of growth-promoting effects in children with achondroplasia up to 7 years: update from a Phase 2 extension study with vosoritide

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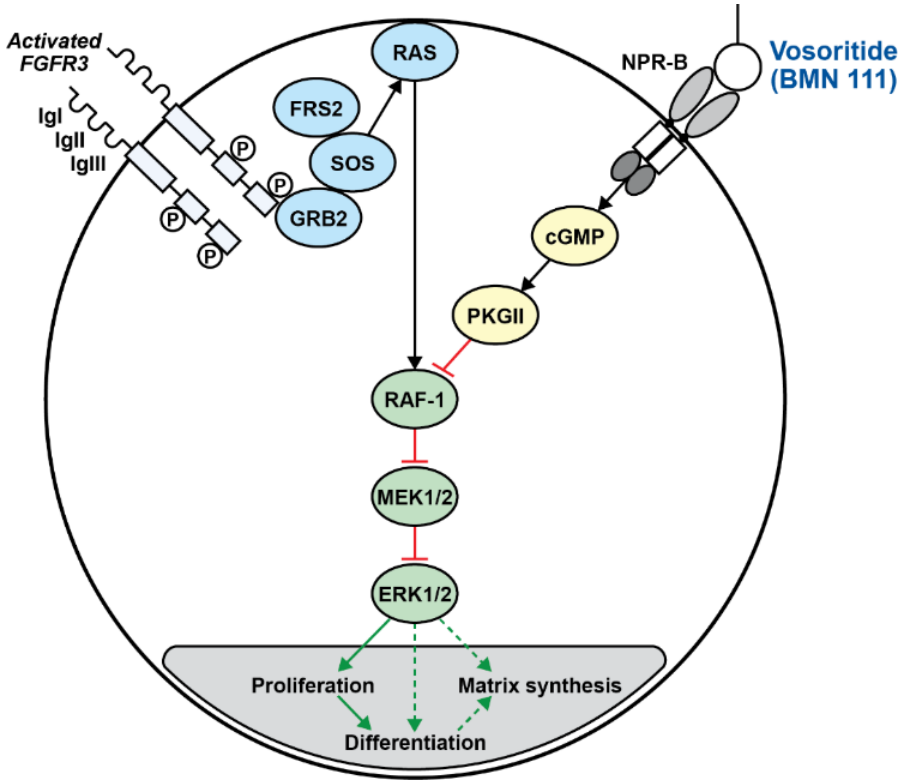
Vosoritide: targeted therapy for achondroplasia

- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- ACH is caused by a pathogenic variant in *FGFR3* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth and multiple complications[1,2]
- CNP down-regulates aberrant FGFR3 signaling in chondrocytes by inhibiting the MAPK-ERK pathway[3,4]
- Vosoritide is based on naturally-occurring CNP engineered to resist degradation and increase the half-life[5]



CNP, C-type natriuretic peptide; ERK, extracellular signal-regulated kinase; FGFR3, fibroblast growth factor receptor 3; MAPK, mitogen-activated protein kinase

1. Horton WA *et al. Lancet* 2007;370:162–72; 2. Hoover-Fong J *et al. Bone* 2021;146:115872; 3. Yasoda A *et al. Nat Med* 2004;10:80–6; 4. Kreji P *et al. J Cell Sci* 2005;118:5089–100; 5. Lorget F *et al. Am J Hum Genet* 2012;91:1108–14

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Increase in growth was demonstrated with vosoritide in clinical trials in ACH

- An open-label, 52-week Phase 2 trial (BMN 111-202) and its extension study (BMN 111-205) in children with ACH showed that vosoritide treatment resulted in sustained increases in AGV[1]
- A Phase 3 randomized placebo-controlled trial (BMN 111-301) in children with ACH showed a statistically significant improvement in AGV with vosoritide after 52 weeks compared with placebo[2]; AGV improvement sustained after 2 years of vosoritide treatment in extension study (BMN 111-302)[3]
- In children with ACH 0–5 years of age, improvement in height Z-score was seen with vosoritide compared with placebo after 52 weeks (111-206)[4]
- Vosoritide is approved for use in children with ACH and open epiphyses from birth in the USA, Japan and Australia, and aged ≥4 months in EU and ≥6 months in Brazil

ACH, achondroplasia; AGV, annualized growth velocity; EU, European Union

1. Savarirayan R *et al. N Engl J Med* 2019;381:25–35; 2. Savarirayan R *et al. Lancet* 2020;396:684–92; 3. Savarirayan R *et al. Genet Med* 2021;23:2443–7; 4. Savarirayan R *et al. Lancet Child Adolesc Health* 2024;8:40–50

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BMN 111-202: a Phase 2 open-label study in children with ACH

- **Primary objective**
  - Evaluate the safety and tolerability of daily subcutaneous injections of vosoritide administered for 6 months and up to 24 months

- **Secondary objectives**
  - Evaluate change from baseline in annualized growth velocity (AGV)
  - Evaluate changes from baseline in growth parameters
  - Evaluate changes from baseline in body proportions
  - Evaluate dose-exposure and PK profiles of vosoritide in children with ACH

ACH, achondroplasia; PK, pharmacokinetics

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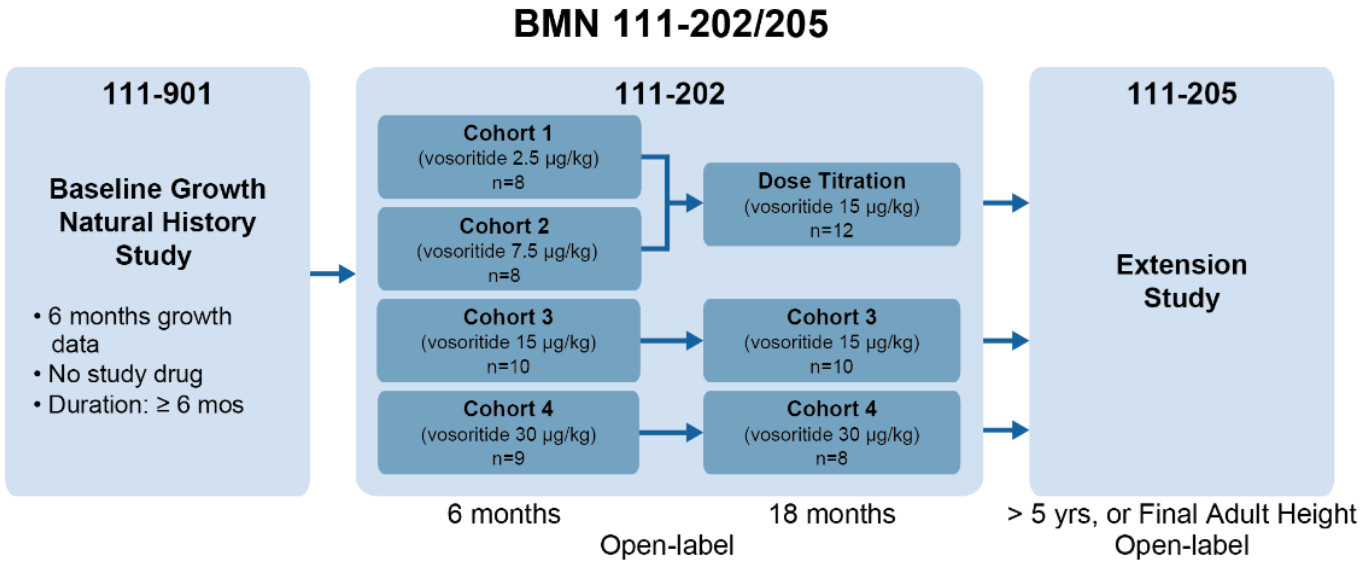
BMN 111-205: a Phase 2 open-label extension study of 202 in children with ACH with follow-up to final adult height

BMN 111-202/205 key eligibility criteria

- Age 5 to 14 years old at screening
- ACH, documented by clinical grounds and confirmed by genetic testing
- At least a 6-month period of pre-treatment growth measurements in BMN 111-901, a clinical assessment study to establish baseline growth in children with ACH



ACH, achondroplasia

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Analyses methods

- Data cut off February 25, 2023
- **Safety**
  - Overall safety profile
  - Bone age/chronological age over time
- **Efficacy**
  - 12-month interval AGV by age intervals referenced to ACH and average stature AGV[1]
  - Height Z-score using reference ranges in the untreated ACH population (CLARITY[2])
  - A comparative analysis was conducted for all subjects with at least 7 years follow-up (N=17) on treatment from the start of receiving 15 or 30 µg/kg. This was a cross sectional analysis and the untreated subjects were matched to each of the subjects in the vosoritide arm at baseline (N=390) and at the 7-year timepoint (N=173) by age (±1 month) and sex. To adjust for baseline differences, the difference at baseline was subtracted from the difference determined at 7 years
  - Upper to lower body segment ratio
    - Sensitivity summary provided which only includes assessments at <11 years (females) and <12 years (males)

ACH, achondroplasia; AGV, annualized growth velocity; CLARITY, achondroplasia natural history study

1. Kelly A *et al. J Clin Endocrinol Metab* 2014;99:2104–12; 2. Hoover-Fong J *et al. Orphanet J Rare Dis* 2021;16:522

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Demographics of BMN-205 study population based on first dose in 111-202 study

	205 C1 (N=6)	205 C2 (N=6)	205 C3 (N=10)	205 C4 (N=8)
Age at Day 1 of treatment (y)				
Mean (SD)	8.07 (1.43)	8.49 (2.37)	8.54 (1.54)	7.50 (0.95)
Min, Max	6.9, 10.9	6.0, 10.8	6.3, 11.1	5.8, 8.7
Age subgroups (%)				
≥5 to <8 years	4 (66.7)	3 (50.0)	4 (40.0)	4 (50.0)
≥8 to <11 years	2 (33.3)	3 (50.0)	5 (50.0)	4 (50.0)
≥11 to <15 years	0	0	1 (10.0)	0
≥15 to <18 years	0	0	0	0
Sex (%)				
Male	2 (33.3%)	4 (66.7%)	4 (40.0)	3 (37.5)
Female	4 (66.7%)	2 (33.3%)	6 (60.0)	5 (62.5)

C, cohort; SD, standard deviation

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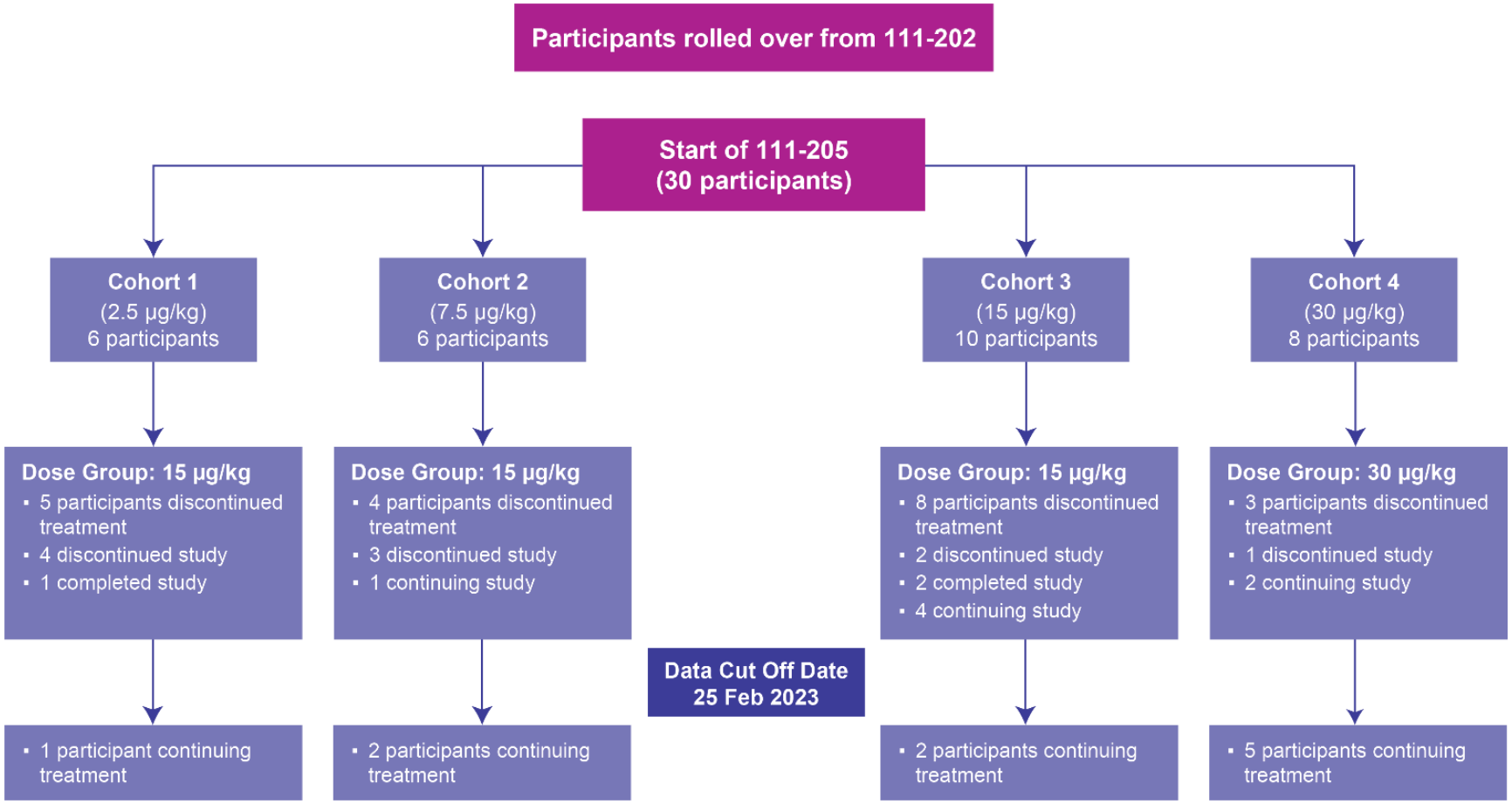
BMN 111-202/205 study disposition



5 of those who discontinued reached FAH

FAH, final adult height

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BMN 111-202 and 205 safety summary

	Overall N=30; Exposure: 200.26 person-years	
	Incidence n (%)	**Event Rate (AEs/person-year)**
AE, n (%)	30 (100.0)	1215 (6.07)
Treatment-related AEs	24 (80.0)	81 (0.40)
AEs leading to study drug discontinuation	1 (3.3)	1 (0.00)
SAEs	8 (26.7)	9 (0.04)
AEs CTCAE Grades ≥3	8 (26.7)	10 (0.05)
Event of interest		
Injection site reactions CTCAE grade ≥2	1 (3.3)	1 (0.00)
Avascular necrosis or osteonecrosis	0	0
Slipped capital femoral epiphysis	0	0
Fractures	1 (3.3)	2 (0.01)

- ISRs continue to remain most common AE, majority remain grade 1 and self-limiting. No long-term sequelae related to daily injections
- None of the SAEs were treatment-related or led to discontinuation of study drug, and were generally attributed to underlying achondroplasia
- There were no deaths in the study

AE, adverse event; CTCAE, common terminology criteria for adverse events; ISRs, injection site reactions; SAEs, serious adverse events

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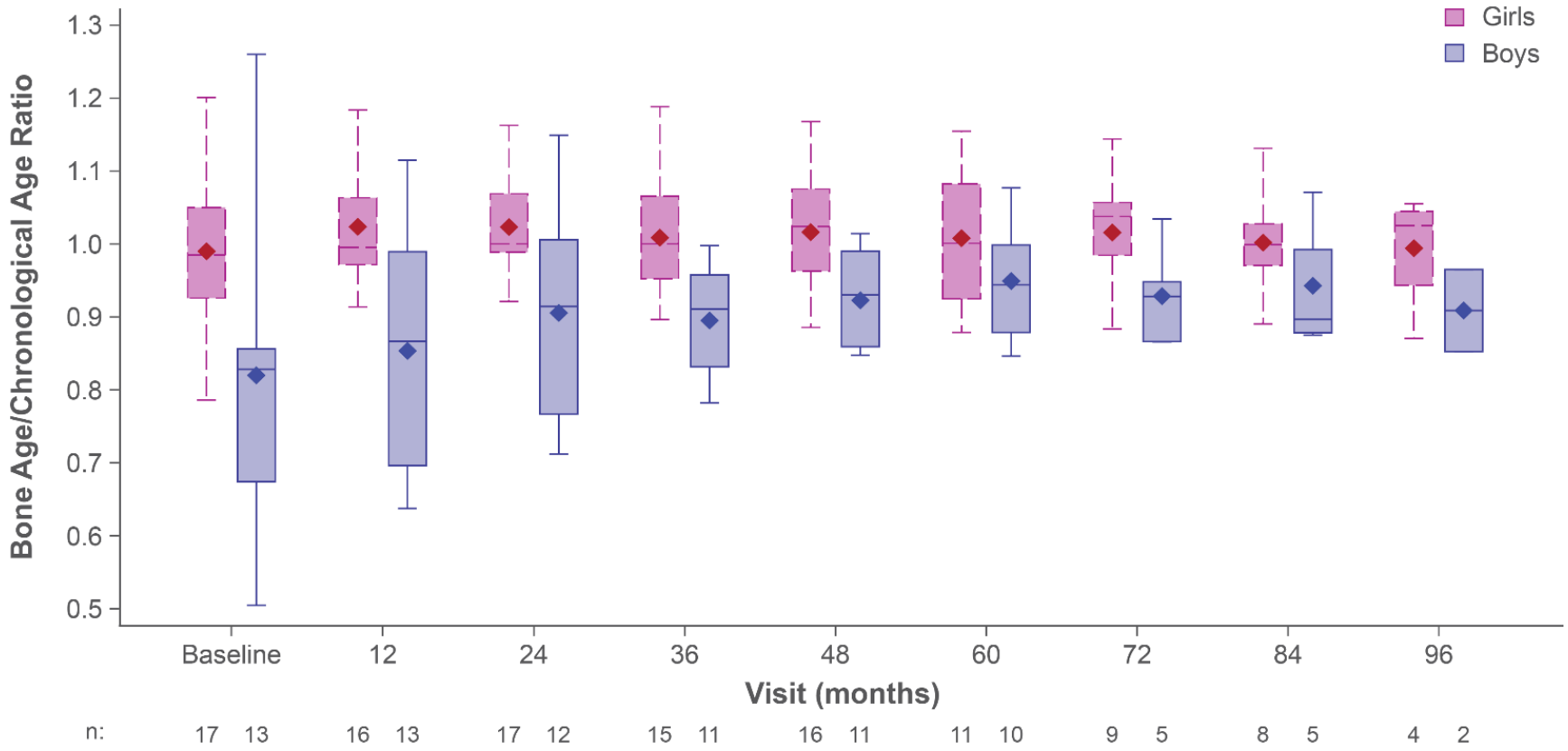
No acceleration of bone age with vosoritide treatment



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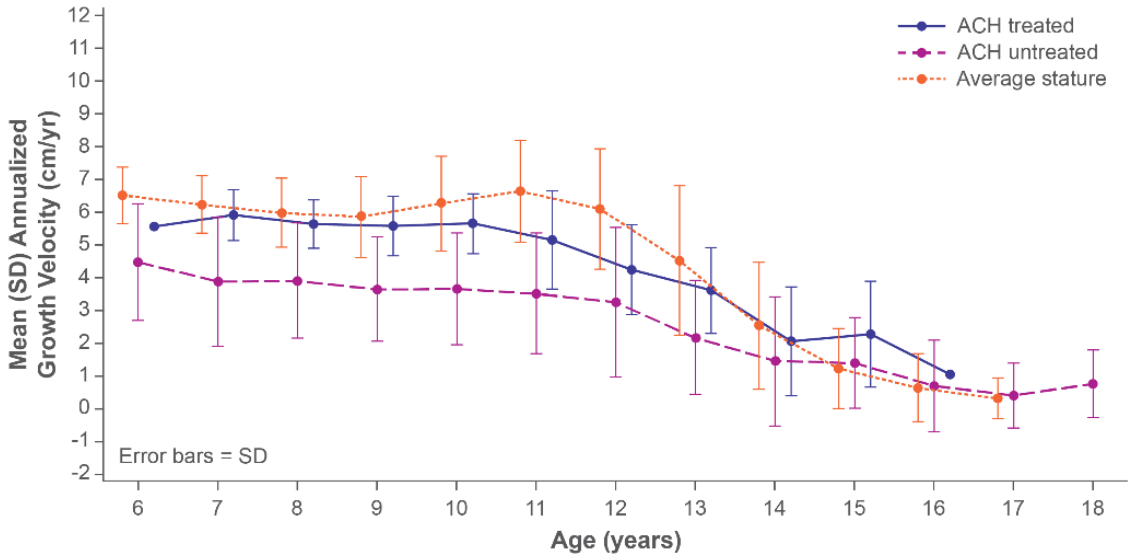
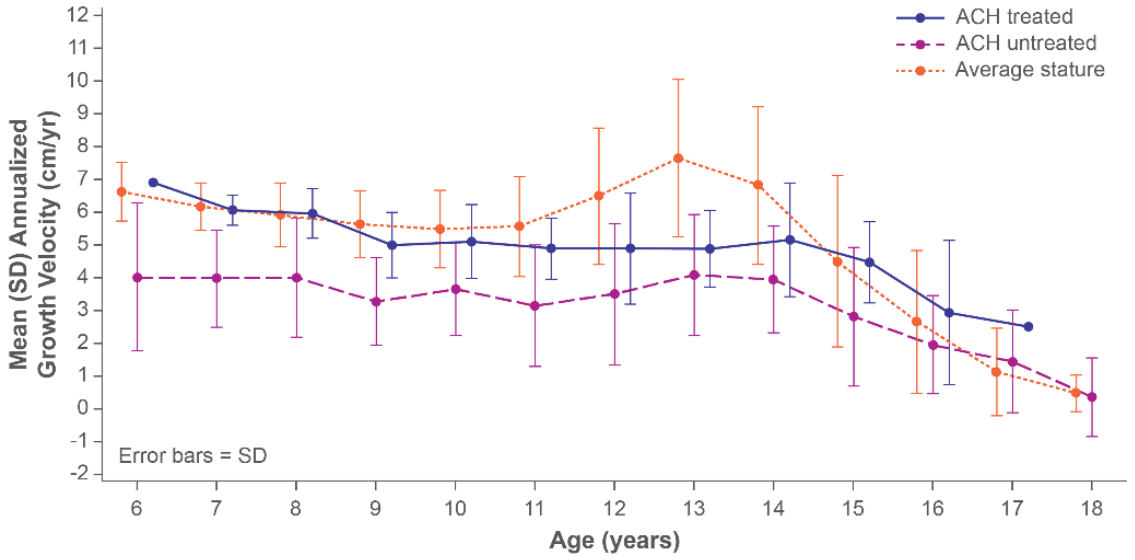
Mean 12-month interval AGV in children treated with vosoritide is higher compared with age-matched untreated children

Girls



	6	7	8	9	10	11	12	13	14	15	16	17	18
ACH treated:	1	4	10	14	15	14	14	14	11	5	1	0	0
ACH untreated:	102	82	77	72	61	48	37	39	33	26	17	13	6
Average stature:	43	107	90	111	140	161	192	187	163	171	192	154	0

Boys



	6	7	8	9	10	11	12	13	14	15	16	17	18
ACH treated:	1	4	7	9	9	11	12	11	7	6	2	2	0
ACH untreated:	117	88	79	62	62	52	45	35	24	20	21	19	8
Average stature:	37	105	85	100	116	144	186	150	151	168	163	163	105

ACH, achondroplasia; AGV, annualized growth velocity; CLARITY, achondroplasia natural history study
ACH untreated reference derived from CLARITY (Hoover-Fong J *et al. Orphanet J Rare Dis* 2021;16:522)
Average stature reference is non-African American data from Kelly A *et al. J Clin Endocrinol Metab* 2014;99:2104–12

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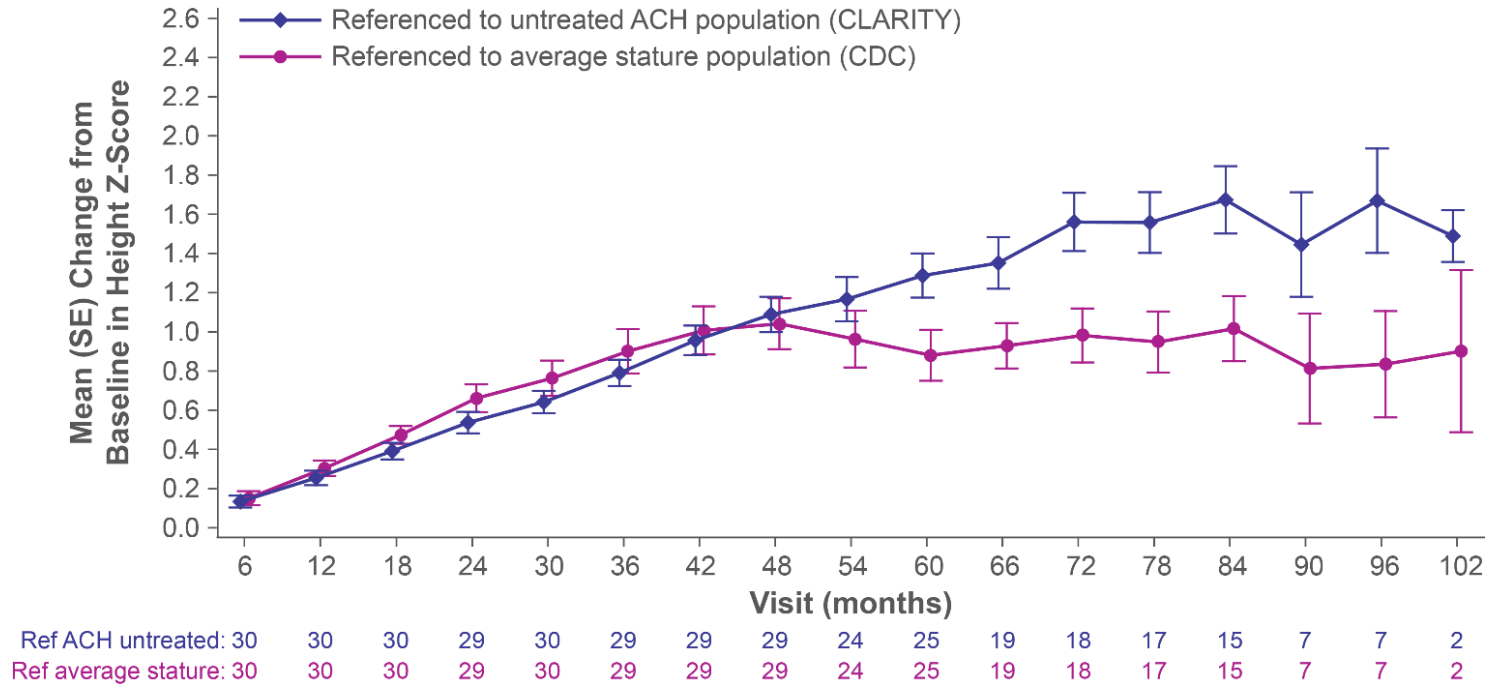
Height Z-score increased over time



- Additional height gain of 11.03 cm (95% CI [8.62, 13.45]) in 17 subjects treated with 15 µg/kg or 30 µg/kg vosoritide for 7 years versus untreated age- and sex-matched ACH controls

ACH, achondroplasia; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLARITY, achondroplasia natural history study; SE, standard error
Z-Scores were derived using age-sex specific reference data (means and standard deviations) from CLARITY (Hoover-Fong J *et al. Orphanet J Rare Dis* 2021;16:522)

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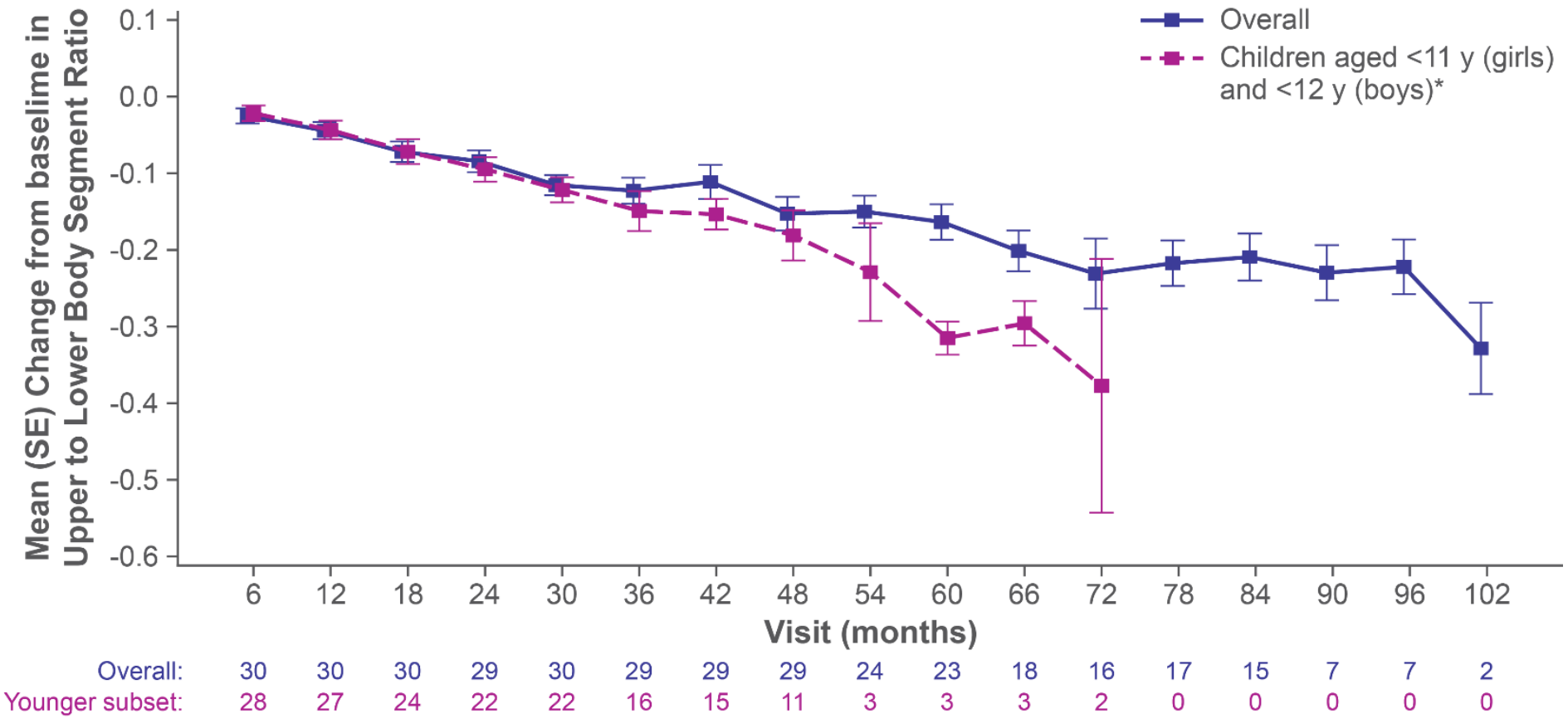
Upper to lower body segment ratios continued to decrease over time



*Assessments beyond these ages are excluded from analysis given any treatment is unlikely to impact proportionality
SE, standard error

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Conclusions

- Vosoritide continued to be well-tolerated, with no evidence of accelerated skeletal maturation or serious adverse events attributable to study drug over 7 years of treatment
- Vosoritide treatment was consistently associated with higher AGVs in males and females with ACH aged 6–17 years compared with age-matched untreated children with ACH. Mean AGVs of treated children are comparable to that of average stature children prior to puberty but are maintained over a longer duration. There is no evidence of a pubertal growth spurt in children with ACH (treated and untreated).
- Durability of treatment effect is also reflected in improvements in height Z-scores over time
- Upper to lower body segment ratios continued to improve over time, with changes particularly marked in the subset of children aged <11 years (girls)/<12 years (boys) in whom there may be more opportunity to impact this parameter

ACH, achondroplasia; AGVs, annualized growth velocities

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