Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 4 years: Update from phase 3 extension study

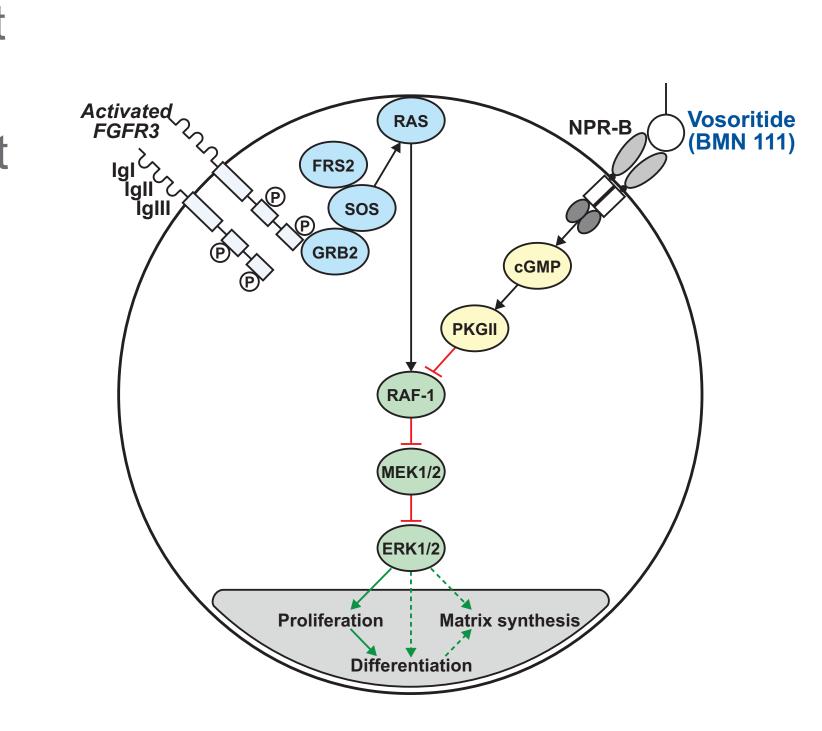
Savarirayan R¹, Tofts L², Irving M³, Wilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch F⁸, Carroll RS⁹, Polgreen LE¹⁰, Mohnike K¹¹, Vilcox WR⁴, Bacino CA⁵, Hoover-Fong JE⁶, Harmatz P⁷, Rutsch RS¹⁰, White KK¹⁰, White K Leiva-Gea A²¹, Mochizuki H²², Tajima A²², Basel D²³, Fisheleva E²⁴, Low A²⁵, Lawrinson S²⁴, Day J²⁴

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Background

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 naturallyoccurring CNP engineered to resist degradation and increase the half-life⁵



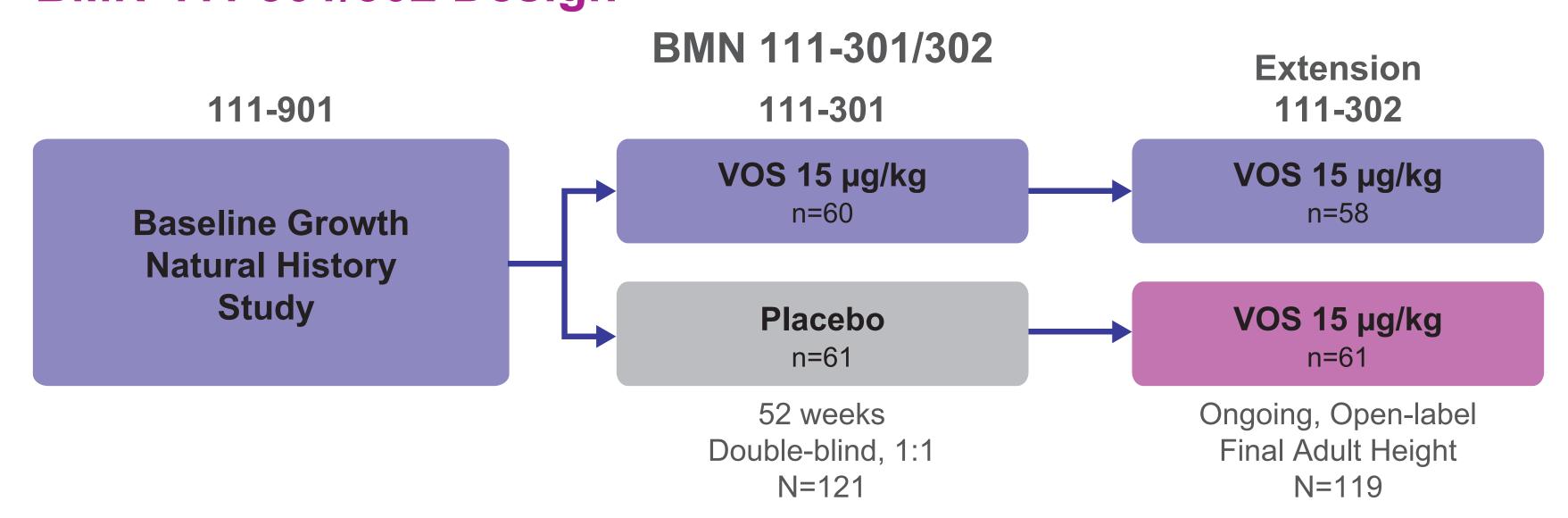
Increase in growth was demonstrated with vosoritide in clinical trials in ACH

- 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 annualized growth velocity (AGV)⁶
- 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 to placebo⁷; AGV improvement sustained after 2 years of vosoritide treatment in extension study (BMN 111-302)8
- In children with ACH 0–5 years of age, improvement in height Z-score was seen with vosoritide compared to placebo after 52 weeks (111-206)9
- 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

Design and Methods

Key Objectives: Evaluate the long-term safety, tolerability, and efficacy (linear growth, proportionality) of daily subcutaneous injections of vosoritide in children with ACH

BMN-111 301/302 Design



Key Eligibility Criteria

- Age 5 to <18 years old at screening
- ACH, documented by clinical grounds and confirmed by genetic testing
- Stratified capped enrollment ≤20% Tanner >I

Primary Efficacy Endpoint: Annualized Growth Velocity (AGV)

Secondary Efficacy Endpoints: Height Z-score; Upper to Lower Body segment ratio

Analyses methods

- All on treatment data for all participants (n=119) by data cut off February 25, 2023
- Efficacy
- 12 month interval AGV by age intervals referenced to untreated AGV and average stature AGV¹⁰
- Height Z-score using reference ranges in the untreated ACH population (CLARITY¹¹)

- A comparative analysis was conducted for all participants still on treatment with 3 years follow up (N=111) versus a matched untreated control. This was a cross-sectional analysis whereby the untreated participants were matched to each of the participants in the vosoritide arm at baseline (N=690) and at the 3 year timepoint (N=520) by age (±1 month) and sex. To adjust for baseline differences, the difference at baseline was subtracted from the difference determined at 3 years

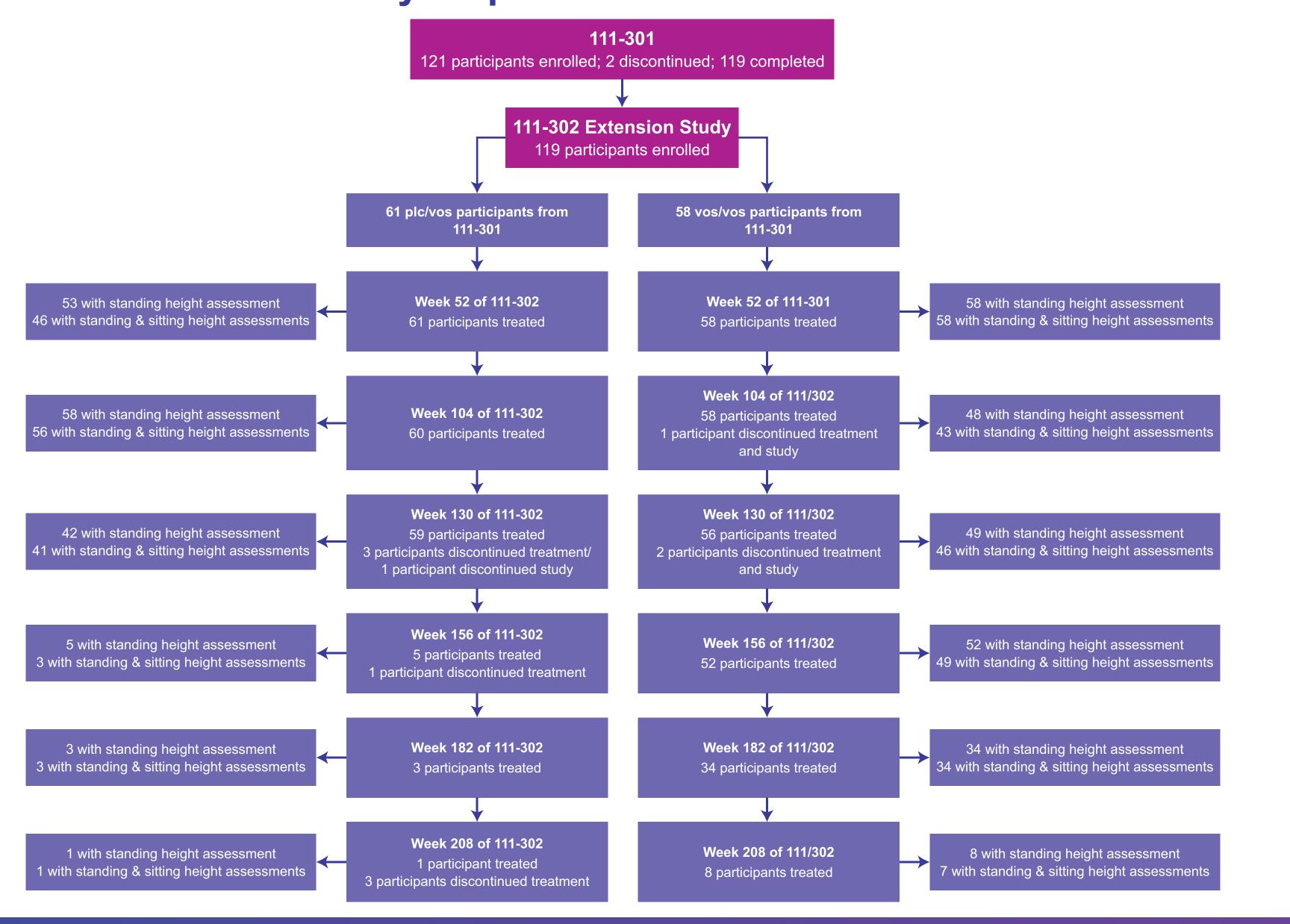
- Upper to lower body segment ratio
- Sensitivity summary provided which only includes assessments at <11 years (females) and <12 years (males)
- Overall safety profile
- Bone age/Chronological age over time

Results

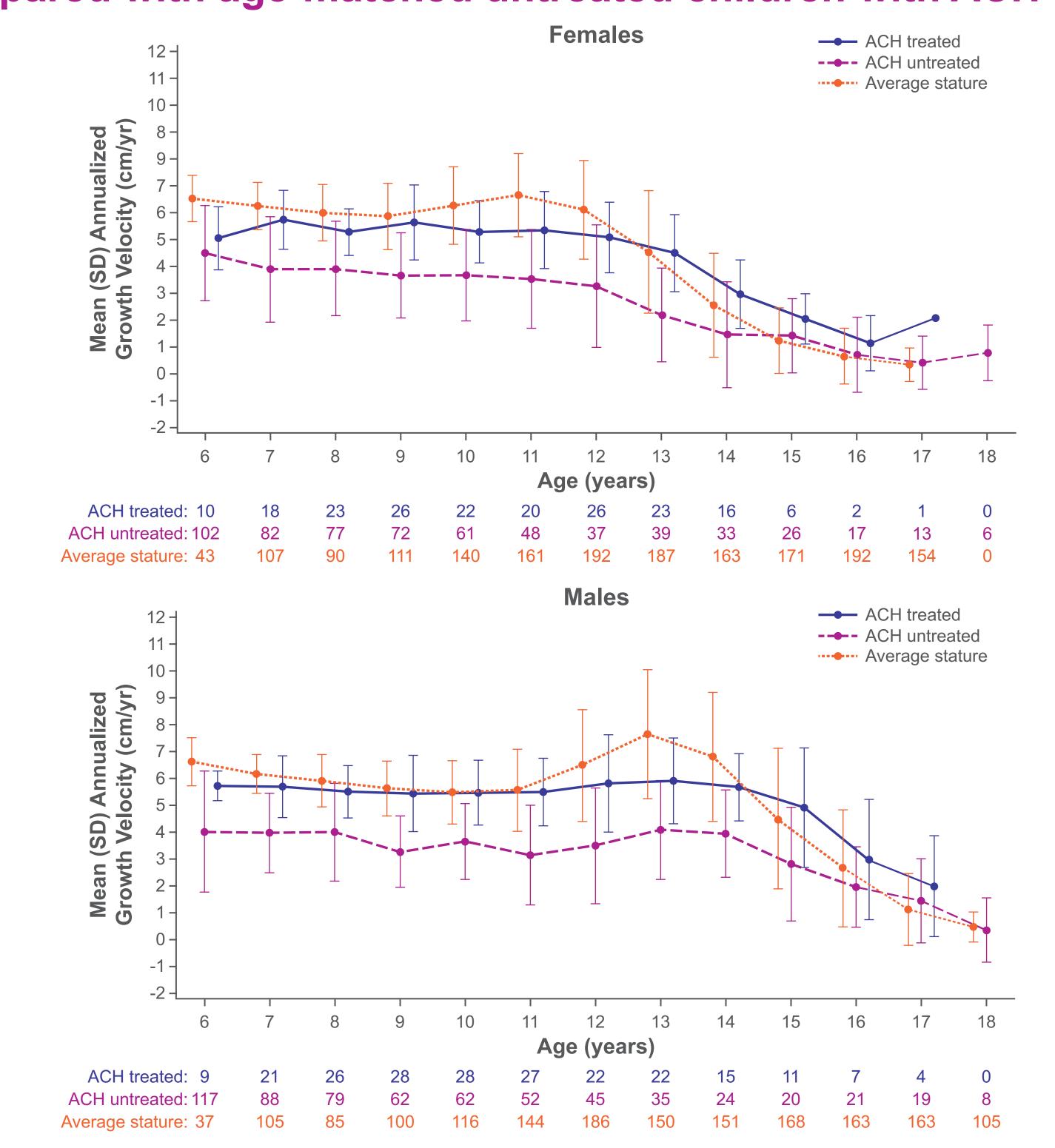
Demographics of BMN 111-301/302 study population (at the first day of vosoritide)

| | 301/302 (N=119) | |
|-------------------------------|--------------------|--|
| Age at Day 1 of treatment (y) | | |
| Mean (SD) | 7.50 (0.95) | |
| Min, Max | 5.8, 8.7 | |
| Age subgroups (%) | | |
| ≥ 5 to < 8 years | 4 (50.0) | |
| ≥ 8 to < 11 years | 4 (50.0) | |
| ≥ 11 to < 15 years | 0 | |
| ≥ 15 to < 18 years | 0 | |
| Sex (%) | | |
| Male | 3 (37.5) | |
| Female | 5 (62.5) | |

BMN 111-301/302 study disposition



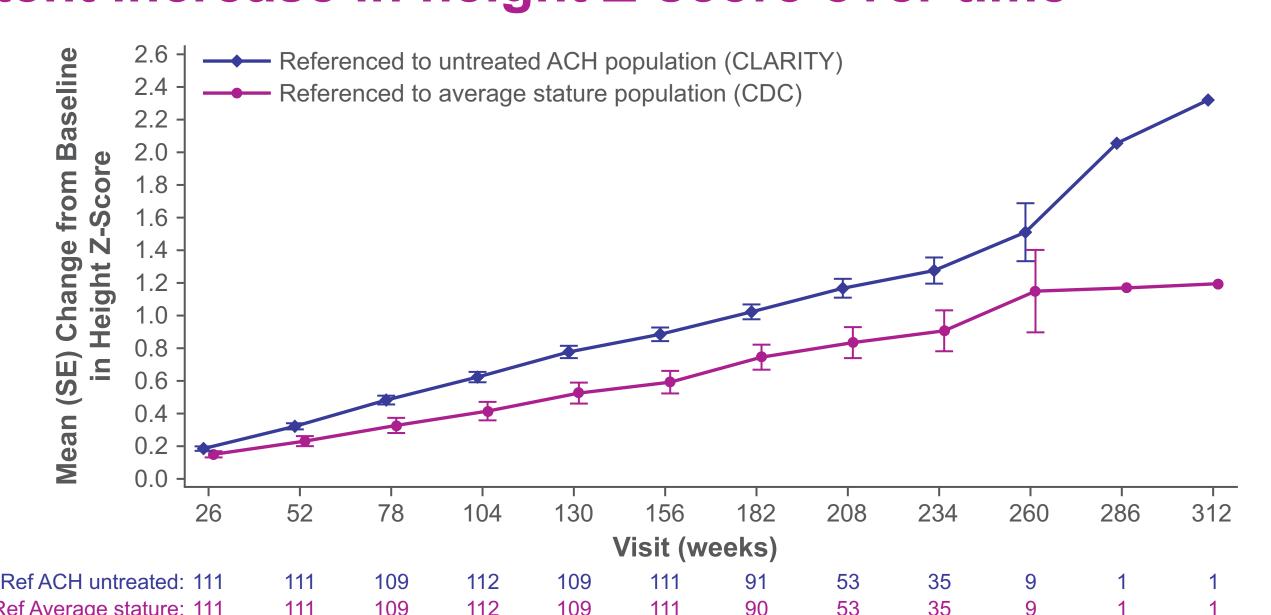
AGV on treatment with vosoritide is consistently higher compared with age-matched untreated children with ACH



ted reference derived from CLARITY (Hoover-Fong J et al. Orphanet J Rare Dis. 2021).

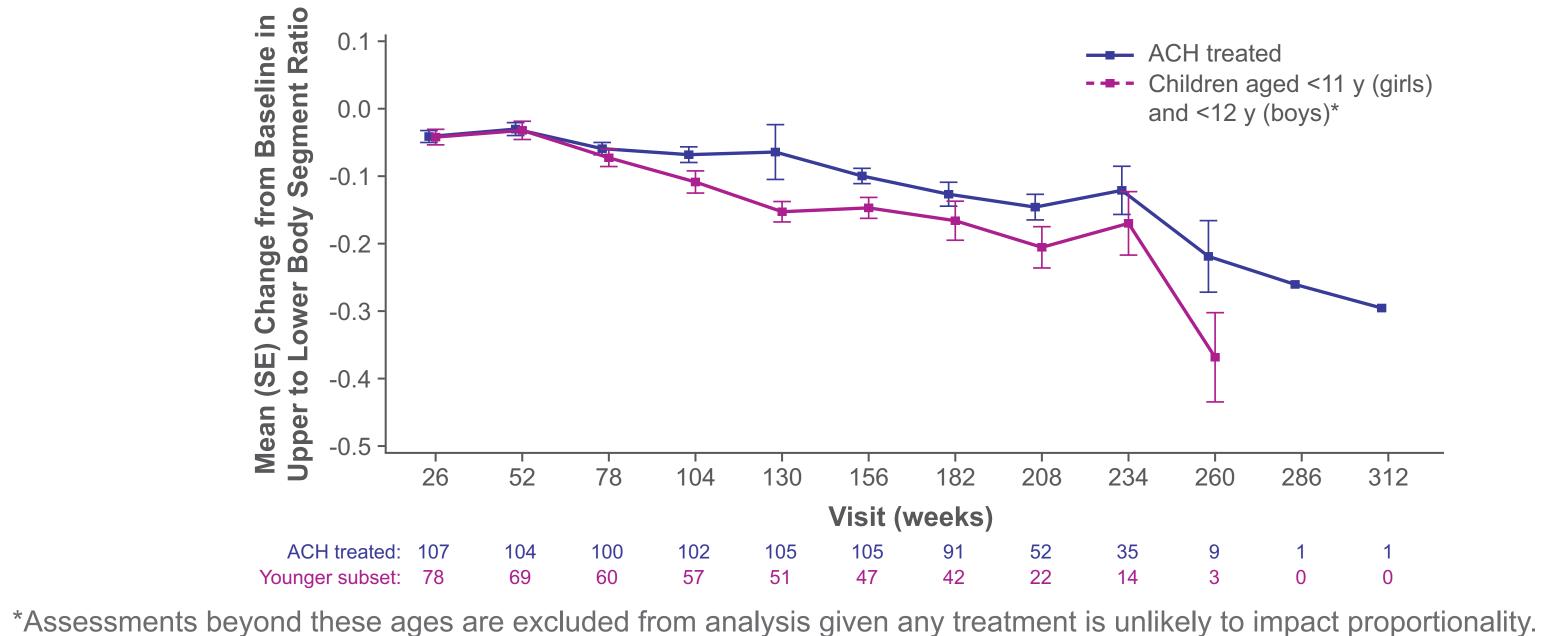
Mean (SD) of the mean differences in AGV between treated and untreated across integer ages 6-17 years is 1.46 (0.61) cm/yr in females and 1.73 (0.52) cm/yr in males

Consistent increase in height Z-score over time

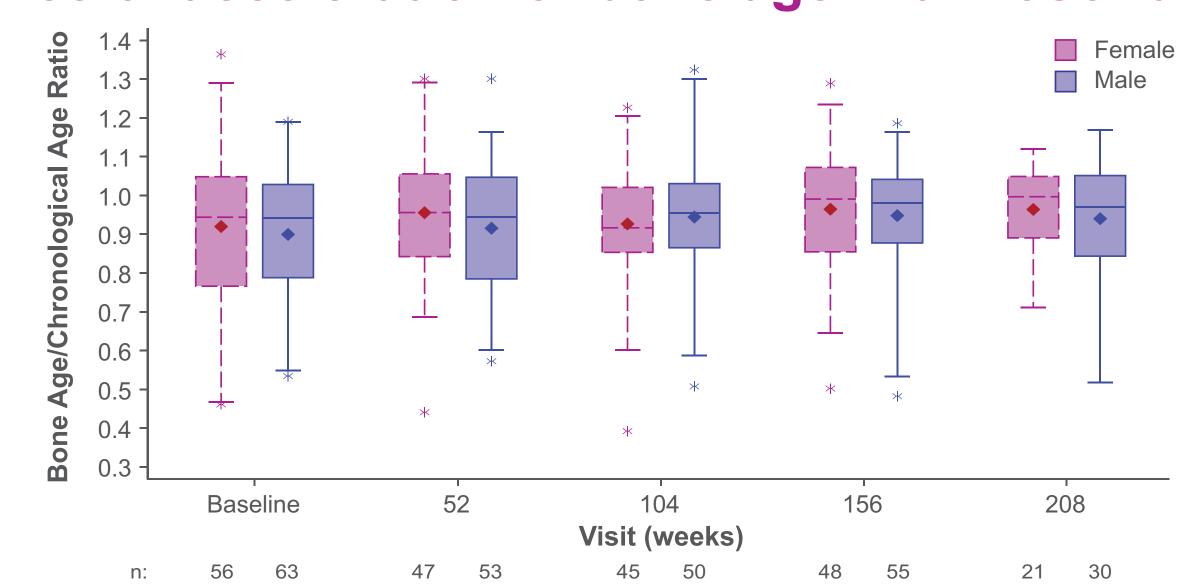


 Additional height gain of 5.75 cm (95% CI 4.93, 6.57) over 3 years for treated children vs. untreated ACH age- and sex-matched controls

Change in upper to lower body segment ratio in the overall population and in subset of children under 11(F)/12(M) years old



No evidence of acceleration of bone age with vosoritide



BMN 111-302 safety summary

| | Overall N=119; Exposure: 464.05 person-years | |
|--|---|---------------------------------|
| | Incidence n (%) | Event Rate (AEs/person-year) |
| AE, n (%) | 118 (99.2) | 1834 (3.95) |
| Treatment-related AEs | 37 (31.1) | 95 (0.20) |
| AEs leading to study drug discontinuation | 1 (0.8) | 1 (0.00) |
| SAEs | 22 (18.5) | 28 (0.06) |
| Treatment-related SAEs | 2 (1.7) | 3 (0.01) |
| SAEs leading to study drug discontinuation | 1 (0.8) | 1 (0.00) |
| AEs CTCAE Grades ≥3 | 20 (16.8) | 27 (0.06) |
| Event of interest | | |
| Injection site reactions CTCAE grade ≥2 | 2 (1.7) | 5 (0.01) |
| Avascular necrosis or osteonecrosis | 0 | 0 |
| Slipped capital femoral epiphysis | 0 | 0 |
| Fractures | 7 (5.9) | 8 (0.02) |

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; SAE, serious adverse event. Safety data for subjects in 302 is included for the entire duration of 301 and 302

- ISR continue to remain most common AE, majority remain grade 1 and self-limiting. No long term sequalae related to daily injections
- SAEs reported were generally attributed to underlying achondroplasia. Two participants had 3 SAE assessed as related to vosoritide: genu valgum and kyphoscoliosis in 1 participant, and femur fracture in 1 participant. The SAE of kyphoscoliosis led to discontinuation of vosoritide. No other participants discontinued drug due to AEs in 302; 2 subjects discontinued in 301
- Rates of fractures comparable to background rates in ACH. Participants continue treatment during healing without complications
- There were no deaths in the study

BioMarin, Ultragenyx, and Ascendis. The other authors declare no competing interests.

Conclusions

- Treatment with vosoritide was consistently associated with higher AGVs in males and females with ACH aged 6-17 years compared to 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 was further demonstrated by continuous increase in height Z-score
- Long term treatment with vosoritide was not associated with serious or treatmentlimiting adverse events. No pathological acceleration in bone age was seen

References

1. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet 2007; 370(9582):162-72. 2. Hoover-Fong J et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. Bone 2021; 146:115872. 3. Yasoda A et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. Nat Med 2004; 10(1):80-86. 4. Kreji P et al. Interaction of fibroblast growth factor and C-natriuretic peptide signaling in regulation of chondrocyte proliferation and extracellular matrix proliferation. J Cell Sci. 2005, 118(Pt 21):5089-100. 5. Lorget F et al. Evaluation of the Therapeutic Potential of a CNP Analog in a Fgfr3 Mouse Model Recapitulating Achondroplasia. Am J Hum Genet 2012; 91(6):1108-1114. 6. Savarirayan R et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. N Engl J Med 2019;381:25-35. 7. Savarirayan R et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet* 2020; 396:684-692. 8. Savarirayan R et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet Med 2021; 23, 2443–2447. 9. Savarirayan R et al. Vosoritide therapy in children with achondroplasia aged 3-59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Child Adolesc Health 2024; 8(1):40-50. 10. Kelly A et al. Age-based reference ranges for annual height velocity in US children. J Clin Endocrinol Metab. 2014;99(6):2104-12. 11. Hoover-Fong J et al. Growth in achondroplasia including stature, weight, weight-for-height and head circumference from CLARITY: achondroplasia natural history study-a multi-center retrospective cohort study of achondroplasia in the US. Orphanet J Rare Dis. 2021:16(1):522.

Disclosures

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