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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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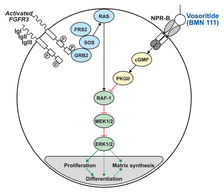
Background

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 naturally-occurring CNP engineered to resist degradation and increase the half-life[5]



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 placebo[7]; 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

BMN 111-202: A phase 2 open-label study in children with ACH

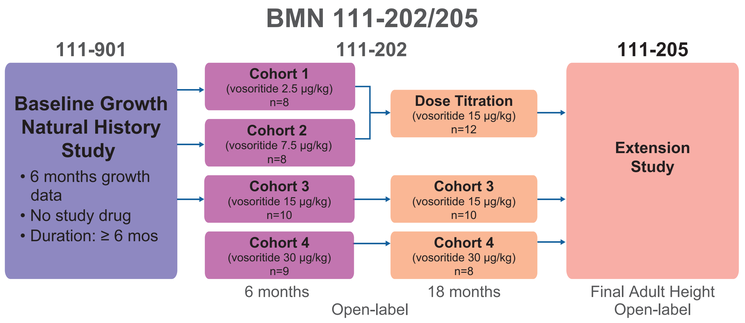
Primary Objective

- 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

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

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[10]
- Height Z-score using reference ranges in the untreated ACH population (CLARITY[11])
- 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 (girls) and <12 years (boys)

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.** Krejci 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

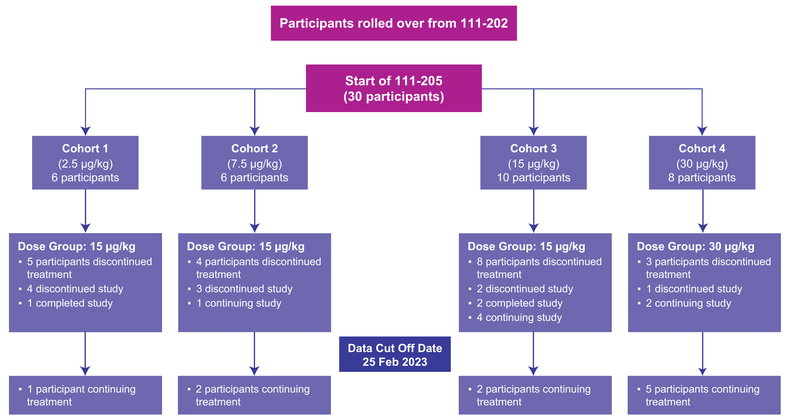
All authors are investigators in this clinical trial with the exception of SG, EF, AL and JD, who are employees of BioMarin. JHF has received consulting fees from BioMarin, Therachon AG, Innoskel, QED, Alexion and Ascendis, and grants from BioMarin and Alexion. RS has received consulting fees and grants from BioMarin. MI has received consulting fees from BioMarin. JC has received grants from BioMarin. LEP and VCD have received honoraria from BioMarin. CB and PH have received consulting fees, honoraria, and grants from BioMarin. Other authors declare no competing interests.

Results

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)

BMN 111-202/205 study disposition



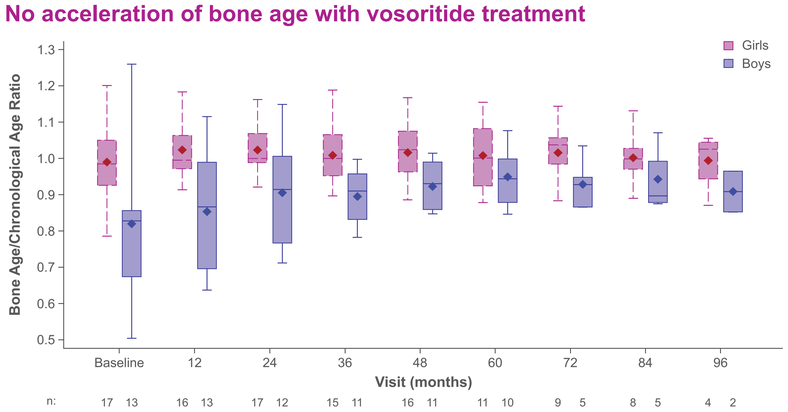
5 of those who discontinued reached FAH.

BMN 111-202 and 205 safety summary

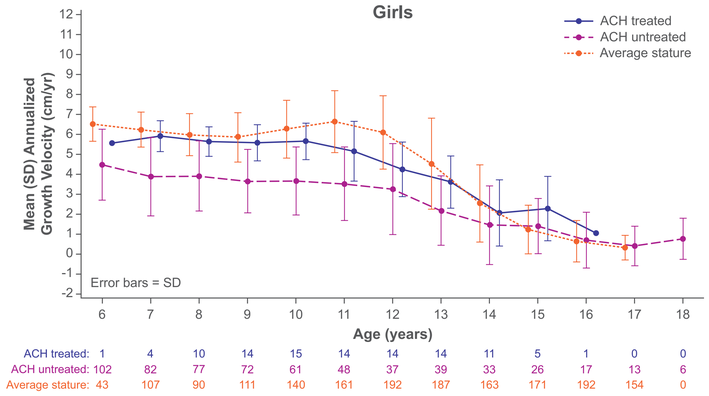
	Overall N=30; Exposure: 200.26 person-years	
	Incidence n (%)	Event Rate (AEs/person-year)
AE, n (%)	30 (100.0)	1215 (6.07)
Treatment-related AEs	24 (80.0)	81 (0.40)
AEs leading to study drug discontinuation	1 (3.3)	1 (0.00)
SAEs	8 (26.7)	9 (0.04)
AEs CTCAE Grades ≥3	8 (26.7)	10 (0.05)
Event of interest		
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)

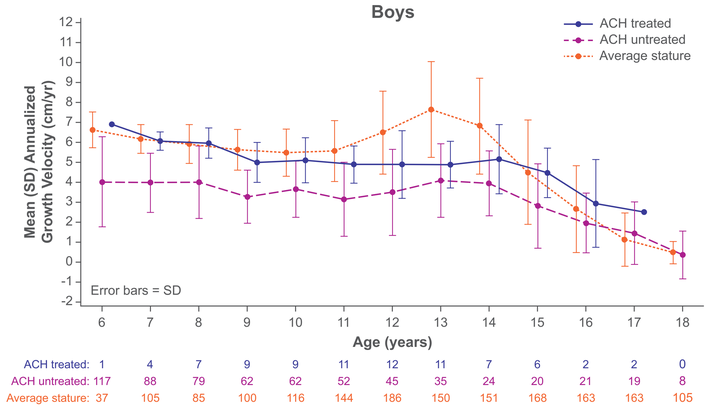
- ISRs continue to remain most common AE, majority remain grade 1 and self-limiting. No long-term sequelae related to daily injections
- None of the SAEs were treatment-related or led to discontinuation of study drug, and were generally attributed to underlying achondroplasia
- There were no deaths in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

No acceleration of bone age with vosoritide treatment



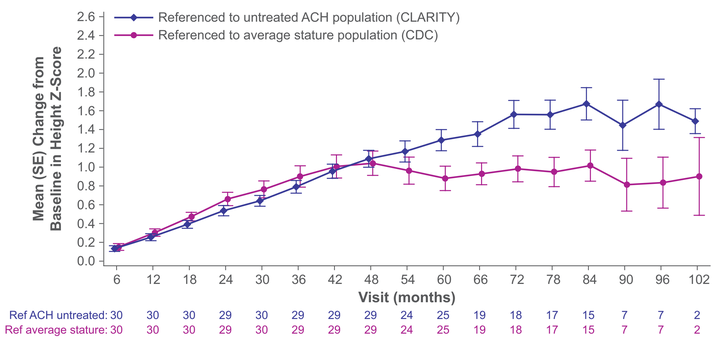
Mean 12-month interval AGV in children treated with vosoritide is higher compared to age-matched untreated children





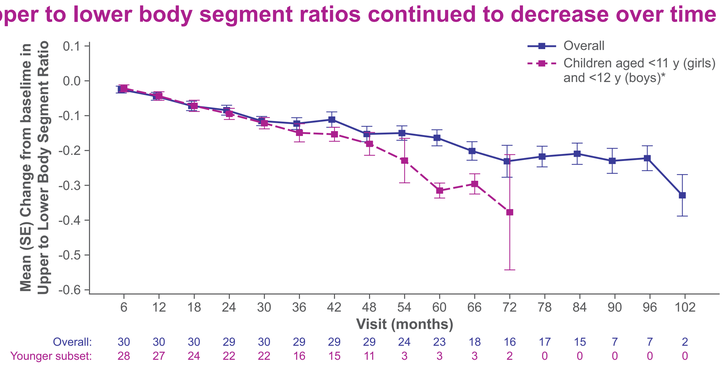
ACH untreated reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021). Average stature reference is non-African American data from Kelly A et al. *J Clin Endocrinol Metab.* 2014.

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

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.

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 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 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

Presented at the 2024 ACMG Annual Clinical Genetics Meeting: Mar 12–16, 2024, Toronto, ON, Canada