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

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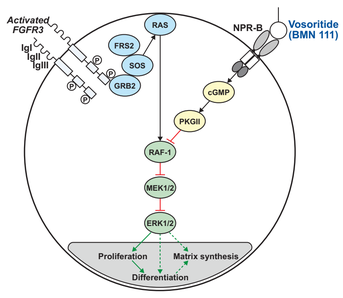
Background

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]



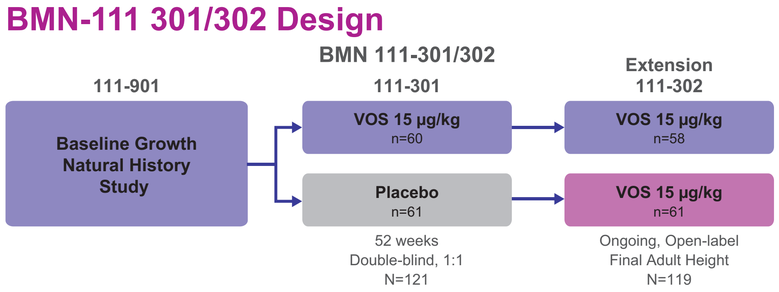
Increase in growth was demonstrated with vosoritide in clinical trials in ACH

- 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

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

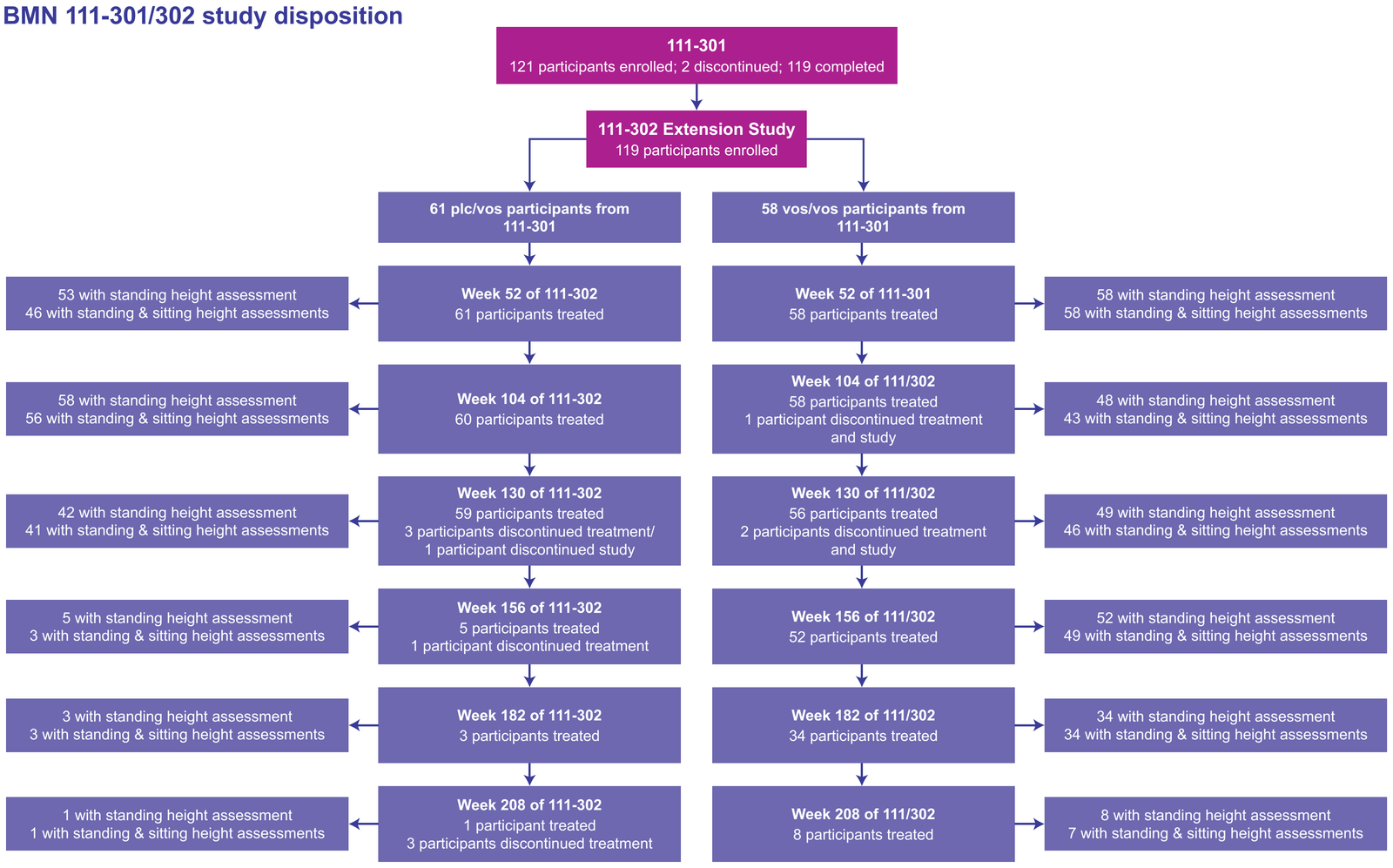
- All on treatment data for all participants (n=119) by data cut off February 25, 2023
- Efficacy
  - 12 month interval AGV by age intervals referenced to untreated AGV and average stature AGV[10]
  - Height Z-score using reference ranges in the untreated ACH population (CLARITY[11])
  - A comparative 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)
- Safety
  - Overall safety profile
  - Bone age/Chronological age over time

Results

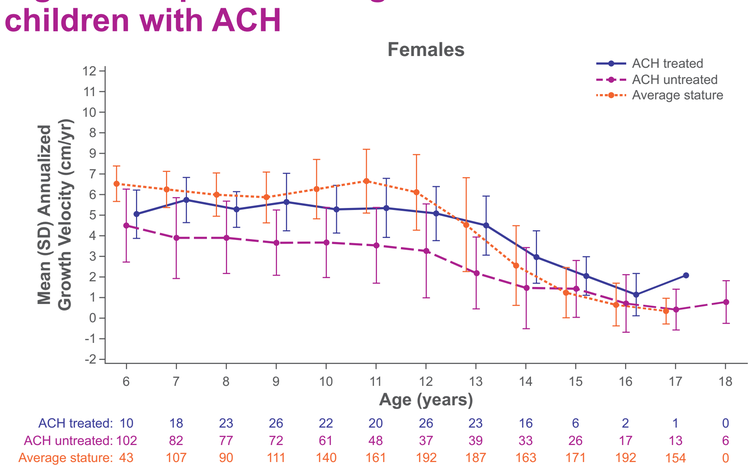
Demographics of BMN 111-301/302 study population (at the first day of vosoritide)

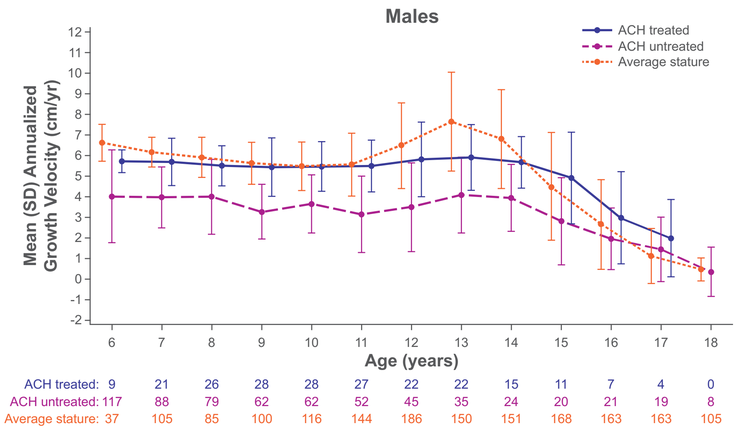
	301/302 (N=119)
Age at Day 1 of treatment (y)	
Mean (SD)	7.50 (0.95)
Min, Max	5.8, 8.7
Age subgroups (%)	
≥ 5 to < 8 years	4 (50.0)
≥ 8 to < 11 years	4 (50.0)
≥ 11 to < 15 years	0
≥ 15 to < 18 years	0
Sex (%)	
Male	3 (37.5)
Female	5 (62.5)

BMN 111-301/302 study disposition



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

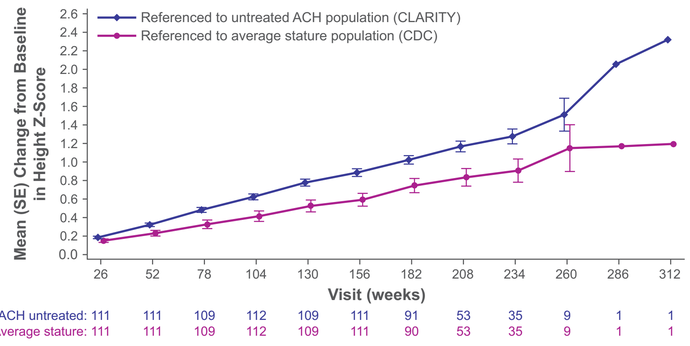




ACH untreated reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021).
Average stature reference is non-African American data from Kelly A et al. *J Clin Endocrinol Metab.* 2014.

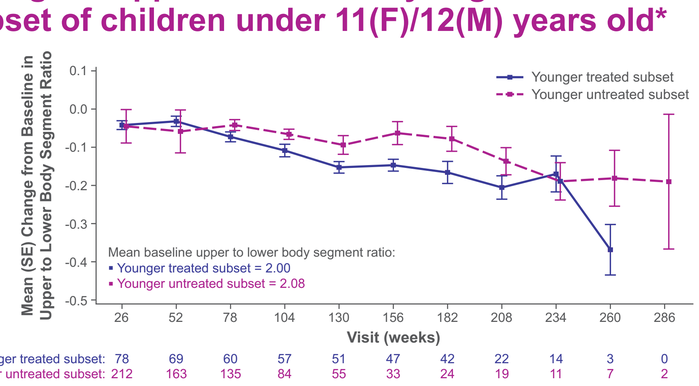
Mean (SD) of the mean differences in AGV between treated and untreated across integer ages 6–17 years is 1.46 (0.61) cm/yr in females and 1.73 (0.52) cm/yr in males

Consistent increase in height Z-score over time



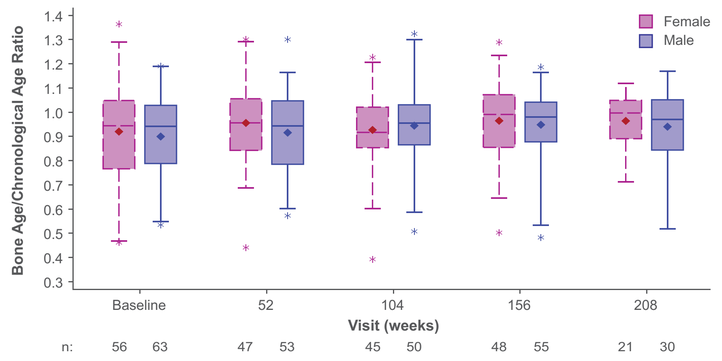
- Additional height gain of 5.75 cm (95% CI 4.93, 6.57) over 3 years for treated children vs. untreated ACH age- and sex-matched controls

Change in upper to lower body segment ratio in a subset of children under 11(F)/12(M) years old*



*Assessments beyond these ages are excluded from analysis given any treatment is unlikely to impact proportionality.

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

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 treatment-limiting adverse events. No pathological acceleration in bone age was seen

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Disclosures

All authors are investigators in this clinical trial except for EF, AL, SL and JD, who are employees of the funder (BioMarin). RS, LT, FR, and KM have received consulting fees and grants from BioMarin. MI and WW have received consulting fees from BioMarin. JC and DB have received grants from BioMarin. LP, PA and RC have received honoraria from BioMarin. CB and PH have received consulting fees, honoraria and grants from BioMarin. JHF has received consulting fees from BioMarin, Therachon AG, Innoskel, QED, Alexion and Ascendis, and grants from BioMarin and Alexion. KW has received consulting fees from BioMarin and Sanofi/Genzyme, and grants from BioMarin, Ultragenyx, and Ascendis. The other authors declare no competing interests.

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