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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

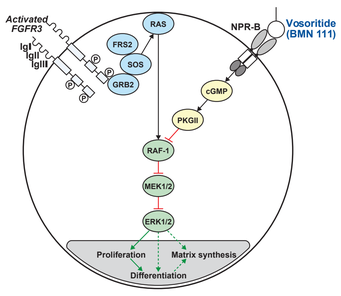
Savarirayan R[1], Tofts L[2], Irving M[3], Wilcox WR[4], Bacino CA5, Hoover-Fong JE6, Harmatz P[7], Rutsch F[8], Carroll RS[9], Polgreen LE[10], Mohnike K[11], Charrow J[12], Prada C[12], Hoernschemeyer D[13], Ozono K[14], Kubota T[14], Alanay Y[15], Arundel P[16], Kotani Y[17], Yasui N[17], White KK[18], Brandstetter S[19], Saal HM[20], Leiva-Gea A[21], Mochizuki H[22], Tajima A[22], Basel D[23], Fisheleva E[24], Low A[25], Lawrinson S[24], Day J[24], Bolzan T[27]

[1]Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, Australia; [2]Kids Rehab, The Children's Hospital at Westmead, Westmead, Australia; [3]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK; [4]Emory University, Atlanta, GA, USA; [5]Baylor College of Medicine, Houston, TX, USA; [6]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [7]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA; [8]Department of General Pediatrics, Muenster University Children's Hospital, Münster, Germany; [9]Nemours Children's Hospital, Wilmington, DE, USA; [10]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, David Geffen School of Medicine – UCLA, Los Angeles, CA, USA; [11]Otto-von-Guericke Universität, Universitätskinderklinik, Magdeburg, Germany; [12]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, USA; [13]University of Missouri-Columbia, Columbia, MI, USA; [14]Osaka University Hospital, Osaka, Japan; [15]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [16]Sheffield Children's NHS Foundation Trust, Sheffield Children's Hospital, Sheffield, UK; [17]Tokushima University Hospital, Tokushima, Japan; [18]Colorado Children's Hospital, Aurora, CO USA; [19]Seattle Children's Hospital, Seattle, WA, USA; [20]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [21]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [22]Saitama Children's Hospital, Saitama, Japan; [23]Medical College of Wisconsin, Milwaukee, WI, USA; [24]BioMarin (U.K.) Limited, London, UK; [25]BioMarin Pharmaceutical Inc., Novato, CA, USA, [27]BioMarin Farmacêutica do Brasil LTDA, São Paulo, Brasil

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]

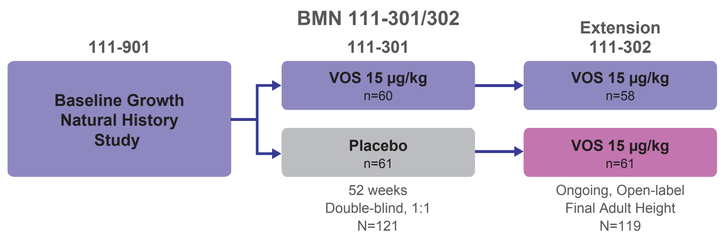
Increase in growth was demonstrated with vosoritide in clinical trials in ACH

- 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

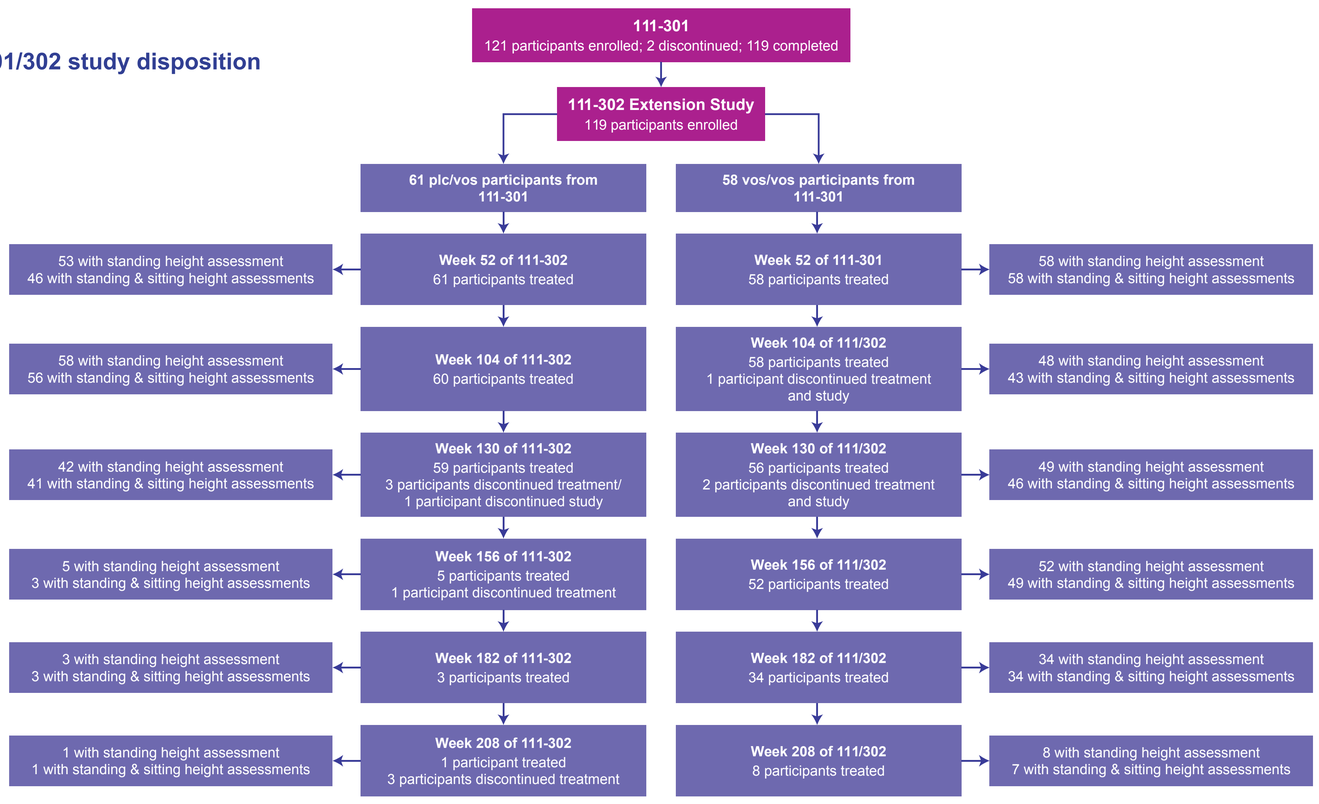
- All on treatment data for all participants (n=119) by data cut off February 25, 2023
- Efficacy
  - 12 month interval AGV by age intervals referenced to untreated AGV and average stature AGV[10]
  - Height Z-score using reference ranges in the untreated ACH population (CLARITY[11])
  - A comparative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

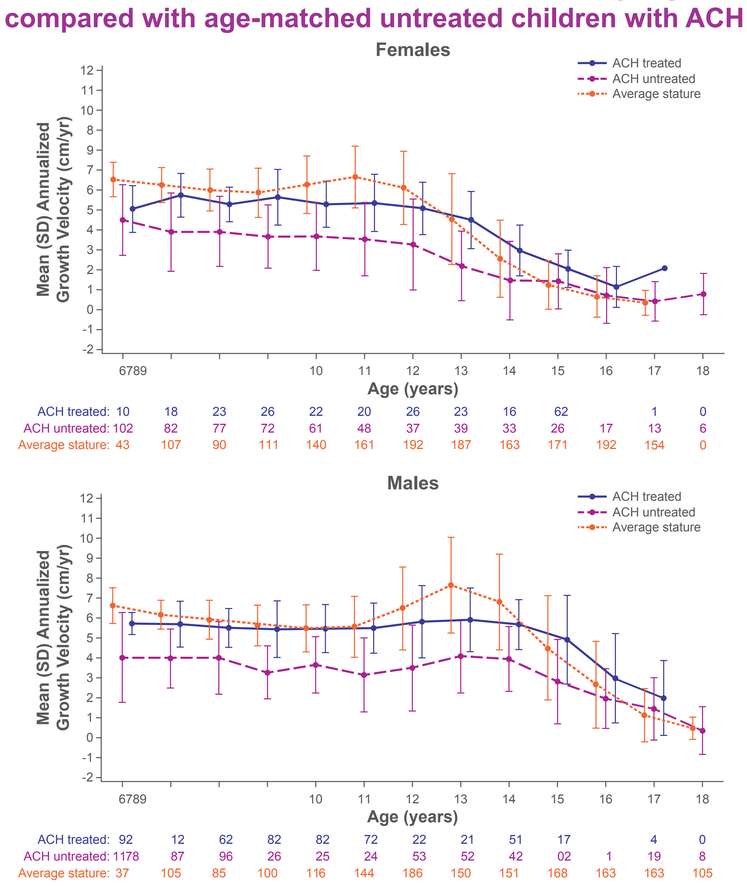
Demographics of BMN 111-301/302 study population (at the first day of vosoritide)

	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)
Female5	(62.5)

BMN 111-301/302 study disposition



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



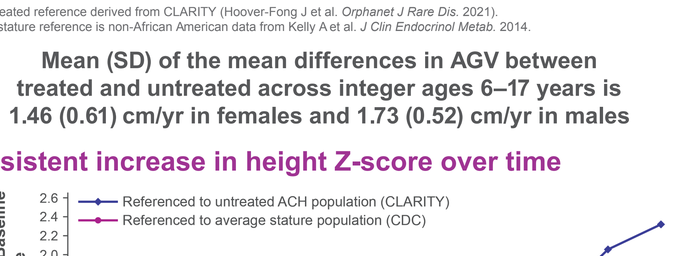
ACH untreated reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021).
Average stature reference is non-African American data from Kelly A et al. *J Clin Endocrinol Metab.* 2014.

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

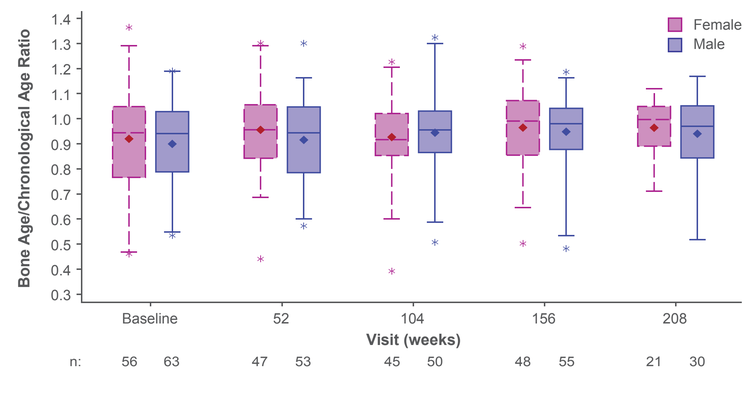
- Additional height gain of 5.75 cm (95% CI 4.93, 6.57) over 3 years for treated children vs. untreated ACH age- and sex-matched controls

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

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