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Persistent and stable growth promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: results from an ongoing Phase 3 extension study

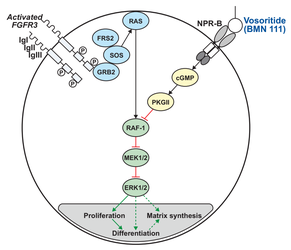
Hoover-Fong J[1], Savarirayan R[2], Tofts L[3], Irving M[4], Wilcox WR[5], Bacino CA[6], Font RU[7], Harmatz P[8], Rutsch F[9], Bober MB[10], Polgreen LE[11], Ginebreda I[12], Mohnike K[13], Charrow J[14], Hoernschemeyer D[15], Ozono K[16], Alanay Y[17], Arundel P[18], Kagami S[19], Yasui N[19], White K[20], Saal HM[21], Leiva-Gea A[22], Luna-González F[23], Mochizuki H[23], Basel D[24], Porco DM[25], Jayaram K[25], Fisheleva E[26], Lawrinson S[26], Day J[26]

[1]Johns Hopkins University School of Medicine, Baltimore, USA; [2]Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, Australia; [3]Kids Rehab, The Children's Hospital at Westmead, Westmead, Australia; [4]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, United Kingdom; [5]Emory University, Atlanta, USA; [6]Baylor College of Medicine, Houston, USA; [7]Hospital Sant Joan de Déu, Barcelona, Spain; [8]UCSF Benioff Children's Hospital Oakland, Oakland, USA; [9]Department of General Pediatrics, Muenster University Children's Hospital, Münster, Germany; [10]Nemours/Alfred I. du Pont Hospital for Children, Wilmington, USA; [11]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, USA; [12]Hospital Universitario Quirón Dexeus, Barcelona, Spain; [13]Otto-von-Guericke Universität, Universitätskinderklinik, Magdeburg, Germany; [14]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, USA; [15]University of Missouri-Columbia, Columbia, USA; [16]Osaka University Hospital, Osaka, Japan; [17]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [18]Sheffield Children's NHS Foundation Trust, Sheffield Children's Hospital, Sheffield, United Kingdom; [19]Tokushima University Hospital, Tokushima, Japan; [20]Colorado Children's Hospital, Aurora, USA; [21]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, USA; [22]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [23]Unidad de Cirugía Ortopédica y Traumatología del Complejo Hospitalario de Málaga, Málaga, Spain; [24]Saitama Children's Hospital, Saitama, Japan; [25]Medical College of Wisconsin, Milwaukee, USA; [26]BioMarin Pharmaceutical Inc., Novato, USA; [27]BioMarin (U.K.) Limited, London, United Kingdom

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]

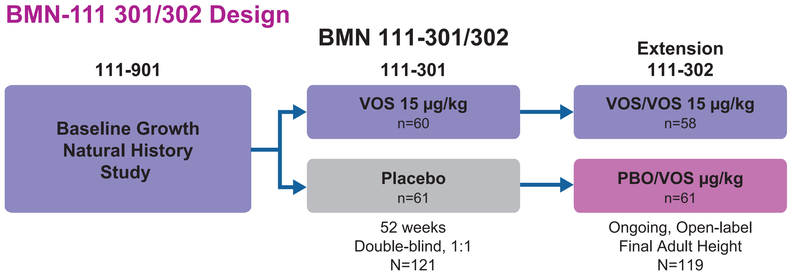
Increase in growth was demonstrated with vosoritide in clinical trials in ACH

- 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]
- Vosoritide is approved for use in children with ACH and open epiphyses aged ≥5 years in the USA; ≥2 years in Brazil, EU and Australia and from birth in Japan

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 subjects (n=119) by data cut off February 25, 2022
- Efficacy
  - 12 month interval AGV by age intervals referenced to untreated AGV and average stature AGV[9]
  - Height Z-score using reference ranges in the untreated ACH population (CLARITY[10])
  - 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

Study 111-301 – Importance of longer term follow-up in growth disorders: Lessons from early data

	Baseline AGV Category (cm/y)					
	Placebo ≤3.5 (n=19)	Vosoritide ≤3.5 (n=18)	Placebo >3.5 to ≤4.5 (n=18)	Vosoritide >3.5 to ≤4.5 (n=14)	Placebo >4.5 (n=24)	Vosoritide >4.5 (n=26)
Baseline AGV Mean (SD)	2.64 (0.67)	2.55 (1.06)	4.03 (0.30)	3.96 (0.24)	5.20 (0.58)	5.61 (0.74)
Change from Baseline in AGV at Week 26 Mean (SD)	+1.63 (1.96)	+4.06 (2.37)	+0.16 (1.18)	+1.74 (0.91)	-1.37 (1.47)	+0.05 (1.60)
Change from Baseline in AGV at Week 52 Mean (SD)	+1.34 (1.77)	+3.07 (1.14)	+0.06 (0.97)	+1.83 (1.05)	-1.40 (1.11)	+0.03 (1.07)

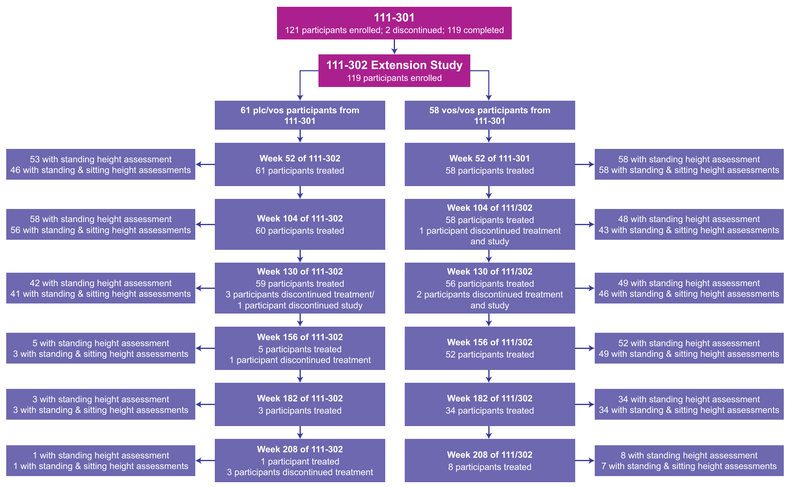
- Lower baseline AGV results in a higher magnitude change from baseline for both vosoritide- and placebo-treated patients, especially during the first 6 months of treatment
- A comprehensive understanding of the treatment effect requires evaluation over a longer duration of time and proper comparison with untreated patients

Results

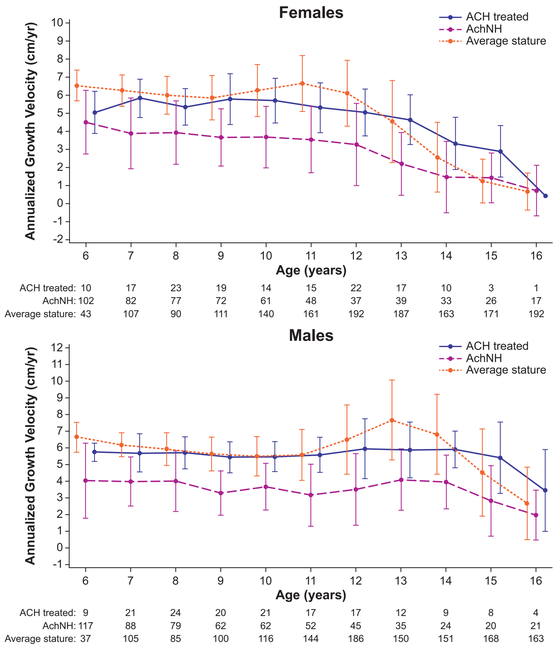
Demographics of BMN 111-301/302 study population (at the first day of vosoritide)

	301/302 (N=119)
Age at Day 1 of treatment (y)	
Mean (SD)	9.18 (2.60)
Min, Max	5.1, 15.9
Age subgroups (%)	
≥ 5 to < 8 years	46 (38.7)
≥ 8 to < 11 years	37 (31.1)
≥ 11 to < 15 years	35 (29.4)
≥ 15 to < 18 years	1 (0.8)
Sex (%)	
Male	63 (52.9)
Female	56 (47.1)

BMN 111-301/302 study disposition



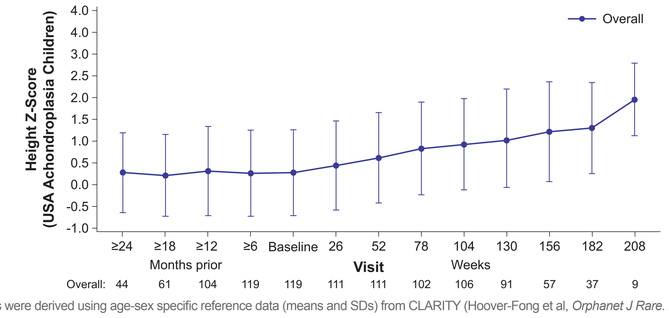
AGV on treatment with vosoritide is consistently higher compared to age-matched untreated children



- Females – The difference in the mean integer AGVs across each integer age (6-16 yrs) between treated and untreated = 1.55 (0.78) cm/y
- Males – The difference in the mean integer AGVs across each integer age (6-16 yrs) between treated and untreated = 1.98 (0.37) cm/y

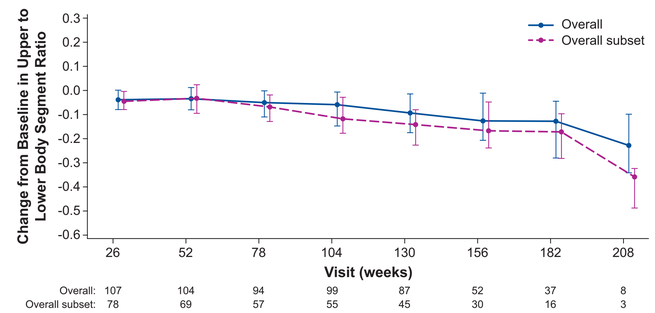
AchNH (Ach Natural History) reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021).
Average stature reference is non-African American data from Kelly A et al. *J Clin Endocrinol Metab.* 2014.

Consistent increase in height Z-score (referenced to untreated ACH population) over time



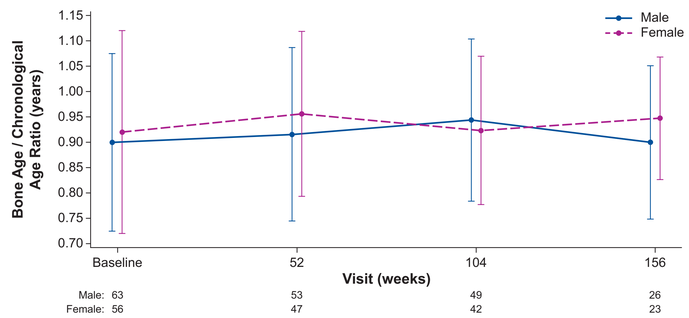
Z-Scores were derived using age-sex specific reference data (means and SDs) from CLARITY (Hoover-Fong et al, *Orphanet J Rare. Dis.* 2021).

Change in upper to lower body segment ratio (median, Q1Q3) in the overall population and in subset of children under 11(f)/12(m) years old



Proportionality changes up to ~age 11 (girls) / 12 (boys). Older children excluded from analysis given any treatment is unlikely to impact proportionality beyond this point.

No evidence of acceleration of bone age with vosoritide



BMN 111-301/302 safety summary

	Overall (N=119)	
	Incidence n (%)[a]	Event Rate (AEs/person-year)[b]
Any AE	116 (97.5)	1469 (4.05)
AEs leading to study drug discontinuation	0	0
AEs leading to study discontinuation	0	0
Any SAE	14 (11.8)	18 (0.05)
Any treatment-related AE	36 (30.3)	93 (0.26)
Treatment-related SAEs	1 (0.8)	1 (0.00)
Any AE of CTCAE Grade ≥ 3	12 (10.1)	16 (0.04)
Participants who died	0	0
Events 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	5 (4.2)	6 (0.02)

AE, adverse event; EOI, event of interest; CTCAE, common terminology criteria for adverse events; SAE, serious adverse event

Favourable safety profile with continuous treatment

- No subjects discontinued drug due to an AE and no subjects died
- 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.
  - One treatment related SAE of genu valgum, attributed to growth and underlying joint damage due to ACH
- Rate of fractures comparable to background rate in ACH and literature
  - Subjects continue treatment during healing without complications

Conclusions

- Treatment with vosoritide consistently associated with higher growth velocities in males and females aged 6-16 years with ACH with average increase of 1.55 cm/y (F) and 1.98 cm/y (M)
  - No obvious pubertal growth spurt observed
- Durability of treatment effect after > 3 years on treatment has been demonstrated by continuous increase in height Z-score referenced to untreated children with ACH
- Long term treatment with vosoritide was not associated with serious or treatment-limiting 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.** Kelly A et al. Age-based reference ranges for annual height velocity in US children. *J Clin Endocrinol Metab.* 2014;99(6):2104-12. **10.** 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.

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