P4

Persistence of growth promoting effects in children with achondroplasia over seven years: Update from phase II extension study with vosoritide

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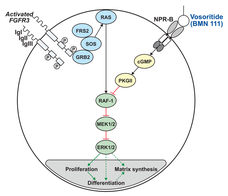
Background

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]
- 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

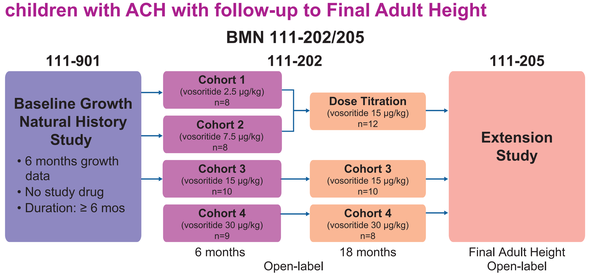
BMN 111-202: A phase 2 open-label study in children with ACH

- 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, 2022

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[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 (girls) and <12 years (boys)

Natural History Study for comparison with vosoritide data – CLARITY (A Multicentre Retrospective study of Achondroplasia in the US)[10]

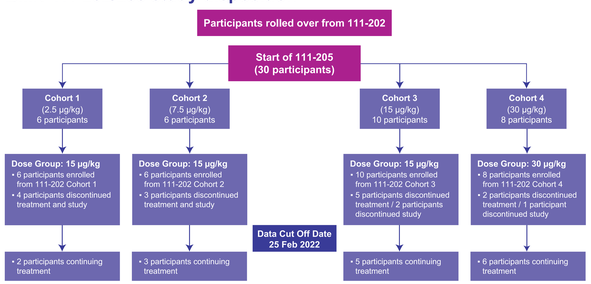
- 1374 participants with 14123 height assessments included, across 4 skeletal dysplasia centres in the US
  - Molecular or clinical diagnosis of ACH
  - All available medical records for past and present clinical patients
  - Cross sectional and longitudinal patient level height data
- Age Range
  - Spanning the entire pediatric age-range with some data beyond Final Adult Height
  - High data density in pediatric growth period
- Study Quality
  - Four large US skeletal dysplasia centres with expertise in ACH and anthropometry
  - RedCAP database with audit trail
  - Data collected to a common protocol using standardized methodologies

Results

Demographics of BMN-202 study population (at the first day of vosoritide)

	202 C1 (N=6)	202 C2 (N=6)	202 C3 (n=10)	202 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 (8.16)
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

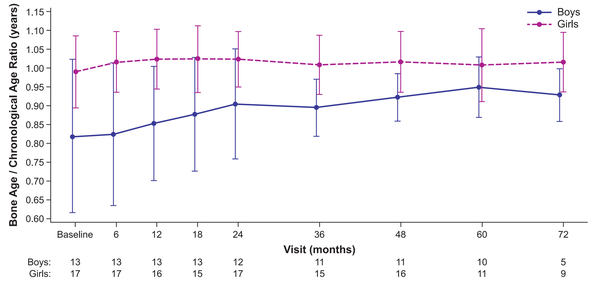


5 of those who discontinued reached FAH.

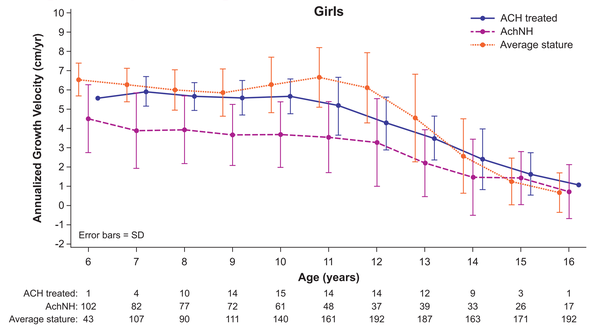
BMN 111-202 and 205 safety summary

	Overall (N=30)
Total treatment exposure (person-years)	186.23
AEs, n (rate per person-year)	1175 (6.31)
AEs leading to study drug discontinuation	1 (0.01)
SAEs, n (rate per person-year)	7 (0.04)
SAEs leading to study drug discontinuation	0
Treatment-related SAEs	0

No acceleration of bone age with vosoritide treatment

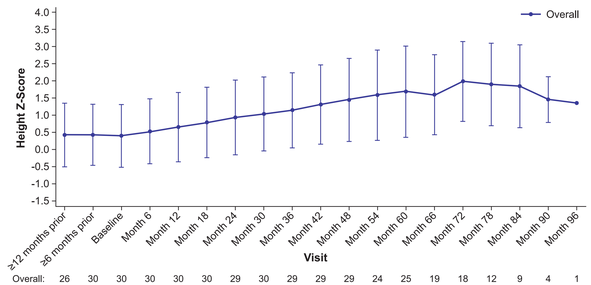


Mean 12-month interval AGV in children treated with vosoritide is higher compared to age-matched untreated children



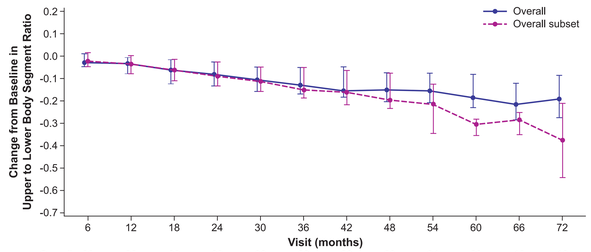
AchNH (Ach Natural History) reference derived from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis.* 2021). Average stature reference is non-African American data from Kelly A et al. *J Clin Endocrinol Metab.* 2014.

Height Z-score (referenced to untreated ACH population) increased 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).

Upper to lower body segment ratios continued to decrease over time



Overall subset: 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.

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 maintained its positive effect on growth: across integer age groups AGV exceeded that seen in a reference population and approached that seen in an average stature population. This was 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

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.** Krejі 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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