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Vosoritide for Children with Achondroplasia: Growth Velocity and Pubertal Milestones

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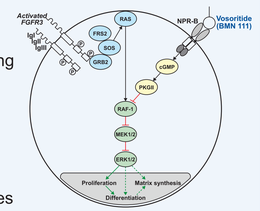
Introduction

Achondroplasia Disease Overview

- Achondroplasia is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- Achondroplasia is caused by a pathogenic variant in *FGFR3* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth[1]
- Complications of achondroplasia impact multiple systems and occur throughout the lifespan[3]
  - Complications include cervicomedullary compression, sleep apnea, genu varum, spinal stenosis

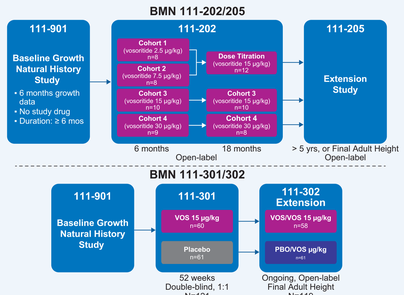
Vosoritide: Targeted therapy for achondroplasia

- CNP down-regulates aberrant FGFR3 signaling in chondrocytes by inhibiting the MAPK-ERK pathway[4,5]
- Vosoritide is based on naturally-occurring CNP engineered to resist degradation and increase the half-life[6]
- An open-label, 52-week phase 2 trial (BMN 111-202) and its extension study (BMN 111-205) in children with achondroplasia showed that vosoritide treatment resulted in sustained increases in annualized growth velocity (AGV)[7]



- A phase 3 randomized placebo-controlled trial (BMN 111-301) in children with achondroplasia showed treatment with vosoritide resulted in a statistically significant improvement in AGV after 52 weeks compared to placebo[8]; AGV improvement sustained after 2 years of vosoritide treatment in extension study (BMN 111-302)[9]
- Vosoritide is approved for use in children with achondroplasia aged ≥5 years in the US and ≥2 years in the EU until closure of epiphyses

Studies in achondroplasia with vosoritide



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 achondroplasia.

BMN 111-202/205 Key Eligibility Criteria

- Age 5 to 14 years old at screening
- Achondroplasia, documented by clinical grounds and confirmed by genetic testing

BMN 111-301/302 Key Eligibility Criteria

- Age 5 to <18 years old at screening
- Achondroplasia, documented by clinical grounds and confirmed by genetic testing
- Stratified capped enrollment ≤ 20% Tanner I

Objective

- To report on the pubertal growth velocity and milestones in children with achondroplasia treated with vosoritide

Methods

- Data for all subjects in studies 111-202/205 and 111-301/302 whilst receiving 15µg/kg or 30µg/kg doses were considered (n=149)
- Tanner staging was determined by trained physicians
- Mean standing heights, derived from duplicate or triplicate measures taken at each 6-month visit, were used to assess growth and calculate AGV when the subjects progress to the next Tanner stage

Tanner Stage-Age

- Age at which subjects transitioned to next Tanner stage was defined as the mid-time point between two consecutive visits where Tanner stage progressed

Tanner Stage-AGV

- AGV is derived over a 6 month interval
- AGV for Tanner stages II-V is growth velocity at the time the Tanner stage is first recorded
- AGV for Tanner stage I is derived over the last recorded 6 months for this Tanner stage

Results

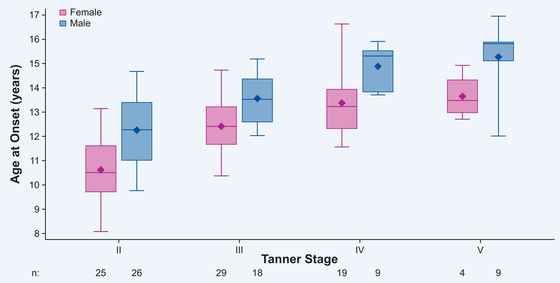
Demographics of enrolled population — by study (at the first day of vosoritide)

	202 C1 (N=6)	202 C2 (N=6)	202 C3 (n=10)	202 C4 (N=8)	301/302 (N=119)
Age at Day 1 of treatment (y)					
	8.07 (1.43)	8.49 (2.37)	8.54 (1.54)	7.50 (8.16)	9.18 (2.60)
	6.9, 10.9	6.0, 10.8	6.3, 11.1	5.8, 8.7	5.1, 15.9
Age subgroups (%)					
≥5 to <8 years	4 (66.7)	3 (50.0)	4 (40.0)	4 (50.0)	46 (38.7)
≥8 to <11 years	2 (33.3)	3 (50.0)	5 (50.0)	4 (50.0)	37 (31.1)
≥11 to <15 years	0	0	1 (10.0)	0	35 (29.4)
≥15 to <18 years	0	0	0	0	1 (0.8)
Sex (%)					
Male	2 (33.3)	4 (66.7)	4 (40.0)	3 (37.5)	63 (52.9)
Female	101 (66.7)	2 (33.3)	6 (60.0)	5 (62.5)	56 (47.1)

Duration on treatment at the time of analyses

Duration	202/205 C1 15 µg/kg	202/205 C2 15 µg/kg	202/205 C3 15 µg/kg	202/205 C4 30 µg/kg	301/302 15 µg/kg
N	6	6	10	8	119
Mean (SD), months	57.33 (16.79)	67.97 (8.12)	70.90 (14.86)	66.69 (2.18)	30.00 (7.22)
Median	59.32	69.54	79.31	66.05	28.75
Min, Max	33.6, 75.0	54.9, 74.8	33.7, 80.4	63.7, 70.9	20.0, 54.6

Tanner Stage by age in children treated with vosoritide in studies 202/205 and 301/302



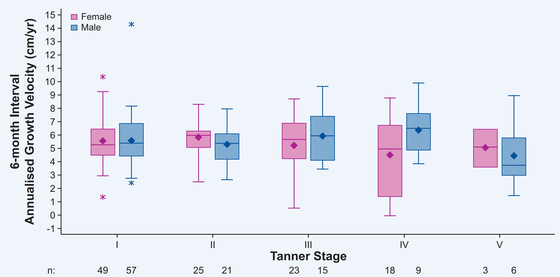
Whiskers indicate min and max.

Age at entry of Tanner Stage of pubertal development in reference to average stature Non-Hispanic White population in USA (NHANES data)[10]

	Average stature white females	Females with achondroplasia treated with VOS	Average stature white males	Males with achondroplasia treated with VOS
Age at Tanner Stage II*, mean (SE)	11.05 (0.18)	10.45 (1.27)	11.08 (0.18)	12.25 (1.34)
Age at Tanner Stage III*, mean (SE)	12.80 (0.19)	12.36 (1.13)	12.55 (0.29)	13.50 (0.98)
Age at Tanner Stage IV* mean (SE)	15.16 (0.32)	13.06 (1.42)	15.29 (0.19)	14.79 (0.88)
Age at Tanner Stage V*, mean (SE)	16.25 (0.18)	13.65 (0.95)**	16.64 (0.15)	15.27 (1.39)**

*Breast development in Girls; Genitalia development in Boys. **Small sample at Tanner V F=4; M=9

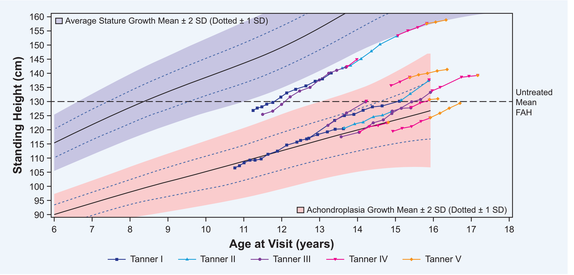
AGV over 6 month intervals by Tanner Stage in children treated with vosoritide in studies 202/205 and 301/302



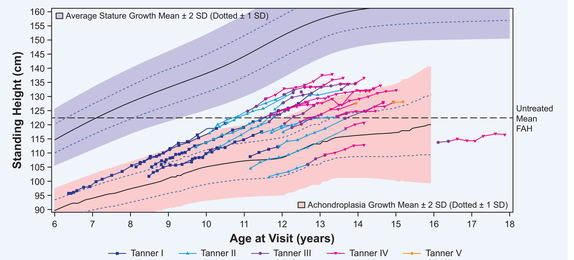
Whiskers indicate 2.5th and 97.5th percentiles. Of note, the peak growth velocity in the general US population is 6.65 and 7.66 cm/year for females and males, respectively[11].

- Mean peak growth velocity on vosoritide was 5.81 and 6.36 cm/year for females and males, respectively
- Mean peak growth velocity occurred at Tanner II for females and Tanner IV for males

Individual plots of height for males on vosoritide treatment who reached Tanner IV*



Individual plots of height for females on vosoritide treatment who reached Tanner IV*



*Achondroplasia growth data derived from Hoover-Fong JE et al[12]. Average stature growth data derived from Centers for Disease Control and Prevention (CDC) reference values:National Center for Health Statistics[13].

Conclusions

- More data are required to determine if the timing of pubertal development in children with achondroplasia treated with vosoritide follows that of average stature children, as well as to understand how the timing compares to that of untreated children with achondroplasia
- Data suggest presence of a growth spurt at Tanner stage II for females and Tanner stage IV for males, but small numbers do not allow a definitive conclusion
- Monitoring of these subjects will continue until subjects reach their adult height in order to help us better understand the potential impact of vosoritide on pubertal development and final height

References

1. Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet* 2007; 370(9582):162-72. **2.** Foreman P et al. Birth prevalence of achondroplasia: A systematic literature review and meta-analysis. *Am J Med Genet A*. 2020;182:2297-2316. **3.** Hoover-Fong J et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. *Bone* 2021; 146:115872. **4.** Yasoda A et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med* 2004; 10(1):80-86. **5.** Krecji 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. **6.** 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. **7.** Savarirayan R et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med* 2019;381:25-35. **8.** 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. **9.** 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 (2021). **10.** Sun SS et al, National estimates of the timing of sexual maturation and racial differences among US children. *Pediatrics*. 2002;110(5):911-9. **11.** Kelley A et al. Age-based reference ranges for annual height velocity in US children. *J Clin Endocrinol Metab.* 2014;99(6):2104-12. **12.** Hoover-Fong JE 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. **13.** Centers for Disease Control and Prevention (CDC) reference values:National Center for Health Statistics, https://www.cdc.gov/growthcharts/index.htm.

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