A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia

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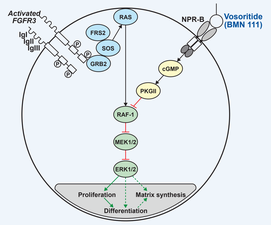
Introduction

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]

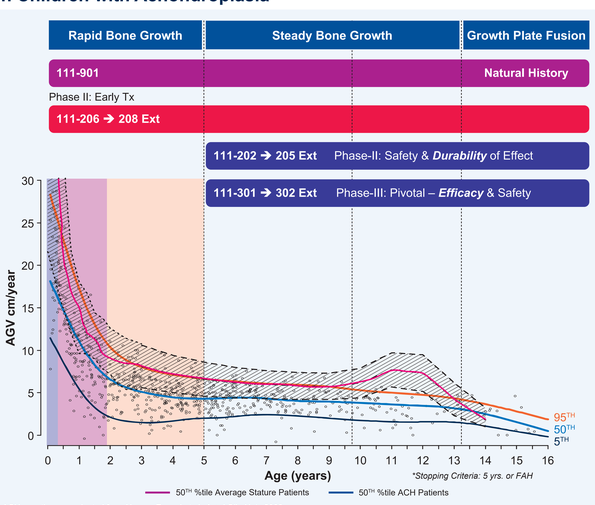
Vosoritide: Targeted therapy for achondroplasia

- 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

Vosoritide Clinical Development Program in Context of Growth Pattern in Children with Achondroplasia



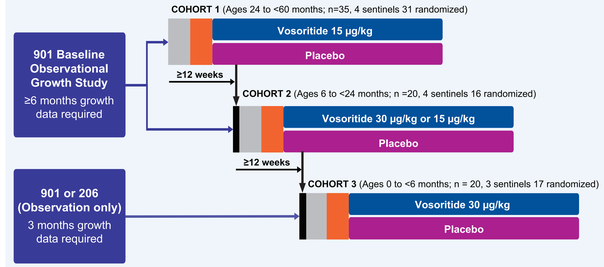
ACH growth curve adapted from Hoover-Fong J et al. *Am J Clin Nutr.* 2008.

Methods

BMN 111-206 Study in Children with Achondroplasia aged 0 to 5 years

- Primary Objectives:
  - Evaluate safety and tolerability of vosoritide in children with achondroplasia
  - Evaluate the effect of vosoritide on change from baseline in height/body length Z-scores
- Secondary Objectives include Height, AGV, Upper to Lower body segment ratio

BMN 111-206 Study Design



Sentinel subjects: lead in Phase for safety, PK, with potential dose adjustment for each cohort

Sentinel subjects complete 8 days dosing in all cohorts. If stopping criteria are not met, remaining subjects in each cohort enrol and randomise to treatment with vosoritide or placebo (1:1 ratio) and receive daily dosing for 52 weeks

DMC reviews safety and available PK data for the sentinels, prior to enrolment in the next cohort. Upon approval by the DMC, the next younger cohort opens and the sentinel subjects are enrolled

Statistical Methods

- Randomization by Age Strata
  - Cohort 1: age stratification ≥ 24 to < 36, ≥ 36 to < 60 months
  - Cohort 2: age stratification ≥ 6 to < 15, ≥ 15 to < 24 months
  - Cohort 3: age stratification 0 to < 6 months
- Population Analyzed
  - All enrolled (randomized + sentinels)
- Comparative Analysis vs Placebo using ANCOVA model
  - Baseline covariates: Sex, Age, Age Stratum, AGV + baseline for each endpoint
  - No formal statistical hypothesis for efficacy comparisons and no type 1 error control
  - ITT principle (imputation of missing data, n=2)
- Pre-specified Subgroup Analyses by cohort

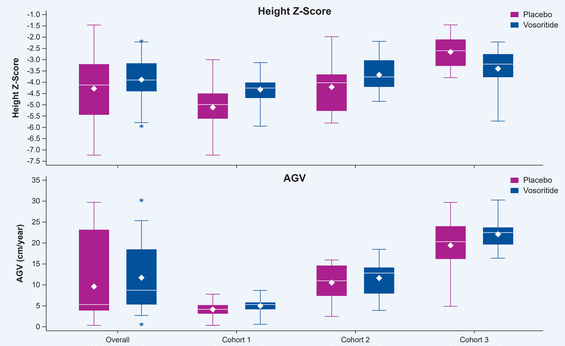
Results

Subject Demographics

	Overall		Cohort 1		Cohort 2		Cohort 3	
	Vosoritide (N=43)	Placebo (N=32)	Vosoritide (N=19)	Placebo (N=16)	Vosoritide (N=12)	Placebo (N=8)	Vosoritide (N=12)	Placebo (N=8)
Age on Day 1, Months								
Mean (SD)	24.47 (17.66)	27.82 (19.25)	41.48 (11.07)	44.33 (11.54)	16.59 (5.11)	16.87 (6.21)	5.41 (0.53)	5.76 (0.59)
Median	21.82	26.43	40.02	40.39	16.54	18.56	5.62	5.91
Q1, Q3	5.91, 36.86	7.67, 40.39	30.19, 51.06	34.55, 56.36	11.63, 21.42	10.46, 22.16	4.86, 5.86	5.72, 5.95
Sex, n (%)								
Male	25 (58.1)	13 (40.6)	10 (52.6)	7 (43.8)	9 (75.0)	5 (62.5)	6 (50.0)	1 (12.5)
Female	18 (41.9)	19 (59.4)	9 (47.4)	9 (56.3)	3 (25.0)	3 (37.5)	6 (50.0)	7 (87.5)
Race*								
White	29 (67.4)	25 (78.1)	12 (63.2)	13 (81.3)	9 (75.0)	6 (75.0)	8 (66.7)	6 (75.0)
Asian	11 (25.6)	6 (18.8)	6 (31.6)	3 (18.8)	2 (16.7)	1 (12.5)	3 (25.0)	2 (25.0)
Japanese	4 (9.3)	4 (12.5)	2 (10.5)	3 (18.8)	1 (8.3)	1 (12.5)	1 (8.3)	0

*Not all race categories are presented here.

Baseline Growth Characteristics



Box plot displays the 25th and 75th percentiles (box edges), the median (midline), the mean (diamond symbol) and the 2.5th and 97.5th percentiles (whiskers). Asterisks represent outliers.

Safety

Overview of SAEs

	Sentinel (N=11)	Vosoritide (N=32)	Placebo (N=32)	All Vosoritide Treated (N=43)
Subjects with any SAE, n (%)	**0**	**3 (9.4)**	**6 (18.8)**	**3 (7.0)**
Infections and infestations, n (%)	0	2 (6.3)	3 (9.4)	2 (4.7)
Pneumonia	0	1 (3.1)	0	1 (2.3)
Respiratory syncytial virus bronchiolitis	0	1 (3.1)	0	1 (2.3)
Gastroenteritis	0	0	1 (3.1)	0
Otitis media	0	0	1 (3.1)	0
Parainfluenzae virus infection	0	0	1 (3.1)	0
General disorders and administration site conditions, n (%)	0	1 (3.1)	0	1 (2.3)
Sudden death (respiratory arrest)	0	1 (3.1)	0	1 (2.3)
Investigations, n (%)	0	1 (3.1)	0	1 (2.3)
Oxygen saturation decreased	0	1 (3.1)	0	1 (2.3)
Gastrointestinal disorders, n (%)	0	0	1 (3.1)	0
Vomiting	0	0	1 (3.1)	0
Injury, poisoning and procedural complications, n (%)	0	0	1 (3.1)	0
Skull fracture	0	0	1 (3.1)	0
Nervous system disorders, n (%)	0	0	1 (3.1)	0
Petit mal epilepsy	0	0	1 (3.1)	0
Psychiatric disorders, n (%)	0	0	1 (3.1)	0
Autism spectrum disorder	0	0	1 (3.1)	0
Respiratory Disorders n (%)	0	0	1 (3.1)	0
Respiratory distress	0	0	1 (3.1)	0

SAE: Serious Adverse Events.

Incidence of TEAE by SOC by Cohort

SOC	Cohort 1		Cohort 2		Cohort 3	
	Vosoritide (N=19)	Placebo (N=16)	Vosoritide (N=12)	Placebo (N=8)	Vosoritide (N=12)	Placebo (N=8)
General disorders and administration site conditions	16 (84.2)	10 (62.5)	10 (83.3)	6 (75.0)	12 (100.0)	8 (100.0)
Infections and infestations	17 (89.5)	15 (93.8)	11 (91.7)	8 (100.0)	9 (75.0)	7 (87.5)
Gastrointestinal disorders	11 (57.9)	12 (75.0)	6 (50.0)	7 (87.5)	8 (66.7)	7 (87.5)
Respiratory, thoracic and mediastinal disorders	13 (68.4)	8 (50.0)	5 (41.7)	5 (62.5)	7 (58.3)	6 (75.0)
Skin and subcutaneous tissue disorders	6 (31.6)	6 (37.5)	4 (33.3)	2 (25.0)	6 (50.0)	4 (50.0)
Injury, poisoning and procedural complications	10 (52.6)	7 (43.8)	3 (25.0)	2 (25.0)	1 (8.3)	2 (25.0)
Ear and labyrinth disorders	4 (21.1)	7 (43.8)	3 (25.0)	4 (50.0)	4 (33.3)	1 (12.5)
Musculoskeletal and connective tissue disorders	5 (26.3)	3 (18.8)	1 (8.3)	1 (12.5)	2 (16.7)	3 (37.5)
Immune system disorders	3 (15.8)	0	0	1 (12.5)	2 (16.7)	1 (12.5)
Investigations	2 (10.5)	2 (12.5)	1 (8.3)	1 (12.5)	1 (8.3)	0
Nervous system disorders	2 (10.5)	5 (31.3)	1 (8.3)	0	1 (8.3)	3 (37.5)
Psychiatric disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0
Vascular disorders	0	0	1 (8.3)	1 (12.5)	1 (8.3)	0
Blood and lymphatic system disorders	1 (5.3)	0	0	0	0	1 (12.5)
Eye disorders	1 (5.3)	0	0	0	0	0
Metabolism and nutrition disorders	0	2 (12.5)	0	0	1 (8.3)	1 (12.5)
Reproductive system and breast disorders	1 (5.3)	0	0	0	0	0
Cardiac disorders	0	1 (6.3)	0	0	0	0
Endocrine disorders	0	0	0	0	0	1 (12.5)

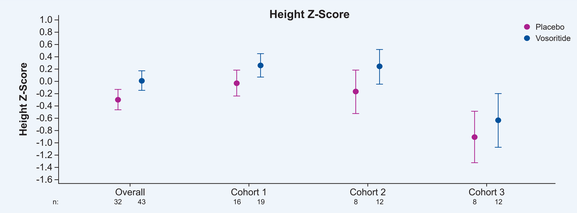
TEAE: Treatment Emergent Adverse Event; SOC: System Organ Class

Incidence of TEAE Reported with >5% Higher Frequency in Vosoritide vs Placebo

Preferred Term	Placebo (N=32)		Vosoritide (N=43)	
	Incidence n (%)	Events m (rate)	Incidence n (%)	Events m (rate)
Injection site reaction	13 (40.6)	154 (4.8)	34 (79.1)	3057 (71.5)
Injection site erythema	13 (40.6)	1738 (54.3)	33 (76.7)	5100 (119.4)
Injection site swelling	2 (6.3)	3 (0.1)	8 (18.6)	36 (0.8)
Injection site urticaria	1 (3.1)	1 (0.0)	6 (14.0)	22 (0.5)
Injection site induration	0	0	5 (11.6)	14 (0.3)
Viral Infection	4 (12.5)	8 (0.2)	8 (18.6)	28 (0.7)
Fall	3 (9.4)	5 (0.2)	7 (16.3)	9 (0.2)
Arthropod bite	2 (6.3)	2 (0.1)	6 (14.0)	7 (0.2)
Constipation	2 (6.3)	4 (0.1)	5 (11.6)	7(0.2)
Dermatitis Diaper	1 (3.1)	1 (0.0)	4 (9.3)	5 (0.1)
Lower respiratory tract infection	1 (3.1)	3(0.1)	4 (9.3)	4 (0.1)
Rhinitis	0	0	4 (9.3)	8 (0.2)
Sleep apnea syndrome	0	0	3 (7.0)	3 (0.1)
Viral upper respiratory tract infection	0	0	3 (7.0)	3 (0.1)
Epistaxis	0	0	3 (7.0)	3 (0.1)

Improvement in Growth with Vosoritide vs Placebo

- Vosoritide (n=43), compared to placebo (n=32):
  - Increased height Z-score by 0.30 SD (95% CI 0.07, 0.54)
  - Increased AGV by 0.92cm/year (95% CI 0.24, 1.59)
  - Did not significantly change upper-to-lower body segment ratio, which changed by -0.06 (95% CI -0.15, 0.03)
- Positive change in height Z-score in children treated with vosoritide across all cohorts



- Increased variability at youngest age group reflects rapidly changing growth pattern in young children

Conclusions

- Daily injections of vosoritide were well tolerated with no treatment limiting adverse events with the safety profile consistent with that in treated children over 5 years of age
- Most common adverse events observed were mild and self-limiting injection site reactions
  - No clinically relevant differences in safety profile of vosoritide between cohorts (doses)
- SAEs more frequent in Placebo group (18%) compared to Vosoritide-treated group (7%). All SAEs including fatal event in treatment group were unrelated to treatment
- In children with achondroplasia 0-5 years of age, improvement in height Z-score of + 0.30 (95%CI 0.07; 0.54) SDS was seen with vosoritide vs placebo after 52 weeks, and was consistent with improvement observed after one year treatment in children over 5 years of age[8]
- There was no significant change in body proportions

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).

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