#27

Growth-promoting effects of vosoritide in children with achondroplasia aged ≥10 years at treatment initiation: results from a phase 3 extension study

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Background

Vosoritide: targeted therapy for achondroplasia

- Achondroplasia (ACH) is the most common form of disproportionate short stature (approximately 1:25,000 live births)[1,2]
- ACH is caused by a pathogenic variant in *fibroblast growth factor receptor 3 (FGFR3)* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth and multiple complications[1,2]
- C-type natriuretic peptide (CNP) down-regulates aberrant FGFR3 signaling in chondrocytes by inhibiting the mitogen-activated protein kinase (MAPK)-extracellular-signal-regulated kinases 1 and 2 (ERK1/2) pathway (**Figure 1**)[3,4]
- Vosoritide, a potent stimulator of endochondral bone growth, is based on a naturally-occurring CNP engineered to resist degradation and increase the half-life.[5] It is approved for use in children with ACH and open epiphyses from birth in the USA, Japan, and Australia, aged ≥4 months in the European Union, and ≥6 months in Brazil

Figure 1. Vosoritide is a CNP pharmacologic analogue that inhibits FGFR3 downstream signaling

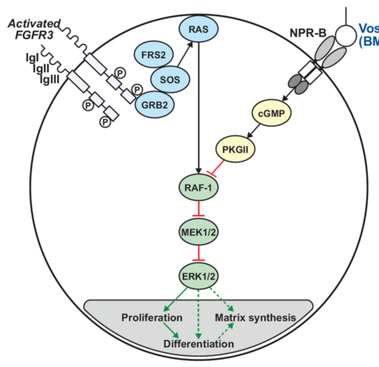


Figure modified from Lorget F, et al. *Am J Hum Genet.* 2012;91(6):1108-14.
cGMP, guanosine 3',5'-cyclic monophosphate; CNP, C-type natriuretic peptide; ERK1/2, extracellular signal-regulated kinase 1 and 2; FGFR3, fibroblast growth factor receptor 3; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; Ig, immunoglobulin module; MEK1/2, mitogen-activated protein kinase kinase 1 and 2; NPR-B, natriuretic peptide receptor B; PKGII, protein kinase G II; RAF-1, rapidly accelerated fibrosarcoma-1; RAS, rat sarcoma; SOS, son of sevenless.

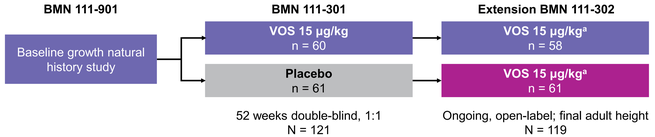
Increase in growth for children with ACH was demonstrated with vosoritide in clinical trials

- An open-label, 104-week, phase 2 trial (BMN 111-202; NCT02055157) and its extension study (BMN 111-205; NCT02724228) in children with ACH showed that vosoritide treatment resulted in sustained increases in annualized growth velocity (AGV)[6]
- In children with ACH of 0 to 5 years of age, improvement in height Z-score was seen with vosoritide compared to placebo after 52 weeks (BMN 111-206; NCT03583697)[7]
- A phase 3, randomized, placebo-controlled trial (BMN 111-301; NCT03197766) in children with ACH showed a statistically significant improvement in AGV with vosoritide after 52 weeks compared to placebo[8]; AGV improvement was sustained after 2 years of vosoritide treatment in the extension study (BMN 111-302; NCT03424018)[9]
- Here, we report efficacy and safety data from the subset of children in a phase 3 trial (BMN 111-301) and its extension (BMN 111-302) who started vosoritide treatment at age 10 years or older

Methods

- After completion of a 52-week, phase 3, placebo-controlled trial (BMN 111-301), participants transitioned to an open-label extension study (BMN 111-302), where they continued to receive vosoritide (**Figure 2**)
  - Key objectives: evaluate the long-term safety, tolerability, and efficacy (linear growth, proportionality) of daily subcutaneous injections of vosoritide in children with ACH

Figure 2. BMN 111-301/302 study design



[a]The majority of individuals had transitioned to weight-band dosing.
VOS, vosoritide.

Key eligibility criteria for BMN 111-301

- Age 5 to <18 years old at screening
- ACH, documented by clinical grounds and confirmed by genetic testing
- Stratified capped enrollment ≤20% Tanner stage >1
- Primary efficacy endpoint: AGV
- Secondary efficacy endpoints: height Z-score; upper to lower body segment ratio

Subgroup analysis

- Of the 119 participants who entered the extension study, 49 participants received their first dose of vosoritide when they were ≥10 years of age on day 1 of BMN 111-301 or day 1 of BMN 111-302 (if they were previously receiving placebo in BMN 111-301)
- Per protocol, participants were required to discontinue vosoritide when they reached near-final adult height (defined as evidence of growth plate closure and <1.5 cm/y AGV)
- Efficacy was assessed using 12-month-interval AGV by age intervals referenced to ACH untreated AGV[10] and average-stature AGV[11]
- Safety was assessed with rate of adverse events (AEs)
- The data cutoff date for this analysis was February 25, 2023

Results

Participants

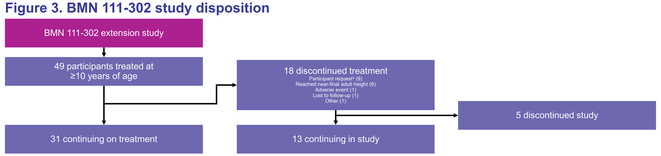
Table 1. Demographics of BMN 111-301/302 study participants who received their first vosoritide dose at ≥10 years of age

	301/302 (N = 49)
Age at day 1 of treatment (y)	
Mean (SD)	11.81 (1.32)
Min, max	10.0, 15.9
Age subgroups (%)	
≥10 to <11 years	13 (26.5)
≥11 to <15 years	35 (71.4)
≥15 to <18 years	1 (2.0)
Sex (%)	
Male	24 (49.0)
Female	25 (51.0)

max, maximum; min, minimum; SD, standard deviation.

- There were 25 females and 24 males who received their first dose of vosoritide by ≥10 years of age (**Table 1**)
- At treatment start, there were 19 females and 8 males at a Tanner stage >1

Figure 3. BMN 111-302 study disposition

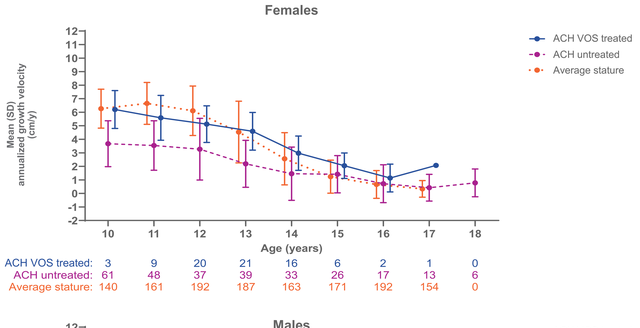


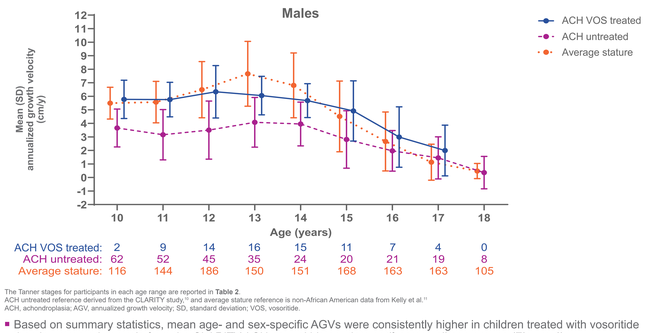
*Nearing final adult height, limb lengthening, injection burden, other.

- The mean (standard deviation [SD]; range) treatment exposure time was 3.57 (0.80; 2.00–4.83) years for females and 3.87 (0.52; 2.97–5.03) years for males, with 31 (63%) still on treatment at the time of the data cut (**Figure 3**)

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

Figure 4. Mean age- and sex-specific AGVs for children treated with vosoritide compared with untreated ACH and average-stature children





The Tanner stages for participants in each age range are reported in **Table 2**.
ACH untreated reference derived from the CLARITY study,[10] and average stature reference is non-African American data from Kelly et al.[11]
ACH, achondroplasia; AGV, annualized growth velocity; SD, standard deviation; VOS, vosoritide.

- Based on summary statistics, mean age- and sex-specific AGVs were consistently higher in children treated with vosoritide than in untreated controls from the CLARITY ACH natural history data set[10] across all age groups (**Figure 4**)
- The mean (SD) difference in AGV across integer ages 10 to 17 years between children with ACH who were treated and untreated was 1.47 (0.63) cm/y in females and 1.71 (0.63) cm/y in males

Table 2. Tanner stages for each sex-specific AGV year assessed in Figure 4

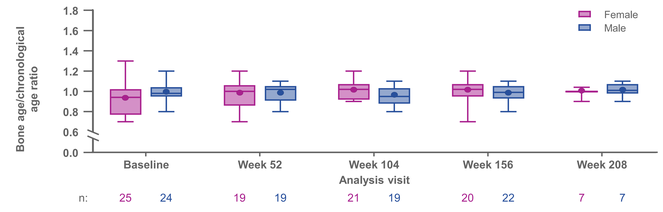
	Tanner stages for females						Tanner stages for males					
	I	II	III	IV	V	Total	I	II	III	IV	V	Total
10 years	1		2			3	2					2
11 years	1	5	1	2		9	4	5				9
12 years		4	8	7	1	20	3	3	8			14
13 years		1	4	13	3	21	2	3	6	5		16
14 years			2	5	9	16		4	2	6	3	15
15 years					6	6			1	4	6	11
16 years				1	1	2				2	5	7
17 years				1		1					4	4

The Tanner stages at each integer year are reported for female and male participants with AGV assessments shown in **Figure 4**.
AGV, annualized growth velocity.

- The growth benefits depicted in **Figure 4** occurred regardless of the individual's Tanner stage (**Table 2**)

No evidence of acceleration of bone age with vosoritide

Figure 5. Mean sex-specific bone age/chronological age ratio for children treated with vosoritide



Data are the interquartile range (boxes), median value (horizontal line), mean value (circle symbol), and minimum and maximum values (whiskers).

- Vosoritide treatment had no adverse effects on bone age in male or female children (**Figure 5**)

BMN 111-301/302 safety summary

Table 3. BMN 111-301/302 incidence of AEs for individuals who received their first dose of vosoritide at ≥10 years of age

	Overall N = 49; 176.77 person-years	
	Incidence n (%)	Event rate (AEs/person-year)
AE, n (%)	49 (100)	656 (3.71)
Treatment-related AEs	13 (26.5)	37 (0.21)
AEs leading to study drug discontinuation	1 (2.0)	1 (0.01)
SAEs	9 (18.4)	11 (0.06)
Treatment-related SAEs	1 (2.0)	2 (0.01)
SAEs leading to study drug discontinuation	1 (2.0)	1 (0.01)
AEs CTCAE grade ≥3	7 (14.3)	10 (0.06)
Event of interest		
Injection site reactions CTCAE grade ≥2	2 (4.1)	5 (0.03)
Injection site reactions lasting >24 hours (excluding bruising)	1 (2.0)	11 (0.06)
Hypotension	7 (14.3)	9 (0.05)
Heart rate change	1 (2.0)	1 (0.01)
Hypersensitivity (SMQ narrow terms)	7 (14.3)	14 (0.08)
Avascular necrosis or osteonecrosis	0	0
Slipped capital femoral epiphysis	0	0
Fractures	4 (8.2)	5 (0.03)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standard MedDRA query.

- Most AEs were mild and generally comparable to the experience of younger children (**Table 3**)
- One participant discontinued vosoritide due to a serious AE of kyphoscoliosis that was assessed as related to vosoritide by the investigator
- No other participant discontinued vosoritide due to an AE

Conclusions

- Vosoritide was well tolerated and improved AGV in children even when starting treatment at adolescence
- Additionally, the AGV improvement persisted during the later stages of puberty
- Treatment with vosoritide was not associated with serious or treatment-limiting adverse drug reactions, and no pathological acceleration was observed in bone age

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Disclosures

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References

1. Horton WA, et al. *Lancet.* 2007;370(9582):162-72. **2.** Hoover-Fong J, et al. *Bone.* 2021;146:115872. **3.** Yasoda A, et al. *Nat Med.* 2004;10(1):80-6. **4.** Krejci P, et al. *J Cell Sci.* 2005;118(pt 21):5089-100. **5.** Lorget F, et al. *Am J Hum Genet.* 2012;91(6):1108-14.
6. Savarirayan R, et al. *N Engl J Med.* 2019;381(11):25-35. **7.** Savarirayan R, et al. *Lancet Child Adolesc Health.* 2024;8(1):40-50.
8. Savarirayan R, et al. *Lancet.* 2020;396(10252):684-92. **9.** Savarirayan R, et al. *Genet Med.* 2021;23(12):2443-7.
10. Hoover-Fong JE, et al. *Orphanet J Rare Dis.* 2021;16(1):522. **11.** Kelly A, et al. *J Clin Endocrinol Metab.* 2014;99(6):2104-12.

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