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Persistent growth-promoting effects of vosoritide in children with achondroplasia is accompanied by improvement in physical aspects of quality of life

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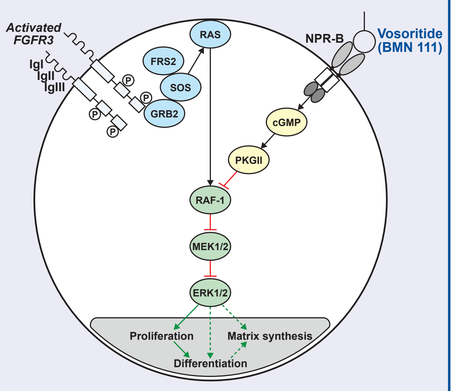
Background and Objectives

Vosoritide: Targeted therapy for achondroplasia

- Achondroplasia (ACH) is the most common form of disproportionate short stature (1:25,000 live births)[1,2] and is associated with a high burden of medical complications[2-5] and a reduced quality of life[6]

- 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[7,8]
- Vosoritide is based on naturally occurring CNP engineered to resist degradation and increase the half-life[9]



- Vosoritide, a CNP analog, has been shown to increase growth in children with ACH
  - An open-label, 52-week phase 2 trial (BMN 111-202) and its extension study (BMN 111-205) in children with ACH aged ≥5 years showed that vosoritide treatment resulted in sustained increases in annualized growth velocity (AGV) for over 7 years[10,11]
  - A phase 3 randomized placebo-controlled trial (BMN 111-301) in children with ACH aged ≥5 years showed a statistically significant improvement in AGV with vosoritide after 52 weeks compared to placebo[12]; AGV improvement was sustained after 3 years of vosoritide treatment in extension study BMN 111-302[13,14]
  - In children with ACH aged 0-5 years, improvement in height Z-score was seen with vosoritide compared to placebo after 52 weeks (111-206)[15]
- Vosoritide is approved for use in children with ACH and open epiphyses from birth in the USA, Japan, and Australia, and aged ≥4 months in the EU and ≥6 months in Brazil
- Our objective was to evaluate the impact of vosoritide on health-related quality of life (HRQoL) in children with ACH using Quality of Life in Short Stature Youth (QoLISSY) questionnaires[16]

Design and Methods

Design

- After completion of the phase 3 placebo-controlled study (BMN 111-301), 119 children were enrolled into the extension study (BMN 111-302) and received 15 µg/kg/day of vosoritide

Assessments

- Children and/or their caregivers completed the QoLISSY questionnaire at baseline and at 6-month intervals
- Self-reported QoLISSY assessments were not available at baseline for all participants because they were designed for use from 8 years of age

Data Collection

- Data collection was completed up to Year 3 as of February 2023

Analysis

- Descriptive summaries assessed mean annual changes from baseline for each domain and total score (based on physical, social, and emotional domains) for caregiver- and self-reported questionnaires for:
  - All children with an assessment at baseline, and
  - Children with ≥1 SD ACH height Z-score improvement at Year 3

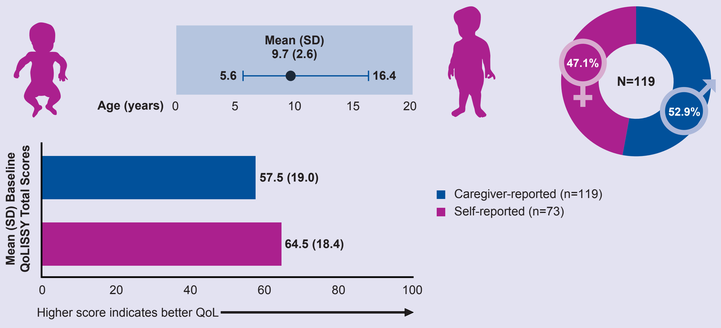
Modeling and Comparison

- Comparative analyses were not performed; however, to facilitate interpretation of changes observed in the treated population, mixed models with fixed effects for age and sex and random subject effects were used to estimate an annual change in each domain score in the untreated setting (observational data from completed study BMN 111-901 and placebo data from study BMN 111-301)

Results

Participant characteristics

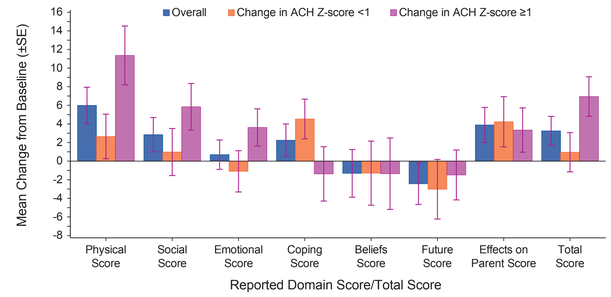
	Untreated Population (N=150)	Treated Population (N=119)
Age at first assessment (years)		
Mean (SD)	8.0 (2.4)	9.7 (2.6)
Median (Min, Max)	7.7 (5.0, 13.9)	9.7 (5.6, 16.4)
Age subgroup, n (%)		
≥5 to <8 years	79 (52.7)	40 (33.6)
≥8 to <11 years	51 (34.0)	39 (32.8)
≥11 to <15 years	20 (13.3)	37 (31.1)
≥15 to <18 years	-	3 (2.5)
Sex, n (%)		
Female	72 (48.0)	56 (47.1)
Race, n (%)		
White	118 (78.7)	85 (71.4)
Asian	18 (12.0)	21 (17.6)
Black or African American	7 (4.7)	5 (4.2)
Location, n (%)		
United States	60 (40.0)	53 (44.5)
Spain	34 (22.7)	12 (10.1)
Australia	19 (12.7)	22 (18.5)
United Kingdom	16 (10.7)	13 (10.9)
Germany	11 (7.3)	9 (7.6)
Japan	6 (4.0)	6 (5.0)
Turkey	4 (2.7)	4 (3.4)
Number of assessments		
Median	4	
25th, 75th percentile	3, 5	
Duration between first and last assessments (months)		
Median	13.2	
25th, 75th percentile	9.2, 21.6	



Mixed-effect analysis of QoLISSY parameters

Reported Domain Score/Total Score	Estimated Annual Slope (SE) in the Untreated Population
Caregiver-reported	
Physical Score	0.16 (0.55)
Social Score	0.16 (0.50)
Emotional Score	-1.40 (0.57)
Coping Score	1.41 (0.48)
Beliefs Score	-0.70 (0.66)
Future Score	-1.45 (0.63)
Effects on Parent Score	1.53 (0.50)
Total score	**-0.27 (0.48)**
Self-reported	
Physical Score	1.45 (0.77)
Social Score	1.92 (0.77)
Emotional Score	1.19 (0.70)
Coping Score	-0.75 (0.93)
Beliefs Score	1.94 (1.09)
Total score	**1.63 (0.63)**

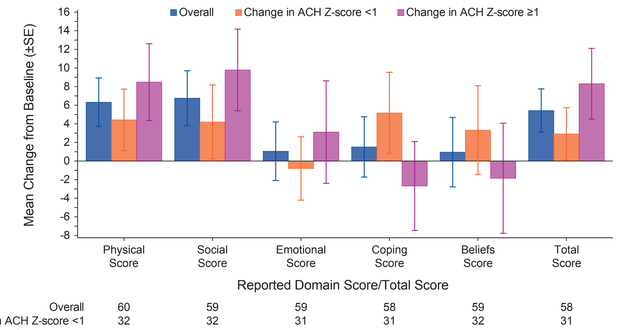
Mean change from baseline in caregiver-reported QoLISSY scores at Year 3 in the treated population



Overall	99	99	100	93	95	97	99	99
Change in ACH Z-score <1	61	61	62	57	58	60	61	61
Change in ACH Z-score ≥1	38	38	38	36	37	37	38	38

Data cut-off February 25, 2023. A positive change in QoLISSY score is indicative of an improvement in QoL. Z-scores were derived using ACH age/sex-specific reference data (means and SDs) from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis* 2021).

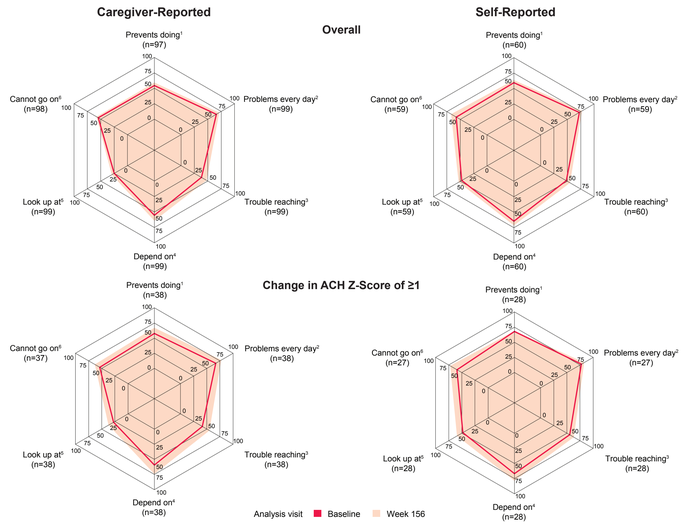
Mean change from baseline in self-reported QoLISSY scores at Year 3 in the treated population



Overall	60	59	59	58	59	58
Change in ACH Z-score <1	32	32	31	31	32	31
Change in ACH Z-score ≥1	28	27	28	27	27	27

Data cut-off February 25, 2023. A positive change in QoLISSY score is indicative of an improvement in QoL. Z-scores were derived using ACH age/sex-specific reference data (means and SDs) from CLARITY (Hoover-Fong J et al. *Orphanet J Rare Dis* 2021).

Distribution of mean physical domain scores at baseline and Year 3 in the treated population



[1]Prevents doing things; [2]Problems every day; [3]Trouble reaching things; [4]Depend on others; [5]Look up at others when talking; [6]Cannot go on fairground rides.

Conclusions

- These data suggest that vosoritide improves HRQoL among children with ACH, particularly for the physical domain scores
- There was a more pronounced change in participants with significant improvement in their ACH height Z-score (≥1 SD)

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.** Stender M et al. Comprehensive literature review on the prevalence of comorbid conditions in patients with achondroplasia. *Bone* 2022;162:116472. **4.** Maghnie M et al. Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study. *Orphanet J Rare Dis* 2023;18(1):56. **5.** Hoover-Fong JE et al. Achondroplasia Natural History Study (CLARITY): a multicenter retrospective cohort study of achondroplasia in the United States. *Genet Med* 2021;23(8):1498-505. **6.** Murton MC et al. Burden and Treatment of Achondroplasia: A Systematic Literature Review. *Adv Ther* 2023;40(9):3639-80. **7.** Yasoda A et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med* 2004;10(1):80-6. **8.** 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. **9.** 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):1108-14. **10.** Savarirayan R et al. C-type natriuretic peptide analogue therapy in children with achondroplasia. *N Engl J Med* 2019;381:25-35. **11.** Hoover-Fong J et al. Persistence of Growth Promoting Effects in Children with Achondroplasia Over Seven Years: Update from Phase II Extension Study with Vosoritide. *Genet Med Open* 2023;1(1):100223. **12.** 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;396:684-92. **13.** 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;23:2443-7. **14.** Polgreen LE et al. 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. *Horm Res Paediatr* 2023;96(suppl 2):FC4.1. **15.** Savarirayan R et al. Vosoritide therapy in children with achondroplasia aged 3-59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Child Adolesc Health* 2024;8(1):40-50. **16.** The European QoLISSY Group. Quality of Life in Short Stature Youth. The QoLISSY Questionnaire User's Manual. Lengerich: Pabst Science Publishers; 2013.

Disclosures

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