Persistent growth in children with achondroplasia treated with vosoritide for two years: further evidence supporting the first precision therapy for this condition

Ravi Savarirayan[1], Louise Tofts[2], Melita Irving[3], William Wilcox[4], Carlos A. Bacino[5], Julie Hoover-Fong[6], Rosendo Ullot Font[7], Paul Harmatz[8], Frank Rutsch[9], Michael B. Bober[10], Lynda E. Polgreen[11], Ignacio Ginebreda[12], Klaus Mohnike[13], Joel Charrow[14], Daniel Hoernschemeyer[15], Keiichi Ozono[16], Yasemin Alanay[17], Paul Arundel[18], Shoji Kagami[19], Natsuo Yasui[19], Klane White[20], Howard M. Saal[21], Antonio Leiva-Gea[22], Felipe Luna-González[22], Hiroshi Mochizuki[23], Donald Basel[24], Dania M. Porco[25], Kala Jayaram[25], Elena Fisheleva[26], Lynn Han[25], Jonathan Day[26]

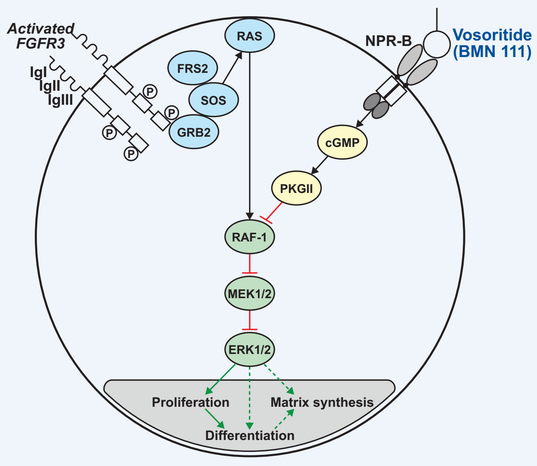
[1]Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, Victoria, Australia; [2]Kids Rehab, The Children's Hospital at Westmead, Westmead, New South Wales, Australia; [3]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK; [4]Department of Human Genetics, Emory University, Atlanta, Georgia, USA; [5]Baylor College of Medicine, Houston, Texas, USA; [6]McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University, Baltimore, USA; [7]Hospital Sant Joan de Déu, Barcelona, Spain; [8]UCSF Benioff Children's Hospital Oakland, Oakland, California, USA; [9]Department of General Pediatrics, Muenster University Children's Hospital, Muenster, Germany; [10]Nemours/Alfred I. du Pont Hospital for Children, Wilmington, Delaware, USA; [11]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California, USA; [12]Hospital Universitario Quirón Dexeus, Barcelona, Spain; [13]Otto-von-Guericke-Universität, Magdeburg, Germany; [14]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA; [15]University of Missouri-Columbia, Columbia, Missouri, USA; [16]Osaka University Hospital, Osaka, Japan; [17]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [18]Sheffield Children's NHS Foundation Trust, Sheffield Children's Hospital, Sheffield, UK; [19]Tokushima University Hospital, Tokushima, Japan; [20]Seattle Children's Hospital, Seattle, Washington, USA; [21]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [22]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [23]Saitama Children's Hospital, Saitama, Japan; [24]Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [25]BioMarin Pharmaceutical Inc., Novato, California, USA; [26]BioMarin (U.K.) Limited, London, UK

Background

- Achondroplasia is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- 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 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]
- Open-label, phase 2 trials in children with achondroplasia showed that administration of vosoritide resulted in sustained increases in annualized growth velocity (AGV)[7]
- In a phase 3 randomized placebo controlled trial (Study BMN 111-301) in children with achondroplasia, treatment with vosoritide resulted in a statistically significant improvement in AGV after 52 weeks compared to placebo[8]



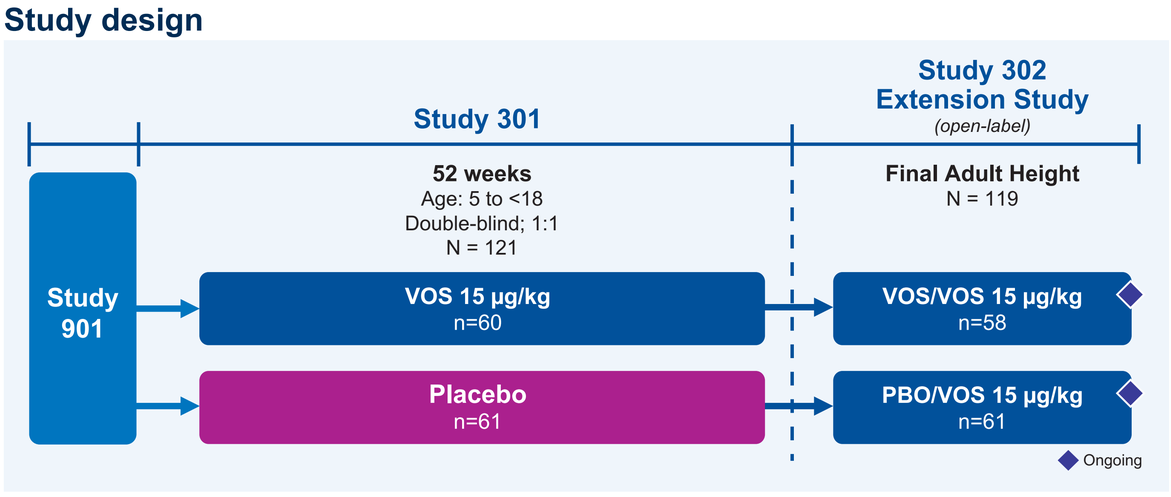
- Vosoritide is approved for use in children with achondroplasia aged ≥5 years in the US, aged ≥2 years in the EU, Brazil, and Australia, and from birth in Japan, until closure of epiphyses

Objectives and Methods

Objective of Study BMN 111-302

- Evaluate the long-term safety, tolerability, and efficacy for growth of daily subcutaneous injections of vosoritide in children with achondroplasia

Study design



- **Primary Efficacy Endpoint:** Annualized Growth Velocity (AGV)
- **Secondary Efficacy Endpoints:** Height Z-score; Upper to lower body segment ratio

Statistical Methods

- Six 6-month interval mean AGV assessments were derived from standing height measurements starting -52 weeks prior to randomization into the placebo controlled study and concluding 104 weeks post-randomization
  - Imputation for discontinued children was conducted by applying the baseline (pre-treatment) AGV to the last available height assessment. Linear interpolation was applied for children who had missed an assessment but in whom an assessment at a later time point was available
- Standing height was converted to an age-appropriate and sex-appropriate Z-score by comparison with Centers for Disease Control and Prevention reference standards (https://www.cdc.gov/growthcharts/index.htm)
- Upper to lower body segment ratio was calculated as the ratio between sitting height and standing height minus sitting height
- Comparative analyses at two years were performed using an ANCOVA model, which adjusted for covariates, as pre-specified for the primary and key secondary analyses of the randomized placebo controlled study. Similarly, comparative analyses were also conducted to assess height Z-score and upper to lower body segment ratio

Results

BMN 111-301/302 Study Disposition (up to Week 52 in 111-302)

Subject Category	Placebo/Vosoritide N=61	Vosoritide/Vosoritide N=60
Enrolled (%)	**61 (100)**	**60 (100)**
Discontinued	0	2 (3.3)*
Enrolled in extension 111-302 study	**61 (100)**	**58 (96.7)**
Discontinued	0	2 (3.3)**
No height assessment at Week 52 due to COVID-19	7 (11.5)	4 (6.7)
Subjects with standing height data at Week 52	54 (88.5)	52 (86.7)

*Reasons for discontinuation: One subject withdrew due to an adverse event (procedural anxiety); another withdrew by request due to pain intolerance from injection.

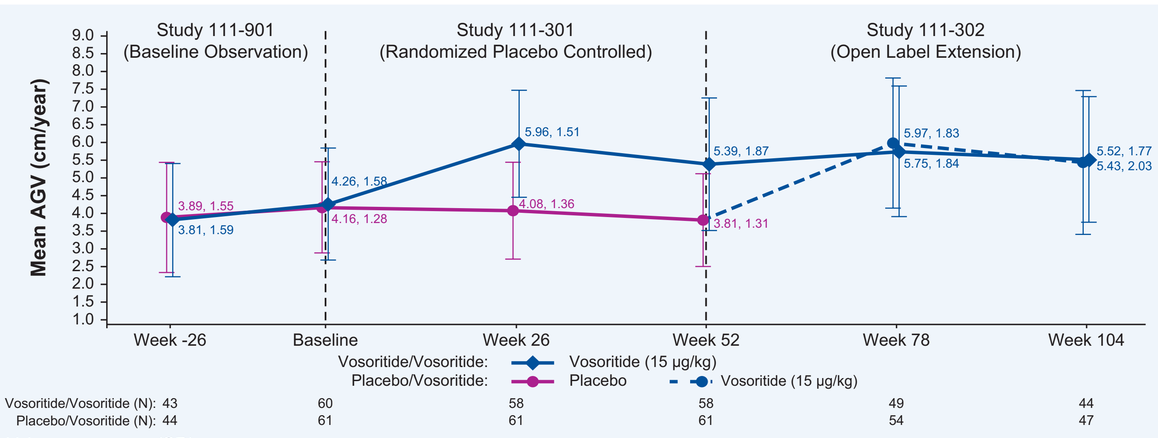
**Reasons for discontinuation: Withdrew by subject, one with "subject and family decided to exit the study" and another with "Participant is very resistant to daily injections".

BMN 111-301/302 Subject Demographics (at start of vosoritide treatment)

Subject Category	Placebo/Vosoritide N=61	Vosoritide/Vosoritide N=60
Age at first dose of vosoritide (years)		
N	61	58
Mean (SD)	10.07 (2.48)	8.26 (2.42)
Median	10.29	7.59
25th,75th Perc	8.07, 11.67	6.08, 10.16
Min, Max	6.1, 15.9	5.1, 13.1
Age category (%)		
≥5 to<8	15 (24.6)	31 (53.4)
≥8 to<11	21 (34.4)	16 (27.6)
≥11 to <15	24 (39.3)	11 (19.0)
≥15 to <18	1 (1.6)	0
Sex (%)		
Male	33 (54.1)	30 (51.7)
Female	28 (45.9)	28 (48.3)
Tanner Stage >1 (%)	18 (29.5)	11 (19.0)
Male Tanner Stage >1	6 (9.8)	3 (5.2)

SD, standard deviation.

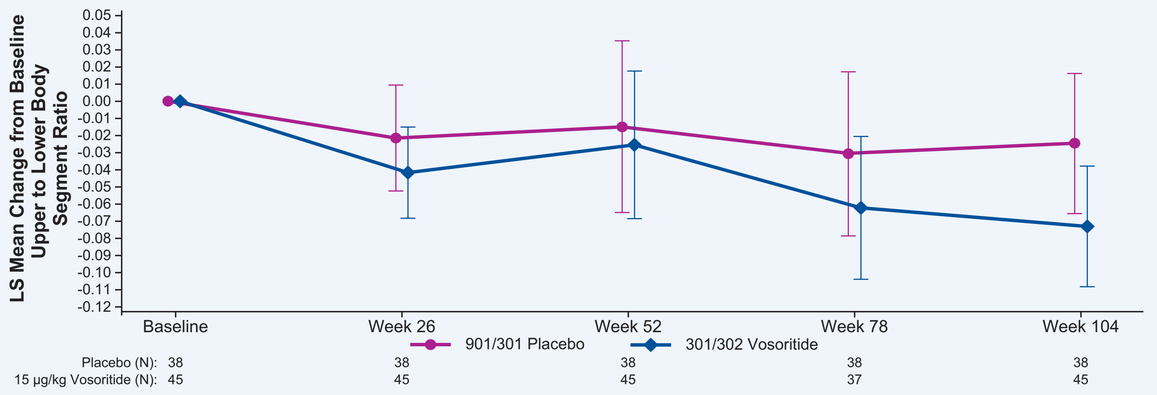
Increase in AGV is Maintained in the Second Year of Treatment with Vosoritide[9]



Values are means (SD).

- Cumulative height gain over 2 years was 3.52 cm in children on active treatment with a height assessment at Week 104 (n=52) compared to children on placebo with a two year untreated observation period (n=38)

Trend Towards Improvement in Upper to Lower Body Segment Ratio after 2 Years of Treatment[9]



Baseline defined as time of initiation of vosoritide treatment.

Comparative analyses (ANCOVA): Treated vs Untreated[9]

	Week 104 LS mean change from baseline (95% CI)
Height gain	3.34 cm (2.76, 3.93)
Height Z-score	+0.44 SDS (0.25, 0.63)
Upper:lower body segment ratio	-0.05 (-0.09, -0.01)

Comparative analyses assessed participants on active treatment for 2 years versus participants in the placebo arm with two years of being untreated (including time in observational study 901).

Safety of 2 Years of Vosoritide Treatment

- A total of 14 SAEs reported on treatment in 111-301/302 by November 2, 2020
  - None related to vosoritide
  - Common childhood illnesses/infections or manifestations of achondroplasia
  - Surgeries
- Safety profile consistent with observations to date
  - ISRs remain most commonly reported AEs without change in severity over time
  - No drug-related hypersensitivity events
  - No change in severity of blood pressure decreases
  - No AEs related to disproportionate bone growth or bone pathology

Conclusions

- During the second year of treatment with 15 µg/kg/day of vosoritide, the improvement in AGV was maintained, resulting in further increase in height Z-score and positive trend in body proportion ratios
- In subjects who switched from placebo to vosoritide in study 302, similar efficacy was observed as in those subjects on vosoritide treatment from the start of study 301
- Vosoritide was well tolerated with no reported drug-related SAEs
- Mean difference in height gain after 2 years treatment with vosoritide compared to no treatment was 3.34 cm (95% CI:2.76, 3.93)
- Participants continue treatment with vosoritide in the extension study where long-term effects of treatment can be evaluated until final adult height
- The studies of vosoritide in younger children with achondroplasia (0–60 months)[10] and those at risk of FM decompression surgery are ongoing[11,12]

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 Oct;182(10):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.** 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. **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 Dec;23(12):2443-2447. **10.** https://clinicaltrials.gov/show/NCT03583697. **11.** https://clinicaltrials.gov/show/NCT04554940. **12.** Savarirayan R et al. Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery. *Sci Prog*. 2021;104(1):368504211003782.

Presented at the 15th Skeletal Dysplasia Society Meeting: 24–27 August 2022, Santiago, Chile