OC4.3

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

Ravi Savarirayan[1], Louise Tofts[2], **Melita Irving**[3], William R. Wilcox[4], Carlos A. Bacino[5], Julie E. Hoover-Fong[6], Paul Harmatz[7], Frank Rutsch[8], Ricki S. Carroll[9], Lynda E. Polgreen[10], Klaus Mohnike[11], Joel Charrow[12], Carlos Prada[12], Daniel Hoernschemeyer[13], Keiichi Ozono[14], Takuo Kubota[14], Yasemin Alanay[15], Paul Arundel[16], Yumiko Kotani[17], Natsuo Yasui[17], Klane K. White[18], Shelley Brandstetter[19], Howard M. Saal[20], Antonio Leiva-Gea[21], Hiroshi Mochizuki[22], Asako Tajima[22], Donald Basel[23], Elena Fisheleva[24], Richard Rowell[25], Alice Huntsman-Labed[24], Jonathan Day[24]

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[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, Australia; [3]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK; [4]Emory University, Atlanta, GA, USA; [5]Baylor College of Medicine, Houston, TX, USA; [6]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [7]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA; [8]Department of General Pediatrics, Muenster University Children's Hospital, Münster, Germany; [9]Nemours Children's Hospital, Wilmington, DE, USA; [10]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA; [11]Otto-von-Guericke Universität, Universitätskinderklinik, Magdeburg, Germany; [12]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [13]University of Missouri-Columbia, Columbia, SC, USA; [14]Osaka University Hospital, Osaka, Japan; [15]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey; [16]Sheffield Children's NHS Foundation Trust, Sheffield Children's Hospital, Sheffield, UK; [17]Tokushima University Hospital, Tokushima, Japan; [18]Colorado Children's Hospital, Aurora, CO, USA; [19]Seattle Children's Hospital, Seattle, WA, USA; [20]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [21]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [22]Saitama Children's Medical Center, Saitama, Japan; [23]Medical College of Wisconsin, Milwaukee, WI, USA; [24]BioMarin (U.K.) Limited, London, UK; [25]BioMarin Pharmaceutical Inc., Novato, USA

Disclosures

- I am an investigator in this clinical trial and have also received consulting fees from BioMarin Pharmaceutical Inc.
- The results of this study were previously presented at the 2023 ACMG Annual Clinical Genetics Meeting, March 14–18, 2023, Salt Lake City, UT, USA.

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Background and objective

- 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 the fibroblast growth factor receptor 3 gene (*FGFR3*) that constitutively activates the downstream inhibitory signalling pathway in chondrocytes, leading to impaired endochondral bone growth and multiple complications[1,2]
- Vosoritide is based on naturally occurring C-type natriuretic peptide engineered to resist degradation and increase the half-life[7]
- In clinical trials, vosoritide has been shown to increase growth in children with ACH of all ages with growth potential[8–13]
- Vosoritide is approved for use in children with ACH and open epiphyses:
  - From birth in the USA, Japan, and Australia
  - From ≥4 months in the EU and from ≥6 months in Brazil

Objective: 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[14]

ACH, achondroplasia; HRQoL, health-related quality of life; QoLISSY, Quality of Life in Short Stature Youth

1. Horton WA et al. *Lancet.* 2007;370:162-172. **2.** Hoover-Fong J et al. *Bone.* 2021;146:115872. **3.** Stender M et al. *Bone.* 2022;162:116472. **4.** Maghnie M et al. *Orphanet J Rare Dis.* 2023;18:56. **5.** Hoover-Fong JE et al. *Genet Med.* 2021;23:1498-1505. **6.** Murton MC et al. *Adv Ther.* 2023;40:3639-3680. **7.** Lorget F et al. *Am J Hum Genet.* 2012;91:1108-1114. **8.** Savarirayan R et al. *Lancet Child Adolesc Health.* 2024;8:40-50. **9.** Savarirayan R et al. *N Engl J Med.* 2019;381:25-35. **10.** Hoover-Fong J et al. *Genet Med Open.* 2023;1:100223. **11.** Savarirayan R et al. *Lancet.* 2020;396:684-692. **12.** Savarirayan R et al. *Genet Med.* 2021;23:2443-2447. **13.** Polgreen LE et al. *Horm Res Paediatr.* 2023;96(suppl 2):FC4.1. **14.** The European QoLISSY Group. Quality of Life in Short Stature Youth. The QoLISSY Questionnaire User's Manual. Lengerich: Pabst Science Publishers; 2013.

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Design and methods

Design

- **Phase 3 OLE study (vosoritide 15 µg/kg/day) in 119 children aged ≥5 years**
- Secondary endpoint: change in HRQoL using QoLISSY questionnaire at baseline and at 6-month intervals*
- Data collection completed up to Year 3 (February 2023)

Methodology

- **Mean annual changes from baseline for each domain score and Total Score** for caregiver- and self-reported questionnaires for:
  - All children assessed at baseline
  - Children with ≥1 SD ACH height Z-score improvement at Year 3
- To understand changes in the treated population, mixed models estimated annual changes in each domain score in the untreated setting†

*Self-reported QoLISSY was not available at baseline for participants aged <8 years; †Using placebo and observational data

ACH, achondroplasia; HRQoL, health-related quality of life; OLE, open-label extension; QoLISSY, Quality of Life in Short Stature Youth

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Quality of Life in Short Stature Youth (QoLISSY)

	Self-reported	Caregiver-reported
Population	Children/adolescents with short stature (aged 8–18 years)	Caregivers (of children with short stature aged 4–18 years)
Domains (number of items)	Core domains: • Physical (6)* • Social (8)† • Emotional (8)†	
Recall period	Last week and currently	
Response options	5-point Likert scale (‘not at all’ to ‘extremely’; ‘never’ to ‘always’)	
Scoring	Subscale scores and Total Scores; raw scores are transformed to a 0–100 scale with **higher scores indicating higher HRQoL**	

QoLISSY has good content validity and psychometric properties in the ACH population

*Minimum score: 6; maximum score: 30; †Minimum score: 8; maximum score: 40
ACH, achondroplasia; COA, clinical outcome assessment; HRQoL, health-related quality of life
Data on file from regulatory submissions (COA evidence dossier)

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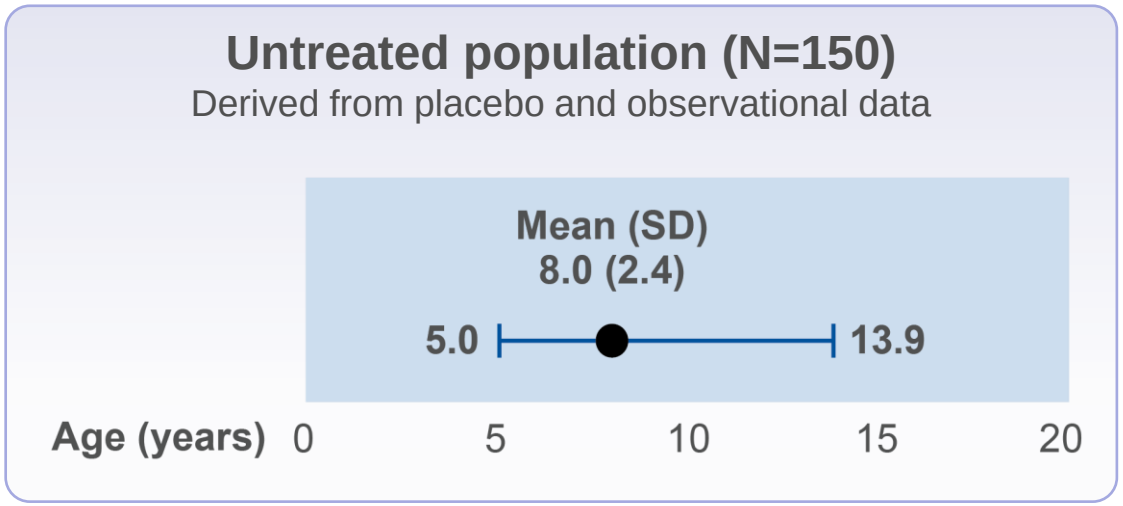
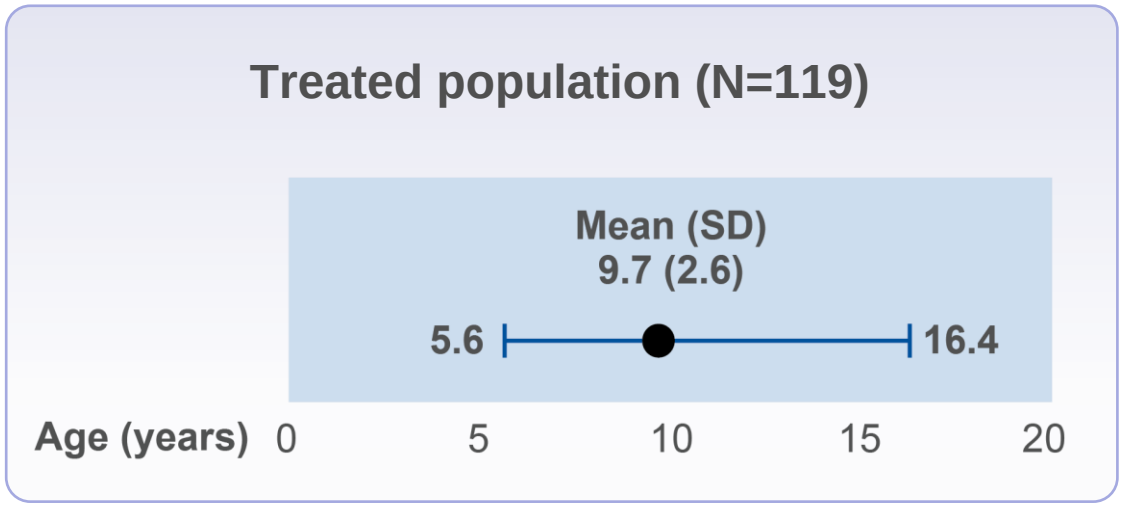
Results: Patient characteristics and demographics





	Untreated population (N=150)	Treated population (N=119)
Sex, n (%)		
Female	72 (48.0)	56 (47.1)
Ethnicity, 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)

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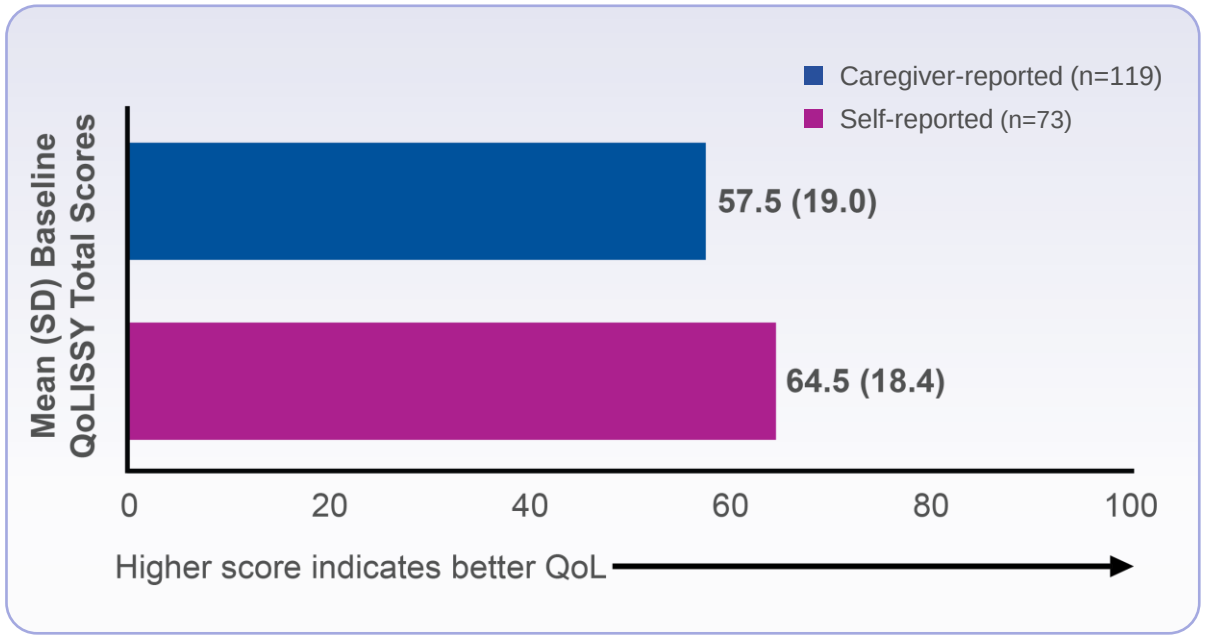
Results: Mean baseline QoLISSY scores



Reported domain score	Mean baseline (SD)	
	Caregiver-reported (n=119)	Self-reported (n=73)
Physical Score	49.2 (20.5)	59.0 (19.7)
Social Score	59.0 (21.4)	64.7 (22.3)
Emotional Score	64.2 (20.5)	69.7 (22.2)
Coping Score	45.9 (19.0)*	49.0 (22.1)
Beliefs Score	62.2 (28.1)	59.0 (28.0)
Future Score	69.0 (26.8)†	-
Effects on Parent Score	61.0 (21.7)	-

QoLISSY Total Score‡ at baseline was consistent with previous findings in the ACH population,[1,§] and lower than that seen in children with average stature[2,¶]

ACH population in the LIAISE study[1]:

- Caregiver-reported (n=91): **52.8**
- Self-reported (n=51): **60.5**

Average stature children[2]:

- Caregiver-reported (n=35): **75.5**
- Self-reported (n=30): **80.0**

*n=116; †n=117; ‡QoLISSY Total Score is the sum of physical, social, and emotional domains; §Children with ACH who had not undergone limb-lengthening surgery in the LIAISE study; ¶Children with ISS and height > –2 SD

ACH, achondroplasia; ISS, idiopathic short stature; QoL, quality of life; QoLISSY, Quality of Life in Short Stature Youth

1. Maghnie M et al. *Orphanet J Rare Dis.* 2023;18:56. **2.** Bullinger M et al. *Health Qual Life Outcomes.* 2015;13:43.

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Results: Change in QoLISSY in the treated population at Year 3 and estimated annual change in untreated population

Reported domain score/Total Score*	Estimated annual slope (SE) in the untreated population	Change in QoLISSY score in the treated population at Year 3		
		Overall	Change in ACH height Z-score <1	Change in ACH height Z-score ≥1
Caregiver-reported				
Physical Score	0.16 (0.55)	6.0	2.7	11.4
Social Score	0.16 (0.50)	2.9	1.0	5.8
Emotional Score	–1.40 (0.57)	0.7	–1.1	3.6
Coping Score	1.41 (0.48)	2.3	4.5	–1.4
Beliefs Score	–0.70 (0.66)	–1.3	–1.3	–1.4
Future Score	–1.45 (0.63)	–2.4	–3.0	–1.5
Effects on Parent Score	1.53 (0.50)	3.9	4.2	3.3
Total Score*	**–0.27 (0.48)**	**3.3**	**1.0**	**6.9**
Self-reported				
Physical Score	1.45 (0.77)	6.3	4.4	8.5
Social Score	1.92 (0.77)	6.8	4.2	9.8
Emotional Score	1.19 (0.70)	1.1	–0.8	3.1
Coping Score	–0.75 (0.93)	1.5	5.2	–2.7
Beliefs Score	1.94 (1.09)	1.0	3.3	–1.9
Total Score*	**1.63 (0.63)**	**5.4**	**2.9**	**8.3**

*QoLISSY Total Score is the sum of physical, social, and emotional domains

ACH, achondroplasia; QoLISSY, Quality of Life in Short Stature Youth

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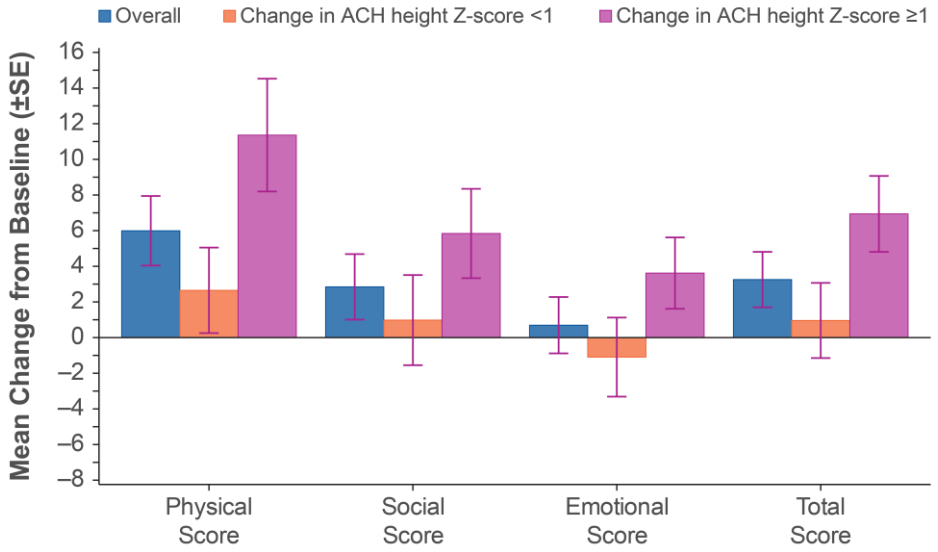
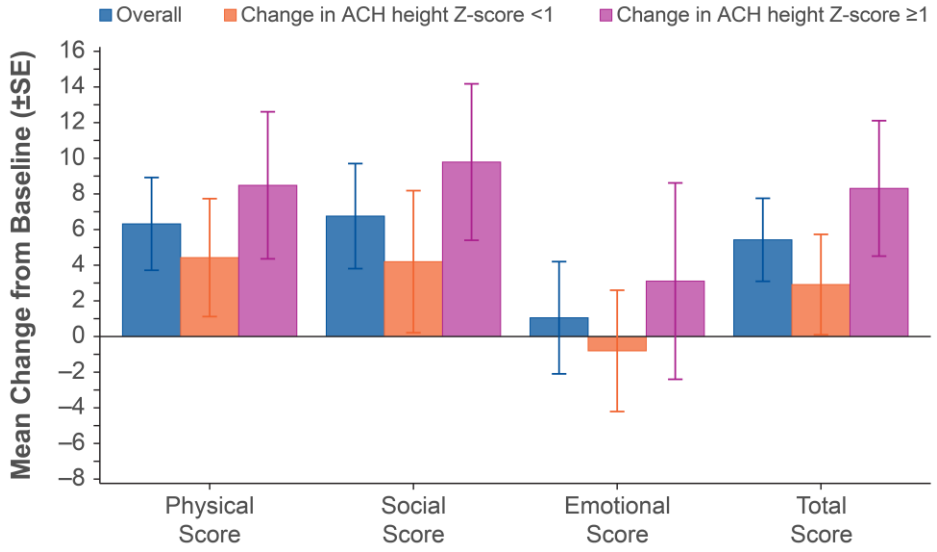
Results: Change from baseline in QoLISSY scores at Year 3 in the treated population

Caregiver-reported



Self-reported



Positive changes observed in QoLISSY **physical** and **social** domain scores (and **Total Score**) were indicative of an improvement in QoL; **improvement was particularly pronounced in participants with ACH height Z-score ≥1 SD**

Data cut-off 25 February 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)

ACH, achondroplasia; QoL, quality of life; QoLISSY, Quality of Life in Short Stature Youth

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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 **greater improvement** in their ACH height Z-score (≥1 SD)

Additional analyses are required to further evaluate and interpret the observed changes in QoLISSY scores

ACH, achondroplasia; HRQoL, health-related quality of life; QoLISSY, Quality of Life in Short Stature Youth

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