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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 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 *FGFR3* that constitutively activates the downstream inhibitory signaling pathway in chondrocytes, leading to impaired endochondral bone growth and multiple complications[1,2]
- Vosoritide is based on naturally occurring CNP 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 HRQoL in children with ACH using QoLISSY questionnaires[14]**

ACH, achondroplasia; CNP, C-type natriuretic peptide; EU, European Union; *FGFR3,* fibroblast growth factor receptor 3 gene; HRQoL, health-related quality of life; QoLISSY, Quality of Life in Short Stature Youth

1. Horton WA *et al. Lancet* 2007;370:162–72; 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;23:1498–505; 6. Murton MC *et al. Adv Ther* 2023;40:3639–80; 7. Lorget F *et al. Am J Hum Genet* 2012;91:1108–14; 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;396:684–92; 12. Savarirayan R *et al. Genet Med* 2021;23:2443–7; 13. Polgreen LE *et al. Horm Res Paediatr* 2023;96(Suppl 2):FC4.1; 14. Bullinger *et al.* 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; SD, standard deviation

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# 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:<br>• Physical (6)*<br>• Social (8)†<br>• 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; QoLISSY, Quality of Life in Short Stature Youth
Data on file from regulatory submissions (COA evidence dossier)

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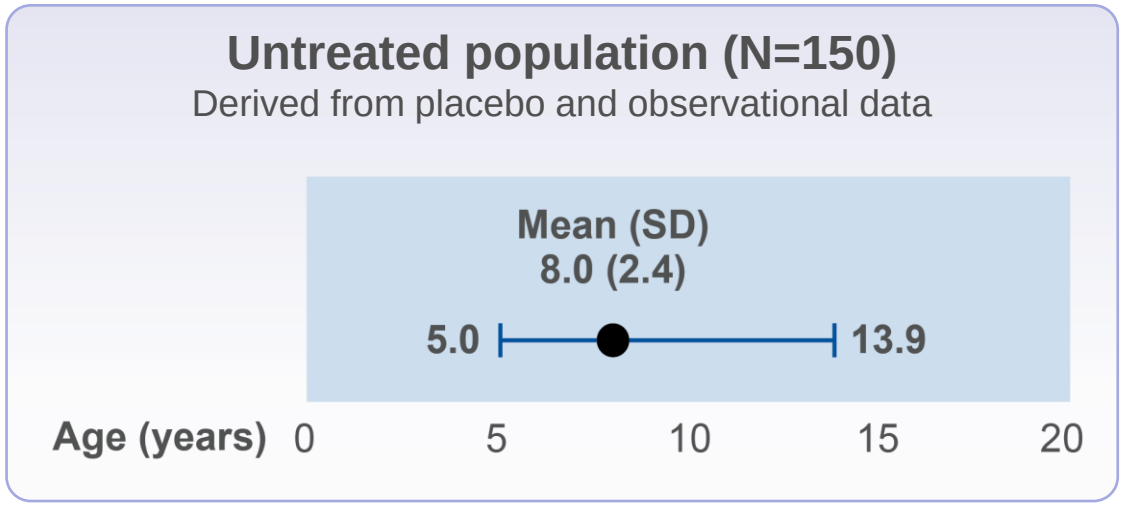
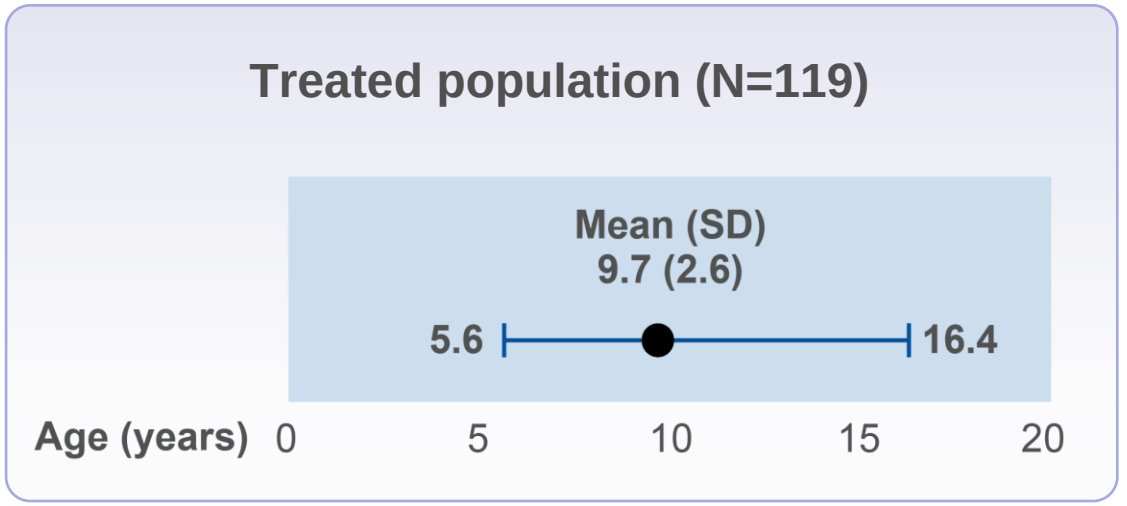
# Results: patient characteristics and demographics




| | 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) |

SD, standard deviation

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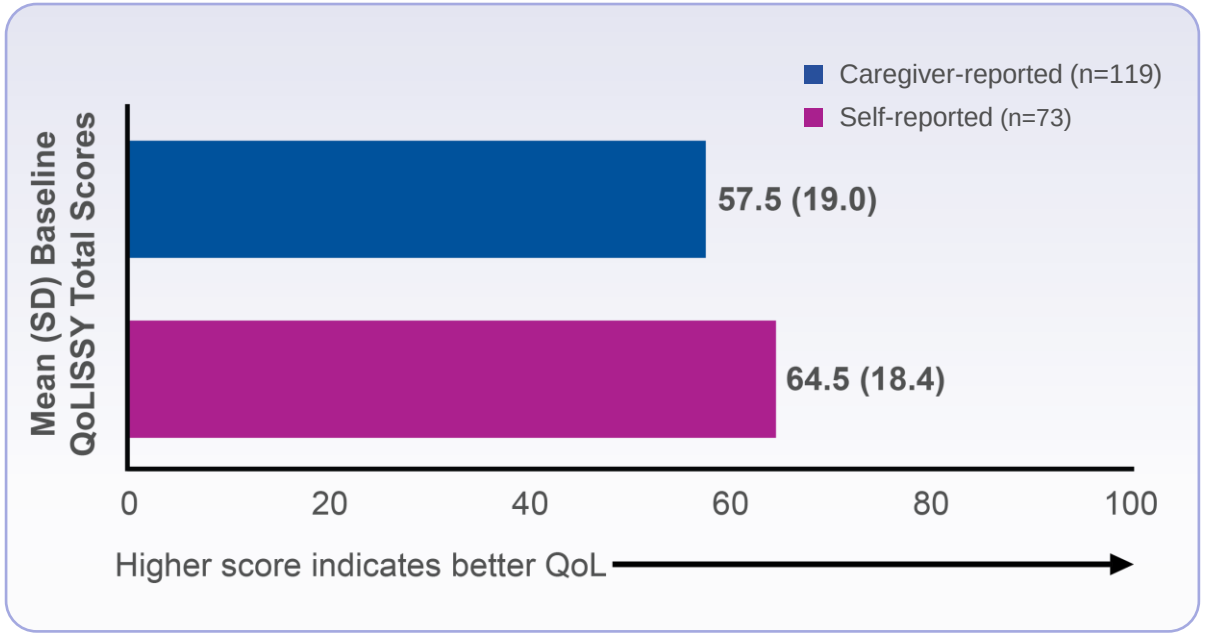
# Results: mean baseline QoLISSY scores




| 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; SD, standard deviation

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; SE, standard error

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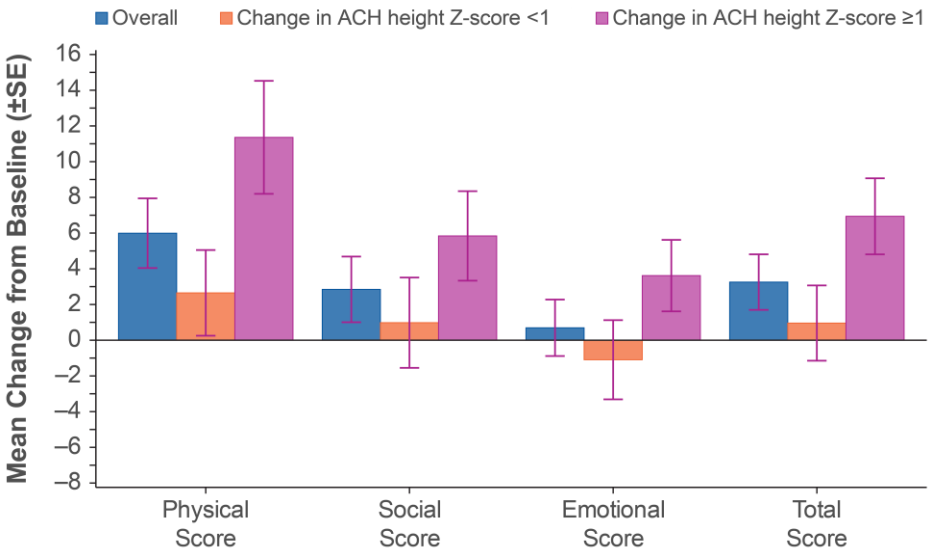
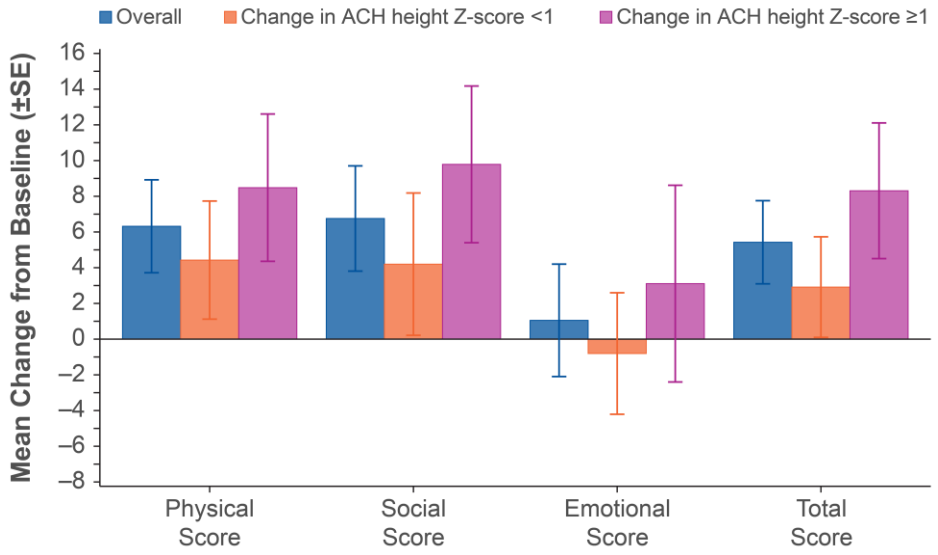
# Results: change from baseline in QoLISSY scores at Year 3 in the treated population

**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 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;16:522)
ACH, achondroplasia; CLARITY, achondroplasia natural history study; QoL, quality of life; QoLISSY, Quality of Life in Short Stature Youth; SD, standard deviation; SE, standard error

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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; SD, standard deviation

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