Characterizing Weight Distribution Patterns in Individuals With Achondroplasia Across Age: Evidence From the CLARITY Cohort With Implications for Economic Modeling

Andrew Howe, Paul Miner, Carol Zhao, Longwen Zhao, Domenic Mantella, Kaysen Bala, Terry Cozza, Zeinab Choucair

Ascendis Pharma, Palo Alto, CA, United States of America

EE102

Background

- Achondroplasia (ACH) is a rare genetic condition characterized by skeletal dysplasia, disproportionate short stature, and serious muscular, neurological, and cardiorespiratory complications. ACH is associated with distinct growth trajectories that differ from general pediatric populations.[1] In the United States and Europe, ACH has an estimated pediatric prevalence (<18 years) of 3.5 and 3.3 per 100,000, respectively[2-5]
- Navepegritide is a prodrug of CNP approved by the FDA to increase linear growth in children 2 years and older with ACH with open epiphyses that is administered once weekly with weight-based dosing[6]
- Weight is an important determinant of dose for therapies used in children with ACH. However, published evidence describing age-specific weight-band distributions of children living with ACH remains limited
- The CLARITY natural history study[7] represents the largest published US dataset of growth-related measurements in individuals with untreated ACH and provides an opportunity to characterize weight distributions across age strata using condition-specific reference data
- Understanding weight distribution may provide critical information to improve the precision and clinical relevance of economic models, health technology assessments, and treatment utilization estimates

Objective

To characterize the proportion of children with ACH within navepegritide weight-based dose bands across pediatric age strata using CLARITY natural history data and statistical simulations to inform implications for health economic modeling estimations

Conclusions

This analysis further expands the literature pool on age-specific weight-based distributions in children with ACH using the largest natural history database of untreated children with ACH and relevant weight-based dosing bands from an FDA-approved treatment for ACH.

Our results show weight distribution in children with ACH likely follows a predictable and age-dependent pattern. Distinct dominant weight bands emerged across age strata with higher weight categories occurring predominantly in adolescence, which may have implications for medication dosing.

Quantification of age-specific weight distributions across navepegritide USPI-aligned weight bands provides a practical framework for weight-based dosing assessments and economic modeling in ACH, improving model input assumptions and supporting reimbursement decision-making.

Methods

- Sex- and age-in-month specific weight distributions were obtained from the CLARITY natural history study[7]
- Weights for 100 males and 100 females from age 2 years (24 months) through age of epiphyseal closure were generated for each age-month based on sex- and age-in-month-specific weight distributions from the CLARITY data
  - Skeletal maturity thresholds for this analysis were modeled using upper-age limits for epiphyseal closure of 16 years for females and 18 years for males[8,9]
- Weight bands were aligned to the navepegritide USPI[6]
  - Weight bands were 8 to 9.9 kg, 10 to 13.4 kg, 13.5 to 17.5 kg, 17.6 to 23 kg, 23.1 to 30.5 kg, 30.6 to 41.2 kg, 41.3 to 55.9 kg, 56 to 73.5 kg, and 73.6 to 90 kg
- Sample observations were stratified across 5 age groups, including 2 to <3 years, 3 to <5 years, 5 to <10 years, 10 to <15 years, and 15 to <18 years

Statistical Analysis

- A parametric simulation was conducted[10] whereby body weight within each age (in months) and sex stratum was simulated from a normal distribution and parameterized using the CLARITY data table
- Simulated weight values were constrained using a 0.5 kg clipping rule to cap values to reduce variance and prevent outlier dominance. Observations were classified into the prespecified weight categories
- Monte Carlo simulation with 100 iterations was conducted.[10] For each age group and overall, the proportion of observations in each weight category was calculated within every iteration and then averaged across the 100 iterations
- The percentage of observations allocated to each weight band was calculated within each age stratum and across all age strata. In addition, the percentage of observations with weight ≥56 kg was summarized

Sensitivity Analysis

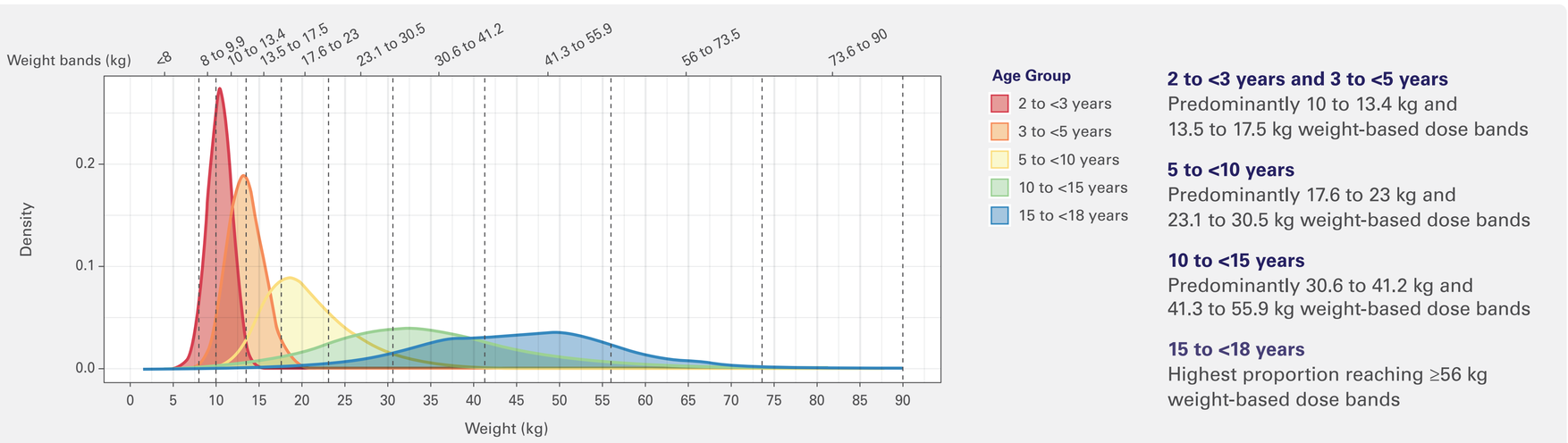
- To account for variation in the proportion of children reaching skeletal maturity at each age, a sensitivity analysis was conducted using different assumptions of age- and sex- specific probabilities of complete epiphyseal closure based on published biological growth-plate data in children of average stature at different anatomical sites[11] including the radius, proximal tibia, and distal tibia with a focus on validating the proportion of children with ACH expected to weigh ≥56 kg

Results

Simulated Population Age-Specific Weight Band Evolution

- Simulated weights for 100 males and 100 females from age 2 years (24 months) through age of epiphyseal closure for each age-month based on sex- and age-in-month-specific weight distributions are shown in Figure 1
- Most age groups were within the lower weight ranges, which may be reflective of the majority of children with ACH in typical US health plans

Figure 1. **Simulated Population Age-Specific Weight-Band Distribution**



Primary Analysis Results

- Across all ages, the largest proportions of simulated observations were in the 17.6 to 23 kg (17.9%), 23.1 to 30.5 kg (16.9%), and 30.6 to 41.2 kg (17.4%) weight bands. Only 3.4% of observations occurred in weight bands ≥56 kg **(Figure 2)**
- Dominant weight bands were higher with increasing age
  - 56.1% of simulated 2 to <3-year-olds were in the 10 to 13.4 kg band
  - 49.5% of simulated 3 to <5-year-olds were in the 10 to 13.4 kg band and 43.8% were in the 13.5 to 17.5 kg band
  - 42.7% of simulated 5 to <10-year-olds were in the 17.6 to 23 kg band
  - 46.2% of simulated 15 to <18-year-olds were in the 41.3 to 55.9 kg band, while 19.5% were ≥56 kg

Figure 2. **Weight Distribution by Age Group**

Age group	<8 kg	8–9.9 kg	10–13.4 kg	13.5–17.5 kg	17.6–23 kg	23.1–30.5 kg	30.6–41.2 kg	41.3–55.9 kg	56–73.5 kg	73.6–90 kg	>90 kg
All ages	**0.5%**	**3.1%**	**11.8%**	**15.6%**	**17.9%**	**16.9%**	**17.4%**	**13.4%**	**3.3%**	**0.1%**	**—**
2 to <3 years	5.4%	36.9%	56.1%	1.7%	—	—	—	—	—	—	—
3 to <5 years	0.2%	3.9%	49.5%	43.8%	2.6%	—	—	—	—	—	—
5 to <10 years	—	0.1%	3.5%	25.9%	42.7%	23.4%	4.3%	0.1%	—	—	—
10 to <15 years	0.2%	0.2%	1.0%	2.9%	9.3%	24.5%	37.8%	21.6%	2.5%	—	—
15 to <18 years	0.1%	—	0.1%	0.5%	1.7%	6.7%	25.2%	46.2%	18.6%	0.9%	—

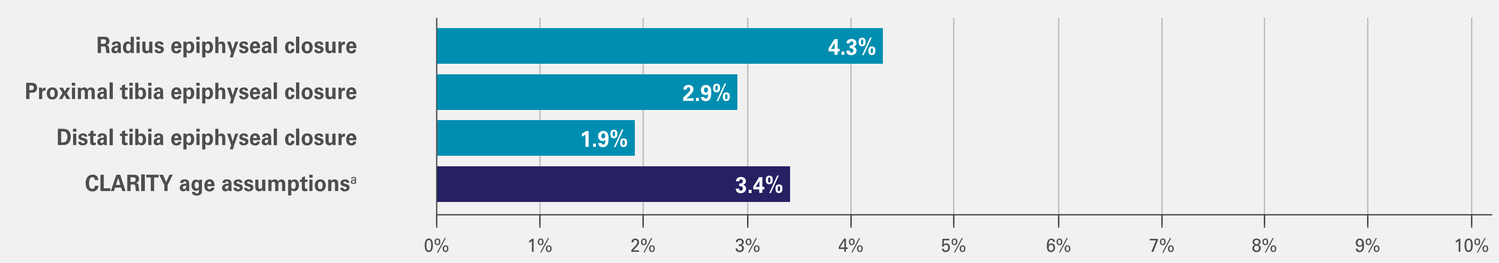
Proportion of observations: 0% – 60%+

Note: cell values represent the mean proportion of observations across 100 simulations, including 100 males and 100 females per age-month. Epiphyses were estimated to be closed at 16 years of age for females and 18 years of age for males.

Sensitivity Analysis Results

- Across epiphyseal closure timepoint assumptions (by age and by published data for radius, distal tibia, and proximal tibia), 1.9% to 4.3% of simulated observations were of children with ACH weighing ≥56 kg **(Figure 3)**
- Results from the primary analysis showing an estimated 3.4% of weight distribution observations ≥56 kg were validated in the sensitivity analysis, as the result was within the range of simulated observations based on published data

Figure 3. **Estimated Proportion of Observations ≥56 kg Under Varying Epiphyseal Closure Assumptions**



[a]CLARITY age assumptions were epiphyseal closure at 16 years of age for females and 18 years of age for males.

Limitations

- Body weight simulations assumed an age-specific normal distribution symmetric around a central mean, which may lead to errors if the real-world data deviate from this assumption
- There is a gap in the literature for site-specific epiphyseal fusion data in children with ACH. As such, we utilized published data from a population of children with average stature for the sensitivity analysis
- Weight was based on the weight distribution estimated in the CLARITY study. While CLARITY is the largest contemporary ACH dataset, it was derived from a retrospective chart review that may have incomplete or missing data. Additionally, the weight assessments were evaluated between 1957 and 2017 and may not reflect the current pediatric ACH population. Finally, the cohort includes untreated participants at specialized US skeletal dysplasia referral centers, potentially limiting generalizability

Abbreviations

ACH = achondroplasia; **CNP** = C-type natriuretic peptide; **FDA** = Food and Drug Administration; **US** = United States; **USPI** = United States prescribing information

References

1. Pauli RM. *Orphanet J Rare Dis*. 2019;14:1. **2.** Stevenson DA, et al. *Am J Med Genet A*. 2012;158:1046-54. **3.** Waller DK, et al. *Am J Med Genet A*. 2008;146A:2385-9. **4.** Coi A, et al. *Am J Med Genet A*. 2019;179:1791-98. **5.** Stoll C, et al. *Eur J Med Genet*. 2022;65:104612. **6.** Yuviwel. Prescribing information. Ascendis Pharma Endocrinology, Inc; 2026. **7.** Hoover-Fong JE, et al. *Orphanet J Rare Dis*. 2021;16:522. **8.** Crowder C, Austin D. *J Forensic Sci*. 2005;50:1001-7. **9.** Scheuer L, Black S. *Developmental Juvenile Osteology*. Academic Press; 2000. doi:10.1016/B978-0-12-624000-9.X5000-X. **10.** Morris TP, White IR, Crowther MJ. *Stat Med*. 2019;38:2074-2102. **11.** Kvist O, et al. *Acta Paediatr*. 2020;110:1249-56.

Disclosures and Funding

Ascendis Pharma, LLC funded this analysis and participated in the trial design, research, analysis, data collection, interpretation of the data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Bridgette Kanz Schroader, PharmD, MPA, BCOP, of Ascendis Pharma.

Financial arrangements of the authors with companies whose products may be related to this presentation are listed as declared by the authors: **AH, PM, CZ, DM, KB, TC,** and **ZC**: Full-time employees of Ascendis Pharma. **LZ**: consultant to Ascendis Pharma.

Ascendis, Ascendis Pharma, and the Ascendis Pharma logo are trademarks owned by the Ascendis Pharma group.
© 2026 Ascendis Pharma A/S