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Growth parameters in children with achondroplasia: A 7-year, prospective, multinational, observational study

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ABSTRACT

Purpose: This study was undertaken to collect baseline growth parameters in children with achondroplasia who might enroll in interventional trials of vosoritide, and to establish a historical control.

Methods: In this prospective, observational study, participants (≤17 years) underwent a detailed medical history and physical examination and were followed every 3 months until they finished participating in the study by enrolling in an interventional trial or withdrawing.

Results: A total of 363 children were enrolled (28 centers, 8 countries). Mean (SD) follow up was 20.4 (15.0) months. In participants <1 year, mean annualized growth velocity (AGV) was 11.6 cm/year for girls and 14.6 cm/year for boys. By age 1 year, mean AGV decreased to 7.4 cm/year in girls and 7.1 cm/year in boys. By age 10 years, mean AGV decreased to 3.6 cm/year for both sexes. Mean height *z*-score in participants <1 year was −2.5 for girls and −3.2 for boys and decreased up to the age 5 years (−5.3 for girls; −4.6 for boys). Girls and boys had a disproportionate upper-to-lower body segment ratio. Mean ratio was highest in participants aged <1 year (2.9 for girls; 2.8 for boys) and decreased gradually to approximately 2 in both sexes from 4 years of age onward.

Conclusion: This study represents one of the largest datasets of prospectively collected medical and longitudinal growth data in children with achondroplasia. It serves as a robust historical control to measure therapeutic interventions against and to further delineate the natural history of this condition.

Introduction

Achondroplasia is the most frequently occurring type of disproportionate short stature,[1,2] with an estimated worldwide birth prevalence of 4.6 per 100,000.[3] It is an autosomal dominant skeletal disorder caused by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene (*FGFR3*).[4] *FGFR3* is a key physiological negative regulator of linear bone growth.[2] Disordered endochondral ossification is responsible for the skeletal changes that cause disproportionate short stature in addition to other medical and functional manifestations experienced by people with achondroplasia over their life course.[2] Narrowing of the foramen magnum is one of the medical complications that can be associated with an excess of sudden deaths secondary to cord compression during infancy and early childhood.[5,6]

Several new treatments, including vosoritide, a recombinant analog of C-type natriuretic peptide, are in development or have recently been approved for the treatment of achondroplasia. Subcutaneous administration of vosoritide[7,8]

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demonstrated increased long-bone and craniofacial growth in murine models of achondroplasia. These findings led to a phase 2 study in 35 children aged 5 to <14 years with achondroplasia,[9] and a 52-week randomized, multinational, double-blind, placebo-controlled phase 3 study in 121 children with achondroplasia aged 5 to <18 years. In the phase 3 confirmatory study, the mean difference in annualized growth velocity (AGV) was 1.57 cm per year (95% CI = 1.22-1.93; 2-sided $P < .0001$) in favor of vosoritide, with similar rates of adverse events in both randomized groups.[10] Both trials have ongoing extension studies where all children continue treatment until they reach near-final adult height. In the phase 3 open-label extension study,[11] subcutaneous administration of vosoritide at a dose of 15.0 ug/kg/day for 2 years demonstrated that the increase in AGV was maintained at 2 years and showed trends in improved upper-to-lower segment body proportions; vosoritide was well tolerated, with no reported serious treatment-related adverse effects.

Prospectively collected high-quality longitudinal growth data are needed to improve understanding of the natural history of achondroplasia and to evaluate clinical outcomes associated with emerging pharmacologic therapies. We undertook an observational study to collect growth parameters and establish baseline AGV in children with achondroplasia who might subsequently enroll in vosoritide interventional trials and to establish a historical control. We report here the baseline growth parameters in children enrolled in this study.

Materials and Methods

Study design

This multinational, prospective, observational study collected data on growth parameters in children with achondroplasia being considered for enrollment in future interventional studies sponsored by BioMarin Pharmaceutical. Approximately 500 children were planned to be enrolled, with approximately equal numbers of boys and girls, to generate a large data set of prospectively collected longitudinal growth data using predefined standardized anthropometric techniques. The study is registered at ClinicalTrials.gov (Identifier: NCT01603095).

As an observational study, no treatments were administered. Participants who were in screening for an interventional study remained enrolled in the observational study until they passed the screening. For children who did not enroll in, or who failed screening for, an interventional study could choose whether to continue participating.

Study population

Participants eligible for enrollment were age ≤17 years, had achondroplasia documented by clinical diagnosis, were ambulatory and able to stand without assistance (unless younger than 5 years and <104 cm in length), and were willing and able as physically possible to perform all study procedures. Study exclusion criteria included: hypochondroplasia or short stature conditions other than achondroplasia; an unstable condition likely to lead to medical intervention during the study; fused growth plates; history of renal insufficiency or anemia; history of cardiac or vascular disease; specified pharmacologic therapies, including growth therapies; use of any other investigational product or investigational medical device for the treatment of achondroplasia or short stature; planned bone-related surgery; any condition likely to reduce compliance with the visit schedule or study completion; or concurrent disease or condition that, in the view of the investigator, would have interfered with study participation. Participants with previous limb-lengthening surgery could have been enrolled if surgery occurred ≥18 months before the study and healing was complete without sequelae. The complete list of enrollment criteria is detailed in the Supplemental Appendix.

Data collection and frequency

During screening, participants underwent a detailed medical history review and physical examination, and data were collected on concomitant treatments, vital signs, growth parameters, serum 25-hydroxy vitamin D and alkaline phosphatase measurements, and other blood and urine biomarkers of bone metabolism and endochondral ossification (including serum collagen X biomarker),[12] Tanner stage of pubertal development (measured in participants aged ≥5 years), health-related quality of life, and adverse events. This manuscript will focus on the growth parameters only. Patients were followed at day 1 (month 0) and every 3 months (±10 days) thereafter until they finished participating in the study (defined as reaching the end of this observational protocol [up to 7 years] or at enrollment in an interventional study, discontinuation of participation, or study termination).

The COVID-19 pandemic resulted in sites being closed for visits during part of the study. Consequently, some protocol-scheduled visits were replaced by home or virtual visits or were missed entirely. For participants who did not attend a final on-site end-of-study visit, the site contacted the family by telephone to collect all adverse event information. The study was terminated by the sponsor on February 11, 2021, after the last participant was enrolled in a phase 2, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov number, NCT03583697) of vosoritide in infants and younger children with achondroplasia (aged 3 months to <60 months).

Growth parameters were collected by a trained study staff member at approximately the same time at each scheduled visit (±2 hours). These parameters included, but were not limited to, standing height, sitting height (total body length/crown to rump if aged <2 years and unable to walk), weight, head circumference, upper and lower arm length, leg length, and arm span. These measurements were taken in triplicate

with the exception of weight, which was taken once. Standardized measuring equipment and measurement techniques were used with mandatory training and revalidation occurring every 6 to 12 months.

Data quality

Sponsor personnel or designees visited sites before study initiation to review with the personnel information about the study and other regulatory document requirements, source document requirements, electronic case report forms, monitoring requirements, and procedures for reporting adverse events. At visits during and after the study, a contract research organization monitored sites for compliance with regulatory documentation. This monitoring focused on accurate and complete recording of data on the case report forms from source documents, adherence to protocol, and serious adverse event reporting. Data quality control and analysis were performed by the sponsor or a designee based on a predefined analysis plan. Audits were performed at 7 sites during the study.

Statistical analysis

The primary analysis population for outputs was the full analysis set, and included all enrolled participants with a signed informed consent. All assessments from baseline up to the date of study discontinuation/study completion were considered in the analyses. Growth parameters were measured 3 times for each assessment and the mean of these 3 assessments (or 2 if only 2 were recorded) was retained for analyses. In the event only one measure was available, this individual assessment was included. The growth endpoints of length/height, AGV, height z-score and upper-to-lower body segment ratio are summarized in the manuscript. Each end point was categorized by integer age (0, 1, 2 to maximum year of age) at the time of the assessment. When summarizing the growth endpoints of height, height z-score and upper-to-lower body segment ratio, the earliest assessment at that integer age was taken. The descriptive summaries by sex and integer age include the number of participants with assessable data, mean (SD), median (Q1, Q3), minimum and maximum.

For all endpoints, body length was prioritized for participants aged <24 months and standing height for participants ≥24 months. For upper-to-lower body segment ratio, crown-to-rump length was prioritized for participants aged <24 months and sitting height for participants ≥24 months. For the derivation of the end point AGV, all pairs of assessments that were 12 ± 3 months apart were identified, where AGV was derived according to the formula:

$$\text{AGV} = \frac{\textit{Standing height end of 12 months} - \textit{Standing height start of 12 months}}{\textit{Date at end of 12 months} - \textit{Date at start of 12 months}} \times 365.25$$

The mid timepoint for each interval was determined and the integer age at this time point was identified as the associated summary integer age. In the event a participant had more than one AGV associated with a specific integer age, the AGV interval with maximum overlap for the integer age was retained.

For height z-score, height measurements were converted to an age- and sex-standard score (SDS) referenced to height for average stature children from the Centers for Disease Control and Prevention.[13]

Upper-to-lower body segment ratio was derived according to the formula:

Sitting height/(standing height – sitting height)

Or (if age <2 years)

Crown-to-rump length/(body length – crown-to-rump length)

For AGV and upper-to-lower body segment ratio, assessments over time were plotted by age for each sex separately. Cubic quantile regression was used to model the 5th, 25th, 50th, 75th and 95th percentiles over time. Outliers were excluded from these descriptive plots as well as assessments taken after receiving limb lengthening, growth hormone, or other investigational treatments. All statistical analyses were performed (using SAS version 9.4). The cubic quantile modeling of the percentiles for AGV and upper-to-lower body ratio were post hoc exploratory analyses.

Results

Study population

A total of 363 children were enrolled between April 20, 2012 and November 3, 2020 at 28 study centers in 8 countries; most participants were enrolled in the United States (50.7%), Australia (14.6%), Spain (12.1%), and the United Kingdom (11.6%) (Supplemental Table 1). Of the 363 participants, 225 (62.0%) were subsequently enrolled in an interventional study. Mean duration of follow up was 20.4 (15.0) months (range: 0.0-84.3 months), with a total follow-up of 617.4 patient-years (Supplemental Table 2) and 2689 height assessments (Supplemental Table 3).

Baseline characteristics of the study population are given in Table 1. Participants ranged from newborn to 13.5 years, with a median age of 5.1 years. Half of the participants (50.7%) were male and 74.9% were White. Of the 186 participants in whom pubertal development was measured, 168 (90.3%) had a Tanner stage of I at baseline. No participants had received previous treatment with growth hormone. In total, 6 participants (1.7%) had undergone previous limb-lengthening surgery (1, who had undergone surgery ≤18 months before enrollment, was regarded as a

major protocol deviation). While enrolled in the study, 1 participant received intramuscular triptorelin acetate for approximately 4 months to delay puberty, and 1 received somatropin; both were considered protocol deviations. Sensitivity analyses excluding these participants confirm that inclusion of these data does not affect the overall results or conclusions reported.

Growth parameters

As illustrated in Figure 1 and Supplemental Table 4, a rapid decline in AGV was observed up to 2 years, whereafter a small steady decline was apparent with a rapid decrease when the participants approached near-final adult height. Among participants aged <1 year, mean AGV was 11.6 (1.7) cm/year for girls and 14.6 (0.5) cm/year for boys. By age 1 year, mean AGV decreased to 7.1 (1.7) cm/year in girls and 7.4 (2.1) cm/year in boys. By age 10 years, mean AGV was approximately 3.6 (1.3) cm/year for girls and 3.6 (0.6) cm/year for boys. The number of participants aged >12 years was small and consequently the variability associated to the integer point estimates for the growth parameters increased for the later years.

Height *z*-scores are shown in Supplemental Table 5 (where height refers to standing height or body length if aged <24 months). Mean height *z*-score in those aged <1 year was −2.5 (1.0) SDS for girls and −3.2 (1.2) SDS for boys, compared with average stature children of a similar age and sex. Mean height deficit increased up to the age 5 years (mean *z*-scores of −5.3 [1.1] SDS for girls and −4.6 [0.8] SDS for boys). The height deficit remained high for girls and boys in all age groups.

Standing heights for individual girls and boys over time by age are shown in Supplemental Figure 1. A comparison of height by age and sex in children with achondroplasia in the present study and in other studies is shown in Supplemental Table 6.

Additional growth measurements are given in Supplemental Tables 7 to 18. Mean ratio of upper arm to forearm length remained similar by age on study: 1.06 (0.13) for participants aged <1 year and 1.05 (0.10) for those aged 14 years (Supplemental Table 7). Similar findings were observed for thigh to lower-leg length ratio (0.68 [0.10] and 0.69 [0.08], respectively) (Supplemental Table 8) and arm span to standing height ratio (0.88 [0.03] and 0.91 [0.03]) (Supplemental Table 9).

Mean sitting height by sex and age at the time of assessment for participants aged <1 year was 40.89 (4.10) cm and gradually increased by age on study to 81.61 (5.69) cm in those aged 14 years (Supplemental Table 10). Increases were also observed for mean lower body length (14.52 [2.07] cm and 40.67 [4.04] cm, respectively) (Supplemental Table 11), knee to heel length (12.81 [1.29] and 32.84 [3.12] cm) (Supplemental Table 12), forearm length (12.81 [1.29] cm and 32.84 [3.12] cm) (Supplemental Table 13), upper arm length (8.08 [0.99] and 18.13 [2.21] cm) (Supplemental Table 14), thigh length (8.69 [1.47] cm and 22.80 [3.13] cm) (Supplemental Table 15), and tibial length (8.22 [1.05] cm and 20.34 [2.11] cm) (Supplemental Table 16). Mean body mass index *z*-score (assessed for participants aged ≥24 months) for participants aged 2 years was 2.26 (0.93) SDS above average and generally decreased with age to 1.73 (0.70) for participants aged 14 years (Supplemental Table 17). Median weight *z*-score for participants aged <1 year was 1.14 (−1.84 to −0.37) SDS below average, and varied by age with no clear pattern on study (Supplemental Table 18). Both girls and boys had a disproportionate upper-to-lower body segment ratio (Figure 2 and Supplemental Table 19). Mean ratio was highest for girls and boys aged <1 year (girls 2.9 [0.6]; boys 2.8 [0.4]) and decreased gradually to approximately 2 for both sexes from age 4 years.

Serum collagen X biomarker[12] samples were obtained in 245 participants (128 boys and 117 girls) across visits; their ages at the date of assessment ranged from 1 month to 15 years. The distributions of median collagen X biomarker concentrations for each participant for each year of age are shown in Supplemental Figure 2. Concentrations were relatively higher (median ≫13,000 pg/mL) in the first 2 years of life, with pronounced variability. They remained relatively consistent, with median concentrations ≫11,000 pg/mL across 3 to age 12 years, with a slight elevation between ages 8 and 11 years followed by a marked decrease after age 13 years (median concentration <10,000 pg/mL), albeit observed with smaller sample sizes.

Table 1 Baseline demographics, characteristics, and growth parameters (full analysis set)

Variable	Overall (N = 363)
Age, y	
Mean (SD)	5.1 (3.3)
Median (range)	5.1 (0.0-13.5)
Age group, *n* (%)	
0 to <24 months	81 (22.3)
2 to <5 years	95 (26.2)
5 to <8 years	108 (29.8)
8 to <11 years	60 (16.5)
11 to <15 years	19 (5.2)
Male sex, *n* (%)	184 (50.7)
Race, *n* (%)	
White	272 (74.9)
Asian	51 (14.0)
Japanese	17 (4.7)
Black or African American	14 (3.9)
Other	23 (6.3)
Not provided	3 (0.8)
Tanner stage I	168/186 (90.3)[a]

[a]Not assessed in 1 child ≥5 years; remaining children were aged <5 years.

Discussion

This multinational, observational study prospectively evaluated growth parameters in children with achondroplasia being evaluated for enrollment in future interventional

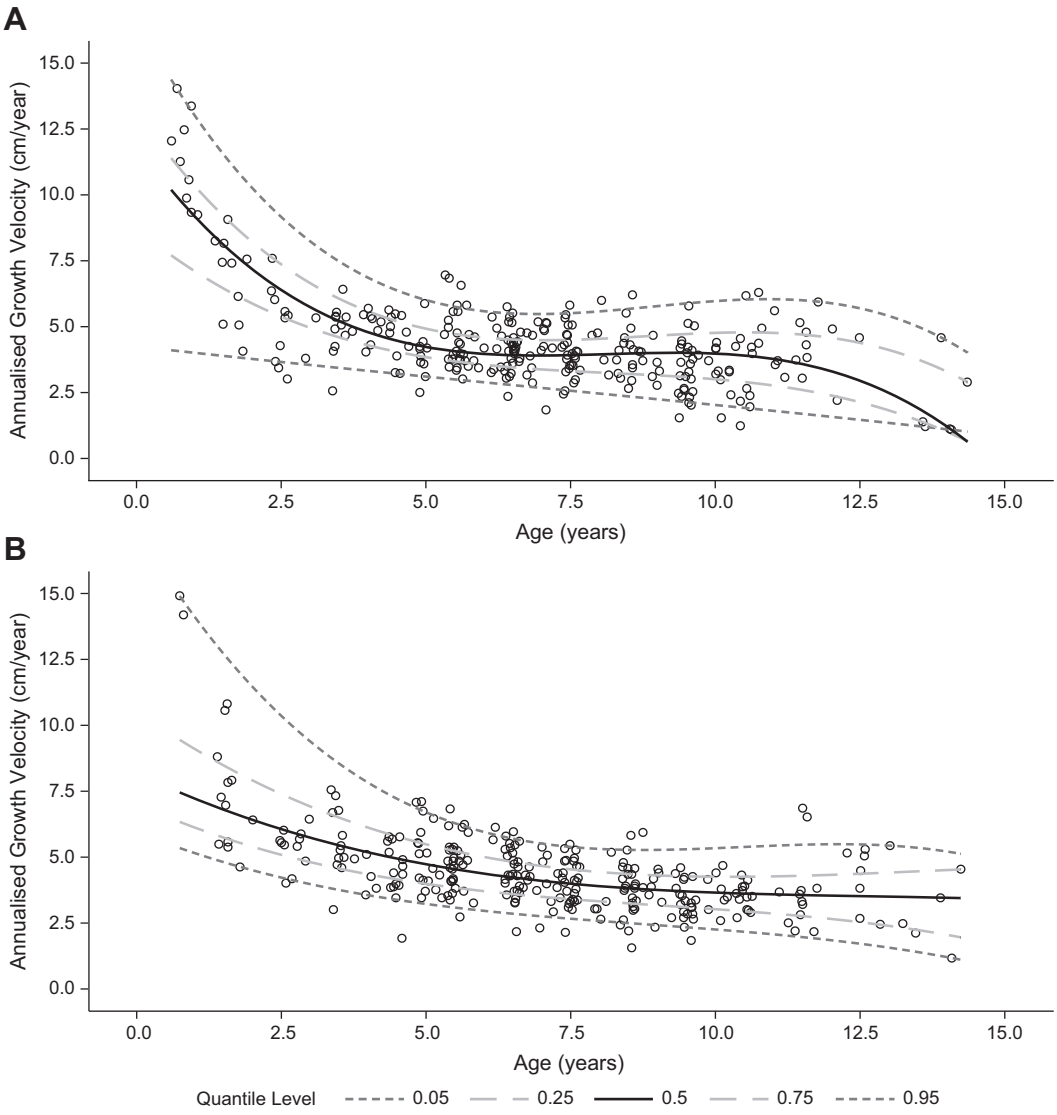

Figure 1 Scatter plots with cubic quantile regression curves of annualized growth velocity (AGV) from birth to 15 years in (A) female children and (B) male children. Black circles represent AGV for an individual participant where age is the midpoint for the AGV interval of 12 months ± 3 months. The dashed lines represent cubic quantile regressions for the 95th, 75th, 50th, 25th, and 5th quantiles. For each participant one AGV associated to each integer year is retained for the plot. Plots based on full analysis set excluding AGV based on height assessments following limb lengthening, growth hormone, or other investigational treatments and erroneous AGV assessments <0.

studies investigating the efficacy and safety of vosoritide for the treatment of achondroplasia. The study population of 363 children represents one of the largest datasets of prospectively collected longitudinal growth data using predefined standardized anthropometric techniques and with regular scheduled assessments.

The demographics of the children reflect the published literature on the epidemiology of achondroplasia.[14-16] There were equal numbers of male and female children, most were Tanner stage I (reflecting the mean age of 5.1 years), and most were White, in line with the geographic locations of the participating sites. Our anthropometric data demonstrate that the children had disproportionate short stature and closely resembled similar aged populations with achondroplasia reported in the literature.[13,15-17] In average stature children, growth velocity during the first years of life is rapid, then decreases and becomes relatively steady before a second rapid growth spurt during puberty.[18] Although the pattern of growth in children in the present study up to 12 years was similar to that of average stature children, the magnitude of growth was smaller in all age groups. Consequently, mean height in both girls and boys was lower from birth compared with average stature children, and remained low in all age groups throughout the study.[14] The magnitude of the height deficit between children in this study and average stature children, measured by the height *z*-score, increased with age. No conclusions can be made on pubertal growth in the present study owing to the small number of patients in the older age groups. The standing height data are consistent with published data on achondroplasia, supporting the close

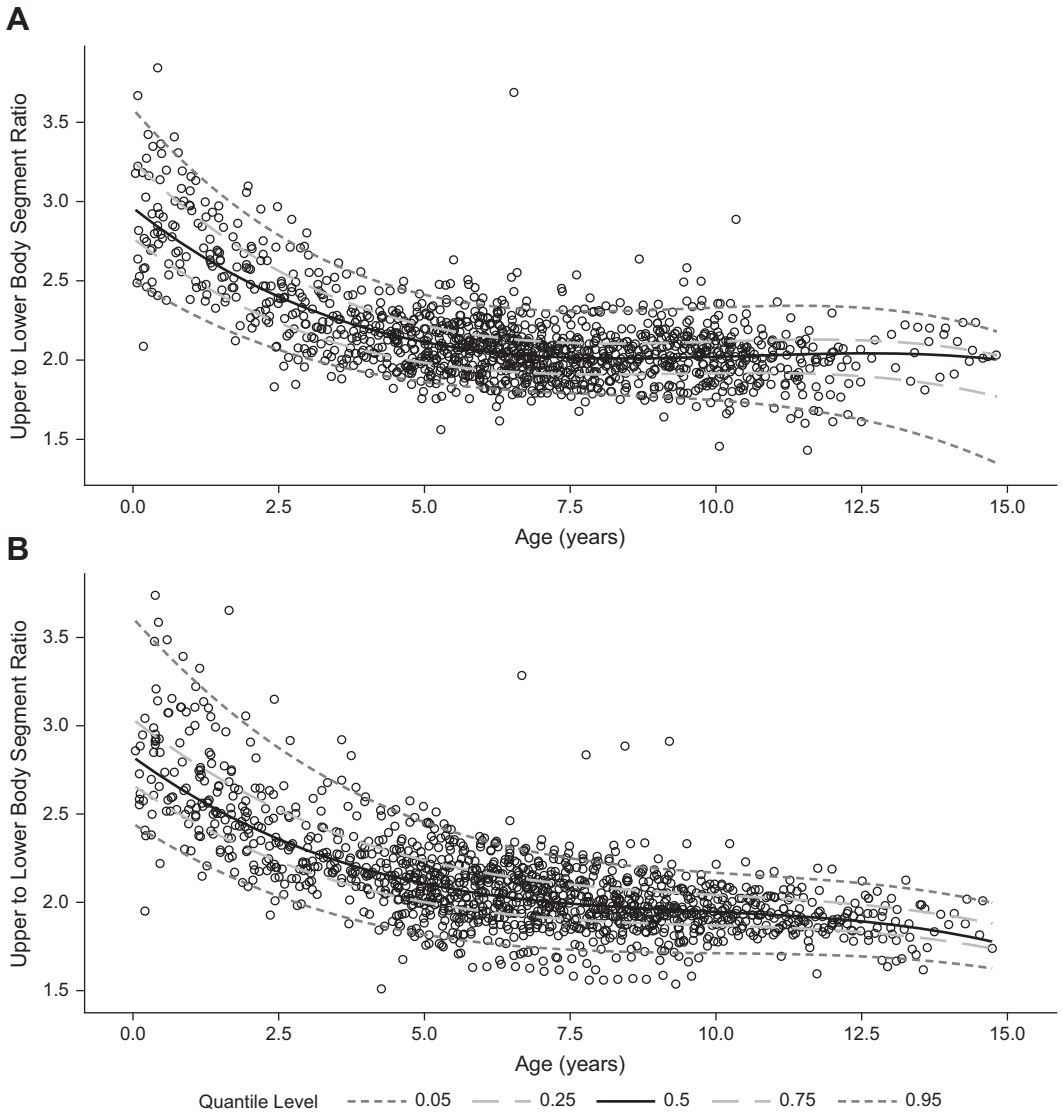

Figure 2 Scatter plots and cubic quantile regression curves of upper-to-lower body segment ratio from birth to 15 years in (A) female children and (B) male children. Black circles represent assessments for upper-to-lower body segment ratio for an individual participant. The dashed lines represent cubic quantile regressions for the 95th, 75th, 50th, 25th, and 5th quantiles. All assessments are included for each participant. Plots based on full analysis set excluding upper-to-lower body segment ratio assessments following limb lengthening, growth hormone, or other investigational treatments and assessments ≤1 or >4.

resemblance of children in our study according to sex and age with the overall population with achondroplasia.[13,15,16]

Analyses on our data show that consideration needs to be given to the nuances of average stature referenced height *z*-scores when used to assess longitudinal height deficit in people with achondroplasia. Height *z*-score is a favored outcome to assess growth because it has the potential advantage that it can summarize data irrespective of age and sex, unlike other growth outcomes (ie, absolute height). Although changes in average stature referenced height *z*-scores over time in a person with achondroplasia can reflect changes in their growth, they also reflect changes in the growth pattern of the average stature reference population. For example, data from this study demonstrate that the height *z*-scores during the period that the average stature population experiences their growth spurt are not stable in children with achondroplasia. *z*-Scores in participants with achondroplasia tended to decline and then increase during this period, solely because of the increased variability (the denominator of the *z*-score) in the reference population caused by the growth spurts (which are less pronounced in children with achondroplasia, who undergo endocrinologic puberty although the accompanying accelerated growth is likely hampered by the *FGFR3* pathogenic variant). As demonstrated by the present analyses, caution is warranted when using the average stature referenced *z*-score as an outcome in an interventional trial to assess treatment benefit over time in pubescent children as its utility is greater in providing an assessment relative to the average stature population at a specified age (Supplemental Figure 3).

An alternative to using the average stature population as the reference for *z*-scores is to use achondroplasia-reference *z*-scores (Supplemental Figure 4). The interpretation of this outcome is potentially less complicated given that the reference population has the same growth pattern, hence changes over time in height deficit are not due to the underlying reference population but rather could reflect external factors (ie, interventions being assessed). Taking a broader view, it must be recognized that *z*-scores of any form are simply a numeric transformation of height and, although potentially useful, clinically the most relevant outcomes are height gains that reduce physical disability/difficulty in daily life and treatments that reduce pain and fatigue.

Consistent with the literature,[17] children in our study had a disproportionate upper-to-lower body ratio. Mean upper-to-lower body segment ratios in both girls and boys were highest for those aged <1 year and decreased to approximately 2 for both sexes at age 4 years and continued to decline gradually after this but never normalizing. People with achondroplasia have a much greater upper-to-lower body ratio compared with average stature age-specific reference data. Because the growth of the extremities is limited in achondroplasia relative to the more typical growth of the trunk, the ratio of the upper-to-lower body in children with achondroplasia never reaches 1.

In this study, concentrations of serum collagen X biomarker, the degradation fragment of type X collagen, were relatively higher in the first 2 years of life (when growth rates are the fastest) with pronounced variability. Concentrations of this biomarker remained relatively consistent across ages 3 to 12 years with a slight elevation between ages 8 and 11 years, followed by a marked decrease after age 13, albeit observed with smaller sample sizes.

Strengths of this multinational prospective observational study include a robust protocol, standardized study procedures, regular (3-monthly) anthropometric measurements, few missing data, and consistency in the techniques and methods used to collect the data, such that the quality is consistent with that of an interventional study. Several limitations must also be discussed. The population comprised children whose caregivers were willing to participate, and half of the participants were enrolled in the United States. Consequently, while this cohort might accurately represent those of European and North American origin,[18] it may not be generalizable to other ethnic groups or nationalities. Pubertal growth, which typically lacks an observed acceleration in children with achondroplasia, could not be evaluated in this study owing to the small number of children in the older age groups and most were Tanner stage I. While this manuscript reports on growth parameters alone, further data on wider health measures, including quality of life, activities of daily living, and frequency and type of medical and surgical interventions performed in children with achondroplasia, are planned for future publications.

Prospectively collected longitudinal growth data ascertained using standardized techniques will represent an important resource to carefully document natural history and evaluate the effects of new therapies such as vosoritide with regards to their effects on modulating growth in children with achondroplasia. These also include emerging therapies, such as a long-acting C-type natriuretic peptide compound (TransCon CNP; NCT04085523),[19] a soluble *FGFR3* ligand trap (recifercept),[20] and an oral tyrosine kinase inhibitor (infigratinib),[21] which are in early stages of clinical development (NCT04638153, NCT05116046, NCT05145010, NCT04265651), as well as several other drugs in preclinical development. The present rigorously collected data set will add to a growing number of reference standards that can be used for this important purpose.

Data Availability

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a website (www.BioMarin.com) beginning at 6 months and ending at 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc. ClinicalTrials.gov (Identifier: NCT01603095).

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Ethics Declaration

The Institutional Review Board or Independent Ethics Committee at each site approved the study protocol and documentation. The main Institutional Review Board was the Royal Children's Hospital Melbourne, Human Research and Ethics Committee, with study approval number HREC32148C. The study was conducted in accordance with the European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, the relevant United States Code of Federal Regulations sections and/or other national and local regulations as applicable, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guideline (Guideline for Good Clinical Practice), and the ethical principles established by the Declaration of Helsinki. Written informed consent from all participants legally authorized representative (parent or legal guardian) and child assent (as appropriate and if required) were obtained prior to enrolment in the study. All individual patient data was de-identified. All authors have signed ethics attestation statements that have been submitted to the editorial staff at *Genetics in Medicine* and are available on request.

Conflict of Interest

All authors were investigators in this clinical trial except for C.A., K.L., K.G., G.J., C.M., E.F., A.H.-L., and J.D., who are employees of the funder (BioMarin). R.S. L.T., F.R., K.M., have received consulting fees and grants from BioMarin. M.I. and W.R.W. have received consulting fees from BioMarin. D.B. has received grants from BioMarin. J.C. has received honoraria from Genzyme, Applied Therapeutics, and CHIESI Farmaceutici S.p.A. P.A. has received honoraria from BioMarin. P.H. and C.B. have received consulting fees, honoraria and grants from BioMarin. J.H.F. has received consulting fees from BioMarin,Therachon AG and Ascendis, and grants from BioMarin. M.B. has received consulting fees and grants from BioMarin, Ascendis, Therachon, QED, Tyra Biosciences, and Alexion Pharmaceuticals, Inc, and grants from BioMarin, Ascendis, Therachon, QED, Medlife, SOBI, and Shire. K.K.W. has received consulting fees from BioMarin, grants from BioMarin, Ultragenyx, Pfizer, and Theracon, and royalties from UptoDate.com. L.P. has received consulting fees from BioMarin, Sanofi/Genzyme, and Therachon, and grants from Sanofi/Genzyme, Takeda/Shire, Pfizer, and SOBI. The other authors declare no conflict of interests.

Additional Information

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