

Vosoritide Treatment Does Not Change the Robust Bone Phenotype of Children with Achondroplasia

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Abstract

Background

Vosoritide is an FDA-approved bone-lengthening treatment for children with achondroplasia, the most common form of disproportionate short stature. Whether this bone-lengthening treatment provides commensurate changes in cross-sectional morphology, to ensure bone strength is not deleteriously affected, is unknown. Thus, we sought to characterize the bone morphological parameters of children with achondroplasia on vosoritide using measurements of the second metacarpal.

Methods

This study included deidentified anteroposterior hand/wrist radiographs from 30 children with achondroplasia (13 males, 17 females; age 5.8 – 11.1 years). Proprietary hand films were collected at screening (pre-treatment) and at 5 years on treatment. Measurements included second metacarpal length and midshaft width, cortical thickness, robustness (total area/length) and cortical area, which correlates with strength. Measurements were compared between the two time-points via non-parametric Wilcoxon tests, and with 378 radiographs from 114 average-statured controls who did not receive vosoritide treatment (61 males, 53 females; age 6 – 16 years) via Kruskal-Wallis tests ($p < 0.05$).

Results

Compared to average-stature controls, children with achondroplasia exhibited a more robust bone phenotype ($p < 0.001$). After 5 years of vosoritide treatment, children with achondroplasia demonstrated increased metacarpal length and cortical area compared to their own baseline values (all $p < 0.05$). No sex differences were observed.

Conclusions

Altogether, increases in metacarpal total area and cortical area kept up with increases in metacarpal length over the course of 5 years of vosoritide treatment. As the bones lengthened, subperiosteal expansion continued at a pace which maintained robustness, allowing the bone to remain strong. This preliminary data suggests that vosoritide did not alter the naturally robust bone phenotype of children with achondroplasia.

Clinical trial registration

Clinical trial registry: ClinicalTrials.gov. Clinical trial numbers: NCT02055157 (registered January 13, 2014) and NCT02724228 (registered January 26, 2016).

BACKGROUND

Achondroplasia is an autosomal dominant disorder of endochondral bone formation caused by gain-of-function variants in the fibroblast growth factor receptor 3 gene (*FGFR3*) [1, 2]. Achondroplasia is one of the most common types of non-lethal skeletal dysplasia, with an estimated prevalence of 1 in 10,000 to 30,000 live births [2]. Constitutive activation of *FGFR3* inhibiting endochondral bone formation leads to a characteristic pattern of skeletal features [2, 3] including disproportionate short stature and macrocephaly [3–5]. The abnormalities in bone growth and development can cause a spectrum of clinical symptoms and complications, including hydrocephalus, foramen magnum stenosis, spinal stenosis, bowing of the legs, midface hypoplasia, obstructive sleep apnea, and recurrent otitis media [4, 6, 7], which require early monitoring and a multidisciplinary approach to reduce morbidity and mortality [2, 3]. Furthermore, children with achondroplasia tend to have altered bone phenotype, specifically changes in cortical thickness, robustness, and length.

C-type natriuretic peptide, encoded by the *NPPC* gene, stimulates endochondral ossification through binding to its receptor, natriuretic peptide receptor 2 (NPR2), thus playing a direct role in regulating chondrocytes in the growth plate [8, 9]. In murine models of achondroplasia, subcutaneous administration of vosoritide, a recombinant analogue of C-type natriuretic peptide [10], showed increased long-bone and craniofacial growth [10, 11], indicating that vosoritide may benefit individuals with achondroplasia. Based on clinical trial evidence that vosoritide is safe and has persistent growth-promoting effects in children [9, 12–14], it has been the first and only pharmacological therapy approved thus far for the treatment of children with achondroplasia and open physes from birth in the USA, Japan and Australia, and from age ≥ 4 months in the European Union and ≥ 6 months in Brazil. However, although vosoritide has been shown to successfully increase the annual growth velocity in children with achondroplasia, our understanding of how this treatment affects bone morphological traits and whether it may alter the bone phenotype of children with achondroplasia remains very limited.

Healthy bones need to be stiff to resist deformation, flexible enough that they do not crack under load, and light enough to enable movement [15]. Changes in the material and structure of bones, due to aging, disease or drug treatment, can lead to fragility and risk of fracture [16]. Morphological parameters such as cortical thickness and cross-sectional geometry influence skeletal stiffness and strength. Clinically, bone health in children is typically assessed using bone mineral density measurements obtained via dual-energy X-ray absorptiometry (DXA) or peripheral quantitative computed tomography (pQCT), which provide quantitative assessments of bone quality beyond linear dimensions. In this study, we use metacarpal length and width as morphological indicators to examine changes over time, recognizing these are research markers rather than clinical diagnostic measures. The second metacarpal is an indicator of overall bone health [15] and robustness (total cross-sectional area/length) [17, 18] and can predict risk of vertebral fracture in women [19]. While metacarpal morphology is not used clinically to assess fracture risk in children, it provides a consistent anatomical region for studying bone morphology in growth disorders. Additionally, cortical area (Ct.Ar) of the second metacarpal measured from hand radiographs has been shown to be a key indicator of bone strength in both males and females [20].

Robustness, defined as total metacarpal cross-sectional area divided by bone length, is a heritable trait which is used to determine the amount of transverse expansion relative to longitudinal growth in long bones (i.e. the relation between periosteal growth and expansion at the growth plate) [21, 22]. Multiple studies have assessed metacarpal robustness using the Bolton-Brush collection of longitudinal hand radiographs from 37 white girls and 32 white boys aged 0–8 years old unaffected by skeletal dysplasia. These studies have shown that bone growth patterns in children in the general population vary across a wide spectrum, from more slender to more robust [18, 23]. Furthermore, genetic and environmental factors have been shown to define the variation in robustness by the age of 2 years old in the general population [23]. Thus, individuals obtain a unique trait set, either a slender or robust phenotype, which in turn may dictate the mechanism of treatment that would optimize their bone strength [24]. For example, individuals with a slender bone phenotype may benefit from therapies meant to increase periosteal expansion, while those with robust bones may benefit from treatments that focus on increasing cortical thickness given their already greater size [24].

In a retrospective study published by our group in 2017, individuals with achondroplasia ($n = 20$; age 5 months to 58 years) had more robust bones than age- and sex-matched controls from the Bolton-Brush collection, likely due to suppressed longitudinal growth [22]. Relative cortical area (RCA) was lower than expected for the increased robustness, suggesting that individuals with achondroplasia do not develop sufficient bone mass (cortical area), likely due to expansion of the marrow space [22]. The study also showed sexual dimorphism in bone morphological traits similar to that of the general population.

The primary objective of the present study is to characterize specific bone morphological traits - specifically, length, width, cortical thickness, and robustness - of the second metacarpal in children with achondroplasia treated with vosoritide. We compare these measurements at baseline and after five years of treatment, as well as to age- and sex-matched controls from the Bolton-Brush collection. By focusing on these defined metacarpal parameters, this study aims to assess whether bone robustness is maintained during vosoritide treatment. Evaluating these targeted morphological traits may provide valuable insights to clinicians considering new therapeutic options for this population.

METHODS

This was an IRB-approved retrospective review of bone age films (anteroposterior hand/wrist) collected during the multinational, phase 2, dose-finding study (Study 111–202, ClinicalTrials.gov number, NCT02055157) and extension study (Study 111–205, NCT02724228). The trial methods and results have been reported elsewhere [12]. As the data presented here was from the initial dose-finding study, it was not designed to have an untreated control arm.

In brief, Study 111–202 was conducted from January 2014 to October 2017 at nine sites in the United States, Australia, France and the United Kingdom. Eligible children were aged 5 – 14 years at screening, had achondroplasia confirmed by genetic testing, and had completed ≥ 6 months of a run-in observational growth study (Study 901, NCT01603095) to establish their baseline annualized growth

velocity. Children who completed the Study 111–202 were eligible to enroll in a long-term extension study (Study 111–205) in which they received daily vosoritide doses of 15.0 µg/kg or 30.0 µg/kg. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate. Studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocols were approved by the relevant ethics boards.

The safety results for Study 111–202 have been reported on ClinicalTrials.gov. The full adverse event profile for the first year of this phase 2, dose-finding study has been previously reported [12]. The most commonly-occurring adverse events were transient injection-site reactions and injection-site erythema, followed by pyrexia, vomiting, and upper respiratory tract infection [12]. The long-term extension study remains ongoing. Under the current protocol, participants receive vosoritide until they reach near final adult height (NFAH) and continue to participate until reaching NFAH and at least 16 years of age for females and 18 years of age for males; adverse events are being reported and monitored on a continuing basis.

Outcome measures

Deidentified anteroposterior (AP) hand/wrist radiographs from children with achondroplasia were reviewed and measured using MicroDicom DICOM Viewer (MicroDicom, Sofia, Bulgaria) at two time-points: screening (pre-treatment) and five years on treatment. X-rays were performed at separate facilities following a standard procedure. A vertical beam was directed at the midway of the subject's hand, perpendicular to the third metacarpal phalangeal joint, and participants' hands were positioned 40 inches from the imaging cassette. A marker was present and calibration bars were visible on all images in order to calibrate pixel dimensions and thus address any variation in the acquisition of the digitized images across sites. All images were evaluated to ensure that the exposure was adequate in order to view the bony detail and soft tissue and that the hand was in correct neutral anatomical position (no rotation), with the back of the hand symmetrical. All images included in the study were of high quality, and none showed concerns related to motion or movement artifacts that may have compromised obtaining image measurements.

Metacarpal length and diaphyseal widths (diameters) were measured directly from the digitized hand X-rays. Dimensional markers included in the hand radiograph were used to calibrate the digitized images, thereby accommodating variation in image acquisition protocols. Metacarpal length (L_e) was measured as the distance between the proximal end to the distal surface of the secondary center of ossification. Marrow diameters ($Ma.Dm$, distance between inner cortices) and outer bone diameters ($B.Dm$, distance between outer cortices) were measured at 50% and 60% of the total metacarpal length and then averaged. Morphological measures were derived from the average marrow and outer diameters and assuming a circular cross-sectional shape. Morphological measures included total cross-sectional area (πR^2 , R = outer bone diameter/2), marrow area (πr^2 (r = inner bone diameter/2)), and cortical area (total area – marrow area). Cortical area served as a measure of bone mass and has been shown to correlate with bone strength measured directly in human adult cadavers without a sex-specific difference [20].

Relative cortical area (RCA, cortical area/total area) and robustness (total area/bone length) were also analysed in order to better understand changes in the bone phenotype and estimate metacarpal size and strength [22].

Measurements were also compared to the second metacarpal morphology reported previously for healthy, ambulatory girls and boys enrolled in the Bolton-Brush study. All radiographs were measured by a single trained investigator (C.D.) using a standardized measurement protocol applied consistently across all images and time points. Details of the imaging protocols for this control group can be found in Pandey et al, JBMR 2009 and Bhola et al, Bone 2011 [18, 23]. Briefly, hand radiographs with calibration markers were digitized for 53 white girls and 61 white boys. Hand radiographs from children in the Bolton-Brush study younger than six years-old and older than sixteen years-old were excluded in order to better match the age range of the treated cohort. Bone length and metacarpal inner and outer diameters of controls were measured at 40, 50, and 60% of bone length, then averaged. Derived morphological traits (Tt.Ar, Ma.Ar, Ct.Ar) were calculated using the formulas described above. Cortical area, Ct.Ar, serves as a dual measure of bone mass and bone strength and does so without a sex-specific discrepancy [20].

Statistical analysis

Statistical analyses included descriptive statistics used to describe the demographics of the study and control populations. Radiograph measurements were compared with radiographs from the Bolton-Brush collection [22] via non-parametric Kruskal-Wallis tests (two-sided). Baseline measurements for children with an x-ray at 5 years on treatment were compared to their treated 5-year measure using a one sample Wilcoxon signed-rank test (two-sided). Testing was descriptive and hypotheses were generated for p values < 0.05. All statistical analyses were conducted using SPSS 29 for Windows (IBM SPSS Statistics, NY, USA). Figures were created using GraphPad Prism 10.2.2.

RESULTS

Deidentified AP hand/wrist radiographs from 30 children with achondroplasia (13 boys, 17 girls; age 5.8 – 11.1 years) were reviewed and measured. Baseline screening x-rays were available for 27 children (13 boys, 14 girls). In addition, 16 children (9 boys, 7 girls) with a baseline x-ray also had an x-ray available to measure at 5 years on treatment. Measurements were compared with 378 hand/wrist radiographs from 114 controls (61 boys, 53 girls; age 6 – 16 years). The baseline characteristics of the study populations are detailed in Table 1.

Table 1
Characteristics of participants with achondroplasia and Bolton-Brush controls at screening.

Average age (years), at screening	Study 202/205 Participants (n = 30)	Bolton-Brush Controls (n = 114)
	8.16 (1.57)	11.31 (3.01)
Age range (years)	5.8–11	6–16
Sex		
Male	13 (43.3)	61 (54)
Female	17 (56.7)	53 (46)
Number of radiographs (total)	130	378
Race		
White	21 (70.0)	114 (100.0)
Asian	6 (20.0)	-
Other	1 (3.3)	-
Unknown	2 (6.7)	
Hispanic or Latino ethnicity	2 (6.7)	-
Weight, kg	21.61 (4.91)	-
Weight Z-score	-1.56 (1.07)	-
Height, cm	100.16 (8.03)	
Height Z-score	-5.12 (1.00)	
Body mass index, kg/m ²	20.31 (2.33)	-
Body mass index Z-score	1.73 (0.42)	-
Annualized growth velocity (cm/yr), 12-month intervals	3.75 (1.28)	-

Characteristics of participants with achondroplasia from study 202/205 and controls from the Bolton-Brush collection at screening. Z-scores were calculated using CDC references. Z-scores were calculated using CDC references. Data are n (%) or mean (SD). SD, standard deviation.

Compared with screening (pre-treatment), participants with achondroplasia demonstrated longer metacarpals at year 5 of treatment with vosoritide (45.03 ± 5.14 mm versus 36.28 ± 4.76 mm; $p < 0.05$) with increased cortical area (35.42 ± 9.87 mm² versus 11.58 ± 6.89 mm²; $p < 0.05$) (Table 2, Fig. 1A, 1B). Participants on five years of treatment also displayed increased cortical thickness (1.76 ± 0.42 versus 1.22 ± 0.25 ; $p < 0.05$) (Fig. 2A). Metacarpal robustness was high at screening and there was significant

increase in robustness after five years on treatment (1.10 ± 0.30 mm to 1.20 ± 0.38 mm; $p < 0.05$) (Fig. 1D). Metacarpal RCA also significantly increased from screening to 5 years on treatment (0.57 ± 0.10 to 0.67 ± 0.12 ; $p < 0.05$) (Fig. 2C). Changes to all metacarpal parameters from screening to five years of treatment are shown in Figs. 1 and 2. No differences in metacarpal parameters were seen between males and females with achondroplasia at screening or at five years on treatment (Table 3).

Comparison of metacarpal (A) length, (B) cortical area (C) robustness and (D) total area for 16 children with achondroplasia at screening and at five years on vosoritide treatment. Box and horizontal line indicate the median with quartile 1 and quartile 3; plus (+) indicates mean, whiskers indicate the 2.5 and 97.5 percentiles.

Comparison of metacarpal (A) cortical thickness, (B) marrow area and (C) relative cortical area (RCA) for 16 children with achondroplasia at screening and at five years on vosoritide treatment. Box and horizontal line indicate the median with quartile 1 and quartile 3; plus (+) indicates mean, whiskers indicate the 2.5 and 97.5 percentiles.

Table 2
Second metacarpal measurements before and after 5 years of vosoritide and in controls.

Measure	Participants with achondroplasia				Bolton–Brush controls (n = 378 radiographs from 114 unaffected children)
	Full Baseline (n = 27)	Baseline for Children with an Assessment at 5 Years (n = 16)	5 Years on Treatment (n = 16)	Change from Baseline (n = 16)	
Second metacarpal length (mm)	35.71 ± 4.51^a	36.28 ± 4.76	45.03 ± 5.14^b	8.75 ± 3.38^d	56.83 ± 9.40
Total area (mm ²)	39.30 ± 12.04	40.65 ± 14.57	54.27 ± 18.2^b	13.63 ± 7.68^d	39.01 ± 11.7
Cortical area (mm ²)	21.80 ± 6.29^a	22.58 ± 6.89	35.42 ± 9.87^b	12.84 ± 6.26^d	29.64 ± 9.57
Marrow area (mm ²)	17.50 ± 7.84^a	18.07 ± 9.04	18.85 ± 12.44^b	0.78 ± 6.53	9.37 ± 4.81
Cortical thickness (mm)	1.20 ± 0.27^a	1.22 ± 0.25	1.76 ± 0.42^b	0.54 ± 0.31^d	1.10 ± 0.35
Relative cortical area	0.57 ± 0.10^a	0.57 ± 0.10	0.67 ± 0.12^b	0.10 ± 0.08^c	0.76 ± 0.10
Robustness (mm)	1.10 ± 0.30^a	1.12 ± 0.36	1.20 ± 0.38^b	0.08 ± 0.13^c	0.68 ± 0.13

Measurements of the second metacarpal (mean ± standard deviation) in participants with achondroplasia before and after 5 years on treatment with vosoritide and in controls from the Bolton–Brush collection. Control population vs. ^ascreening, ^b5 years on treatment (Kruskal-Wallis test), $p < 0.05$. Baseline for children with assessment at 5 years vs. 5 years on treatment (Wilcoxon paired test), ^c $p < 0.05$, ^d $p < 0.001$. Le, second metacarpal length; T.Ar, total area; Ct. Ar, cortical area; M.Ar., marrow area; Ct.Th., cortical thickness; RCA, relative cortical area; T.Ar/Le, robustness.

Table 3
Second metacarpal measurements by sex at screening and after 5 years of vosoritide.

	At Screening		5 Years on Treatment	
	Female	Male	Female	Male
	(n = 14)	(n = 13)	(n = 7)	(n = 9)
Second metacarpal length (mm)	35.90 ± 3.59	35.50 ± 5.57	43.56 ± 4.73	46.17 ± 5.42
Total area (mm ²)	37.97 ± 11.83	40.73 ± 12.97	54.75 ± 20.22	53.90 ± 17.75
Cortical area (mm ²)	22.39 ± 5.74	21.16 ± 7.16	35.67 ± 8.07	35.21 ± 11.57
Marrow area (mm ²)	15.57 ± 7.81	19.57 ± 7.94	19.08 ± 16.82	18.68 ± 8.82
Cortical thickness (mm)	1.27 ± 0.27	1.12 ± 0.27	1.82 ± 0.49	1.72 ± 0.39
Relative cortical area	0.60 ± 0.10	0.53 ± 0.11	0.69 ± 0.15	0.66 ± 0.10
Robustness (mm)	1.07 ± 0.35	1.14 ± 0.27	1.27 ± 0.48	1.15 ± 0.30

Measurements of the second metacarpal (mean ± standard deviation). All comparisons between sexes were non-significant. Le, second metacarpal length; Tt.Ar, total area; Ct.Ar, cortical area; Ma.Ar, marrow area; Ct.Th, cortical thickness; RCA, relative cortical area; robustness, total area/length.

Comparison with Bolton-Brush control population

At screening, participants with achondroplasia had shorter metacarpals than the Bolton-Brush control population (35.71 ± 4.51 mm versus 56.83 ± 9.40 mm; $p < 0.05$), smaller RCA (0.57 ± 0.10 versus 0.76 ± 0.10; $p < 0.05$) and higher robustness (1.10 ± 0.30 versus 0.68 ± 0.13 mm; $p < 0.05$) (Table 2). Robustness remained higher and RCA lower than that of the control population at 5 years on treatment (all $p < 0.001$) (Table 2). Cortical area of the treated children with achondroplasia exceeded that of the Bolton-Brush cohort after 5 years of treatment.

DISCUSSION

To the best of the authors' knowledge, this is the first study that offers important insight into how vosoritide, a newly FDA-approved treatment for bone lengthening in children with achondroplasia, may affect their bone phenotype and morphology. As expected to see in growing children, we found that the second metacarpal length, cortical thickness, and cortical area, which correlates with experimentally-determined metacarpal strength [20], increased over the course of five years. The growth-promoting, bone-lengthening effect of vosoritide in children with achondroplasia, relative to placebo-treated controls, has been established in the randomized, placebo-controlled phase 2 and phase 3 trials [12–14]. Most importantly, children with achondroplasia did not change their naturally robust bone phenotype over the course of five years of treatment designed to increase growth velocity, suggesting that periosteal expansion continued outward at a pace that maintained or even increased robustness. Overall, we observed that increases in total cross-sectional area occurred proportionally with increases in bone length resulting from growth and treatment, such that the robusticity values remained stable over time. This finding is clinically meaningful, as it suggests that bone modeling during vosoritide treatment maintained proportional structural adaptation, rather than resulting in disproportionate elongation or compromised morphology. These preliminary findings suggest that vosoritide treatment does not lead to unfavorable changes in bone structure in children with achondroplasia, though further research is needed to assess functional outcomes such as bone strength or fracture risk.

The present study found no sexual dimorphism in metacarpal parameters at screening or at five years on treatment, in contrast with the general population. Previous work by Pandey and colleagues has shown that prepubertal girls tended to have more slender metacarpals with higher RCA compared to prepubertal boys [23]. This lack of sex-specific differences in metacarpal parameters also contradicts our earlier-reported findings in a smaller cohort of untreated individuals with achondroplasia ($n = 20$; 5 months – 58 years) [22]. The cohort of participants presented here larger than what has been previously published, with a current cohort of $n = 30$ participants compared to $n = 20$ participants [22]. Importantly, the age ranges of the boys and girls are similar at both time-points we investigated, strengthening the comparisons made between sexes. One potential explanation for our observed results may be that the genetically-driven impaired longitudinal growth of the bones due to the *FGFR3* constitutive activation in children with achondroplasia has a more persistent effect on the overall bone morphology compared to the underlying sex-driven trends seen in the general population. Our findings that children with achondroplasia have a pattern of more robust bones with lower RCA compared to the general population does parallel those reported by our group previously in 2017 [22].

Altogether, this study may have important clinical implications in terms of treatment choices for children with achondroplasia. However, this work is not without its limitations. Future work comparing treated and untreated children with achondroplasia over time is necessary to understand the long-term effect of treatment with vosoritide on the development of bone strength. Furthermore, we cannot rule out possible attrition bias within our data as x-rays were not available for review from the full cohort of participants at year 5 on treatment. Moreover, because these radiographs were collected retrospectively within a single-arm, dose-finding clinical trial that did not include an untreated achondroplasia control arm, we cannot exclude bias related to the source of the data. In addition, a larger sample size of children with

achondroplasia on treatment would allow us to ensure the reliability of these findings and validate our initial observations regarding the bone phenotype and morphology of those on vosoritide, as well as whether the lack of sex-specific differences in bone morphological traits holds in this population.

CONCLUSIONS

In this cohort of children with achondroplasia, five years of vosoritide treatment increased second metacarpal length, cortical thickness, and cortical area without altering the naturally robust bone phenotype characteristic of achondroplasia. Increases in total cross-sectional area and cortical area kept pace with gains in metacarpal length, indicating that subperiosteal expansion continued proportionally and that morphological robustness was preserved during treatment. These preliminary findings suggest that vosoritide does not adversely affect bone structure in children with achondroplasia. Further studies comparing treated and untreated children over time, with larger cohorts and direct measures of bone strength, are needed to confirm these observations and to determine the long-term functional implications for fracture risk.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Hospital for Special Surgery Institutional Review Board, New York, New York, USA. The data analyzed in this study were derived from the multinational phase 2 dose-finding clinical trial, Study 111-202 (ClinicalTrials.gov identifier: NCT02055157; registered January 13, 2014), and its long-term extension study, Study 111-205 (ClinicalTrials.gov identifier: NCT02724228; registered January 26, 2016). The original clinical studies were conducted in accordance with the Declaration of Helsinki and were approved by the relevant ethics committees. Written informed consent was obtained from a parent or legal guardian of each participant, and assent was obtained from participants where appropriate.

Clinical trial registration

Clinical trial registry: ClinicalTrials.gov. Clinical trial numbers: NCT02055157 (registered January 13, 2014) and NCT02724228 (registered January 26, 2016).

Consent for publication

Not applicable

Availability of data and materials

The de-identified hand radiographs provided by BioMarin Pharmaceutical from the 202/205 clinical trials may be available upon request to the company. Investigators are able to request access to these radiographs and supporting documents of interest via www.BioMarin.com. The hand radiographs from

the Bolton-Brush collection are part of the Bolton-Brush Growth Study Center at Case Western Reserve University; they are available to interested investigators at Use | School of Dental Medicine | Case Western Reserve University.

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BioMarin Pharmaceutical provided the hand radiographs used for analysis from the Study 202 and Study 205 clinical trials. Measures of bone morphology derived from the hand radiographs and the statistical analyses were conducted by CED. A biostatistician at BioMarin Pharmaceutical evaluated the statistical analysis for accuracy and completeness. A medical writer paid by the sponsor provided a draft version of the paper, which was heavily edited by the co-authors. The final manuscript represents the independent data analysis, interpretations, and perspectives of all authors.

Competing interest

Author CLR has received consulting fees and payment for presentations from BioMarin. Author EMC is a noncompensated member of the Little People of America Medical Advisory Board.

Authors' contributions

CR, KJ, EC, and CD: Conceptualization, methodology, writing of original draft - developed the research concept, designed the methodology, and drafted the initial manuscript. CD: Data curation, formal analysis, visualization - collected, analyzed, and interpreted the data, and contributed to the creation of visual materials (figures, tables). CR, EC, CD: Investigation, resources, project administration – conducted the experiments, provided critical resources, and managed project administration. CR, KJ, EC, CD: Writing, validation, supervision – Writing of the manuscript, validated the findings, and provided oversight and leadership throughout the project. CD and CB: Revision – reviewed the edited and final manuscript. CR, KJ, EC, CD, and CB reviewed the final manuscript and approved the decision to submit for publication.

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References

1. Foldynova-Trantirkova S, Wilcox WR, Krejci P. Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. *Hum Mutat.* 2012;33:29–41. <https://doi.org/10.1002/humu.21636>.
2. Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet.*, London E. 2007;370:162–72. [https://doi.org/10.1016/S0140-6736\(07\)61090-3](https://doi.org/10.1016/S0140-6736(07)61090-3)
3. Ireland PJ, Pacey V, Zankl A, Edwards P, Johnston LM, Savarirayan R. Optimal management of complications associated with achondroplasia. *Appl Clin Genet.* 2014;7:117–25.

<https://doi.org/10.2147/TACG.S51485>.

4. Trotter TL, Hall JG, American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. *Pediatrics*. 2005;116:771–83. <https://doi.org/10.1542/peds.2005-1440>.
5. Carter EM, Davis JG, Raggio CL. Advances in understanding etiology of achondroplasia and review of management. *Curr Opin Pediatr*. 2007;19:32–7. <https://doi.org/10.1097/MOP.0b013e328013e3d9>.
6. Hunter AG, Bankier A, Rogers JG, Sillence D, Scott CI. Medical complications of achondroplasia: a multicentre patient review. *J Med Genet*. 1998;35:705–12. <https://doi.org/10.1136/jmg.35.9.705>.
7. Wright MJ, Irving MD. Clinical management of achondroplasia. *Arch Dis Child*. 2012;97:129–34. <https://doi.org/10.1136/adc.2010.189092>.
8. Olney RC. C-type natriuretic peptide in growth: a new paradigm. *Growth Horm IGF Res*. 2006;16. <https://doi.org/10.1016/j.ghir.2006.03.016>. Suppl A:S6-14.
9. Savarirayan R, Irving M, Bacino CA, Bostwick B, Charrow J, Cormier-Daire V, et al. C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. *N Engl J Med*. 2019;381:25–35. <https://doi.org/10.1056/NEJMoa1813446>.
10. Lorget F, Kaci N, Peng J, Benoist-Lasselin C, Mugniery E, Oppeneer T, et al. Evaluation of the therapeutic potential of a CNP analog in a Fgfr3 mouse model recapitulating achondroplasia. *Am J Hum Genet*. 2012;91:1108–14. <https://doi.org/10.1016/j.ajhg.2012.10.014>.
11. Yasoda A, Komatsu Y, Chusho H, Miyazawa T, Ozasa A, Miura M, et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. *Nat Med*. 2004;10:80–6. <https://doi.org/10.1038/nm971>.
12. Savarirayan R, Wilcox WR, Harmatz P, Phillips J, Polgreen LE, Tofts L, et al. Vosoritide therapy in children with achondroplasia aged 3–59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Child Adolesc Health*. 2024;8:40–50. [https://doi.org/10.1016/S2352-4642\(23\)00265-1](https://doi.org/10.1016/S2352-4642(23)00265-1).
13. Savarirayan R, Tofts L, Irving M, Wilcox WR, Bacino CA, Hoover-Fong J, 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 Sci*. 2021;23:2443–7. <https://doi.org/10.1038/s41436-021-01287-7>.
14. Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet Lond Engl*. 2020;396:684–92. [https://doi.org/10.1016/S0140-6736\(20\)31541-5](https://doi.org/10.1016/S0140-6736(20)31541-5).
15. Chavassieux P, Seeman E, Delmas PD. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. *Endocr Rev*. 2007;28:151–64. <https://doi.org/10.1210/er.2006-0029>.

16. Barnett E, Nordin BE. The radiological diagnosis of osteoporosis: a new approach. *Clin Radiol*. 1960;11:166–74. [https://doi.org/10.1016/s0009-9260\(60\)80012-8](https://doi.org/10.1016/s0009-9260(60)80012-8).
17. Pearson OM. Activity, climate, and postcranial robusticity: implications for modern human origins and scenarios of adaptive change. *Curr Anthropol*. 2000;41:569–607.
18. Bhola S, Chen J, Fusco J, Duarte GF, Andarawis-Puri N, Ghillani R, et al. Variation in childhood skeletal robustness is an important determinant of cortical area in young adults. *Bone*. 2011;49:799–809. <https://doi.org/10.1016/j.bone.2011.07.018>.
19. Meema HE, Meindok H. Advantages of peripheral radiogrametry over dual-photon absorptiometry of the spine in the assessment of prevalence of osteoporotic vertebral fractures in women. *J Bone Min Res*. 1992;7:897–903. <https://doi.org/10.1002/jbmr.5650070806>.
20. Bigelow EMR, Goulet RW, Ciarelli A, Schlecht SH, Kohn DH, Bredbenner TL, et al. Sex and External Size Specific Limitations in Assessing Bone Health From Adult Hand Radiographs. *JBMR Plus*. 2022;6:e10653. <https://doi.org/10.1002/jbm4.10653>.
21. Tommasini SM, Nasser P, Hu B, Jepsen KJ. Biological co-adaptation of morphological and composition traits contributes to mechanical functionality and skeletal fragility. *J Bone Min Res*. 2008;23:236–46. <https://doi.org/10.1359/jbmr.071014>.
22. Citron K, Veneziale C, Marino J, Carter EM, Jepsen KJ, Raggio C. Bone robusticity in two distinct skeletal dysplasias diverges from established patterns. *J Orthop Res*. 2017;35:2392–6. <https://doi.org/10.1002/jor.23543>.
23. Pandey N, Bhola S, Goldstone A, Chen F, Chrzanowski J, Terranova CJ, et al. Interindividual variation in functionally adapted trait sets is established during postnatal growth and predictable based on bone robustness. *J Bone Min Res*. 2009;24:1969–80. <https://doi.org/10.1359/jbmr.090525>.
24. Schlecht SH, Bigelow EMR, Jepsen KJ. Mapping the natural variation in whole bone stiffness and strength across skeletal sites. *Bone*. 2014;67:15–22. <https://doi.org/10.1016/j.bone.2014.06.031>.

Figures

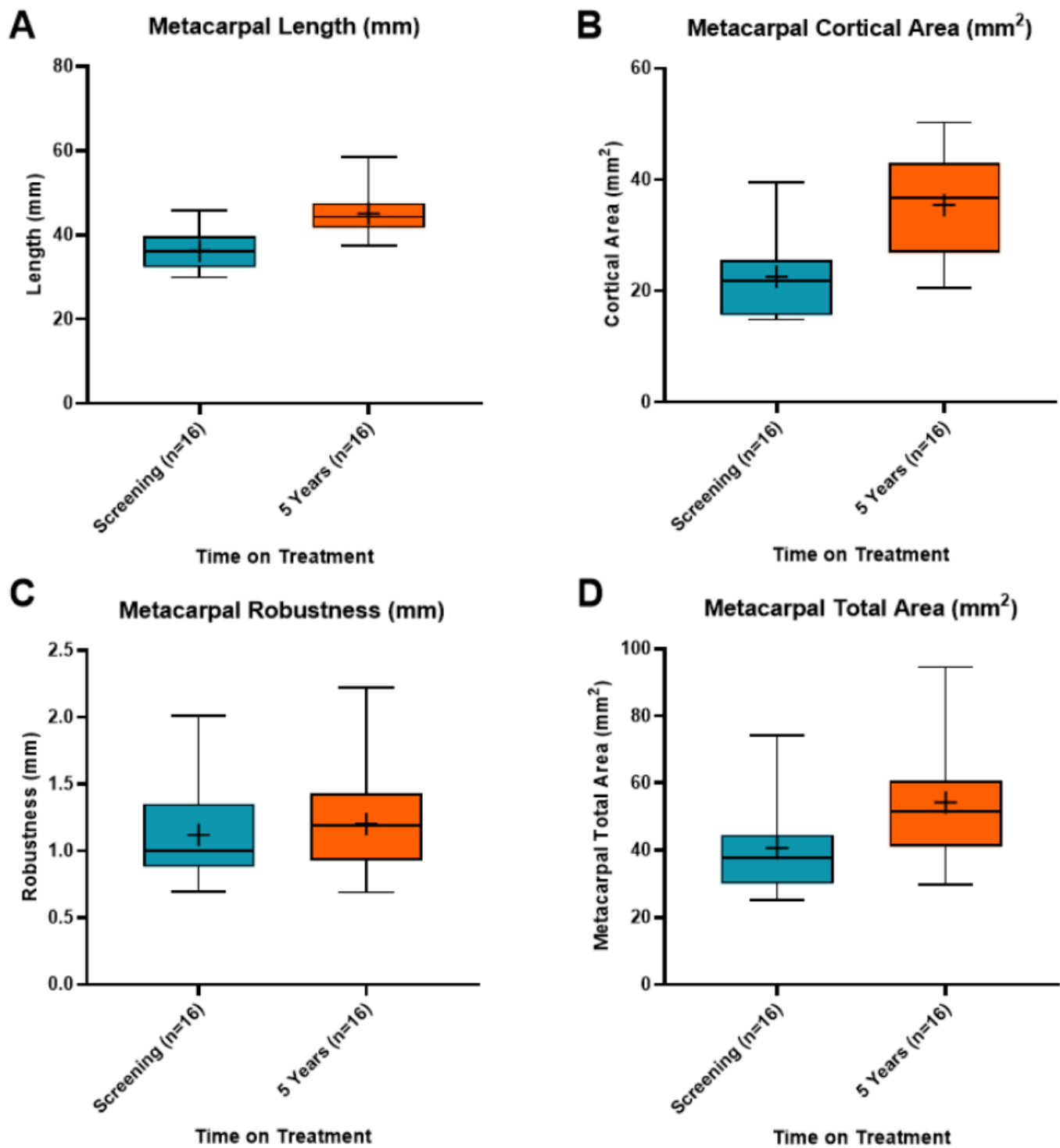


Figure 1

Second metacarpal size parameters at screening and after 5 years of vosoritide

Comparison of metacarpal (A) length, (B) cortical area (C) robustness and (D) total area for 16 children with achondroplasia at screening and at five years on vosoritide treatment. Box and horizontal line

indicate the median with quartile 1 and quartile 3; plus (+) indicates mean, whiskers indicate the 2.5 and 97.5 percentiles.

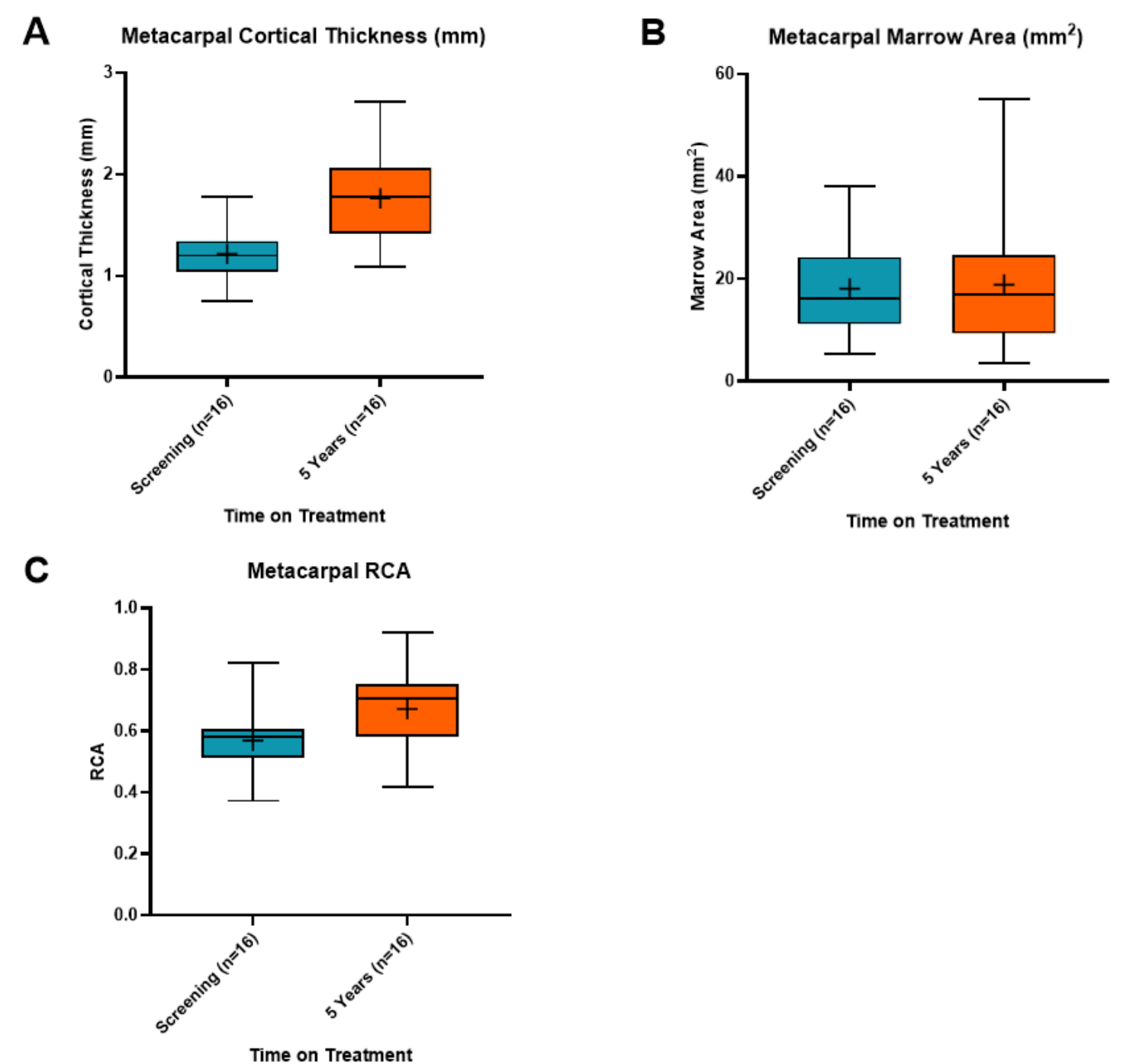


Figure 2

Second metacarpal cortical parameters at screening and after 5 years of vosoritide.

Comparison of metacarpal (A) cortical thickness, (B) marrow area and (C) relative cortical area (RCA) for 16 children with achondroplasia at screening and at five years on vosoritide treatment. Box and

horizontal line indicate the median with quartile 1 and quartile 3; plus (+) indicates mean, whiskers indicate the 2.5 and 97.5 percentiles.