

Original Article

Development of Muscle Function in Children with Achondroplasia Under Vosoritide Treatment: A Retrospective Single-Centre Observational Study

Susanna Reincke¹, Stefanie Stasek¹, Shino Junghänel-Welzing¹, Oliver Semler¹, Mirko Rehberg¹, Ibrahim Duran^{1,2}, Heike Hoyer-Kuhn¹

¹University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Pediatrics, Cologne, Germany;

²Center for Pediatric and Adolescent Rehabilitation, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Abstract

Objectives: Vosoritide, a C-type natriuretic peptide analog, is the first approved pharmacological treatment for achondroplasia that targets the overactive *FGFR3* pathway and promotes longitudinal bone growth. As increased body height may improve biomechanical leverage and influence muscle function, this retrospective, monocentric, observational study aimed to evaluate changes in muscle performance parameters during long-term vosoritide treatment. **Methods:** Nineteen (19) children with achondroplasia treated with vosoritide for at least 12 months were included. Muscle function was assessed via two-legged jump tests on a ground reaction force plate at baseline, month 12, 24 and 36. Jumping parameters, 6-minute walking distances and auxological measurements were converted to z-scores. Longitudinal changes were detected using a linear mixed-effects model. **Results:** Vosoritide treatment resulted in significant gains in height z-scores over 36 months ($p < 0.001$). Raw values of jumping parameters increased numerically over time for all parameters except relative force; however, no significant changes were observed in z-scores. Similarly, no significant changes were detected in 6-minute walking distances. **Conclusions:** While vosoritide produced significant height gains, no significant changes in muscle function z-scores were observed in this cohort. These findings are exploratory and suggest that muscle function may develop in parallel with that of unaffected children.

Keywords: Achondroplasia, *FGFR3*, Jumping Mechanography, Muscle-bone Unit, Single Two-legged Jump

Introduction

Achondroplasia is the most common skeletal dysplasia, with a prevalence estimated at 3.7-4.6 per 100.000 births^{1,2}. It is caused by gain-of-function mutations in the

fibroblast growth factor receptor 3 gene (*FGFR3*), which lead to an impaired endochondral ossification resulting in a disproportionate short stature³⁻⁵. The disproportionality, alongside a macrocephaly and a generalized muscular hypotonia – whose underlying cause remains unclear – contribute to atypical motor development and delayed motor milestones in children with achondroplasia compared to unaffected peers^{5,6}. These motor impairments persist into later childhood, as older children with achondroplasia also show reduced functional ability on the Activity Scale for Kids compared to those without skeletal dysplasia⁷. Given the importance of motor function for autonomy and daily living, improving muscle function in individuals with achondroplasia is of clinical importance. In male adults, greater muscle strength is associated with longer six-minute walking distances⁸. Moreover, higher levels of physical activity correlate with improved outcomes across multiple

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Corresponding author: Susanna Reincke, Dr. med., Department of Pediatrics and Adolescent Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50937 Cologne, Germany
E-mail: susanna.reincke@uk-koeln.de
ORCID iD: 0000-0003-2286-5761

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domains of health-related quality of life – particularly relevant given the lower average health-related quality of life reported in adults with achondroplasia⁹.

In recent years, several medical approaches targeting the underlying pathophysiology of achondroplasia have emerged: Since 2021, vosoritide has been approved as the first targeted therapy. As a C-type natriuretic peptide (CNP) analog, vosoritide inhibits the overactive FGFR3 signaling, promoting endochondral ossification and increasing longitudinal bone growth^{10,11}. Clinical trials^{12–14} and real-world data^{15–18} have confirmed its efficacy in increasing the annualized growth velocity.

As new medical therapies for achondroplasia emerge with improved outcomes regarding bone growth, it becomes increasingly important to explore their potential impact on muscle function. Muscle and bone development are closely interrelated: Bones provide the mechanical leverage necessary for muscles to generate force, while the mechanical forces exerted by muscles stimulate bone remodeling, thereby enhancing bone mass and strength. This bidirectional interaction, often referred to as the functional muscle-bone unit, ensures the alignment and functional optimization of both systems¹⁹. Indeed, muscle strength measured by fixed dynamometry has been shown to correlate strongly with height²⁰. In children with achondroplasia, there is also evidence suggesting that improved growth may support motor development. One study found that the ability to transition from lying to sitting occurred earlier in children who were taller and heavier at 12 months and later in those with pronounced head-to-body disproportion²¹.

Given the close interaction between muscle and bone, we hypothesized that the increased bone length resulting from vosoritide treatment in our cohort may positively influence muscle function in children with achondroplasia.

Material and Methods

Patients and inclusion criteria

This retrospective, monocentric observational study included all patients with achondroplasia who were treated with vosoritide at the specialized skeletal dysplasia clinic of the University Hospital Cologne, Germany, between October 2021 and April 2025, and who met the following inclusion criteria:

1. A minimum treatment duration of 12 months with vosoritide,
2. Completion of baseline muscle function testing prior to treatment initiation,
3. At least one follow-up assessment of muscle function at 12, 24, or 36 months,
4. Age above 6 years to allow comparison with available reference data.

Vosoritide doses were administered as approved by national authorities. Clinical data of all patients with achondroplasia treated with vosoritide were collected systematically during routine follow-up visits and documented in an institutional registry. As of June 2025, 54

Table 1. Clinical data of the cohort at Baseline.

Patients n	19
Sex (female/male)	6/13
Mutation n (%)	
c.1138G>A (p.Gly380Arg) in FGFR3	19 (100)
Age at Baseline (years)	
median (IQR)	8.9 (8.0 – 10.0)
range	6.7 – 15.25
Height	
median (IQR) (cm)	107 (99 – 114)
ACH z-scores median (IQR)	0.55 (-0.85 – 1.26)
CDC z-scores median (IQR)	-5.01 (-5.96 – -4.24)
Weight	
median (IQR) (kg)	22 (20 – 28)
CDC z-scores median (IQR)	-2.09 (-2.92 – -0.86)
BMI	
median (IQR) (kg/m ²)	21 (20 – 23)
CDC z-scores median (IQR)	1.40 (1.16-1.78)
Patients with ACH-related/growth-affecting surgeries before/during vosoritide treatment n (female/male)	
Limb lengthening surgery (lower extremity, no upper extremity procedures) n (female/male)	5 (2/3)
Corrective osteotomy n (female/male)	3 (1/2)
Foramen magnum decompression n (female/male)	6 (2/4)
Ventriculoperitoneal (VP) shunt surgery n (female/male)	2 (0/2)
Corrective spinal fusion surgery n (female/male)	1 (0/1)
General medical conditions	
Intermittent low vitamin D levels requiring supplementation n (female/male)	6 (3/3)
Hereditary spherocytosis n (female/male)	1 (0/1)
Prematurity n (female/male)	1 (1/0)
<i>Abbreviations: IQR – interquartile range.</i>	

patients in the registry had received vosoritide treatment for at least 12 months, 37 for at least 24 months, and 19 for at least 36 months. Of these, 19 patients met the full inclusion criteria at baseline, 17 at 12 months, 15 at 24 months, and 8 at 36 months (Figure S1). For the latter group, complete muscle function data were available for 8 patients, while 1 patient had data on only two parameters (maximum velocity and maximum relative force). None of the included patients were concurrently enrolled in other interventional clinical trials during the study period. The most frequent reason for exclusion was a young age at the initiation of treatment,

Table 2. Longitudinal changes in auxological data. Median (IQR) and LMM-estimated mean (95% CI) are shown. Δ vs. Baseline = estimated mean change from baseline. P-values are Bonferroni-adjusted. n = number of patients per timepoint. ACH z-scores = achondroplasia references²⁸; CDC z-scores = general population references²⁵.

Parameter	Timepoint	n	Descriptive	LMM			
			Median (IQR)	Estimated Mean	95% CI (Estimated Mean)	Δ vs. Baseline	p-value (Δ vs. Baseline, Bonferroni)
Absolute Height (cm)	Baseline	19	106.5 (99.1 – 113.9)	105.9	101.2 – 110.5		
	Month 12	17	113.0 (104.1 – 120.1)	112.2	107.6 – 116.9	6.3	<0.001
	Month 24	15	116.9 (111.3 – 127.4)	118.2	113.5 – 122.9	12.3	<0.001
	Month 36	9	125.0 (112.4 – 134.4)	124.0	119.3 – 128.8	18.2	<0.001
Height ACH z-score	Baseline	19	0.55 (-0.85 – 1.26)	0.34	-0.38 – 1.06	–	–
	Month 12	17	1.13 (-0.34 – 1.80)	0.92	0.20 – 1.64	0.57	<0.001
	Month 24	15	1.87 (0.23 – 2.37)	1.37	0.65 – 2.10	1.03	<0.001
	Month 36	9	2.02 (-0.64 – 2.66)	1.81	1.07 – 2.54	1.46	<0.001
Height CDC z-score	Baseline	19	-5.01 (-5.96 – -4.24)	-5.00	-5.54 – -4.45	–	–
	Month 12	17	-4.40 (-5.61 – -3.65)	-4.54	-5.09 – -3.99	0.46	<0.001
	Month 24	15	-3.83 (-4.97 – -3.57)	-4.23	-4.78 – -3.68	0.77	<0.001
	Month 36	9	-3.84 (-5.63 – -3.29)	-4.00	-4.57 – -3.44	0.99	<0.001
Weight CDC z-score	Baseline	19	-2.09 (-2.92 – -0.86)	-1.87	-2.40 – -1.34	–	–
	Month 12	17	-1.39 (-2.82 – -0.55)	-1.67	-2.20 – -1.14	0.20	0.096
	Month 24	15	-1.88 (-2.52 – -0.42)	-1.47	-2.00 – -0.94	0.40	0.006
	Month 36	9	-1.60 (-2.43 – -0.58)	-1.41	-1.96 – -0.86	0.47	0.030
BMI CDC z-score	Baseline	19	1.40 (1.16 – 1.78)	1.36	1.01 – 1.71	–	–
	Month 12	17	1.43 (1.14 – 1.69)	1.23	0.88 – 1.59	-0.13	0.106
	Month 24	15	1.25 (0.72 – 1.66)	1.18	0.82 – 1.53	-0.18	0.094
	Month 36	9	1.06 (0.83 – 1.41)	1.12	0.76 – 1.49	-0.24	0.128

when mechanography was not possible. To assess potential attrition bias, baseline characteristics of completers versus non-completers were compared descriptively (Table S1).

Study objectives

The primary objective of this study was to evaluate the two-legged jump test in patients with achondroplasia in comparison to reference values from the general population published by Martakis et al.²², and to analyze longitudinal changes in jumping parameter in relation to growth during vosoritide treatment. Secondary objectives were to assess the 6-minute walking test as a measure of overall functional mobility and the longitudinal development of auxological data during vosoritide treatment.

Muscle function parameters

Muscle function was assessed using the two-legged jump test performed on the Leonardo Ground Reaction Force Platform (Novotec Medical GmbH, Pforzheim, Germany; software version 4.4b03.58). This test is part of our clinic's standardized annual assessment protocol for children with achondroplasia receiving growth-affecting therapy. The two-legged jump test was selected due to its applicability

in pediatric populations, its sensitivity to detect subtle changes in functional strength over time, and its high reproducibility in children²³. Prior to testing the Leonardo Ground Reaction Force Platform was calibrated according to manufacturer guidelines. All tests were supervised by trained physiotherapists. Participants were instructed to perform a natural countermovement jump with a free arm swing, aiming to jump as high as possible. Jumps were performed without shoes, with feet hip-width apart, using both legs. Each participant completed three consecutive jumps, landing with both feet fully on the platform and remaining still until a signal indicated the trial was complete; the highest jump was used for analysis. The following parameters were derived from the two-legged jump test: maximal total power (kW), maximal relative power (W/kg), maximal velocity (m/s), maximal jump height (m), maximal total force (kN) and the Neve-Muscle-Index (NMI). Maximal relative force was calculated by normalizing total force to body weight (N/kg). The NMI²² was calculated as the ratio of velocity to maximal relative force and serves as a surrogate for jump efficiency: For two jumps with the same velocity, the jump performed with lower force corresponds to a higher NMI, reflecting greater neuromuscular efficiency.

To ensure comparability across different ages and sexes,

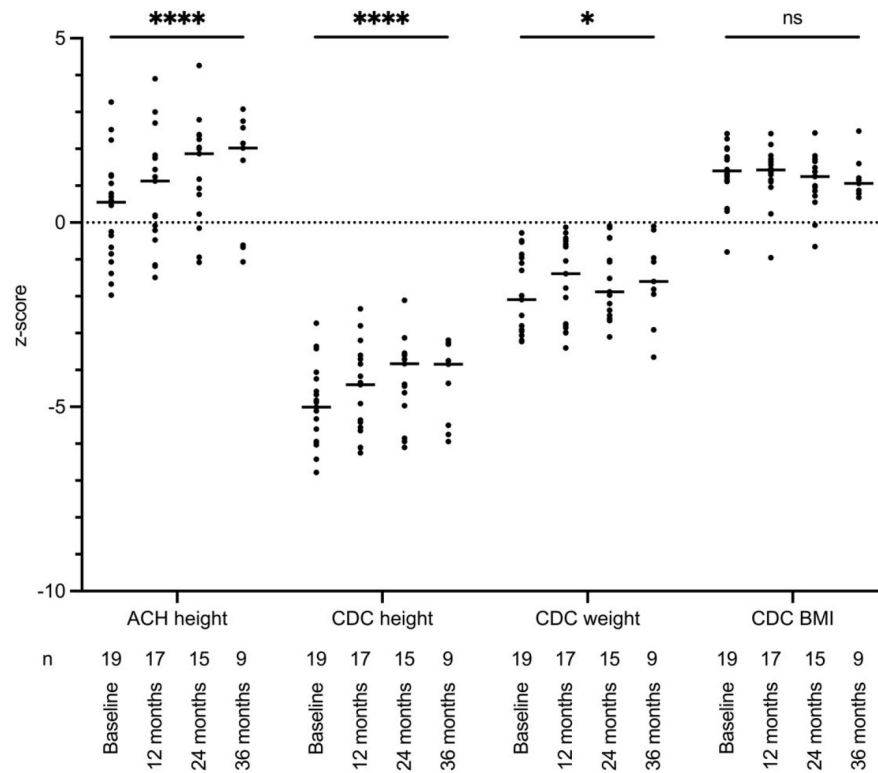


Figure 1. Auxological development in children with achondroplasia treated with vosoritide. Longitudinal changes of height, weight, and BMI z-scores (ACH and CDC) over the observation period. Data points represent individual patients. Horizontal bars indicate the median values at each time point (baseline, 12, 24, and 36 months). The dotted line corresponds to the reference median of unaffected children. Sample sizes (n) for each time point are shown below the x-axis. Statistical significance was assessed using linear mixed models with FDR-Bonferroni adjustment. P-values for the change (Δ) of the estimated mean from baseline to 36 months are shown above the data. $p \leq 0.001$ (****), $p \leq 0.05$ (*), not significant (ns).

muscle function parameters – including maximal relative power, maximal velocity, jump height, and maximal relative force – were transformed into age- and sex-adjusted z-scores using the Box-Cox power transformation (L), the median (M), and the coefficient of variation (S), based on reference data published by Martakis et al.²², which were derived from the German DONALD study, a longitudinal cohort study investigating nutritional and anthropometric development in healthy children. To our knowledge, no disease-specific reference data for these parameters are currently available for patients with achondroplasia.

6-minute walking test

Additional to muscle function measured with the two-legged-jump test, overall functional mobility was assessed with the 6-minute walking test. For the 6-minute walking test, patients were instructed to walk continuously for six minutes along a flat, straight corridor at their own pace, with running or jogging not permitted. The total distance within six minutes was recorded in meters. Z-scores for

the 6-minute walking distance were calculated based on reference data from an unaffected cohort²⁴.

Auxological parameters

Auxological data were obtained by trained nurses using a stadiometer and a calibrated sitting scale, with height measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI was calculated as weight divided by the square of height. Height, weight, and BMI were converted into z-scores using the LMS method with reference data from unaffected children (Centers for Disease Control and Prevention; CDC z-scores)²⁵ and achondroplasia-specific reference values reported by Merker et al. (ACH z-scores)²⁶.

Statistical Analysis

Z-score calculations were performed using Microsoft Excel (version 16.87). Statistical analyses were conducted using GraphPad Prism (version 10.3.0) and IBM SPSS Statistics

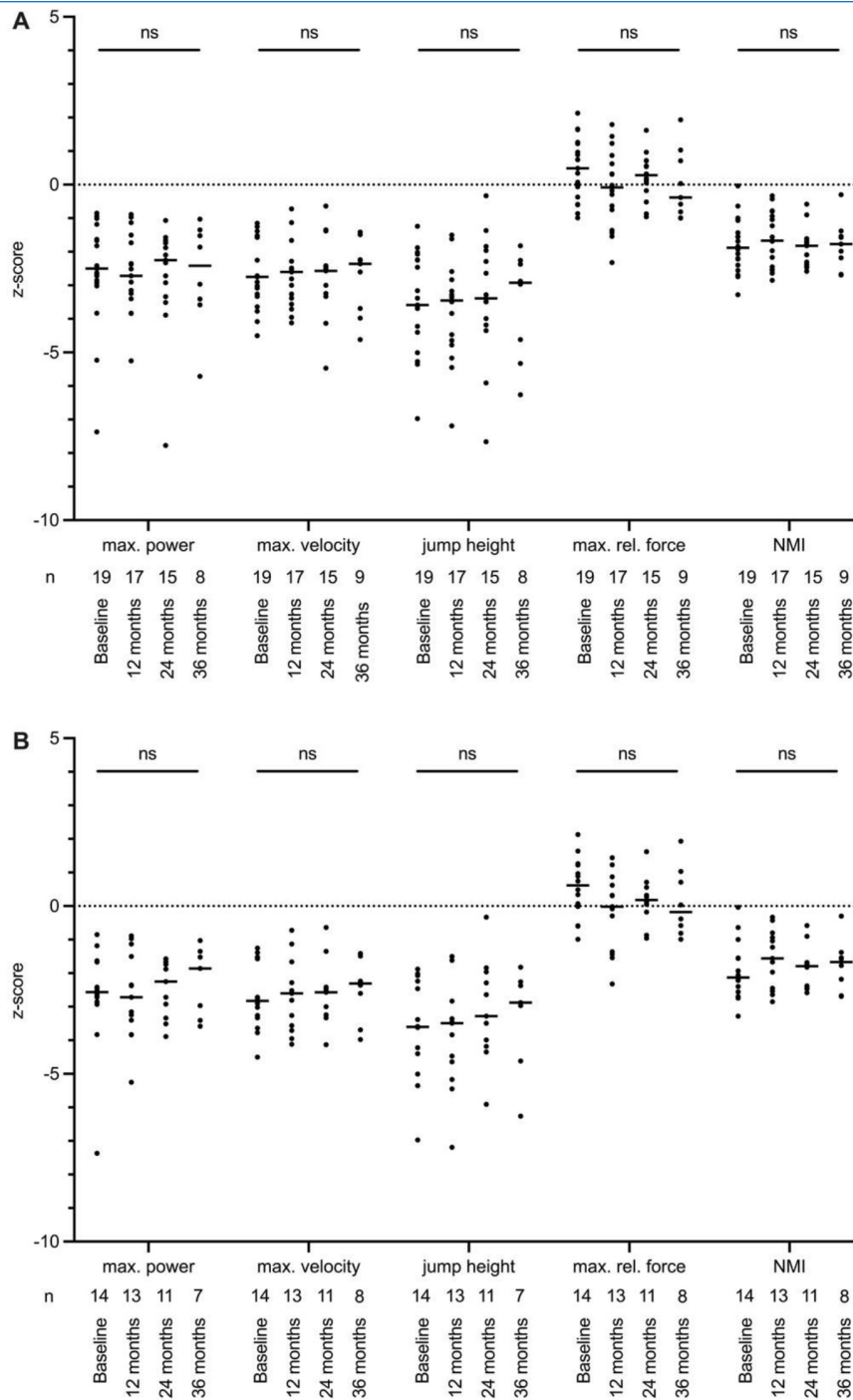


Figure 2. Jumping mechanography in children with achondroplasia treated with vosoritide. Longitudinal changes of jump parameter z-scores (maximal power, maximal velocity, jump height and maximal relative force) over the observational period in the entire cohort (A) and excluding children who underwent limb lengthening surgeries (B). Data points represent individual patients. Horizontal bars indicate the median values at each time point (baseline, 12, 24, and 36 months). The dotted line corresponds to the reference median of unaffected children. Sample sizes (n) for each time point are shown below the x-axis. Statistical significance was assessed using linear mixed models with FDR-Bonferroni adjustment. P-values for the change (Δ) of the estimated mean from baseline to 36 months are shown above the data: not significant (ns).

Table 3. Longitudinal changes in two-legged jump test parameters. Median (IQR) and LMM-estimated mean (95% CI) are shown. Δ vs. Baseline = estimated mean change from baseline. P-values are Bonferroni-adjusted. n = number of patients per timepoint.

Parameter	Timepoint	n	Descriptive		LMM		
			Median (IQR)	Estimated Mean	95% CI (Estimated Mean)	Δ vs. Baseline	p-value (Δ vs. Baseline, Bonferroni)
Max. Power z-score	Baseline	19	-2.50 (-2.93 -- -1.63)	-2.62	-3.34 -- -1.89	-	-
	Month 12	17	-2.72 (-3.32 -- -1.62)	-2.84	-3.57 -- -2.11	-0.23	1.000
	Month 24	15	-2.25 (-3.34 -- -1.74)	-2.77	-3.51 -- -2.02	-0.15	1.000
	Month 36	8	-2.42 (-3.54 -- -1.39)	-2.30	-3.12 -- -1.47	0.32	1.000
Max. Velocity z-score	Baseline	19	-2.75 (-3.33 -- -1.55)	-2.66	-3.14 -- -2.18	-	-
	Month 12	17	-2.60 (-3.47 -- -2.39)	-2.85	-3.34 -- -2.37	-0.20	1.000
	Month 24	15	-2.57 (-3.24 -- -2.42)	-2.74	-3.24 -- -2.24	-0.08	1.000
	Month 36	9	-2.36 (-3.84 -- -1.87)	-2.57	-3.14 -- -1.99	0.09	1.000
Jump height z-score	Baseline	19	-3.59 (-4.40 -- -2.24)	-3.50	-4.25 -- -2.74	-	-
	Month 12	17	-3.45 (-4.71 -- -2.71)	-3.81	-4.58 -- -3.04	-0.31	1.000
	Month 24	15	-3.39 (-4.18 -- -1.96)	-3.42	-4.21 -- -2.64	0.07	1.000
	Month 36	8	-2.93 (-5.15 -- -2.29)	-2.97	-3.91 -- -2.04	0.52	1.000
Max. Relative force z-score	Baseline	19	0.49 (-0.37 -- 1.22)	0.44	0.00 -- 0.88	-	-
	Month 12	17	-0.08 (-1.06 -- 0.75)	-0.16	-0.62 -- 0.30	-0.60	0.708
	Month 24	15	0.28 (-0.18 -- 0.71)	0.21	-0.28 -- 0.69	-0.24	1.000
	Month 36	9	-0.38 (-0.90 -- 0.87)	-0.07	-0.67 -- 0.53	-0.51	0.201
NMI z-score	Baseline	19	-1.88 (-2.40 -- -1.43)	-1.83	-2.17 -- -1.49	-	-
	Month 12	17	-1.67 (-0.87 -- -2.49)	-1.65	-2.00 -- -1.29	0.19	1.000
	Month 24	15	-1.82 (-2.39 -- -1.68)	-1.85	-2.22 -- -1.48	-0.02	1.000
	Month 36	9	-1.77 (-2.43 -- -1.46)	-1.75	-2.23 -- -1.27	0.08	1.000

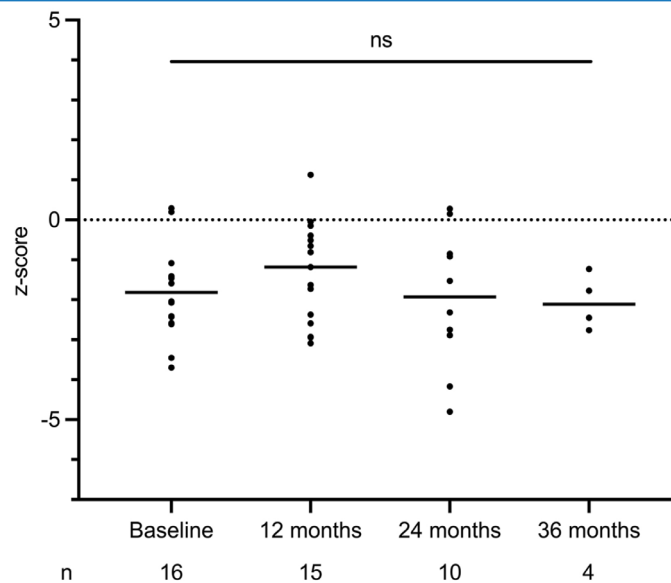
**Figure 3.** 6-minute walking test in children with achondroplasia treated with vosoritide. Longitudinal changes of 6-minute walking distance z-scores over the observational period in the entire. Data points represent individual patients. Horizontal bars indicate the median values at each time point (baseline, 12, 24, and 36 months). The dotted line corresponds to the reference median of unaffected children. Sample sizes (n) for each time point are shown below the x-axis. Statistical significance was assessed using linear mixed models with FDR-Bonferroni adjustment. P-values for the change (Δ) of the estimated mean from baseline to 36 months are shown above the data: not significant (ns).

Table 4. LMM estimates for mechanography outcomes. Shown are estimates, 95% confidence intervals (CI), and p-values for LMMs using baseline age, sex, baseline ACH height z-score, and limb-lengthening surgery status as covariates. Dependent variables were z-scores of maximal power, maximal velocity, jump height, maximal relative force, and NMI. Positive estimates indicate higher z-scores associated with the covariate.

	LMM			
	Parameter	Estimate	95% CI	p-value
Max. Power Z-Score	Age at Baseline	0.052	-0.244 – 0.349	0.709
	Sex (1=female; 0=male)	-1.461	-2.786 – -0.136	0.33
	ACH height z-score at Baseline	0.929	0.397 – 1.460	0.002
	Limb lengthening surgery (1=yes; 0=no)	-1.887	-3.584 – -0.189	0.032
Max. Velocity Z-Score	Age at Baseline	-0.003	-0.172 – 0.166	0.969
	Sex (1=female; 0=male)	-0.642	-1.400 – 0.116	0.091
	ACH height z-score at Baseline	0.679	0.380 – 0.977	<0.001
	Limb lengthening surgery (1=yes; 0=no)	-1.438	-2.398 – -0.477	0.006
Jump Height Z-Score	Age at Baseline	0.092	-0.186 – 0.370	0.487
	Sex (1=female; 0=male)	-1.199	-2.446 – -0.049	0.059
	ACH height z-score at Baseline	0.984	0.487 – 1.480	<0.001
	Limb lengthening surgery (1=yes; 0=no)	-1.734	-3.321 – -0.147	0.034
Max. Relative Force Z-Score	Age at Baseline	-0.085	-0.256 – 0.086	0.300
	Sex (1=female; 0=male)	-0.824	-1.595 – -0.052	0.038
	ACH height z-score at Baseline	0.380	0.072 – 0.687	0.020
	Limb lengthening surgery (1=yes; 0=no)	-0.874	-1.861 – 0.113	0.078
NMI z-score	Age at Baseline	0.037	-0.083 – 0.157	0.523
	Sex (1=female; 0=male)	0.505	-0.037 – 1.047	0.066
	ACH height z-score at Baseline	0.204	-0.006 – 0.414	0.057
	Limb lengthening surgery (1=yes; 0=no)	-0.434	-1.117 – 0.249	0.200

(version 31.0.1.0 (49)). Data normality was assessed using the Shapiro–Wilk test. Because sample sizes decreased over time and the number of measurements per participant varied, longitudinal changes in anthropometric parameters, 6-minute walking distance, and muscle function parameters were analyzed using linear mixed-effects models (LMMs) with timepoint as a fixed effect and patient ID as a random effect. For muscle function parameters, an additional LMM was fitted including the following covariates: baseline age, sex, baseline ACH height z-score, and limb-lengthening surgery status. Model parameters were estimated using restricted maximum likelihood (REML). Post-hoc pairwise comparisons were Bonferroni-adjusted, and results are reported as estimated marginal means with 95% confidence intervals (95% CI). To compare the median baseline muscle function z-scores in our cohort with the reference median, a Wilcoxon signed-rank test was applied. A p-value of < 0.05 was considered statistically significant.

Results

Clinical Data

Clinical characteristics of the cohort are summarized in Table 1. All patients carried the same disease-causing

mutation. Among the 19 patients, 6 were female. The median age at therapy start was 8.9 years (IQR: 8.0–10.0). The median height was 106.5 cm (99.1 – 113.9), corresponding to a median height z-score of 0.55 (-0.85–1.26) based on ACH references, and -5.01 (-5.96 – -4.24) based on CDC references. 12 patients had undergone ACH-related growth-affecting surgeries. Of these, one patient had tibial lengthening surgery during the first 12 months of vosoritide treatment; all other surgeries were performed prior to treatment initiation. 7 patients had additional medical conditions, as detailed in Table 1.

Auxological Parameters

Absolute height and height z-scores based on both ACH and CDC reference data increased significantly from baseline to month 36 (Table 2, Figure 1). In the LMM, absolute height increased at all timepoints compared to baseline (all $p < 0.001$). Median height rose from 106.5 cm (99.1 – 113.9) ($n=19$) at baseline to 125.0 cm (112.4 – 134.4) ($n=9$) at month 36.

Median ACH height z-score improved from 0.55 (-0.85 to 1.26) ($n=19$) at baseline to 2.02 (-0.64 to 2.66) ($n=9$) at month 36, with significant model-estimated increases

Table 5. Longitudinal changes in 6-minute walking distance z-scores. Median (IQR) and LMM-estimated mean (95% CI) are shown. Δ vs. Baseline = estimated mean change from baseline. P-values are Bonferroni-adjusted. n = number of patients per timepoint.

Timepoint	n	Descriptive	LMM			
		Median (IQR)	Estimated Mean	95% CI (Estimated Mean)	Δ vs. Baseline	p-value (Δ vs. Baseline, Bonferroni)
Baseline	16	-1.82 (-2.54 – -1.42)	-1.84	-2.51 – -1.16	–	–
Month 12	15	-1.18 (-2.59 – -0.39)	-1.40	-2.08 – -0.71	0.44	0.608
Month 24	10	-1.93 (-3.21 – -0.60)	-1.82	-2.57 – -1.06	-0.02	1.000
Month 36	4	-2.11 (-2.68 – -1.37)	-1.98	-3.01 – -0.95	-0.14	1.000

at all timepoints compared with baseline (all $p < 0.001$). Similarly, CDC height z-score improved from -5.01 (-5.96 – -4.24) at baseline to -3.84 (-5.63 – -3.29) at month 36, with significant improvements observed in the LMM for all follow-up visits (all $p < 0.001$).

CDC weight z-score showed a significant increase at month 24 ($p = 0.006$) and month 36 ($p = 0.030$), while BMI z-score showed no significant model-based changes over time.

Two-legged-jump test

Compared to general population reference data, this cohort showed significantly lower baseline values for maximal relative power, as well as velocity, jump height and NMI than the median of unaffected children ($p < 0.0001$ for each parameter; $n = 19$). The median maximal relative force at baseline was 0.49 (-0.37 – 1.22), which was higher than the reference median, although the difference was not statistically significant ($p = 0.0712$; $n = 19$).

In the LMM based on raw values, maximal velocity and jump height showed significant changes over time ($p = 0.014$ and 0.003 , respectively). Maximal power and NMI showed continuously numerically increasing estimated means over the treatment period, but these changes were not statistically significant. Maximal relative force showed no significant change over time (Table S2 and Figure S2).

Regarding z-scores, no significant changes were observed in any of the five parameters after 12, 24, or 36 months of treatment (Table 3, Figure 2a, Figure S2). Excluding children with previous limb lengthening surgery yielded similar results, with no significant longitudinal changes in any parameter (excluded patients: $n = 5$ at baseline, $n = 4$ at months 12 and 24, and $n = 1$ at month 36; all patients underwent lower extremity limb lengthening; no upper extremity procedures were performed; Table S3, Figure 2b).

An additional LMM including baseline age, sex, baseline ACH height z-score, and limb-lengthening surgery status as covariates revealed several significant associations (Table 4). Higher baseline ACH height z-scores were

positively associated with better performance across most parameters, including maximal power (estimate 0.929, $p = 0.002$), maximal velocity (0.679, $p < 0.001$), jump height (0.984, $p < 0.001$), and maximal relative force (0.380, $p = 0.020$). Limb-lengthening surgery status was associated with lower z-scores in maximal power (-1.887, $p = 0.032$), maximal velocity (-1.438, $p = 0.006$), and jump height (-1.734, $p = 0.034$) after adjusting for ACH height at baseline, age and sex. Sex showed a significant association only for maximal relative force (-0.824, $p = 0.038$), with girls demonstrating lower values. NMI z-scores showed no significant associations with any covariates.

6-minute walking test

6-minute walking test data were available for 16 of 19 patients at baseline, 15 of 17 at 12 months, 10 of 15 at 24 months, and 4 of 9 at 36 months. Walking distances were converted into age- and sex-specific z-scores using reference data from an unaffected cohort²⁴. The median z-score at baseline was 1.8 (2.5 – 1.4; $n = 16$). No significant longitudinal changes in 6-minute walking distance z-scores were observed over time (Figure 3, Table 5).

Discussion

In this study, we analyzed the development of muscle function using the two-legged jump test in children with achondroplasia during vosoritide treatment. While vosoritide treatment led to significant height gains over 36 months, no statistically significant improvement in jumping parameters was observed. Similarly, evaluation of the 6-minute walking test as a secondary outcome revealed no significant changes.

The two-legged jump test measures four parameters: maximal relative power, maximal velocity, maximal relative force, and jump height. These parameters reflect different but interrelated aspects of muscle function and neuromuscular performance. For instance, jump height is directly determined by the vertical take-off velocity, which in turn depends on the force applied against the ground and

the time over which this force is generated. Consequently, the same jump height can be achieved with different combinations of force and velocity outputs, depending on individual muscular capacities and motor control. This interplay of parameters, captured by mechanographic measurements, allows for a comprehensive evaluation of muscle function. Improved muscle performance may therefore be reflected by increases in jump height, maximal velocity, and maximal power, along with unchanged or reduced maximal relative force, indicating that less force is required to achieve the same performance output. Additionally, a lower relative force with consistent jump velocity, corresponds to a higher NMI, reflecting greater neuromuscular efficiency.

In our cohort of children with achondroplasia, baseline values of maximal relative power, maximal velocity, and jump height were significantly lower than age- and sex-specific reference values from unaffected children. These findings could be consistent with previous reports of reduced muscle strength in children with achondroplasia measured by hand-held dynamometry⁷, as well as reduced muscle volume and diminished functional strength in adults with achondroplasia assessed by ultrasonography and the 30-second sit-to-stand test, respectively^{8,27}. Interestingly, maximal relative force at baseline was above the reference median, although this difference was not statistically significant. This could suggest a compensatory mechanism, whereby increased force is exerted to enhance jump performance and thereby reduce the impact of biomechanical and functional limitations.

We observed a significant positive association between greater baseline ACH height and higher z-scores of most jump test parameter. This indicates that taller children tend to perform better, suggesting a functional relationship between stature and muscle performance. This observation could correspond with data from typically developing children, where muscle strength measured by fixed dynamometry shows a strong correlation with height²⁰.

Previous limb-lengthening surgery, however, was associated with lower maximal power, velocity, and jump height z-scores after adjusting for baseline ACH height z-score, age, and sex. This indicates that these children had lower z-scores for the above jump parameters than the rest of the cohort, despite their taller stature. One possible explanation is that sufficient time may be required after surgery for muscles and neuromotor systems to adapt to altered limb lengths and biomechanics; however, in our cohort, the interval between surgery and jump testing was not available. Another possible explanation could be that all surgeries involved only the lower extremities, which could have altered the biomechanics of jumping, including the coordination of the countermovement and force generation. However, these explanations remain speculative, and further studies are needed to confirm these findings and elucidate potential underlying mechanisms.

Over the observational period, there was a significant height gain compared to both ACH and CDC reference

values. Notably, the median height z-score increase in our cohort was comparable to that reported in the ongoing phase 3 extension study of vosoritide³ (median height z-score increase after 36 months: 1.17, n = 9 vs. 1.06, n = 111). However, the considerable difference in cohort sizes should be taken into account.

Regarding longitudinal changes in muscle function during vosoritide treatment, raw values of jumping parameters increased numerically over time for all parameters except relative force, and significant increases were observed for maximal velocity and jump height. This pattern – increasing maximal power, velocity, and jump height with unchanged relative force – may reflect improved neuromuscular efficiency, where the same force output is sufficient to achieve greater performance. However, in the absence of a control group or achondroplasia-specific reference data for the two-legged jump test, it is not possible to determine whether these changes differ from non-treated children with achondroplasia. Compared to age- and sex-specific reference values from unaffected children, no significant changes in muscle function parameter z-scores were observed. Importantly, one might expect that children with achondroplasia would show a decline in muscle performance relative to unaffected peers over time, due to increasing differences in stature and biomechanical constraints. The fact that z-scores remained stable suggests that gains in height under vosoritide treatment may help maintain muscle function, and that muscle function in our cohort developed similarly to unaffected peers who had comparable baseline z-scores. Likewise, the 6-minute walking distance z-scores as an indicator for overall functional mobility did not change significantly in this cohort and remained stable in comparison to unaffected children.

Several limitations of this study must be acknowledged. The cohort size was small, although relatively large for a rare disease such as achondroplasia. Due to the retrospective design, data were incomplete at later time points. Moreover, the absence of an untreated control group and of achondroplasia-specific reference values for mechanographic parameters limits the ability to attribute findings solely to vosoritide treatment and prevents disease-specific comparisons. The study cohort also showed an uneven sex distribution, and the minimum age requirement of 6 years excluded younger children who had already initiated vosoritide treatment, introducing selection bias and potentially limiting the generalizability of the findings.

However, this study provides for the first time longitudinal data on muscle function under vosoritide treatment in children with achondroplasia who were treatment naïve at baseline. The relatively long observation period of up to 36 months, combined with repeated standardized assessments, enhances the reliability of the findings. Being a single-center study, all measurements were conducted by the same experienced and consistently trained staff, further supporting data consistency. In addition, the use of a validated and highly reproducible test method (two-legged jump test) ensures a consistent and objective evaluation of

muscular function.

Taken together, our findings suggest that the height gain achieved under vosoritide treatment may prevent a further decline in muscle function in comparison to unaffected children. This could potentially contribute to improved motor performance, activity levels, and quality of life over time. Larger studies with longer follow-up are warranted to validate these findings and to clarify whether improvements in functional parameters translate into meaningful benefits in daily living.

Ethics approval

This retrospective study analyzed anonymized, pre-existing patient data collected during routine clinical care. No additional interventions were performed, and all data were fully de-identified prior to analysis. The study was approved by the Ethics Committee of the Medical Faculty, University of Cologne (TEMP798939-retro). The presented data analysis was conducted in accordance to data protection regulations and the Declaration of Helsinki.

Authors' contributions

SR wrote the first draft of the manuscript. OS and HHK conceptualized and designed the study. Data collection was conducted during clinical visits with contributions from all authors. Data analysis was performed by SR with support from ID and reviewed by OS and HHK. Revision and final approval of the manuscript were done by all authors.

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Supplemental Files

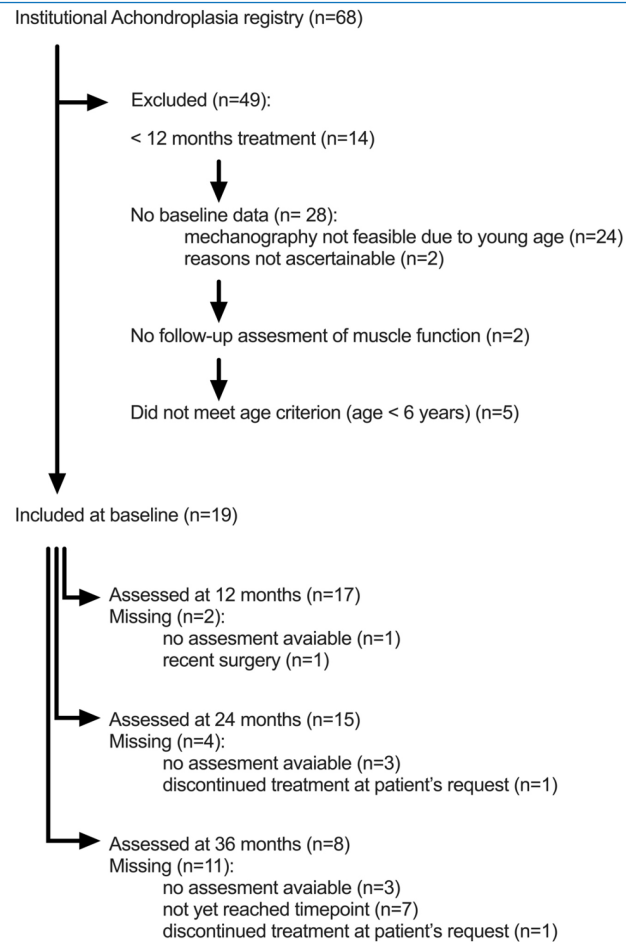


Figure S1. Flowchart of patient inclusion and exclusion in the study.

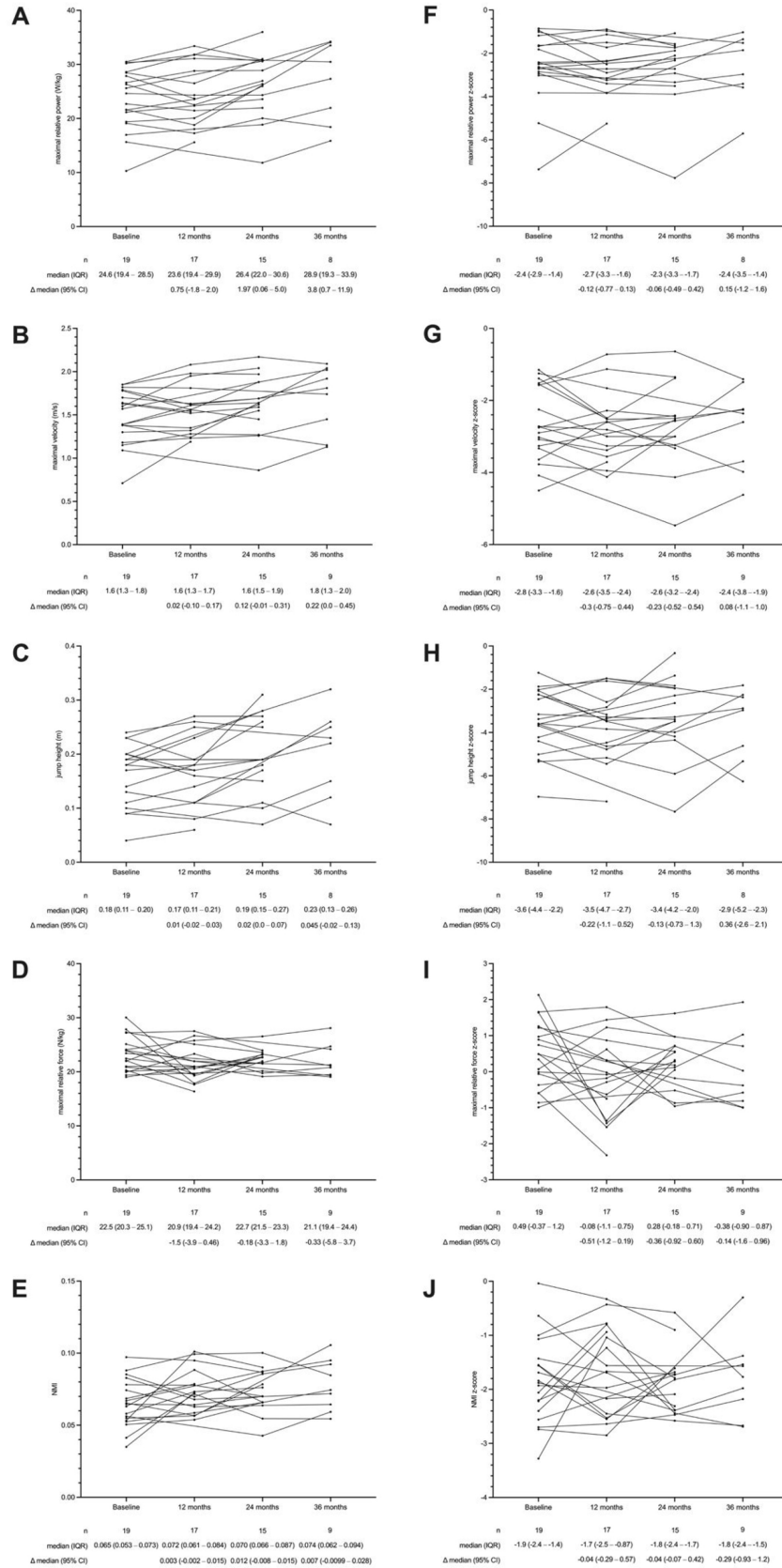


Figure S2. Trajectory plots of jumping parameters maximal power, maximal velocity, jump height, maximal relative force and NMI, shown as raw values (A-E) and z-scores (F-J). Below each plot, the number of patients (n), median (IQR) per timepoint, and Δ median versus baseline median with 95% CI are provided.

Table S1. Baseline characteristics of completers vs non-completers of month 24. Baseline characteristics are presented descriptively as median (interquartile range) or number (female/male). The comparison was performed at month 24, as seven patients had not yet reached month 36 at the time of analysis and are therefore not considered non-completers. Given the small sample size, no formal statistical testing was conducted.

Characteristic	Completers	Non-Completers
Patients n	15	4
Sex (female/male) n	3/12	3/1
Age at Baseline (years)		
median (IQR)	9.3 (8.5 – 11.0)	8.2 (7.0 – 9.8)
range	6.7 – 15.3	6.8 – 10.1
Height		
median (IQR) (cm)	107 (100 – 116)	102 (94 – 107)
ACH z-scores median (IQR)	0.55 (-0.85 – 1.26)	0.41 (-1.54 – 1.95)
CDC z-scores median (IQR)	-5.01 (-5.94 – -4.24)	-5.27 (-3.71 – -6.58)
Weight		
median (IQR) (kg)	22.4 (19.6 – 27.6)	21.2 (20.0 – 25.9)
CDC z-scores median (IQR)	-2.09 (-2.95 – -1.10)	-0.91 (-2.42 – -0.43)
BMI		
median (IQR) (kg/m ²)	20.9 (19.6 – 22.3)	22.8 (19.4 – 23.7)
CDC z-scores median (IQR)	1.38 (1.11 – 1.76)	1.85 (1.30 – 2.20)
Limb lengthening surgery (lower extremity, no upper extremity procedures) n (female/male)	4 (1/3)	1 (1/0)
Maximal power z-score	-2.50 (-1.29 – -1.67)	-1.93 (-6.26 – -0.87)
Maximal velocity z-score	-2.75 (-3.26 – -1.57)	-2.44 (-4.21 – -1.33)
Maximal jump height z-score	-3.59 (-4.22 – -2.07)	-3.43 (-6.33 – -2.30)
Maximal relative force z-score	0.49 (-0.37 – 1.22)	0.28 (-0.43 – 1.07)
Maximal NMI z-score	-3.92 (-4.04 – -3.34)	-2.78 (-3.75 – -2.70)
6-minute walking test z-score	-1.8 (-2.5 – -1.4) (n=14)	-3.45 and -1.08 (n=2)

Table S2. Longitudinal changes in two-legged jump test parameters (raw values). Median (IQR) and LMM-estimated mean (95% CI) are shown. Δ vs. Baseline = estimated mean change from baseline. P-values are Bonferroni-adjusted. n = number of patients per timepoint.

Parameter	Timepoint	n	Descriptive	LMM			
			Median (IQR)	Estimated Mean	95% CI (Estimated Mean)	Δ vs. Baseline	p-value (Δ vs. Baseline, Bonferroni)
Max. power (W/kg)	Baseline	19	24.63 (19.39 – 28.46)	23.47	20.51 – 26.42	–	–
	Month 12	17	23.56 (19.44 – 29.95)	24.02	21.07 – 26.97	0.98	1.000
	Month 24	15	26.37 (21.96 – 30.63)	25.71	22.67 – 28.74	2.67	0.303
	Month 36	8	28.91 (19.30 – 33.94)	26.69	23.34 – 30.04	3.22	0.188
Max. velocity (m/s)	Baseline	19	1.57 (1.30 – 1.78)	1.48	1.34 – 1.63	–	–
	Month 12	17	1.56 (1.30 – 1.72)	1.53	1.39 – 1.68	0.05	1.000
	Month 24	15	1.64 (1.45 – 1.88)	1.63	1.47 – 1.78	0.14	0.096
	Month 36	9	1.81 (1.30 – 2.03)	1.74	1.57 – 1.91	0.25	0.014
Jump height (m)	Baseline	19	0.18 (0.11 – 0.20)	0.16	0.13 – 0.19	–	–
	Month 12	17	0.17 (0.11 – 0.21)	0.17	0.14 – 0.20	0.01	1.000
	Month 24	15	0.19 (0.15 – 0.27)	0.20	0.17 – 0.23	0.04	0.030
	Month 36	8	0.23 (0.13 – 0.26)	0.22	0.19 – 0.26	0.06	0.003
Max. relative force (N/kg)	Baseline	19	22.46 (20.30 – 25.12)	23.31	21.95 – 24.66	–	–
	Month 12	17	20.94 (19.43 – 24.21)	21.44	20.08 – 22.79	-1.87	0.176
	Month 24	15	22.65 (21.50 – 23.28)	22.14	20.68 – 23.60	-1.17	0.981
	Month 36	9	21.13 (19.39 – 24.44)	21.94	20.13 – 23.76	-1.37	1.000
NMI	Baseline	19	0.065 (0.053 – 0.078)	0.065	0.058 – 0.072	–	–
	Month 12	17	0.072 (0.061 – 0.084)	0.073	0.065 – 0.080	0.008	0.253
	Month 24	15	0.070 (0.066 – 0.087)	0.074	0.066 – 0.081	0.009	0.392
	Month 36	9	0.074 (0.062 – 0.094)	0.079	0.069 – 0.089	0.014	0.116

Table S3. Longitudinal changes in two-legged jump test parameters, excluding patients with limb lengthening surgeries. Median (IQR) and LMM-estimated mean (95% CI) are shown. Δ vs. Baseline = estimated mean change from baseline. P-values are Bonferroni-adjusted. n = number of patients per timepoint.

Parameter	Timepoint	n	Descriptive	LMM			
			Median (IQR)	Estimated Mean	95% CI (Estimated Mean)	Δ vs. Baseline	p-value (Δ vs. Baseline, Bonferroni)
Max. Power z-score	Baseline	14	-2.57 (-2.87 - -1.66)	-2.69	-3.45 - -1.93	-	-
	Month 12	13	-2.72 (-3.62 - -1.32)	-2.65	-3.41 - -1.89	0.04	1.000
	Month 24	11	-2.25 (-3.34 - -1.74)	-2.61	-3.38 - -1.84	0.08	1.000
	Month 36	7	-1.86 (-3.41 - -1.35)	-2.26	-3.09 - -1.44	0.43	1.000
Max. Velocity z-score	Baseline	14	-2.83 (-3.41 - -1.56)	-2.74	-3.27 - -2.21	-	-
	Month 12	13	-2.60 (-3.64 - -1.97)	-2.70	-3.23 - -2.17	0.04	1.000
	Month 24	11	-2.57 (-3.24 - -2.42)	-2.66	-3.20 - -2.11	0.08	1.000
	Month 36	8	-2.31 (-3.42 - -1.68)	-2.51	-3.11 - -1.91	0.24	1.000
Jump height z-score	Baseline	14	-3.60 (-4.55 - -2.20)	-3.63	-4.52 - -2.74	-	-
	Month 12	13	-3.49 (-4.91 - -2.13)	-3.69	-4.59 - -2.80	-0.06	1.000
	Month 24	11	-3.28 (-4.18 - -1.96)	-3.29	-4.20 - -2.37	0.35	1.000
	Month 36	7	-2.88 (-4.62 - -2.26)	-3.03	-4.06 - -2.00	0.60	1.000
Max. Relative force z-score	Baseline	14	0.62 (-0.16 - 1.23)	0.54	0.01 - 1.07	-	-
	Month 12	13	-0.02 (-1.40 - 0.75)	-0.18	-0.73 - 0.36	-0.55	0.869
	Month 24	11	0.18 (-0.18 - 0.56)	0.14	-0.45 - 0.72	-0.41	1.000
	Month 36	8	-0.18 (-0.75 - 0.95)	-0.01	-0.68 - 0.66	-0.72	0.263
NMI z-score	Baseline	14	-2.13 (-2.56 - -1.41)	-1.92	-2.35 - -1.49	-	-
	Month 12	13	-1.56 (-2.49 - -0.87)	-1.59	-2.03 - -1.14	0.33	1.000
	Month 24	11	-1.79 (-2.44 - -1.68)	-1.79	-2.27 - -1.32	0.13	1.000
	Month 36	8	-1.67 (-2.55 - -1.42)	-1.73	-2.28 - -1.17	0.19	1.000