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ORIGINAL RESEARCH

# Real-World Safety and Effectiveness of Vosoritide in Achondroplasia: Results from a Single Center in Portugal

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## ABSTRACT

***Introduction***: Achondroplasia, the most common skeletal dysplasia, is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Vosoritide, a C-type natriuretic peptide analog, is a first-in-class targeted treatment for achondroplasia that counteracts overactive FGFR3 signaling to stimulate endochondral bone growth. This retrospective cohort study evaluated growth, safety, and treatment compliance in children with achondroplasia receiving vosoritide under an early access program in Portugal.

***Methods***: Twenty-seven children aged 2–14 years with a genetically confirmed diagnosis of achondroplasia were treated with vosoritide at a single Portuguese center for at least 6 months between January 2022 and June 2024. The analysis included children with severe achondroplasia-associated complications. Anthropometric measurements collected to characterize the effect of vosoritide on growth included height standard deviation score (SDS) and annualized growth velocity (AGV). Student's *t* test was used for statistical comparisons. Safety and tolerability endpoints included adverse drug reactions and treatment adherence.

***Results***: In total, 15 children completed at least 24 months of treatment. After 24 months of treatment, mean variation in height SDS increased from baseline by +0.95 SD ($P \leq 0.0001$), referenced to an untreated achondroplasia-specific population, and +0.56 SD ($P \leq 0.0001$) relative to children of average stature. Additionally, mean AGV from baseline was 5.87 cm/year (95%

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confidence interval 5.14–6.60), resulting in a significant increase of +1.62 cm/year ($P \leq 0.0001$). Injection site reactions were the most common adverse drug reaction observed ($n = 14$); no serious adverse drug reactions were reported. There were no discontinuations due to adverse drug reactions.

***Conclusion***: Vosoritide showed long-term effectiveness in a real-world Portuguese population of patients with achondroplasia. Vosoritide was also well tolerated, and patients showed good adherence to treatment. These findings were consistent with the outcomes of clinical trials and existing real-world experience.

**Keywords:** Achondroplasia; Compliance; Growth; Proportionality; Real-world experience; Safety; Vosoritide

**Key Summary Points**

*Why carry out this study?*

There is limited evidence to date demonstrating the safety and effectiveness of vosoritide in children with achondroplasia in a real-world setting.

This study evaluated growth, safety, and treatment compliance in children with achondroplasia ($n = 27$) receiving vosoritide at a single Portuguese clinic.

*What was learned from the study?*

After 24 months of vosoritide treatment, improvements were observed in height standard deviation score and annualized growth velocity in children with achondroplasia, consistent with clinical trial outcomes and existing real-world evidence.

Vosoritide was well tolerated, and patients showed good adherence to treatment, with no discontinuations due to adverse drug reactions; the most common adverse drug reactions observed were injection site reactions ($n = 14$) and hypertrichosis ($n = 4$).

The preliminary findings of this study contribute to the growing body of evidence supporting the safety and effectiveness of vosoritide in achondroplasia; longer-term follow-up is ongoing.

## INTRODUCTION

Achondroplasia is the most common form of skeletal dysplasia, affecting over 360,000 individuals worldwide [1]. It is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene, leading to overactive FGFR3 signaling and, thus, inhibition of chondrocyte proliferation and differentiation [2]. Consequently, endochondral bone growth is impaired in affected individuals, resulting in disproportionately short stature [3]. Other characteristic features of achondroplasia include macrocephaly with frontal bossing,

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midface hypoplasia, and genu varum [3–5]. Individuals with achondroplasia may experience a variety of medical, functional, and psychosocial challenges requiring lifelong management by a multidisciplinary team [1]. Complications associated with the condition include foramen magnum stenosis, sleep apnea, recurrent otitis media, spinal stenosis, and obesity [6].

Historically, treatment options for achondroplasia were limited and focused on managing disease symptoms, such as ameliorating body disproportion through limb lengthening. However, this procedure is complex, time consuming, and is often associated with complications [1, 7, 8]. Despite only being approved in Japan, human growth hormone was also used off-label in certain countries, with limited efficacy [9–11].

Vosoritide, a C-type natriuretic peptide (CNP) analog, is currently the only approved treatment that targets the underlying pathophysiology of achondroplasia. CNP is a potent stimulator of endochondral bone growth. Vosoritide has been engineered to resist degradation, thereby increasing its half-life, and works by counteracting overactive FGFR3 signaling to stimulate endochondral bone growth [12, 13].

In August 2021, the European Medicines Agency (EMA) approved vosoritide (daily subcutaneous injection, 15 µg/kg) for use in children with achondroplasia aged ≥ 2 years with open epiphyses based on positive data from an extensive clinical trial program. In October 2023, the EMA approved expansion of the indication to children with achondroplasia aged ≥ 4 months [12–14]. Data from phase 2 and 3 trials, and open-label extensions in children with achondroplasia have demonstrated sustained increases in absolute height gain, annualized growth velocity (AGV), and height standard deviation score (SDS) with vosoritide for up to 7 years [15–23]. Decreases in upper to lower body segment ratio have also been observed over time [17, 24]. Additionally, vosoritide was well tolerated across clinical trials; the most common adverse events were mild and transient injection site reactions [15–17, 22].

Following EMA approval of vosoritide, it is important to share experiences of using vosoritide in the clinic to facilitate a better understanding of its safety and effectiveness in a real-world setting. This retrospective cohort study aimed to evaluate growth parameters, safety, and treatment compliance in children with achondroplasia receiving vosoritide under an early access program in Portugal. The program was approved in December 2021.

## METHODS

### Study Design, Participants, and Follow-up

Hospitals in Portugal have been using a vosoritide monitoring protocol adapted from the French early access program [25], while also consulting published practical considerations for clinical practice (which provide expert guidance for the use of vosoritide in a real-world setting, including treatment initiation, clinical assessments, treatment response, and follow-up) [26, 27]. In this study, children aged 2–14 years with a genetically confirmed clinical diagnosis of achondroplasia who were treated with vosoritide at Hospital Pediátrico de Coimbra, Portugal for at least 6 months between January 2022 and June 2024 were included. All data were collected retrospectively by medical record analysis. The study was conducted in accordance with the Declaration of Helsinki, and approval from Unidade Local de Saúde de Coimbra ethics committee was obtained (ref. OBS.SF.140-2022; no. 490/CE; 1 August, 2024).

Vosoritide was administered as a daily subcutaneous injection at a dose of 15 µg/kg. Baseline parameters, clinical characteristics, and historical anthropometric measurements were recorded on the first day of vosoritide administration. Patients were followed up at 1, 3, and 6 months, and at 6-monthly intervals thereafter. Physical assessments, blood analysis, and electrocardiograms (ECGs) were conducted at baseline and month 3. Detailed anthropometric measurements and Tanner stage were collected at baseline and every 6 months thereafter; measurements were performed by the same two trained nurses at each visit. Bone age was assessed at baseline and every 12 months thereafter. The safety and tolerability of vosoritide was recorded at each follow-up visit.

### Study Outcomes

The following anthropometric measurements were collected to characterize the effect of vosoritide on growth: standing height (or supine length), height SDS, and AGV. Arm span, sitting height (or crown–rump length), sitting height to height ratio, upper to lower segment ratio were also recorded to assess vosoritide's impact on body disproportion. Other measurements, including leg length, hand length, weight, body mass index, and head circumference, were also collected but not included in this study. Safety and tolerability endpoints included adverse drug reactions and treatment adherence (pauses in or discontinuation of vosoritide).

### Statistical Analysis

All data analysis was performed using R Statistical Software (v4.2.2; R Core Team 2022). Patient characteristics were described as numbers and percent or means and standard deviations (SDs). Standing height was converted to an age- and sex-appropriate SDS value according to a comparison with the reference standards of the World Health Organization (WHO). Growth of the cohort was compared with children from the general population (WHO standard charts) and to an untreated achondroplasia-specific population using one-sample Student's *t* test [4, 28–30]. AGV, which was based on measurements of standing height, was summarized using descriptive statistics, with AGV at the time of vosoritide administration serving as baseline. The minimum time interval used to calculate baseline AGV was 0.42 years. To compensate for deviations in date of anthropometric measurement (e.g., measurements at month 12, which had been taken at 11 months, 20 days) variations were divided by the number of years since treatment initiation to give annual variations. Adverse drug reactions are presented as incidence and percent.

## RESULTS

### Participants

In total, 27 children with achondroplasia (12 girls, 15 boys) were included in the study (Table 1). Participants were from the following Portuguese regions: North ($n=13$), Center, Lisbon (each $n=6$), Alentejo, Algarve (each $n=1$). Twenty-four participants were White, two participants were Black, and one participant was Asian. Diagnosis was established prenatally in 37.0% of participants and postnatally in 63.0% of participants. In all cases, the *FGFR3* variant occurred de novo. Twenty-one participants had the recurrent *FGFR3* variant c.1138G>A; p.Gly380Arg, and five had c.1138G>C; p.Gly380Arg. The remaining participant, an 8-year-old girl, had the *FGFR3* variant c.1620C>A; p.Asn540Lys, which is more frequently associated with hypochondroplasia [31]. However, as a result of the participant's clinical phenotype, namely early-onset severe short stature (height SDS − 4.91 SD, based on WHO growth curves; 0 SD, based on achondroplasia-specific growth curves), a diagnosis of achondroplasia was considered appropriate.

Considering their medical history, 21 participants had foramen magnum stenosis, of whom seven (25.9%) required decompression surgery. Other achondroplasia-associated complications included ear, nose, and throat problems ($n=19$), obstructive sleep apnea ($n=15$; four patients had ongoing non-invasive ventilation during treatment), persistent kyphosis ($n=5$), genu varum requiring 8-plates ($n=2$), and epilepsy ($n=2$). No individuals were excluded from treatment initiation as a result of the severity of their achondroplasia-related complications.

The mean age at treatment initiation was 7.3 years (range 2.2–14.2 years). All children completed a minimum of 6 months of treatment, 26 (96.3%) completed 12 months, 19 (70.4%) completed 18 months, 15 (55.6%) completed 24 months, and 2 (7.4%) completed 30 months. Of the four patients who started vosoritide aged 12 years or older (Table S1), three discontinued treatment (one at 18 months and two at 24 months). The remaining patient is responding well and is continuing treatment.

### Height Standard Deviation Score

Absolute mean height SDS improved from baseline over time with treatment (Figs. 1, S1, S2). In the overall cohort, mean variation in height

**Table 1** Baseline characteristics

| | **Total (*N* = 27)** | **Boys (*N* = 15)** | **Girls (*N* = 12)** |
|---|---|---|---|
| Age, years, *n* (%) | | | |
| 2–5 | 9 (33.3) | 7 (46.7) | 2 (16.7) |
| 6–9 | 8 (29.6) | 3 (20.0) | 5 (41.7) |
| 10–12 | 6 (22.2) | 4 (26.7) | 2 (16.7) |
| 13–14 | 4 (14.8) | 1 (6.7) | 3 (25.0) |
| Age at treatment initiation, years | | | |
| Mean (SD) | 7.3 (4.07) | 6.3 (4.33) | 8.6 (3.51) |
| Ethnicity, *n* (%) | | | |
| White | 24 (88.9) | 14 (93.3) | 10 (83.3) |
| Black | 2 (7.4) | 1 (6.7) | 1 (8.3) |
| Asian | 1 (3.7) | 0 (0.0) | 1 (8.3) |
| Genetic variant in *FGFR3*, *n* (%) | | | |
| c.1138G>A (p.Gly380Arg) | 21 (77.7) | 14 (93.3) | 7 (58.3) |
| c.1138G>C (p.Gly380Arg) | 5 (18.5) | 1 (6.7) | 4 (33.3) |
| c.1620C>A (p.Asn540Lys) | 1 (3.7) | 0 (0.0) | 1 (8.3) |
| Height SDS (WHO) | | | |
| Mean (SD) | − 5.08 (0.83) | − 4.84 (0.83) | − 5.39 (0.76) |
| Height SDS (ACH) | | | |
| Mean (SD) | − 0.07 (1.13) | 0.14 (1.26) | − 0.33 (0.94) |
| Foramen magnum stenosis, *n* (%) | | | |
| Yes | 21 (77.7) | 13 (86.7) | 8 (66.7) |
| No/not evaluated | 6 (22.2) | 2 (13.3) | 4 (33.3) |
| Foramen magnum stenosis severity, *n* (%) | | | |
| Mild | 13 (48.1) | 9 (60.0) | 4 (33.3) |
| Moderate | 2 (7.4) | 1 (6.7) | 1 (8.3) |
| Severe | 6 (22.2) | 3 (20.0) | 3 (25.0) |
| Foramen magnum decompression, *n* (%) | | | |
| Yes | 7 (25.9) | 5 (33.3) | 2 (16.7) |
| No | 20 (74.1) | 10 (66.4) | 10 (83.3) |

**Table 1** continued

| | Total ($N=27$) | Boys ($N=15$) | Girls ($N=12$) |
|---|---|---|---|
| Ear, nose, and throat complications, *n* (%) | | | |
| Yes | 19 (70.4) | 11 (73.3) | 8 (66.7) |
| No | 8 (29.6) | 4 (26.7) | 4 (33.3) |
| Obstructive sleep apnea, *n* (%) | | | |
| Yes | 15 (55.6) | 9 (60.0) | 6 (50.0) |
| No | 12 (44.4) | 6 (40.0) | 6 (50.0) |
| Ongoing non-invasive ventilation, *n* (%) | | | |
| Yes | 4 (14.8) | 2 (13.3) | 2 (16.7) |
| No | 23 (85.2) | 13 (86.7) | 10 (83.3) |
| Genu varum requiring 8-plates, *n* (%) | | | |
| Yes | 2 (7.4) | 0 (0.0) | 2 (16.7) |
| No | 25 (92.6) | 15 (100.0) | 10 (83.3) |
| Kyphosis, *n* (%) | | | |
| Yes | 13 (48.1) | 7 (46.7) | 6 (50.0) |
| No | 14 (51.9) | 8 (53.3) | 6 (50.0) |
| Neurological complications (epilepsy), *n* (%) | | | |
| Yes | 2 (7.4) | 2 (13.3) | 0 (0.0) |
| No | 25 (92.6) | 13 (86.7) | 0 (0.0) |

*ACH* achondroplasia, *FGFR3* gene encoding fibroblast growth factor receptor 3, *SD* standard deviation, *SDS* standard deviation score, *WHO* World Health Organization

SDS significantly increased from baseline by +0.38 SD ($P \leq 0.001$) after 12 months and +0.95 SD ($P \leq 0.0001$) after 24 months of treatment, referenced to the untreated achondroplasia-specific population [4]. When compared with children from the general population using WHO standard charts [29, 30], mean variation in height SDS significantly increased from baseline by +0.21 SD ($P \leq 0.01$) after 12 months and +0.56 SD ($P \leq 0.0001$) after 24 months.

### Standing Height

Vosoritide treatment resulted in improvements in absolute height in children with achondroplasia. Most treated girls surpassed the 50th percentile on the achondroplasia-specific reference charts, while several boys reached or exceeded the 97th percentile (Fig. 2).

### Annualized Growth Velocity

The overall mean AGV at baseline was 4.25 cm/year (95% confidence interval [CI] 3.58–4.91), which significantly increased to 5.69 cm/year (95% CI 5.02–6.36) after 12 months of vosoritide treatment ($P \leq 0.0001$). After 24 months of treatment, mean AGV was 5.87 cm/year (95% CI 5.13–6.60), resulting in a significant increase of +1.62 cm/year compared with baseline ($P \leq 0.0001$). In girls, mean AGV at

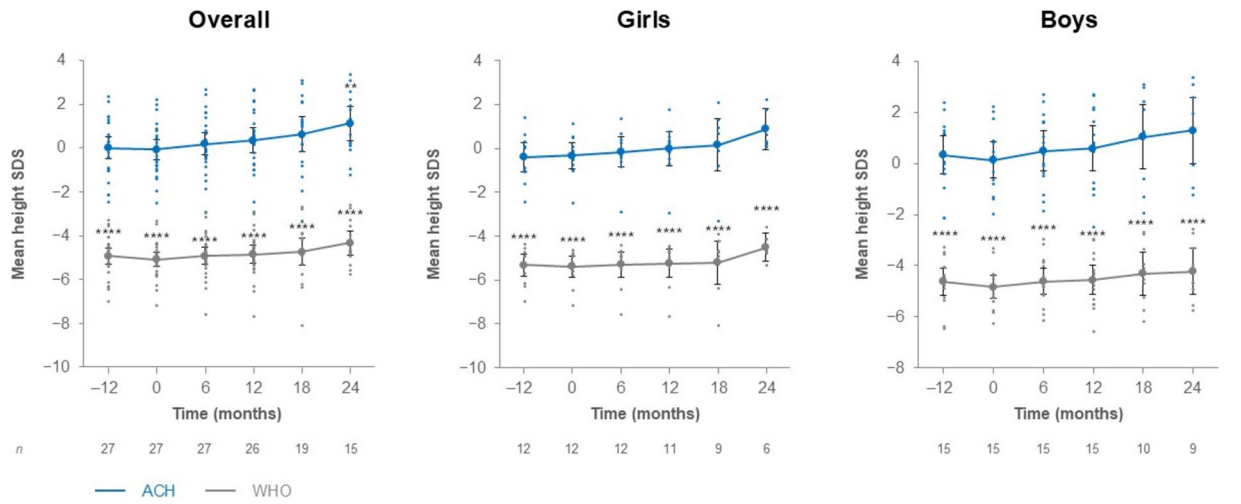


**Fig. 1** Absolute mean height SDS in children ($n = 27$) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals. $^{**}P \le 0.01$ and $^{****}P \le 0.0001$ compared with the ACH or WHO reference growth curves [4, 29, 30]. Individual height SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score, *WHO* World Health Organization

24 months increased by +1.4 cm/year compared with baseline AGV (4.12 cm/year [95% CI 2.89–5.37]; $P \le 0.001$). In boys, mean AGV at 24 months increased by +1.76 cm/year compared with baseline AGV (4.34 cm/year [95% CI 3.52–5.17]; $P \le 0.001$) (Figs 3 and S3).When analyzed by sex, mean variation in height SDS increased significantly from baseline by +0.85 SD ($P \le 0.05$) in girls and +1.01 SD ($P \le 0.001$) in boys at month 24, referenced to the untreated achondroplasia-specific population [4]. Compared with WHO standard growth curves [29, 30], mean variation in height SDS increased significantly from baseline by +0.56 SD ($P \le 0.05$)

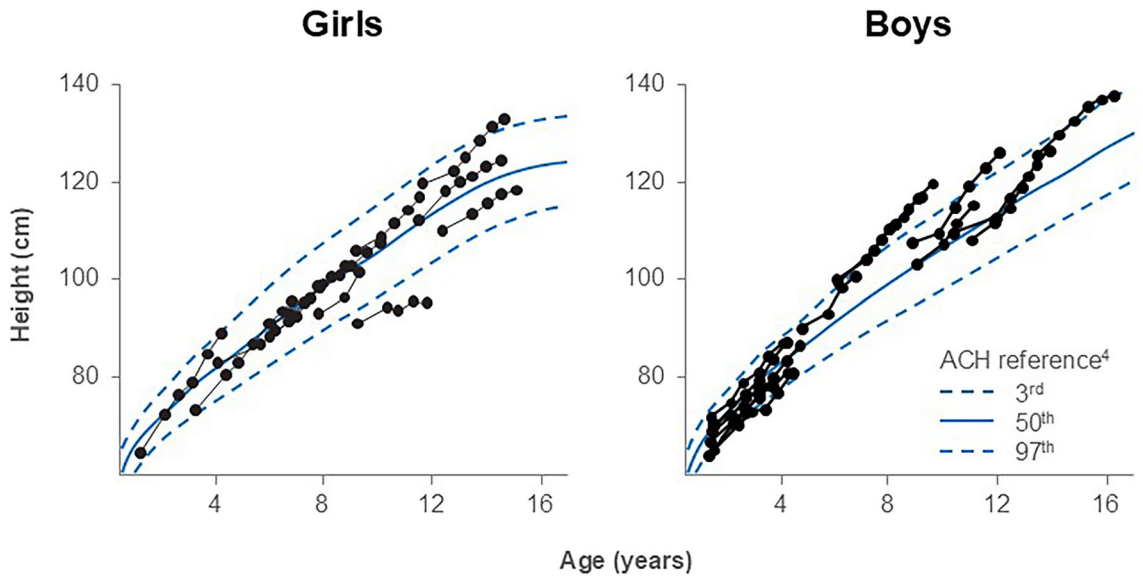


**Fig. 2** Individual height variation following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [4]. *ACH* achondroplasia

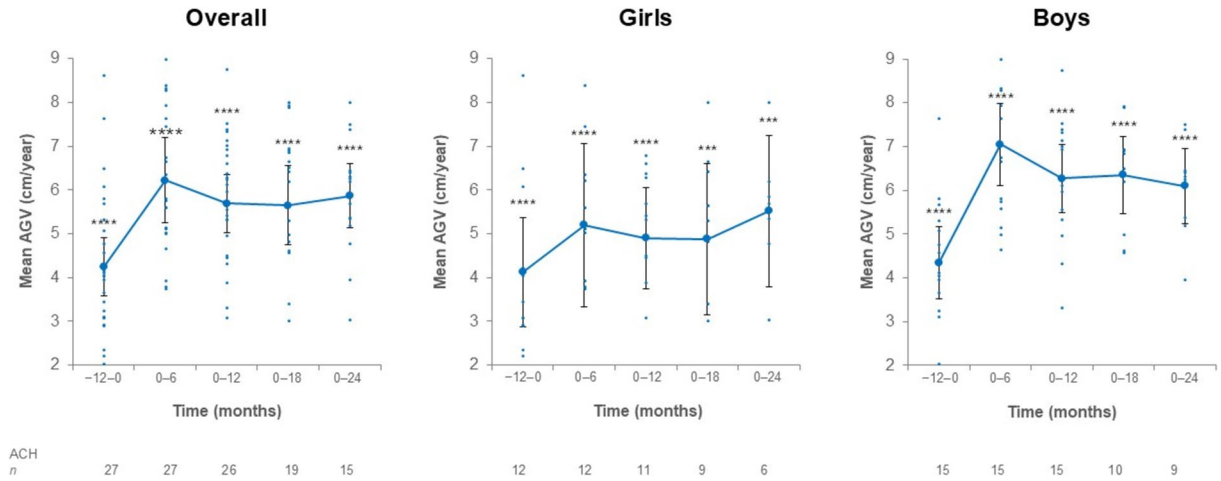


**Fig. 3** Absolute mean AGV in children ($n = 27$) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals; the ranges on the x-axis represent the time points between which AGV was calculated. ***$P \leq 0.001$; ****$P \leq 0.0001$, compared with baseline AGV. Individual AGV values are also plotted. *ACH* achondroplasia, *AGV* annualized growth velocity

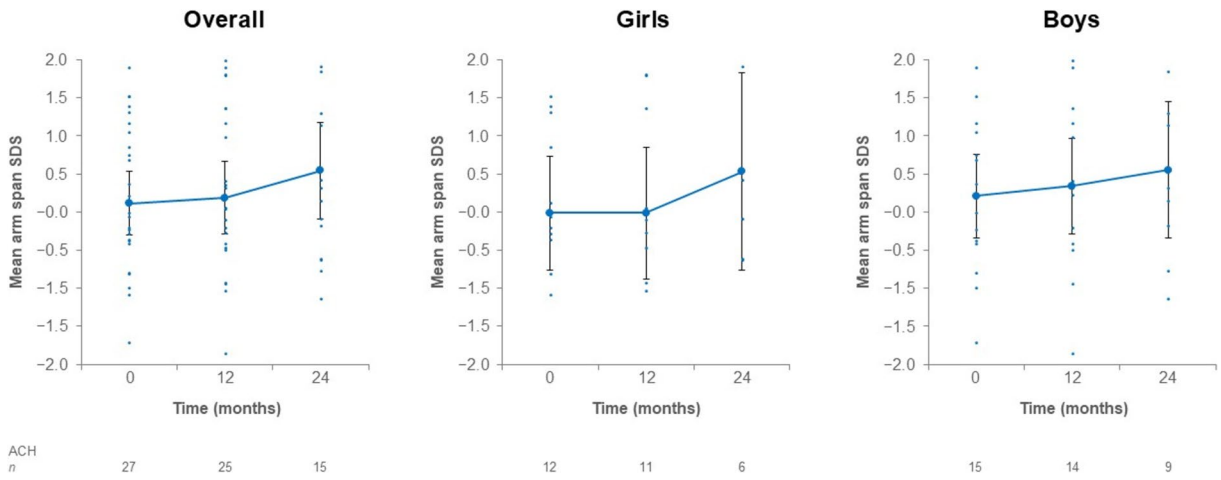


**Fig. 4** Absolute mean arm span SDS in children ($n = 27$) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals. Individual arm span SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score

in girls and +0.56 SD ($P \leq 0.01$) in boys after 24 months of treatment.

## Arm Span

Absolute mean arm span SDS, referenced to the untreated achondroplasia-specific population [28], showed an upward trend from baseline to 24 months (Figs. 4 and S4). While this improvement was not statistically significant overall, there was considerable variability in response between individuals (Fig. 5).

In the overall cohort, mean variation in arm span SDS significantly increased from baseline by +0.13 SD ($P \leq 0.01$) after 12 months of treatment and +0.32 SD ($P \leq 0.01$) after 24 months of treatment compared with the untreated achondroplasia-specific reference population [28]. When analyzed by sex and compared with sex-matched data

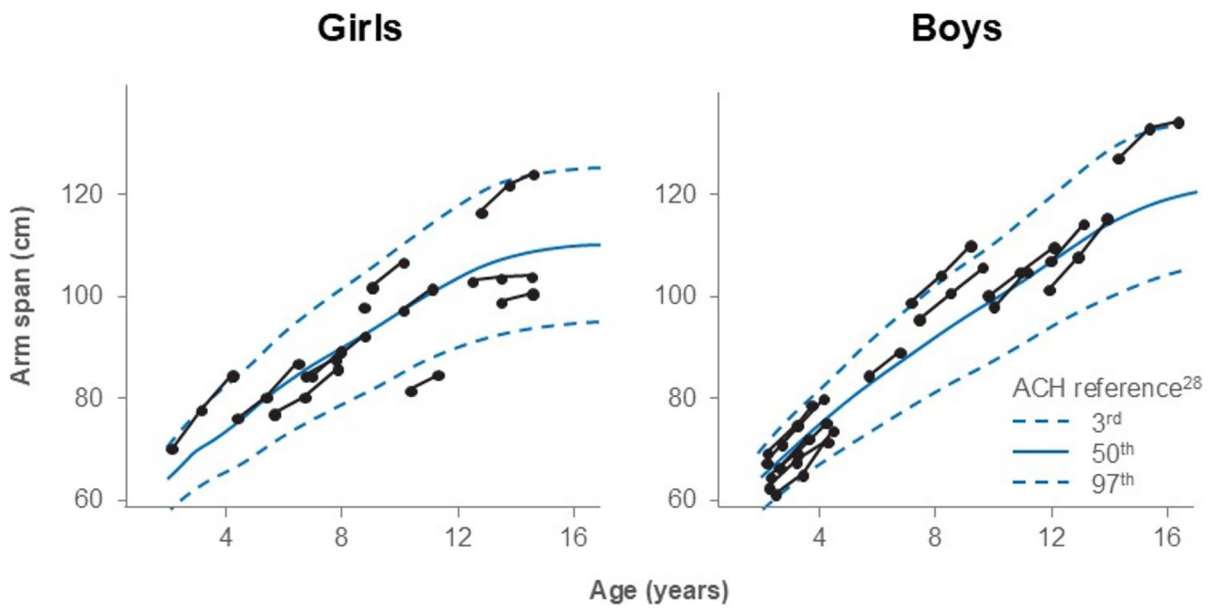


**Fig. 5** Arm span in individual patients following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [28]. *ACH* achondroplasia

from the same reference population, the increase from baseline in mean variation in arm span SDS was significant at 12 months (+0.17 SD; $P \leq 0.05$) and 24 months (+0.38 SD; $P \leq 0.05$) among boys. However, in girls, the improvements from baseline following 12 months (+0.08 SD) and 24 months (+0.24 SD) of vosoritide treatment were not statistically significant.

### Sitting Height

Improvements in absolute sitting height were also observed following vosoritide treatment

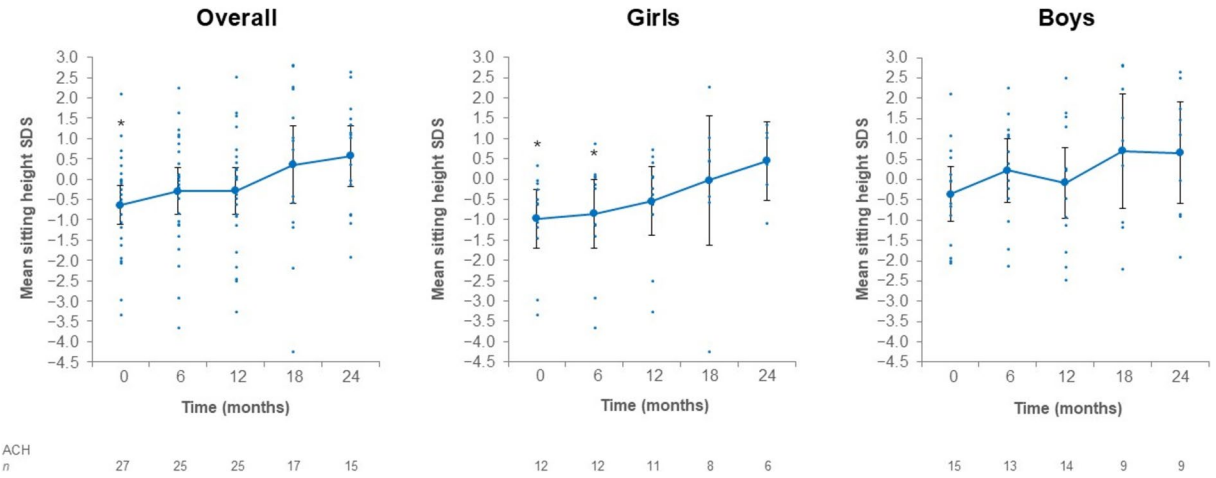


**Fig. 6** Absolute mean sitting height SDS in children ($n = 27$) treated with vosoritide for up to 24 months. Error bars show 95% confidence intervals. $^{*}P \leq 0.05$ compared with the achondroplasia reference growth curve [28]. Individual sitting height SDS values are also plotted. *ACH* achondroplasia, *SDS* standard deviation score

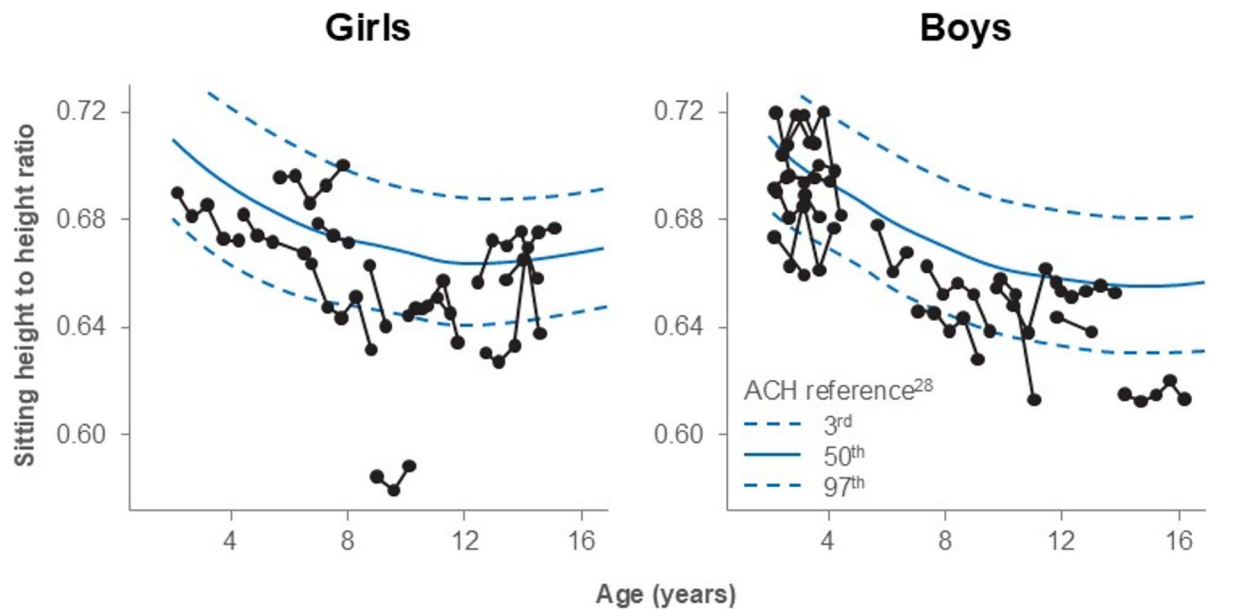


**Fig. 7** Sitting height to height ratio in individual patients following treatment with vosoritide for up to 24 months, referenced to the untreated ACH-specific growth curve [28]. *ACH* achondroplasia

(Figs. 6 and S5). In the overall cohort, mean variation in sitting height SDS, referenced to the untreated achondroplasia-specific population [28], significantly increased from baseline by +0.35 SD ($P \leq 0.01$) after 12 months of treatment and +0.79 SD ($P \leq 0.01$) after 24 months of treatment. When analyzed by sex, the increase from baseline in mean variation in sitting height SDS was significant at 12 months among girls (+0.39 SD; $P \leq 0.01$) and 24 months among boys (+0.80 SD; $P \leq 0.05$) compared with sex-matched data from the same reference population.

### Sitting Height to Height Ratio

No statistically significant differences in variation in sitting height to height ratio were observed between baseline and month 24 of vosoritide treatment. Individual sitting height to height ratios are shown in Fig. 7.

### Upper to Lower Segment Ratio

In the overall cohort, there was a significant improvement in mean variation in upper to lower segment ratio after 24 months of vosoritide treatment (−0.10; $P \leq 0.01$). When analyzed by sex, a significant improvement in mean variation in upper to lower segment ratio was observed in boys at month 24 (−0.11; $P \leq 0.05$), while no significant improvement was seen in girls. Individual upper to lower segment ratios are shown in Fig. S6.

### Safety and Adherence

Adverse drug reactions were reported by 18 (66.7%) individuals. Injection site reactions, including hematomas, erythema, and local edema, were the most common adverse drug reaction observed ($n = 14$; 51.9%). Other adverse drug reactions were recorded in a limited number of children, including headache, rash, itching, and lipothymia (all $n = 1$; 3.7%). Four patients (14.8%) experienced hypertrichosis, mostly at the dorso-lumbar region (Fig. S7). The time of onset varied in relation to treatment initiation. In all four cases, treatment was continued without interruption, and hypertrichosis stabilized or diminished after a few months. No abnormal blood test results or ECGs were

observed during treatment. One individual had elevated liver transaminases at baseline which did not worsen on treatment. No serious adverse drug reactions were observed.

Throughout the study, there were 29 missed doses of vosoritide reported by nine patients, equating to 0.71 missing doses/patient/year. One patient was responsible for 10 of the 29 missed doses. No patients discontinued treatment because of an adverse drug reaction.

## DISCUSSION

This real-world retrospective cohort study aimed to characterize growth and evaluate safety and tolerability in patients with achondroplasia receiving vosoritide in Portugal. The Bone Dysplasia Multidisciplinary Team at Hospital Pediátrico de Coimbra is the most experienced team nationally, following up with approximately 85% of children diagnosed with achondroplasia in Portugal. The study cohort, which included children of all ages, diverse backgrounds, and from all regions of continental Portugal, is representative of the Portuguese population.

According to published reference data from untreated children with achondroplasia, mean height SDS is −2.5 in girls aged < 1 year and −3.2 in boys aged < 1 year, compared with age- and sex-matched average-stature children. It decreases to −5.3 SDS in girls and −4.6 in boys by aged 5 years. Mean AGV is 11.6 cm/year in girls aged < 1 year and 14.6 cm/year in boys aged 1 year, which decreases to 7.1 cm/year in girls and 7.4 cm/year in boys at 1 year, before steadily declining to 3.6 cm/year in girls and 3.6 cm/year in boys at 10 years [32]. In our study, vosoritide treatment led to improvements in growth across several parameters, including height SDS and AGV, while maintaining an acceptable safety and tolerability profile. Increases in arm span and sitting height were also observed on treatment. Growth acceleration became more apparent over time, with some individuals only showing noticeable effects after 18 months of treatment. The most substantial improvements were observed at 24 months.

The effectiveness data from our study are concordant with efficacy data from clinical trials with vosoritide. In a phase 3 randomized, placebo-controlled, double-blind study (NCT03197766) with an open-label extension (NCT03424018), significant improvements were observed in absolute height, AGV (+1.57 cm/year; $P < 0.0001$), and height SDS (+0.28 SD after 1 year of treatment and +0.44 SD after 2 years of treatment, relative to children of average stature) [16, 17, 23]. These improvements were sustained for up to 4 years [19, 23]. In a phase 2 randomized, placebo-controlled, double-blind study (NCT02055157) with an open-label extension (NCT02724228), vosoritide treatment was associated with increases in AGV in children aged ≥ 5 years [15]. An increase in mean (SD) height SDS of +1.02 SD (0.64), referenced to an untreated achondroplasia population, was also observed. Improvements were maintained for up to 7 years [15, 18, 20]. In a separate phase 2 randomized, placebo-controlled, double-blind study in infants and toddlers (NCT03583697) with an open-label extension (NCT03989947), children aged ≥ 2 years ($n = 9$) treated with vosoritide for 4 years achieved 90.45% of the height of children of average stature, while those aged < 2 years ($n = 14$) treated for 3 years reached 80.02% of the height of children of average stature [21].

While vosoritide had a positive effect on absolute arm span and sitting height in the present study, its impact was not statistically significant, and considerable variability was observed between individuals. These data should be interpreted in the context of the small sample size, limited follow-up period to date, and the interpatient variability observed, particularly in sitting height. It should also be noted that the effect of vosoritide on arm span and sitting height has not been described extensively in previous studies. To further characterize vosoritide's effect on proportionality, we determined the sitting height to height ratio, which is considered an accurate method of evaluating body proportionality [33–35]. In infants of average stature, sitting height accounts for approximately

two-thirds of their total height, decreasing to approximately 50% of standing height by adolescence [33]. In children with achondroplasia, the median ratio at birth is 0.73, which reduces to only 0.66 at adolescence [36]. In our study, while we observed no significant improvements in sitting height to height ratio between baseline and 24 months overall, some individual patients showed positive responses to vosoritide when compared with the untreated achondroplasia reference population, and this parameter is worthy of further investigation with a longer follow-up.

Clinical trials have typically used upper to lower body segment ratio to evaluate vosoritide's effects on proportionality, a ratio that should be in accordance to sitting height to height ratio. In children of average stature, the ratio of upper to lower body segments is 1.4 at birth, decreasing to 1.0 by 10 years of age as the long bones lengthen relative to the trunk. In children with achondroplasia, the median ratio at birth is 2.0, which reduces to only 1.7 at skeletal maturity [37]. In a phase 3 clinical trial (NCT03197766) with an open-label extension (NCT03424018), vosoritide treatment for up to 2 years led to a mean change from baseline in upper to lower body segment ratio of −0.05 (95% CI −0.09 to −0.01) in children with achondroplasia aged < 12 years, representing an improvement in proportionality [17]. In our study, significant improvements in mean variation in upper to lower segment ratio were observed in the overall cohort after 24 months of vosoritide treatment (despite seeing no increase in sitting height to height ratio). However, no achondroplasia-specific reference data are available for comparison.

The effectiveness of vosoritide observed in our study was also consistent with real-world data published to date. In the published results from the French early access program, which served as a model for our study design, data were collected from 57 vosoritide-treated children with achondroplasia aged ≥ 5 years, across six referral centers [25]. In the 17 participants with 18 months of follow-up, mean absolute height increased by 8.8 cm and mean height SDS improved by 0.56 SD, referenced to an untreated American achondroplasia population [38]. Preliminary data have also been published from a cohort of patients with achondroplasia ($n = 30$) treated with vosoritide for at least 6 months at IRCCS Giannina Gaslini, Genoa, Italy [39]. As with our study, an increase in height SDS was reported. However, the Italian analysis also documented improvements in additional anthropometric parameters following vosoritide treatment, including weight SDS and upper to lower body segment ratio. Data from children with achondroplasia treated with vosoritide across 30 European centers ($n = 236$) are also being collected as part of the CrescNet registry at the University of Leipzig [40]. Using the European reference cohort [4], an increase of 1.15 SD in mean height SDS was recorded among patients who had been treated with vosoritide for 24 months. In a retrospective observational study, 34 patients with achondroplasia who received vosoritide for at least 12 months at University Hospital Cologne, Germany, were included in the analysis. When referenced to both achondroplasia and average-stature populations, significant increases in height SDS were observed after 12 months of treatment (+0.35 SD and +0.38, respectively; both $P < 0.0001$). AGV exceeded reference values for untreated children with achondroplasia. However, as in our study, no significant differences were seen in sitting height to height ratio [41].

Vosoritide has been well tolerated in clinical trials conducted to date and its safety profile in children aged < 5 years is consistent with that in children aged ≥ 5 years [19, 21]. Similar to our observations, in both clinical trials and previous real-world studies, the most common adverse events were mild and largely limited to transient injection site reactions [15–17, 22, 25, 39, 42]. Hypertrichosis was not identified as an adverse event in clinical trials, but several clinical centers have reported cases following vosoritide use in a real-world setting. In July 2024, hypertrichosis was added to vosoritide's Summary of Product Characteristics as an uncommon adverse reaction in treated patients [43]. In our study, four patients (14.8%) experienced hypertrichosis but in all cases treatment was continued without interruption, and hypertrichosis stabilized or resolved after a few months.

Existing real-world studies have reported no instances of treatment discontinuations, interruptions, or missed doses, although this should

be interpreted in the context of the limited follow-up period [25, 39, 42]. We observed infrequent missed doses (approximately 0.71 per patient per year), and no discontinuations due to adverse drug reactions.

Of the four individuals (three girls, one boy) who started vosoritide aged 12 years or older, three discontinued treatment. In two girls, no significant response was observed. In the male patient, a clear response was seen after 12 months of treatment, but this subsequently diminished at 24 months. Vosoritide should be ceased upon confirmation of no further growth potential, indicated by an AGV of less than 1.5 cm per year and the closure of epiphyses [43]. Although AGV in these individuals was slightly above 1.5 cm per year and they had open growth plates at the time of final treatment, vosoritide was discontinued because of their lack of response expected by the patient/team, progression toward maturity, and/or the burden of daily injections. The remaining female patient is responding well and is continuing treatment.

Among the remainder of our cohort, there were three additional individuals who did not show a clear response to vosoritide. Two boys started vosoritide at 2 years of age and have completed 12 months of treatment with limited response so far. Greater variability in response has been observed in younger children within the cohort, although a later positive response remains possible. The third case was a girl who started vosoritide aged 10 years. Her height worsened from − 2.50 SDS at baseline (referenced to the untreated achondroplasia-specific population) to − 3.29 SDS following 18 months of treatment; vosoritide discontinuation was therefore being considered. She presented with an acute achondroplasia phenotype, including severe foramen magnum stenosis with neurological sequela and significant kyphosis. Although this case may be an outlier, several individuals in the cohort with limited treatment response also have a more severe achondroplasia phenotype, characterized by a greater degree of short stature and associated complications. Nevertheless, it is difficult to determine factors predicting treatment response in this cohort because of its small size.

The main strength of the data is their homogeneity; they were collected by the same physicians and nurses at a single Portuguese center throughout the study period. Additionally, a consistent baseline growth pattern was observed within our cohort; minimal variation in height SDS was recorded prior to vosoritide initiation. Unlike in clinical trials, no patients were excluded from treatment initiation and data analysis as a result of the severity of their achondroplasia-associated complications. It should be acknowledged that our study utilized WHO standard curves and a European achondroplasia reference cohort [4, 29, 30], whereas the growth curves used in vosoritide clinical trials were based on Centers for Disease Control and Prevention (CDC) reference data for average stature and an American cohort of individuals with achondroplasia [38, 44]. However, this is unlikely to have impacted on the findings.

The present study had some limitations. The single-center, retrospective design may influence the external validity of the findings. Retrospective analysis limited the time points used for data analysis. Sample sizes were also small ($n = 27$), especially when considering treatment duration subgroups (e.g., only six girls completed 24 months of treatment). Careful consideration should be made before drawing conclusions from statistical significance in such small subgroups. Small sample sizes were also the reason we did not compare growth and proportionality by age group, which would have been valuable, given they change over time regardless of treatment status. In addition, assessment of health-related quality of life in children with achondroplasia undergoing treatment with vosoritide was not undertaken. A longer follow-up is ongoing to further assess the safety and effectiveness of vosoritide in a real-world setting.

## CONCLUSION

Vosoritide showed long-term effectiveness in a real-world Portuguese population of patients with achondroplasia. Vosoritide was also well

tolerated, and patients showed good adherence to treatment. These initial findings are consistent with clinical trial data and preliminary real-world data from other centers, contributing to the growing body of evidence supporting the safety and effectiveness of vosoritide in managing achondroplasia. Moving forward, it is crucial that vosoritide treatment and subsequent monitoring is integrated into the multidisciplinary care of patients with achondroplasia. Thorough follow-up by an experienced team is also vital. To determine the potential impact of vosoritide on achondroplasia-associated complications, longer-term data collection from larger cohorts in a real-world setting is required.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

### *Declarations*

***Conflict of Interest.*** Inês Rua has received honoraria for lectures and/or travel support from BioMarin and Ascendis; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, BioMarin, and QED. Isabel Silva has received travel support from BioMarin; and has been an investigator in observational studies for BioMarin. Upon completion of the manuscript, Isabel Silva has changed affiliation to Unidade Local de Saúde de São José, Lisbon, Portugal. Christoph Beger has received support for attending meetings and/or travel from BioMarin. Cristina Gomes has received honoraria for lectures and/or travel support from BioMarin; and has been research nurse in observational studies or clinical trials for Pfizer, Ascendis, BioMarin, and QED. Maria J. Pais has been research nurse in observational studies and/or clinical trials for Pfizer, BioMarin, and QED. Alice Mirante has received honoraria for lectures, advisory boards, and/or travel support from BioMarin; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, and BioMarin. Sérgio B. Sousa has received honoraria for lectures, advisory boards, and/or travel support from BioMarin, Ascendis, and Kiowa Kirin; and has been an investigator in observational studies and/or clinical trials for Pfizer, Ascendis, BioMarin, and QED.

***Ethical Approval.*** The study was conducted in accordance with the Declaration of Helsinki, and approval from Unidade Local de Saúde de Coimbra ethics committee was obtained (ref. OBS.SF.140-2022; no. 490/CE; 1 August, 2024).

Written consent was obtained for the use of any identifying information.



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