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SYSTEMATIC REVIEW

Real-world outcomes of vosoritide in achondroplasia: A systematic review and meta-analysis of multinational clinical evidence

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ABSTRACT

Purpose: Achondroplasia is the most common skeletal dysplasia, caused by gain-of-function variants in *FGFR3*, resulting in constitutive receptor activation and downstream inhibition of endochondral ossification. In 2021, the first targeted therapy, vosoritide, was approved in some countries after a landmark randomized trial. Although findings are promising, evidence is limited to modest-sized cohorts. To address this, we conducted a systematic review and meta-analysis of available vosoritide data.

Methods: A systematic search of PubMed, Cochrane, and Embase was conducted. Data were extracted according to Cochrane guidelines. Outcomes consistently reported were synthesized using R (v4.5) to generate forest plots.

Results: Ten studies were analyzed, encompassing 696 pediatric patients. Meta-analysis of single means showed that height *z*-score variation after 12 months of treatment was 0.32 (95% CI 0.25-0.40), annualized growth rate was 1.82 cm/year higher after treatment (95% CI 1.46-2.18), and the ratio between sitting height and height showed −0.0089 decrease (95% CI −0.0157 to −0.0020). Studies reported uniform profiles of adverse events, mostly limited to mild injection-site related issues and no serious complications.

Conclusion: This meta-analysis shows that real-world observational data on vosoritide in children with achondroplasia replicate clinical trial findings, with greater gains in linear growth and a similarly favorable safety profile.

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Introduction

Achondroplasia (ACH) is the most common form of short-limbed skeletal dysplasia, caused by gain-of-function variants in the *FGFR3* gene that results in constitutive activation of the fibroblast growth factor receptor 3 pathway. These variants disrupt endochondral ossification, leading to disproportionate short stature and a range of medical complications that persist throughout the lifespan. Individuals with achondroplasia often face challenges such as foramen magnum stenosis, obstructive sleep apnea, spinal stenosis, recurrent otitis media, obesity, delayed motor milestones, and psychosocial difficulties related to stature and physical limitations.[1,2]

Historically, the management of achondroplasia has relied primarily on supportive care, complication management and limb-lengthening surgeries.[1,3] Growth hormone is approved only in Japan for achondroplasia treatment and has shown limited efficacy in significantly altering final adult height, so that its long-term benefits remain modest.[2,4] Surgical interventions, although effective in increasing limb length, are invasive, costly, and carry substantial physical and psychological burdens. These limitations have underscored the urgent need for targeted, disease-modifying therapies that address the underlying pathophysiology of achondroplasia rather than its complications alone.[1,5]

In recent years, the rise of precision medicine has transformed the landscape of treatment for genetic disorders, enabling therapeutic strategies tailored to molecular defects.[5] A leading example of this progress is the development of vosoritide, a recombinant C-type natriuretic peptide analog designed to counteract the effects of *FGFR3* overactivation. Vosoritide works by binding to natriuretic peptide receptor-B, stimulating cyclic guanosine monophosphate production and thereby inhibiting the MAPK pathway downstream of *FGFR3*, effectively bypassing the constitutively active receptor and restoring chondrocyte proliferation and differentiation in the growth plate.[5]

Although vosoritide represents a breakthrough in targeted therapy for achondroplasia and has demonstrated encouraging results in preclinical studies and clinical trials, current regulatory approvals are largely based on a single pivotal phase 3 trial.[6] This trial was well-designed, rigorously conducted, and comprehensive, providing robust evidence of vosoritide's efficacy in improving growth velocity in children with achondroplasia. Despite being the gold standard for evaluating treatment efficacy, clinical trial populations may not fully capture the heterogeneity of real-world patients across different countries, health care systems, and genetic backgrounds.

To address this gap, we conducted a systematic review and meta-analysis of multinational real-world evidence on vosoritide, aiming to synthesize all available clinical data on the use of vosoritide so far. By integrating observational studies and registry-based cohorts, this study seeks to provide a broader understanding of vosoritide's effectiveness and safety in diverse patient populations and inform its long-term role in the clinical management of achondroplasia.

Materials and Methods

Data sources and search strategy

This systematic review and meta-analysis aimed to analyze available evidence on precision therapies for children with genetic causes of short stature. We followed recommendations from the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (Supplemental Table 2) and registered the study on PROSPERO under the protocol number CRD420251089551.[7] Articles were retrieved using a broad search strategy (Supplemental Table 3), later limited to vosoritide treatment in children with achondroplasia due to meta-analysis viability limitations.

A comprehensive search was conducted in PubMed, Embase, and the Cochrane Library from inception until July 2, 2025. Additional articles were manually identified by examining reference lists of the included publications and published abstract archives from recent genetics and endocrinology conferences. Abstract and title screening was performed blindly by 2 authors (A.A. and M.D.), and conflicts were resolved by a third reviewer (P.R.).

Study selection criteria and data extraction

We included the available randomized control trial[6] and observational studies in form of full articles and abstracts reporting long-term outcomes of treatment with vosoritide for at least 12 months. We applied no restrictions to sample size because of the limited amount of studies and intention to include diverse populations. We excluded reviews, case reports, case series, case-control studies, and preclinical research. Clinical trial registrations and published results were also consulted. Additionally, ongoing studies and abstracts with no published results at the time the search was performed were excluded, as well as studies in languages other than English and results lacking quantitative data.

On full-text analysis, studies were cautiously assessed for population overlap. Two authors (A.A., P.R.) independently collected data from individual studies, and disagreements were resolved by consensus. The primary outcome measure evaluated was increased growth, which was heterogeneously reported among studies. The most prevalent metrics available were selected for statistical synthesis, namely, increase in annualized growth velocity (AGV) after treatment and catch-up growth, represented by height standard deviation score variation (ΔSDS) after at least 12 months of treatment.[6] ΔSDS represents the mean z-score after treatment minus the mean baseline z-score

reported in each cohort. These metrics were referenced to different growth charts specific to each population, including Centers for Disease Control and Prevention, World Health Organization, and population-specific growth charts. Notably, individual patient height at baseline and follow-up were plotted to the same references, reflecting within-study standardized growth variation and minimizing the influence of reference differences across cohorts. A secondary endpoint analyzed was the ratio between sitting height and total height (SH/H), representing upper and lower segment proportionality. To enable comparison across studies, we transformed data originally reported as the ratio of sitting height to sitting height (SH/[H − SH]) into SH/H, using the formula: $SH/H = r/(1 + r)$, in which r represents SH/(H − SH). The standard deviation (SD) of the mean difference between pre- and posttreatment values was estimated using the formula for paired samples: $SD\_diff = \sqrt{(SD\_pre^2 + SD\_post^2 - 2r \times SD\_pre \times SD\_post)}$, in which r is the assumed correlation between pre- and posttreatment measurements. In the absence of reported correlation, we assumed $r = 0.75$, as by the Cochrane Handbook for Systematic Reviews of Interventions.[8,9] SD data not available in text form were extracted from graphs using WebPlotdigitalizer.[10]

Quality assessment

The Risk of Bias in Nonrandomized Studies of Interventions tool[11] was used to assess the quality of nonrandomized studies. For the randomized controlled trial (RCT), we used the Cochrane Risk of Bias 2 Tool.[12] Two independent reviewers (C.R., P.R.) carried out this assessment, and disagreements were resolved by consensus between the authors after reviewing the full article. Following this protocol, each study was classified as low, moderate, serious, critical risk of bias, or no information based on 7 domains: bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended intervention, and missing data and bias in the measurement of outcomes and the selection of the reported results.

Statistical analysis

To aggregate data on vosoritide treatment in various patient populations, we conducted a single-arm meta-analysis using random-effects generalized linear mixed models with logit transformation as the summary measure for proportions and 95% confidence intervals (CI). Statistical significance was defined as P values $< .05$, whereas heterogeneity was assessed using I^2 and Tau^2 estimates. Following Cochrane guidelines, we considered P values $< .10$ in the chi-square test, $Tau^2 > 0$, or $I^2 > 40\%$ as indicators of heterogeneity potentially influencing the estimates. A leave-one-out sensitivity analysis was performed to explore effect modification, study heterogeneity and publication bias, respectively. All analyses were conducted using R version 4.5 (R Foundation for Statistical Computing) using the R packages "meta" and "metafor." When studies reported only the mean and range, standard deviations were estimated using the method described by Hozo et al[9] (2005). This approach is recommended by Cochrane Handbook for Systematic Reviews of Interventions[8] for continuous data when sample sizes are fewer than 70 and standard deviations are not reported.

Results

Study selection

A total of 1759 records were retrieved on July 2, 2025, including 922 from PubMed, 693 from Embase, and 144 from the Cochrane Library (Figure 1). After initial screening, 44 reports were selected for full-text review. Among these, 8 corresponded to study registries in the World Health Organization or National Institutes of Health trial databases. Three additional records were excluded: 1 abstract (Adachi et al,[13] 2024) that did not report quantitative data, 1 that presented only 6-month treatment outcomes (Leonardi et al,[14] 2024), and 1 article published in Croatian (Kero 2025).[15] Ultimately, 10 studies were included in the meta-analysis (Figure 1). The remaining 23 records were excluded because of overlapping study populations with the included articles or because they were abstracts whose results were subsequently published in full. Two studies by Savarirayan were included as separate cohorts for statistical analysis: Cohort 1 comprised patients in the intervention arm of the phase 3 RCT,[6] whereas Cohort 2 included participants from the extension study[16] who were initially in the placebo group but later received vosoritide following completion of the phase 3 RCT.[6] The study selection process is illustrated in Figure 1 and detailed in Supplemental Table 1.

Study and patient characteristics

A total of 10 studies, including 1 RCT and 9 observational cohort studies, were included, encompassing 696 pediatric patients with achondroplasia. These studies span a wide geographic distribution, with data collected from centers in Turkey, Italy, Qatar, China, France, Germany, Portugal, the United States, the United Kingdom, and Australia. Sample sizes ranged from 9 to 319 patients per study. Across the studies that reported sex distribution, the proportion of male participants ranged approximately from 42% to 51%. Mean age at initiation of vosoritide treatment varied between 5.2 and 8.9 years, although age data were not available for all cohorts. Similarly, baseline height SDS was inconsistently reported, with most studies not providing standardized values; in those that did, mean z-scores were typically around −4.7 to −5.1, consistent with the expected growth impairment in achondroplasia. Minor adverse events were reported in 8 studies, the most prevalent being transient

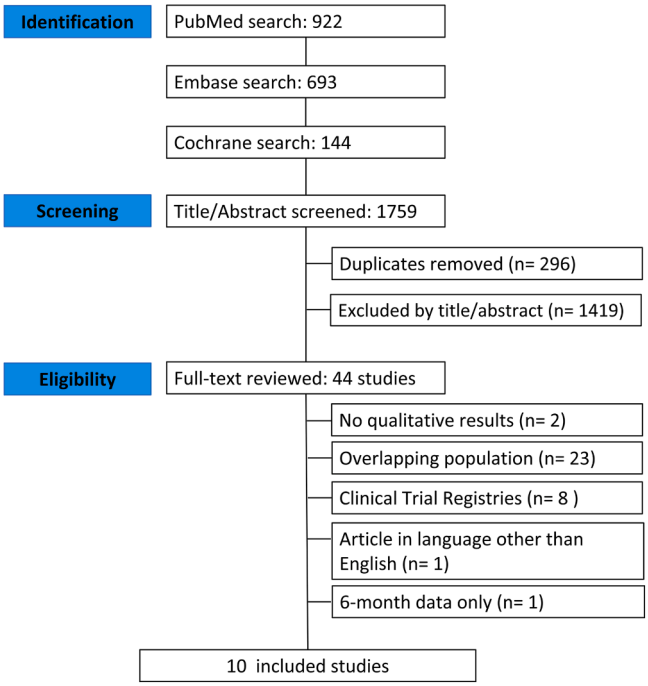

Figure 1 PRISMA flow diagram of meta-analysis articles inclusion.

injection-related reactions. Other self-limiting adverse events (AEs) observed included emesis, hypertrichosis, headache, contact dermatitis, gastric discomfort, hypotension and syncope-spectrum disorders, encompassing presyncope and dizziness. Hypertrichosis ranged from patient-reported mildly increased body hair compared with baseline to frank clinical hirsutism, defined as Ferriman-Gallwey score over 8 points. Notably, no treatment-related serious AEs were reported by any of the studies. Quality-of-life assessments were reported only by Reincke et al[17] and Savarirayan et al.[18] Further details of each cohort are presented in Table 1.

Quality assessment of included studies

Among the 9 nonrandomized studies included, all were judged to have a moderate risk of bias overall (Table 2). The main contributing factor was the consistent lack of adjustment for potential confounding variables across all studies, which resulted in a moderate risk rating for the domain "Bias due to confounding." Additionally, 3 studies (Allegri, Amin, and Rua) presented moderate risk in the domain of "Selection of participants" due to limitations related to sample size and representativeness. All other domains, including classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting, were consistently rated as low risk. The only RCT (Savarirayan Cohort 1[6]) was assessed using the Cochrane Risk of Bias 2 tool and met all criteria across domains, being classified as low risk of bias in all evaluated aspects (Table 3).

AGV variation

A total of 6 studies reported changes in AGV after vosoritide treatment, encompassing 179 children with ACH across 4 real-world treatment settings, the intervention cohort from the BioMarin-sponsored RCT,[6] and the control arm subsequently treated with vosoritide in the extension phase of the same study. The mean AGV increased by 1.82 cm/year (95% CI: 1.46-2.18) compared with baseline growth rates (Figure 2). All studies individually demonstrated increased posttreatment growth velocities, with the most modest improvement observed in the initial phase 3 trial. These findings suggest that, in real-world settings, the efficacy of vosoritide exceeded that observed during late-stage clinical development. To compare real-world and trial-controlled treatment impact and explore study heterogeneity, we performed leave-one-out sensitivity analysis, which revealed that, excluding the results from the intervention group in the phase 3 RCT,[6] the impact of vosoritide treatment in AGV was slightly more expressive, with an increased AGV of 1.91 cm/year (95% CI: 1.53-2.29, n = 121) (Supplemental Figure 1).

ΔSDS after 12 months of treatment

ΔSDS after 12 months of treatment, according to population-appropriate growth charts, were reported in 8 studies comprising a combined sample of 265 patients. After vosoritide therapy, children's height z-scores increased by 0.3229 (95% CI: 0.25-0.40) (Figure 3). Leave-one-out meta-analysis revealed the greatest treatment

Table 1 Baseline characteristics of studies included

Title	Author	Year	Study Design	Country/ Center	Abstract /Full Paper	*N* of Patients	Male (%)	Mean Baseline Height *z*-Score (CDC Classification)	Mean Age at Initiation of Treatment	Adverse Events	Quality-of-Life (QOL) Assessment
Real-world experience with vosoritide treatment in achondroplasia: A single-center report from Turkey[19]	Abali	2024	Observational Cohort	Acibadem University, School of Medicine, Istanbul, Turkey	Abstract	73	37 (50.6%)	NA	5.2 ± 2.65	No treatment-related AEs reported	NA
Vosoritide therapy in children with achondroplasia: Early experience in an Italian cohort[20]	Allegri	2024	Observational Cohort	IRCCS Giannina Gaslini, Genoa (Italy)	Abstract	30	14 (46.7%)	NA	8.9 ± 2-14	Transient injection-site reactions No serious AEs	NA
Vosoritide Therapy in Children with Achondroplasia: Single-Center Experience[21]	Amin	2024	Observational Cohort	Sidra Medicine, Doha (Qatar)	Abstract	9	NA	NA	NA	Transient injection-site reactions No serious AEs	NA
Real-World Data: Effectiveness and Safety of Vosoritide in the Treatment of Achondroplasia in Chinese Population[22]	Chen	2025	Observational Cohort	Ruijin Hospital, Shanghai Jiao Tong University (China)	Full	26	11 (42.3%)	-4.7 ± 0.1	6.52 ± 0.52	Transient injection-site reactions: 7 (26.9%) Increased body hair compared with baseline: 24 (92.3%) Hirsutism: 2 (7.7%) Gastric discomfort: 1 (3.8%) Hypotension: 2 (7.7%) No serious AEs	NA
Real-World Safety and Effectiveness of Vosoritide in Children with Achondroplasia: French Early Access Program[4]	Cormier-Daire	2025	Observational Cohort	University Hospitals of Lyon, Marseille, Nantes, Strasbourg, and Toulouse (France)	Full	57	29 (50.9%)	−5.1 ± 1.04	8.6 ± 2.0	Transient injection-site reactions: 14 (24.5%) Emesis: 3 (5.3%) Contact dermatitis: 1 (1.8%) Headache: 1 (1.8%) Syncope-spectrum disorders: 1 (1.8%) No serious AEs	NA

(continued)

Table 1 Continued

Title	Author	Year	Study Design	Country/ Center	Abstract /Full Paper	*N* of Patients	Male (%)	Mean Baseline Height *z*-Score (CDC Classification)	Mean Age at Initiation of Treatment	Adverse Events	Quality-of-Life (QOL) Assessment
Expansion of the CrescNet Registry Achondroplasia Module: Real-World Demographic Data and Outcomes After up to 2 Years of Vosoritide Treatment[23]	Mohnike	2024	Observational Cohort	CresNet (Germany, Belgium, France, Czech Republic and Estonia)	Abstract	319	163 (51.1%)	NA	6.57 ± 3.7	NA	NA
Real-world Outcome of Vosoritide Treatment in Children With Achondroplasia: A 12-month Retrospective Observational Study[17]	Reincke	2025	Observational Cohort	Specialized clinic for skeletal dysplasia of University Hospital Cologne (Germany)	Full	34	22 (64.7%)	−4.84 ± 1.00	7.52 ± 4.69	Transient injection-site reactions: 12 (35,3%) Syncope-spectrum disorders: 2 (5.9%) No serious AEs	KIDSCREEN-52: no significant change in QOL after 12 months of treatment
Real-World Safety and Effectiveness of Vosoritide in Achondroplasia: Results from a Single Center in Portugal[24]	Rua	2025	Observational Cohort	Hospital Pediátrico de Coimbra, Unidade Local de Saúde de Coimbra, Coimbra (Portugal)	Full	27	15 (55.5%)	−5.08 ± 0.83	7.3 ± 4.07	Transient injection-site reactions: 14 (51.9%) Increased body hair compared with baseline: 4 (14.8%) Contact dermatitis: 1 (3.7%) Headache: 1 (3.7%) Syncope-spectrum disorders: 1 (3.7%) No serious AEs	NA

(continued)

Table 1 Continued

Title	Author	Year	Study Design	Country/ Center	Abstract /Full Paper	*N* of Patients	Male (%)	Mean Baseline Height *z*-Score (CDC Classification)	Mean Age at Initiation of Treatment	Adverse Events	Quality-of-Life (QOL) Assessment
Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomized, double-blind, phase 3, placebo-controlled, multicenter trial-Cohort #1[6]	Savarirayan	2020	Phase 3 RCT	Children's Hospital and Research Center Torrance, Harbor UCLA Medical Center, Ann and Robert H. Lurie Children's	Full	60	31 (52%)	−5·13 ± 1·11	8·35 ± 2·43	Transient injection-site reactions: 44 (77%) Hypotension: 7 (11.67%) Headache: 14 (23.3%) Syncope-spectrum disorders: 4 (6.67%) Emesis: 16 (26.7%) No serious AEs	PedsQL and QoLISSY: no significant changes from baseline in the placebo and vosoritide groups after
Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study-Cohort #2[16]	Savarirayan	2021	Observational extension study	Hospital of Chicago, Johns Hopkins Institute of Genetic Medicine, Vanderbilt University, Baylor College of Medicine (USA); Murdoch Children's Research Institute (Australia); Institut Necker (France); Guys & St. Thomas NHS Foundation Trust Evelina Hospital (UK)	Full	61	33 (54.1%)	NA	10.06 ± 2.47	No new or serious AEs	QoLISSY: consistent improvements in physical and social domains after 3 years of treatment, proportional to improvements in height deficit*

AE(s), adverse event(s); *NA*, nonavailable data; *PedsQL*, Pediatric Quality-of-Life Inventory tool; *QOL*, quality of life; *QoLISSY*, Quality of Life of Short Statured Youth.
*These data were published separately from other outcomes, reporting the effects on quality of life of both cohorts #1 and #2 after 3 years of treatment, after the open-label study.[25]

Table 2 Quality assessment for studies included in this systematic review and meta-analysis—Risk of bias summary for nonrandomized studies (ROBINS-I)

Study/Author	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall Risk of Bias Judgment
Abali et al,[19c] 2024	Moderate[a]	Low	Low	Low	Moderate	Low	Low	Moderate
Allegri et al,[20c] 2024	Moderate[a]	Moderate[b]	Low	Low	Moderate	Low	Low	Moderate
Amin et al,[21c] 2024	Moderate[a]	Moderate[b]	Low	Low	Moderate	Low	Low	Moderate
Chen et al,[22] 2025	Moderate[a]	Moderate[b]	Low	Low	Low	Low	Low	Moderate
Cormier-Daire et al,[4] 2025	Moderate[a]	Low	Low	Low	Low	Low	Low	Moderate
Mohnike et al,[23c] 2024	Moderate[a]	Low	Low	Low	Moderate	Low	Low	Moderate
Reincke et al,[17] 2025	Moderate[a]	Moderate[b]	Low	Low	Low	Low	Low	Moderate
Rua et al,[24] 2025	Moderate[a]	Moderate[b]	Low	Low	Low	Low	Low	Moderate
Savarirayan Cohort 2,[16] 2021	Moderate[a]	Low	Low	Low	Low	Low	Low	Moderate

[a]All nonrandomized studies are subject to bias due to confounding factors.
[b]Moderate due to limited number of patients.
[c]Abstract or conference presentations.

impact and lowest heterogeneity when excluding data from the intervention group of the phase 3 RCT,[6] showing 0.35 (95% CI: 0.27-0.43, $n = 205$) increase in height z-score after treatment with vosoritide among patients from observational studies (Supplemental Figure 2).

SH/H variation

Proportionality changes after treatment were reported using various measures across studies. SH/H was collected directly or estimated from the upper-to-lower segment ratio in 5 studies. Four of these were observational, and 1 was conducted in an experimental setting, comprising a total of 170 individuals. Changes in SH/H after vosoritide treatment varied considerably across studies. Meta-analysis showed a pooled reduction in the SH/H ratio of −0.0089 (95% CI: −0.0157 to −0.0020) after treatment (Figure 4). Leave-one-out analysis did not reveal significantly different results disregarding trial-based data (Supplemental Figure 3).

Discussion

Substantial progress has been achieved in the development of growth-modulating therapies for achondroplasia, as evidenced by the regulatory approval of vosoritide in several countries and ongoing clinical trials of novel agents, such as infigratinib and navepegritide. The revolutionary RCT conducted by Savarirayan et al[6] catalyzed the adoption of vosoritide as a therapeutic strategy in several centers around the world, generating real-world data on treatment efficacy and safety outside controlled experimental settings. Our meta-analysis combining all published data available on the use of vosoritide thus far demonstrated reproducibility of the significant growth-promoting effects and safety profile across study settings. Notably, when synthesizing data from multiple cohorts, the observed effects on mean AGV and height z-scores surpassed the previously published trial results. This apparently enhanced effect of treatment among observational cohorts may reflect broader

Table 3 Quality assessment for studies included in this systematic review and meta-analysis-Risk of bias summary for randomized studies (RoB 2)

Study	Bias From Randomization Process	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Outcome Data	Bias in Measurement of the Outcomes	Bias in Selection of the Reported Result	Overall Risk of Bias
Savarirayan Cohort 1,[6] 2020	Low	Low	Low	Low	Low	Low

Abstract or conference presentations.

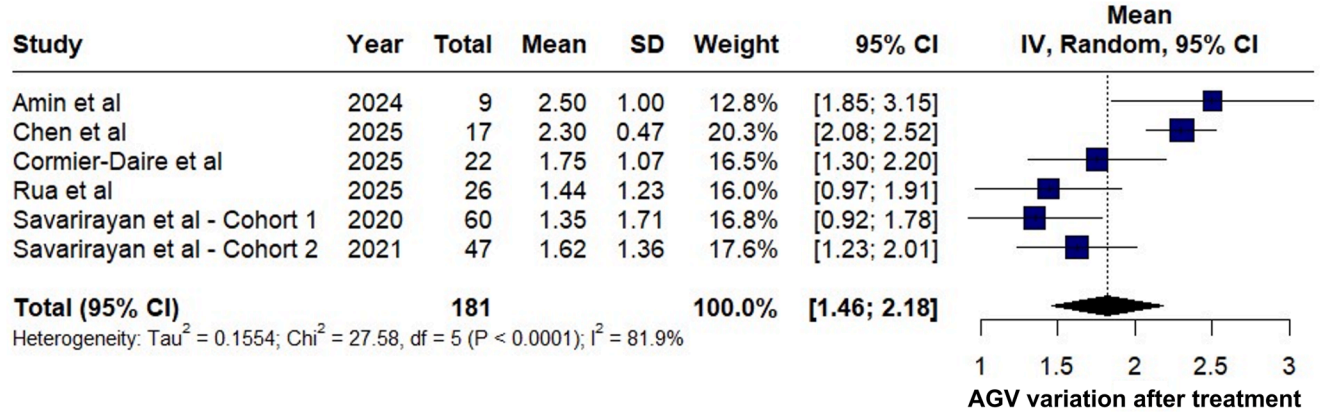

Figure 2 Meta-analysis forest plot of annualized growth velocity variation after vosoritide treatment in pediatric patients with achondroplasia. CI, conference interval; IV, Inverse Variance; SD, standard deviation.

inclusion criteria, particularly the use of vosoritide in younger children and in those with more severe phenotypes than the children enrolled in the original phase 3 RCT,[6] potentially leading to enhanced clinical benefit.

Studies reporting the effects of at least 12 months of treatment with vosoritide showed an increase of 1.82 cm/year (95% CI: 1.46-2.18, $n = 179$) in growth rate. Children with achondroplasia display similar growth rate patterns to their average-stature peers, characterized by more rapid growth throughout the first years of life, which becomes steady until around age 12. However, throughout their childhood, the growth magnitude is consistently smaller, and they lack substantial pubertal growth spurts.[26] The pivotal phase 3 RCT[6] demonstrated an absolute mean increase of 1.35 cm/year (95% CI: 0.91-1.79) in the intervention arm comprising 58 patients aged 5 to 18 years old.[6] In this study, patients with radiographic evidence of closed growth plates, planned bone surgery, severe untreated sleep apnea, and other medical conditions or treatments known to affect growth were excluded. Our results combining trial-derived and real-world data include patients younger than 5 years and patients with complications that would have excluded them from the RCT,[6] that tend to be associated with more severe ACH phenotypes.

Although randomized, placebo-controlled studies remain the gold standard for establishing therapeutic efficacy, real-world observational data offer essential insights into treatment performance in more diverse patient populations and, most importantly, demonstrate the reproducibility of the promising results shown by Savarirayan et al[6] in 2020. Ongoing follow-up studies in infants and children with potentially surgical cervicomedullary compression aim to evaluate the differential effect of vosoritide in specific subgroups with ACH.

Combined height z-score variation (ΔSDS) after 12 months of vosoritide treatment was 0.3229 (95% CI: 0.25-0.40, $n = 265$), whereas the results of the phase 3 RCT[6] showed 0.24 increase (95% CI: 0.16-0.32, $n = 60$). Although the difference is not statistically significant, these results may still hold clinical relevance as height z-scores provide a relative measure of stature that can obscure clinically meaningful growth changes, particularly in children with severe short stature or in

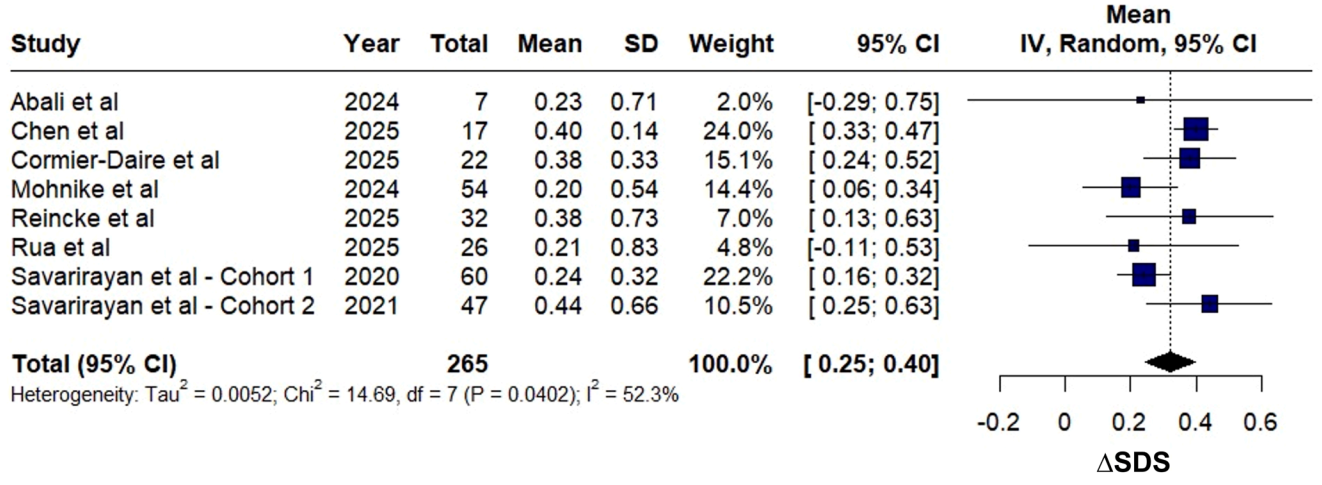

Figure 3 Meta-analysis forest plot of height z-score variation (ΔSDS) after 12 months of vosoritide treatment in pediatric patients with achondroplasia. CI, conference interval; IV, inverse variance; SD, standard deviation.

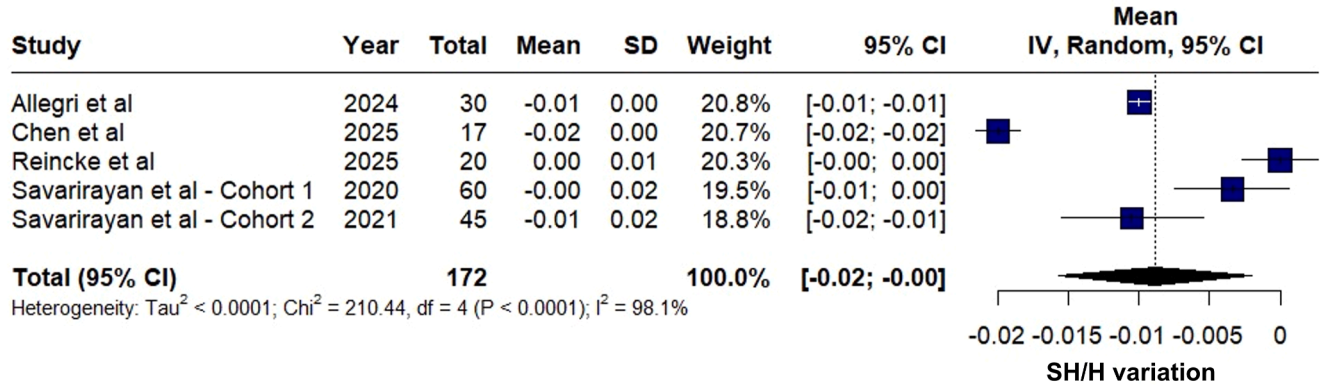

Figure 4 Meta-analysis forest plot of sitting height over total height variation after vosoritide treatment in pediatric patients with achondroplasia. CI, conference interval; IV, Inverse Variance; SD, standard deviation.

response to short-term interventions. Because they normalize height based on population variability, *z*-scores minimize the apparent effect of growth-promoting therapies and exhibit poor sensitivity to short-term improvements. Furthermore, the use of average-stature population reference values for children with ACH has been questioned because they do not follow the same growth patterns and do not exhibit the same pubertal height gains observed in average-stature children.[26,27] ACH-specific *z*-scores have been developed[26] to allow for disease-specific comparison and better reflect height gains or deficits as results of external interventions; however, demographic group-specific *z*-scores were more commonly used in vosoritide treatment reports for consistency and replicability.

Notably, people with achondroplasia have higher upper-to-lower body segment ratios that decrease as they grow but never normalize. This disproportion contributes to developmental motor delays and musculoskeletal complications, including early osteoarthritis, reduced mobility, and various other biomechanical implications.[27,28] This parameter, however, is one that would presumably require very long-term interventions to reflect treatment results, preferably starting in infancy. Our study showed minimal reduction of −0.0089 (95% CI −0.0157 to −0.0020) in sitting height/height ratio, a measure of upper-to-lower body proportionality. These results reinforce the evidence provided by the RCT,[6] showing that the improvements in growth parameters induced by vosoritide may optimize segmental proportionality, nevertheless, these results will be more clearly evaluated after longer-term follow-up.

Regarding safety, the observational studies included in our analysis reported no serious drug-related adverse events. Notably, most studies reported minor but prevalent AEs, such as transient injection-related pain and redness, as well as increased body hair compared with baseline, which rarely met criteria for clinical hirsutism. Other self-limiting AEs included emesis, dizziness, presyncope, and headache. These results were consistent with the favorable safety profile exhibited in the phase 2 and 3 trials findings that lead to drug approval.[6,18]

Although height is a general marker of effect, the ultimate goal in achondroplasia treatment is to improve health and quality of life. It is hoped that the growth-promoting effect of vosoritide will decrease medical complications associated with achondroplasia, such as cervicomedullary compression, sleep-disordered breathing, obesity, delayed motor milestones, and chronic pain, but this has not yet been reported in literature. It is reasonable to assume that the reduction of ACH-related sequelae will be prevented more significantly in children with more severe forms of the disease, who have been recently started gaining access to the drug, now that it has been tested in healthier, older cohorts. At this point, the long-term effect of vosoritide treatment on these outcomes is still unclear, but early quality-of-life assessments suggest mild improvements in patient and parent quality-of-life perspective after initial treatment stages, especially after 3 years of treatment, when growth effects become more substantial,[25,29] which might become more significant as treatment effect accumulates throughout the years. Achondroplasia is a multifaceted disease that compromises much more than height, including severe physical complications and important psychosocial burdens, which represent the most important parameters to evaluate drug efficacy.

Limitations

This meta-analysis has certain limitations inherent to the available body of evidence on vosoritide. Most studies report outcomes after 12 months of treatment, and longer-term data remain limited, which restricts conclusions about sustained efficacy and potential effects on clinical complications or body proportionality. Average-stature population growth references were used across studies to maintain consistency, although they may not fully capture the specific growth trajectories of children with achondroplasia. There was also variability in study populations, including differences in age at treatment initiation, baseline phenotype severity, and eligibility criteria, which may influence treatment

responsiveness and contribute to between-study heterogeneity. The inclusion of real-world observational data introduces variation in data completeness and follow-up standards, which is expected in routine clinical settings. Additionally, although auxological outcomes were well reported, functional and quality-of-life measures remain underrepresented in the literature. The most significant limitation in our study is the inclusion of data from conference abstracts to provide the most current and comprehensive synthesis possible, knowing that these sources may lack methodological detail and completeness, which could introduce reporting bias. Finally, lack of reports on ACH-related complications and effect on quality of life are gaps that must be addressed as treatment with vosoritide becomes more readily available, scarcely reported at this time because of the chronology of growth and natural history of the disease. These considerations reinforce the importance of ongoing long-term studies and the need for standardized, comprehensive outcome reporting in future research.

Conclusion

This meta-analysis of reports on vosoritide treatment outcomes in children with achondroplasia demonstrates reproducibility of trial results in real-world observational settings, with even more pronounced effects on linear growth and similarly favorable safety profile. Our results suggest that, moving on to clinical application, the use of this drug in younger children and children with more severe phenotypes may lead to significant changes in growth that might translate to generally improved health.

Data Availability

The search strategies, detailed methods, and inclusion criteria used in this study are available in the Supplemental Material. The R code used for data processing and statistical analyses is available from the corresponding author upon request.

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Author Contributions

Conceptualization: A.A., M.D.; Data Curation: A.A., C.R., P.R.; Formal Analysis: A.A., P.R.; Methodology: A.A., P.R.; Supervision: A.A, P.R., D.B.; Writing-original draft: A.A., M.D., P.R.; Writing-review and editing: A.A., D.B.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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References

1. Savarirayan R, Ireland P, Irving M, et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. *Nat Rev Endocrinol*. 2022;18(3):173-189. http://doi.org/10.1038/s41574-021-00595-x
2. Shiang R, Thompson LM, Zhu YZ, et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell*. 1994;78(2):335-342. http://doi.org/10.1016/0092-8674(94)90302-6
3. Poskanzer SA, Peña LDM, Niu Z. ACMG Therapeutics Committee6*documents@acmg.net. Vosoritide approved for treatment of linear growth in pediatric patients with achondroplasia: a therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG). *Genet Med Open*. 2023;1(1):100771. http://doi.org/10.1016/j.gimo.2023.100771
4. Cormier-Daire V, Edouard T, Isidor B, et al. Real-world safety and effectiveness of vosoritide in children with achondroplasia: French early access program. *Horm Res Paediatr*. Published online January 25, 2025. http://doi.org/10.1159/000543743
5. Savarirayan R, Hoover-Fong J, Ozono K, et al. International consensus guidelines on the implementation and monitoring of vosoritide therapy in individuals with achondroplasia. *Nat Rev Endocrinol*. 2025;21(5):314-324. http://doi.org/10.1038/s41574-024-01074-9
6. Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial [published correction in *Lancet* 2020;396(10257):1070. http://doi.org/10.1016/S0140-6736(20)32074-2] *Lancet*. 2020;396(10252):684-692. http://doi.org/10.1016/S0140-6736(20)31541-5
7. Garritty C, Hamel C, Trivella M, et al. Updated recommendations for the Cochrane Rapid Review Methods Guidance for Rapid Reviews of Effectiveness. *BMJ*. 2024;384:e076335. http://doi.org/10.1136/bmj-2023-076335
8. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane. Accessed July 19, 2025. https://www.cochrane.org/handbook
9. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13. http://doi.org/10.1186/1471-2288-5-13
10. WebPlotDigitizer RA. *Automeris.io*. version 5.2. Pacifica, CA. 2024. Accessed June 8, 2025. https://automeris.io/

11. Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. John Wiley & Sons; 2019.
12. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. http://doi.org/10.1136/bmj.l4898
13. Adachi N, Sato A, Chiba Y, Tanaka H. Vosoritide therapy in 16 young children with achondroplasia: a retrospective study. *Horm Res Paediatr*. 2024;97(suppl 3):161. http://doi.org/10.1159/000541189
14. Leonardi R, Rapisarda G, Costanza G, Leone G, Nicoletti MC. Single center prospective study on the efficacy and safety of vosoritide therapy in achondroplasia: a comprehensive evaluation at three and six months. *Horm Res Paediatr*. 2024;97(suppl 3):293. http://doi.org/10.1159/000541189
15. Kero M. Treatment of patients with achondroplasia in the Republic of Croatia – first experiences and results. *Paediatr Croat*. 2025;69:108-115. http://doi.org/10.13112/pc.1057
16. Savarirayan R, Tofts L, Irving M, 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 Med*. 2021;23(12):2443-2447. http://doi.org/10.1038/s41436-021-01287-7
17. Reincke S, Semler O, Junghänel-Welzing S, et al. Real-world outcome of vosoritide treatment in children with achondroplasia: a 12-month retrospective observational study. *J Endocr Soc*. 2025;9(5):bvaf041. http://doi.org/10.1210/jendso/bvaf041
18. Savarirayan R, Wilcox WR, Harmatz P, 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(1):40-50. http://doi.org/10.1016/S2352-4642(23)00265-1
19. Abali S, Ozkose GS, Akgun-Dogan O, Semiz S, Alanay Y. Real-world experience with vosoritide treatment in achondroplasia: a single-center report from Turkey. *Horm Res Paediatr*. 2024;97(suppl 3):348-349. http://doi.org/10.1159/000541189
20. Allegri AEM, Tedesco C, Di Iorgi N, et al. Vosoritide therapy in children with achondroplasia: early experience in an Italian cohort. *JBMR Plus*. 2024;8(suppl 2):ii189. http://doi.org/10.1093/jbmrpl/ziae105
21. Amin R, Ben-Omran T, Khalifa A, et al. Vosoritide therapy in children with achondroplasia: single-center experience. *Horm Res Paediatr*. 2024;97(suppl 3):341. http://doi.org/10.1159/000541189
22. Chen L, Zhang X, Zhang X, et al. Real-world data: effectiveness and safety of vosoritide in the treatment of achondroplasia in Chinese population. *Endocr Abstr*. 2025;110:636. http://doi.org/10.1530/endoabs.110.P636
23. Mohnike K, Eibenstein U, Pimenta J, et al. Expansion of the CrescNet registry achondroplasia module: real-world demographic data and outcomes after up to 2 years of vosoritide treatment. 2024;97(suppl 3):38. http://doi.org/10.1159/000541189
24. Rua IB, Silva I, Beger C, et al. Real-world safety and effectiveness of vosoritide in achondroplasia: results from a Single Center in Portugal. *Adv Ther*. 2025;42(8):3726-3742. http://doi.org/10.1007/s12325-025-03223-6
25. Savarirayan R, Irving M, Wilcox WR, et al. Persistent growth-promoting effects of vosoritide in children with achondroplasia are accompanied by improvements in physical and social aspects of health-related quality of life. *Genet Med*. 2024;26(12):101274. http://doi.org/10.1016/j.gim.2024.101274
26. Savarirayan R, Irving M, Harmatz P, et al. Growth parameters in children with achondroplasia: a 7-year, prospective, multinational, observational study. *Genet Med*. 2022;24(12):2444-2452. http://doi.org/10.1016/j.gim.2022.08.015
27. Hoover-Fong J, Cheung MS, Fano V, et al. Lifetime impact of achondroplasia: current evidence and perspectives on the natural history. *Bone*. 2021;146:115872. http://doi.org/10.1016/j.bone.2021.115872
28. Merchant N, Hoover-Fong J, Carroll RS. Approach to the patient with achondroplasia-new considerations for diagnosis, management, and treatment. *J Clin Endocrinol Metab*. 2025;110(7):e2309-e2316. http://doi.org/10.1210/clinem/dgaf017
29. Dentry T, O'Neill J, Raj S, Gardiner K, Savarirayan R. Exploring the family experience of children aged 2-4 years receiving daily vosoritide injections: a qualitative study. *J Pediatr Nurs*. 2024;77:e167-e176. http://doi.org/10.1016/j.pedn.2024.04.007