

## Systematic Review

# Efficacy and safety of Vosoritide in achondroplasia: A systematic review and meta-analysis

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Received August 7, 2025; Accepted November 21, 2025; Published February 28, 2026

**Background and objectives:** Achondroplasia, a rare autosomal dominant disorder caused by FGFR3 mutation, is treated with vosoritide, a C-type natriuretic peptide analogue. This review aimed to assess vosoritide's efficacy and safety to guide clinical practice and healthcare policy decisions.

**Methods:** Advanced search was performed on three databases. The included articles underwent screening, data extraction, and quality evaluation, culminating in a qualitative synthesis. The protocol was registered on PROSPERO (CRD42024541795).

**Results:** Out of 752 records screened, six were incorporated in this systematic review. The trials included daily injections of vosoritide (2.5-30 µg/kg) in phase II study and at 15 µg/kg in all other studies to patients with achondroplasia aged 3 months to 18 years. Safety assessments were done for all patients (n=156) having received vosoritide. Efficacy was assessed using annualised growth velocity and height Z score as the primary outcomes and serum collagen X-marker concentrations, bone age progression, and serum immunogenicity as secondary outcomes. Overall, the articles demonstrated good quality with minimal bias.

**Interpretation and conclusions:** Vosoritide showed significant improvement in the annualised growth velocity, height z score and standing height in patients with achondroplasia aged 3 months to 18 years as compared to placebo. The safety assessment recorded adverse events in all patients (n=156) enrolled, usually mild (grade 1), self-limiting and limited to local injection site reactions. Studies with longer duration (till puberty), a large sample size and its effect on medical complications, are required to establish its effectiveness in the patients of achondroplasia.

**Keywords** Achondroplasia; Annualised growth velocity; Randomised clinical trials; Rare disease; Systematic review; Vosoritide

Achondroplasia is an inherited rare disease with unevenly proportioned short stature marked by shortening of mainly proximal limb segments i.e. femora and humeri.<sup>1-3</sup> The patients experience significant medical complications including foramen magnum stenosis, cervico-medullary compression, hypotonia, hydrocephalus, hearing loss, pain in back and legs, and delayed speech related to recurrent otitis media and chronic middle ear fluid.<sup>4</sup>

Vosoritide is a synthetic protein binds to B type natriuretic peptide receptor and upregulate intracellular cyclic guanosine monophosphate (cGMP) production, it imitates C type natriuretic peptide (CNP) pharmacological activity with extended half-life.<sup>5</sup> In

animal experiments, Vosoritide has been known to promote endochondral bone growth by stimulating proliferation and differentiation of chondrocytes. It increases long-bone and craniofacial growth.<sup>6,7</sup>

The National Policy for Rare Diseases (NPRD), launched by the Ministry of Health and Family Welfare, Government of India, provides up to INR 50 lakhs per patient for lifetime care for treatment of inherited rare diseases. Given India's large population and the economic burden of such conditions, inclusion under NPRD requires strong evidence-based justification of the effectiveness of approved treatment. Achondroplasia, the most common form of disproportionate short stature, currently has only one

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**How to cite this article:** Pahuja M, Prakash C, Umrao A, Chatterjee NS. Efficacy and safety of Vosoritide in achondroplasia: A systematic review and meta-analysis. *Indian J Med Res.* 2026;163:78-87. DOI: 10.25259/IJMR\_2087\_2025.

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approved targeted therapy vosoritide, a CNP analogue that corrects the FGFR3 pathway defect.<sup>8</sup> Although multiple trials have assessed its efficacy and safety, no prior systematic synthesis of the available literature exists. This review and meta-analysis therefore aimed to comprehensively evaluate the efficacy and safety of vosoritide in achondroplasia, providing consolidated evidence to guide clinical and policy decisions under the NPRD framework.

## Methods

This systematic review summarises the efficacy and safety of vosoritide in achondroplasia, including a meta-analysis of available data. The protocol was registered in PROSPERO (CRD42024541795).

*Literature search:* Cochrane, PubMed, and Embase were systematically searched on May 10, 2024, for studies published between January 2000 and May 2024. This timeframe was selected to capture all relevant clinical and translational research on achondroplasia. Since vosoritide, the only approved targeted therapy for achondroplasia, received regulatory approval in late 2021, setting 2000 as the lower limit ensured inclusion of studies contributing to its development as well as other contemporary interventions. In addition to database searches, literature was also searched on Google Scholar to identify grey literature relevant to this systematic review.

*Search strategy:* The title was structured according to the PICOST framework. Controlled vocabulary and Boolean operators were used to define the population (achondroplasia patients) and intervention (vosoritide), following the indexing standards of each database. A detailed search strategy is provided in **Supplementary Material I**.

*Screening the studies:* Following the search, all retrieved records were extracted and added to Rayyan tool. Duplicates were removed and the retrieved records were subsequently screened according to the inclusion/exclusion criteria (**Supplementary Material I**). Titles and abstracts were screened first, followed by full texts, with CP and MP conducting independent screening and resolving discrepancies through NC.

*Data extraction:* PRISMA checklist and PROSPERO registration guidelines were followed and adhered to while doing systematic review and meta-analysis. Data extraction was carried out by CP, and independently reviewed by both CP and AU. The included studies were subjected to qualitative analysis, and when data were

comparable, a quantitative analysis was also performed. Quantitative analyses were performed using RevMan (version 5.4). Missing data, where applicable, were addressed using the RevMan calculator. A fixed-effect model was employed for analyses with heterogeneity less than 50%, and a random-effects model was applied when heterogeneity exceeded 50%.

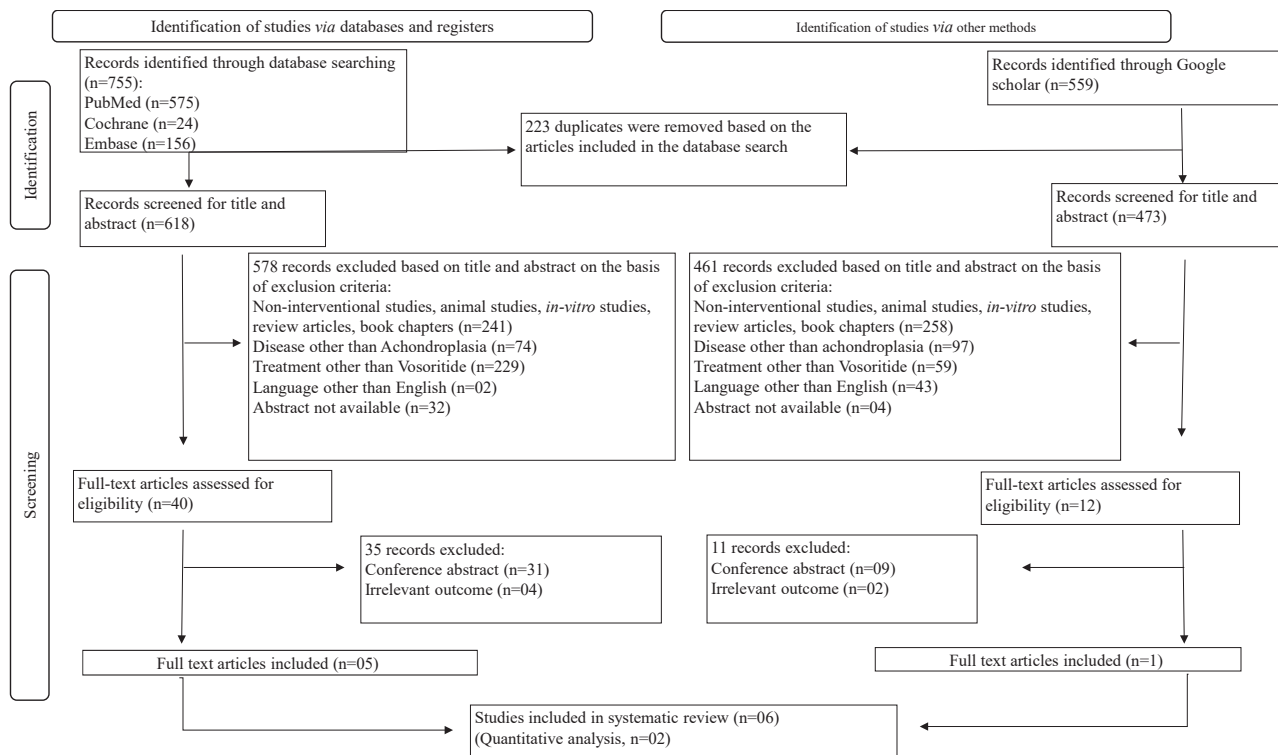
*Quality assessment:* Two reviewers (AU and MP) assessed the quality of included studies using Risk of bias (RoB) to evaluate their methodological validity. Eligible study designs comprised randomised clinical trials (RCTs) and quasi-experimental research published in peer-reviewed journals. The Revised Cochrane Risk of Bias Tool (RoB 2) was applied to RCTs. However, for non-randomised studies with no control group, the NIH quality assessment tool was used. These tools assessed key aspects including study design, methodology, data analysis, and interpretation. Low, moderate, or high risk of bias were thus assessed.

## Results

*Data characterisation and analyses:* A total of 1,314 records were retrieved from four databases (**Supplementary Material I**). After removing duplicates, 1,091 records were screened by title and abstract (**Fig. 1**), and 1,039 were excluded for being descriptive studies, reviews, preclinical work, unrelated conditions, or non-English reports. In the second screening, 52 abstracts were reviewed, of which 46 were excluded (conference abstracts=40; insufficient or irrelevant data=6). Finally, six studies (five clinical trials and one case report) were included for data extraction.

*Risk of bias assessment:* The included studies underwent quality assessment. Both RCTs showed a low risk of bias, while the pre-post studies were rated as fair quality. The RCTs by Savarirayan *et al* (2020, 2024)<sup>9,10</sup> were well conducted, providing reliable evidence for safety and efficacy. The pre-post study, assessed using the NIH quality assessment tool, showed good methodological quality with clear objectives, defined eligibility criteria, consistent interventions, and appropriate analyses. Overall, the studies demonstrated strong methodological rigor, supporting the reliability of the findings and certainty of the evidence. Details are provided in **Table I, Supplementary Tables I, II and III**.

*Study characteristics:* Three multicentre clinical trials, one pharmacokinetic study, and one case report were included for analysis. The phase II dose-escalation



**Fig. 1.** PRISMA flow diagram illustrating the literature search strategy, screening process, and selection of studies included and excluded in the systematic review, detailing the number of records identified, screened, assessed for eligibility, and finally included in the analysis.

study enrolled 35 patients (5–14 yr) treated with daily subcutaneous vosoritide (2.5–30  $\mu\text{g}/\text{kg}$ ) for 42 months. The phase III double-blind, randomised trial included 121 patients (5–18 yr) receiving vosoritide (15  $\mu\text{g}/\text{kg}$ ) or placebo for 52 wk, followed by an open-label extension where all 119 participants received vosoritide. In total, 154 patients were treated for 1–3.5 yr. The pharmacokinetic study included data from phase II and III participants, while the case report described cardiovascular adverse events (AEs) in two infants (**Table II**).

The studies were conducted in seven countries at 24 sites including the Australia (n=2), Europe [Spain (n=3), Germany (n=2), United Kingdom (n=3), Turkey (n=1)], United States (n=10), and Japan (n=3).

Vosoritide injections were given once daily subcutaneously with side rotation. Initially, the drug or placebo was given at study site and afterwards at home by trained caregivers. Full clinical medical assessments were done at each visit at screening, days 1, 2, 3 and 10, then at week 6 and at months 3, 6, 9 and 12.

**Patient characteristics:** Patients with genetically confirmed achondroplasia, ambulatory status, and at least six months of baseline growth data were included across trials with similar criteria. Exclusions included

fused growth plates, planned bone surgery, untreated sleep apnoea, or other growth-affecting conditions. The phase III RCT used 1:1 randomisation stratified by sex and Tanner stage, with separate randomisation for seven Japanese participants. Participants were aged 5–18 yr, primarily of non-Hispanic ethnicity (**Table III**).

**Safety measurement:** Safety measures were assessed, based on the occurrence of unpleasant events and serious adverse events, laboratory findings, clinical examination, ECG and EEG results, and antibody response (if any). Imaging assessments showing spine, arm bone, leg bone measurements, growth plate data, bone mineral density, and bone age data were also collected in the studies. Adverse events (AEs) occurred in all patients across the three trials, with no deaths reported. In the phase II study, safety data were available for six patients each in cohorts 1 and 2 (up to 52 months), 10 patients in cohort 3 (45 months), and eight patients in cohort 4 (34 months). Detailed AEs are shown in **Figure 2**.

In phase III study, the most common AE was non-serious, transient injection-site reactions. Nine serious AEs unrelated to the study drug occurred in seven patients: four placebo participants experienced grade 3 adenoidal hypertrophy, grade 3 appendicitis, grade

**Table I. Risk of bias assessment of RCT as per RoB 2.0 tool**

Risk of bias of included randomised controlled trials						
Study	Outcome	Sequence generation	Allocation sequence concealment	Blinding	Missing outcome data	Publication bias
Savarirayan <i>et al</i> <sup>10</sup> , 2020 (study 111-301; Clinical Trials.gov number NCT03197766)	Safety	Low	Low	Low	Low	Low
Savarirayan <i>et al</i> <sup>10</sup> , 2020 (study 111-901; Clinical Trials.gov number NCT03197766)	Efficacy	Low	Low	Low	Low	Low
Savarirayan <i>et al</i> <sup>9</sup> , 2024 (Clinical Trials.gov number NCT NCT03583697)	Safety	Low	Low	Low	Low	Low
Savarirayan <i>et al</i> <sup>9</sup> , 2024 (study 111-302; Clinical Trials.gov number NCT03583697)	Efficacy	Low	Low	Low	Low	Low

**Table II. Details of clinical trials evaluating the efficacy and safety of Vosoritide injection in patients with achondroplasia, summarising study design, Study duration/follow up, comparator, sample size and endpoints**

Study design	Study duration/follow up	Comparator	Sample size and dose ( $\mu\text{g}/\text{kg b.wt.}$ )	Endpoint
Savarirayan <i>et al</i> <sup>11</sup> , 2019	24 months/follow up till 42 months	Placebo	n= 35 Cohort-1: Dose-2.5 (n=8) Cohort-2: Dose-7.5 (n=8) Cohort-3: Dose-15 (n=10) Cohort-4: Dose-30 (n=9) After 6 months Cohort-1: Dose-7.5 and 15 Cohort-2: Dose-15 Cohort-3: Dose-15 (n=10) Cohort-4: Dose-30 (n=9)	Safety, side effect profile and appropriate dose for further studies
Savarirayan <i>et al</i> <sup>9</sup> , 2024	52 wk	Placebo	n= 75 sentinels = 11 PBO= 32 vosoritide= 32	Safety, efficacy and tolerability of vosoritide
Savarirayan <i>et al</i> <sup>10</sup> , 2020	52 wk	Placebo	n= 121 PBO= 61 Vosoritide= 60	Change from baseline in annualised growth velocity,
Savarirayan <i>et al</i> <sup>12</sup> , 2021	52 wk	Baseline at week 52	n= 119 PBO-Vosoritide= 61 Vosoritide - Vosoritide = 58	Long-term safety and growth promoting effects following completion of Phase study
Chan <i>et al</i> <sup>13</sup> , 2021	Phase 2: 24 months Phase 3: 52 wk	Placebo Placebo	n= 35 n=60	PK parameters – $T_{\max}$ , $t_{1/2}$ , $C_{\max}$ , $AUC_{0-t}$ , $AUC_{0-\infty}$ , $AUC_{0-24}$ , $CL/F$ , $V_z/F$ .

2 dyspnoea, grade 3 increased intracranial pressure, and grade 3 spinal cord compression, while three vosoritide-treated patients had grade 3 influenza, grade 3 sleep apnoea, grade 3 radial fracture, and grade 2 adenoidal hypertrophy.

*Pharmacokinetic profile of vosoritide:* Drug activity using cGMP and its pharmacokinetic profile along

with endochondral ossification markers including serum collagen X marker (CXM), a degradation fragment of type X collagen was studied. PK analysis was performed by plasma vosoritide concentrations in phases II using a validated enzyme-linked immunosorbent assay (ELISA) and III studies using electrochemiluminescence assay (ECLA). Positive correlation was reported for plasma vosoritide

**Table III. Patient characteristics in reported studies evaluating Vosoritide in achondroplasia, including mean age at screening or treatment initiation, sex distribution, ethnicity, and tanner stage**

Study	Mean age ( $\pm$ SD) at screening (yr)/Age at day 1 of treatment (yr)	Sex (%)	Ethnicity (Non-Hispanic or Latino in %)	Tanner stage (values in %)
Savarirayan <i>et al</i> <sup>11</sup> , 2019	Cohort 1: 7.3 $\pm$ 1.6	Cohort 1: F-62 M-38	Cohort 1: 100	Cohort 1: Pubic hair development-100 Breast development-100 Genital development-100
	Cohort 2: 8.3 $\pm$ 2.2	Cohort 2: F-38 M-62	Cohort 2: 100	Cohort 2: Pubic hair development-100 Breast development-100 Genital development-100
	Cohort 3: 8.0 $\pm$ 1.6	Cohort 3: F-60 M-40	Cohort 3: 90	Cohort 3: Pubic hair development-100 Breast development-100 Genital development-100
	Cohort 4: 6.9 $\pm$ 1.2	Cohort 4: F-56 M-44	Cohort 4: 78	Cohort 4: Pubic hair development-100 Breast development-100 Genital development-100
Savarirayan <i>et al</i> <sup>9</sup> , 2024	Cohort 1: PBO: 3.69 Vosoritide: 3.30	Cohort 1: F-54.5 M-45.5	Cohort 1: 6.45	--
	Cohort 2: PBO: 1.40 Vosoritide: 1.41	Cohort 2: F-38 M-63	Cohort 2: 0	
	Cohort 3: PBO: 0.48 Vosoritide: 0.46	Cohort 3: F-66 M-33	Cohort 3: 23.52	
Savarirayan <i>et al</i> <sup>10</sup> , 2020	PBO: 9.06 $\pm$ 2.47	PBO: F-46 M-54	PBO: 90	Stage 1: PBO: 78.7 Vosoritide- 80
	Vosoritide: 8.35 $\pm$ 2.43	Vosoritide: F-48 M-52	Vosoritide: 98	Stage >1: PBO: 21.3 Vosoritide- 20
Savarirayan <i>et al</i> <sup>12</sup> , 2021	PBO: 9.06 $\pm$ 2.47	PBO: F-46 M-54	PBO: 90	Stage 1: PBO: 78.7 Vosoritide- 80
	Vosoritide: 8.35 $\pm$ 2.43	Vosoritide: F-48 M-52	Vosoritide: 98	Stage >1: PBO: 21.3 Vosoritide- 20

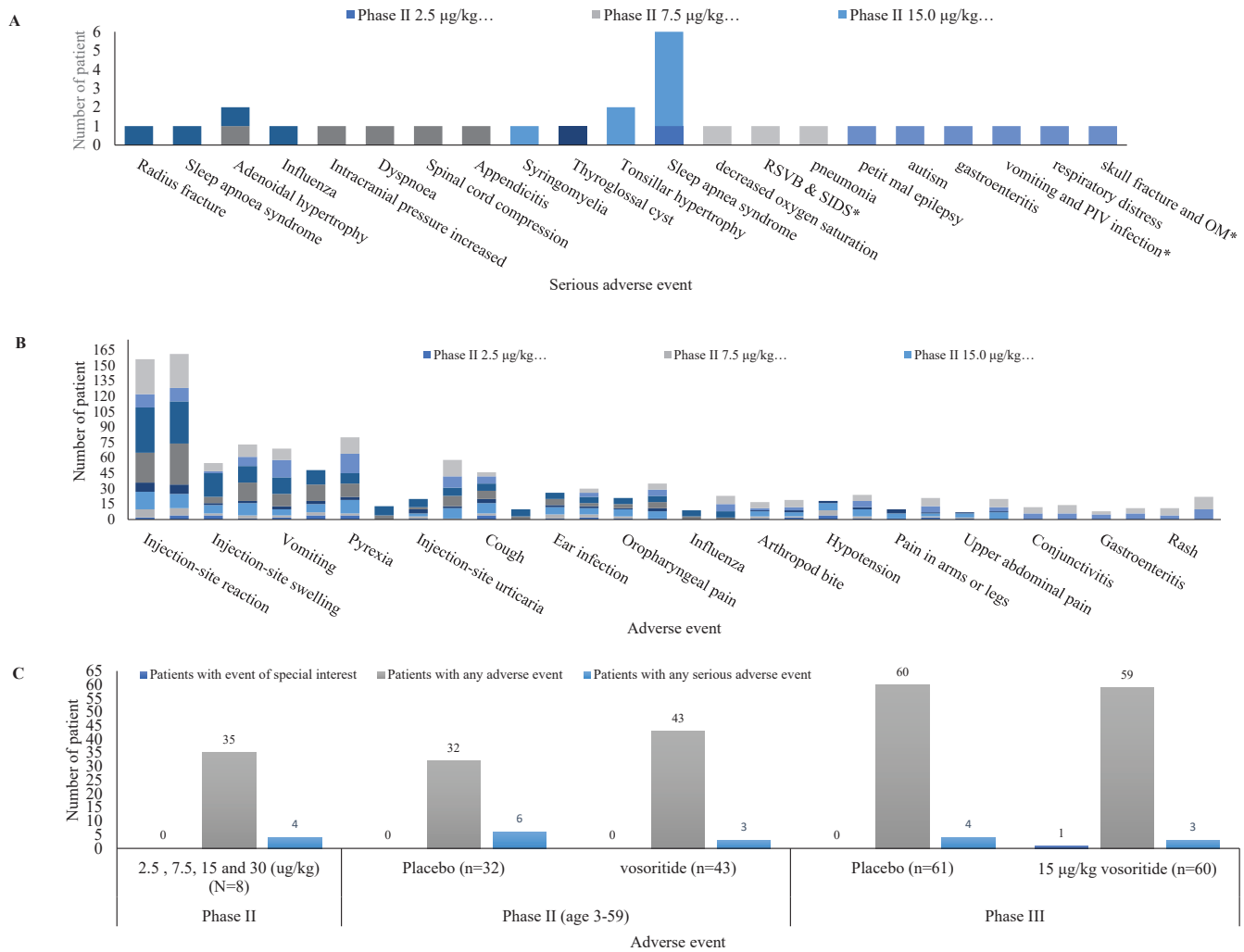
AUC<sub>0-60min</sub> with the body weight and age ( $P < 0.001$ ) and vosoritide exposure was shown to be consistent throughout the study duration of 52 wk (**Fig. 3**). A plateau in the exposure-response curve at 15 $\mu$ g/kg supported the dose chosen for phase III study.

#### Efficacy measures:

**Primary outcomes:** The effect of vosoritide on annualised growth velocity (cm per year), height z score, and the body segment proportionality was

recorded and reported in all 3 clinical trials. Detailed patient characteristics are mentioned in **Table IV**.

In the phase II safety and dose-finding study, four patients discontinued: two in cohort 1 (withdrawal of consent, needle fear) and two in cohort 2 (growth plate closure, needle fear). In cohort 3, one patient discontinued due to grade 1 intermittent Wolff-Parkinson-White syndrome. Efficacy data were thus available for 30 patients after 42 months. Dose



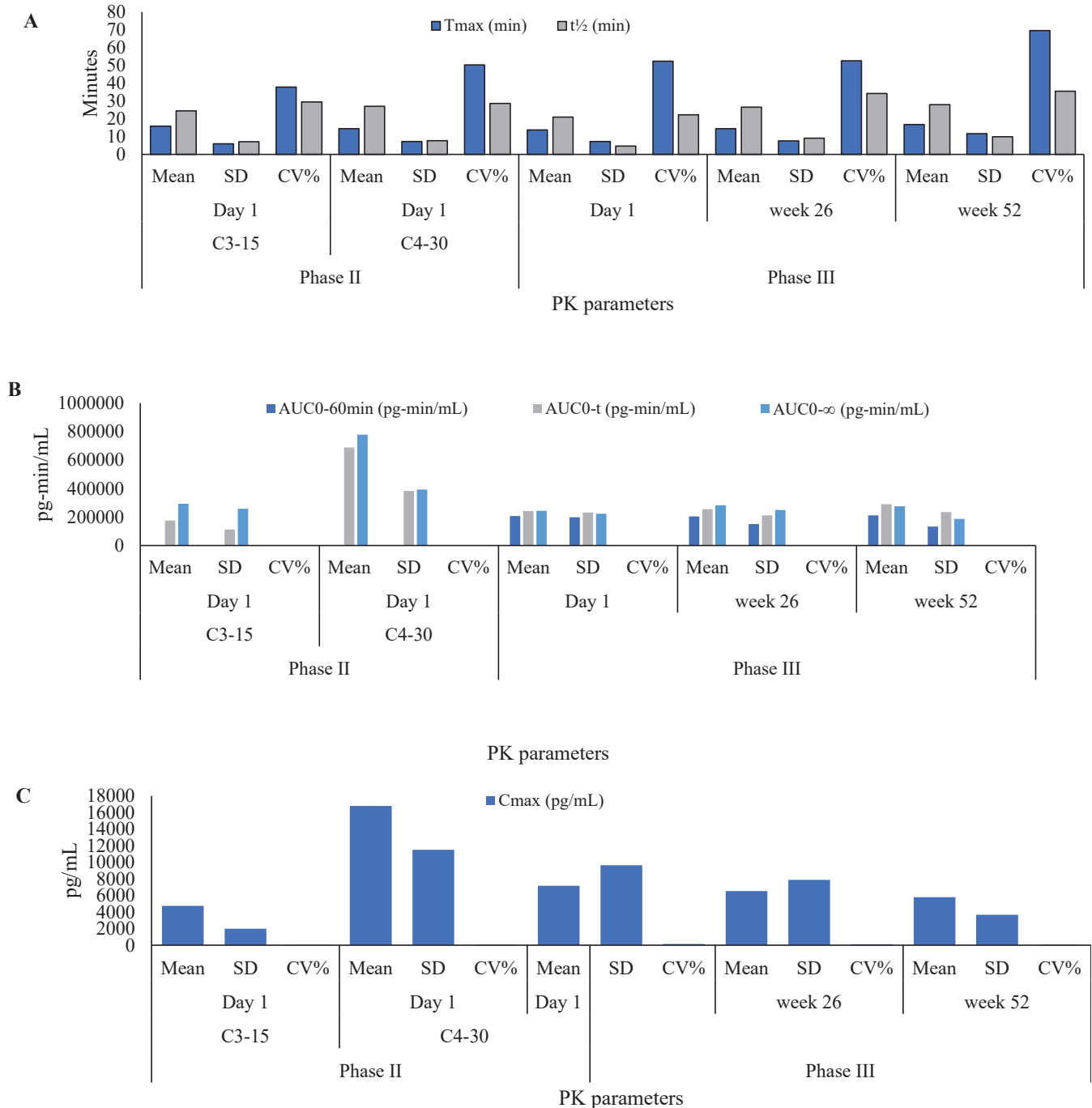
**Fig. 2.** Adverse events reported across clinical trials evaluating Vosoritide in achondroplasia. The figure illustrates the distribution and frequency of adverse events observed among treated participants. Subfigure (A) represents patients with serious adverse events, (B) depicts patients experiencing any adverse events, and (C) shows the total number of patients with reported adverse events across all studies, highlighting the overall safety profile of Vosoritide.

dependent change in the annualised growth velocity was reported in various treatment groups with an increase of -0.37cm (-1.84 to 1.10), 1.28 cm (0.07 to 2.48), 2.01 cm (0.58 to 3.44) and 2.08 cm (0.30 to 3.87) per year in cohorts 1, 2, 3 and 4, respectively from baseline at 95% CI. Detailed results of annualised growth velocity, height Z score and upper to lower body segment ratio is given in **Table IV**.

In phase III study, two patients discontinued within a week due to pain and fear of injections. An increase (two-sided *P* value <0.0001) of 1.57cm/yr (95% CI 1.22–1.93; vosoritide vs. placebo) was reported after 52 weeks of treatment in annualised growth velocity. Baseline adjusted least square mean of 1.71 cm/yr (95% CI 1.40 to 2.01) change was reported in

treated vs. placebo group. A significant change (two-sided *P* value <0.0001; *P*=0.51) in least squares mean difference of +0.28 (95% CI 0.17–0.39) and -0.01 (95% CI -0.05–0.02) in height Z score and the upper to lower body segment, respectively was reported for vosoritide group as compared to placebo (**Table IV**).

In phase III extended study, 58 patients who were initially randomised to vosoritide continued taking it. Standing height measurements were provided for 44 individuals by week 104 to calculate the annualised growth velocity at six-month intervals. Out of 61 patients in placebo in phase III trial, standing height assessments of 47 were available. There is a missing data of 28 patients during the COVID-19 pandemic, where virtual visits replaced many site visits.



**Fig. 3.** Pharmacokinetic parameters evaluated following Vosoritide administration in achondroplasia patients. Subfigures represent (A) time to reach maximum plasma concentration (T<sub>max</sub>), (B) area under the concentration–time curve over different intervals (AUC<sub>0–60</sub>, AUC<sub>0–t</sub>, AUC<sub>0–∞</sub>), and (C) maximum plasma concentration (C<sub>max</sub>), providing an overview of drug absorption and systemic exposure.

**Secondary outcomes:** Analysis of secondary outcomes showed that vosoritide treatment caused a dose-dependent increase in urinary cGMP and serum CXM, sustained over 24 months across all cohorts.<sup>11</sup> The 15 and 30 µg/kg doses elicited the strongest responses,

indicating prolonged pharmacologic activity. Plasma cGMP levels rose significantly within 1 h post-dose in the vosoritide group, with no change in placebo.<sup>9</sup> Serum CXM, a marker of endochondral ossification, remained above baseline for up to 52 wk in treated

**Table IV. Primary outcomes reported in clinical studies evaluating Vosoritide in achondroplasia, presenting mean annualised growth velocity, mean height Z-score, and mean upper-to-lower body segment ratio. Data reflect key efficacy parameters used to assess treatment response across trials**

Study	Mean annualised growth velocity (cm/yr)	Mean height Z score	Mean upper to lower body segment ratio
Savarirayan <i>et al</i> <sup>11</sup> , 2019	Baseline to Month 24 – 1.55±1376 Baseline to Month 42 - 1.49±1.446	Baseline to Month 24 – 0.61±0.449 Baseline to Month 42 – 0.87±0.696	Baseline to Month 24 – -0.09±0.083 Baseline to Month 42 – -0.09±0.0121
Savarirayan <i>et al</i> <sup>9</sup> , 2024	0.78 (LS mean)	0.25 (LS mean)	-0.07 (LS mean)
Savarirayan <i>et al</i> <sup>10</sup> , 2020	PBO: 0.13 Vosoritide: 1.57	PBO: -0.01 Vosoritide: 0.27	PBO: -0.02 Vosoritide: -0.03
Savarirayan <i>et al</i> <sup>12</sup> , 2021	At week 104 PBO- Vosoritide: 5.43±2.03 Vosoritide -Vosoritide: 5.52±1.77	-	At 24 months PBO- Vosoritide: 1.95±0.15 Vosoritide -Vosoritide: 1.88±0.21

patients, highlighting vosoritide's efficacy in promoting endochondral ossification and its potential for long-term therapeutic effects.<sup>10</sup>

**Potential bias:** Participants, study personnel, caregivers administering injections and those assessing the outcome data were all blinded to group assignment in phase II study<sup>10</sup> and phase III study<sup>11</sup> to minimise the potential bias. In addition, in quasi experimental studies<sup>11,12</sup> which were open labelled, hope bias plays a significant role.

**Meta-analysis:** Both mean difference (MD) and least square mean difference (LSMD) were reported across studies. Since LSMD accounts for baseline differences but reflects the same outcome as MD, we treated LSMD values as equivalent to MD for descriptive comparison. Results are presented narratively and in tables, emphasising consistent trends across studies rather than pooled effect estimates. The LSMD with 95% CI, from the control and intervention group of clinical trials<sup>9,12</sup> were evaluated. Two articles included<sup>9,12</sup> for meta-analysis from all the included articles. Four articles which were not RCTs were exempted from the meta-analysis. With random-effects models, the meta-analysis was conducted using RevMan 5.4 software. The results were presented as the mean difference and 95% CI using an inverse-variance.

Two clinical trials including 90 participants in the intervention group and 93 in the control group reported LSMD in annualised growth velocity. Using random-effects models, the LSMD between groups was 2.40 (95% CI: 1.94–2.86), with high heterogeneity ( $I^2 = 96\%$ ,  $P < 0.00001$ ), demonstrating that vosoritide significantly increased annualised growth velocity (**Fig. 4**). For

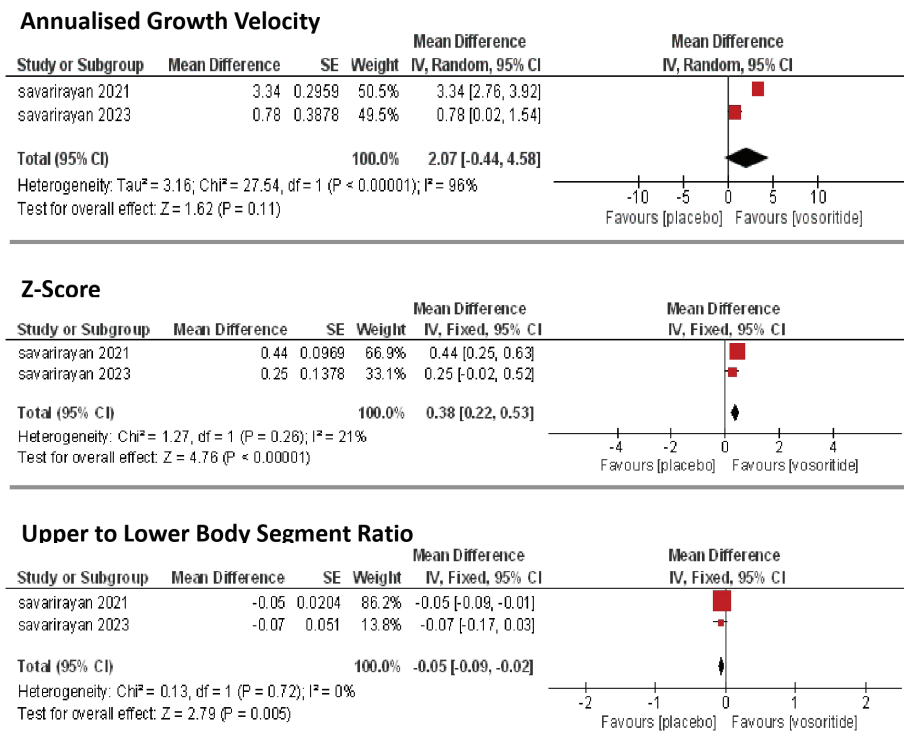
height z-score, the LSMD between the vosoritide and control groups was 0.38 (95% CI: 0.22–0.53), with low heterogeneity ( $I^2 = 21\%$ ,  $P < 0.00001$ ), indicating a significant improvement with vosoritide. For the upper-to-lower body segment ratio, the LSMD between the vosoritide and control groups was -0.05 (95% CI: -0.09 to -0.02), with no heterogeneity ( $I^2 = 0\%$ ,  $P < 0.005$ ), indicating a non-significant effect on z-score.

## Discussion

Vosoritide significantly improved annualised growth velocity in phase II and III trials. Dose escalation from 2.5 to 15  $\mu\text{g}/\text{kg}$  over six months increased growth velocity, with no additional benefit at 30  $\mu\text{g}/\text{kg}$ . The optimal dose of 15  $\mu\text{g}/\text{kg}/\text{day}$  achieved growth velocity comparable to average-height peers. Unlike recombinant human growth hormone (approved in Japan), which shows minimal impact on final height or body proportions, vosoritide promoted proportional linear growth and improved height z-scores.<sup>11</sup>

Treatment response was age-dependent, with children under 5 years showing smaller gains in annualised growth velocity, reflecting natural growth variability. MRI analyses after 52 wk revealed greater increases in facial and cranial volumes, including the foramen magnum, particularly in children under six months, suggesting that early vosoritide intervention may help prevent complications such as brainstem compression, a common cause of morbidity in infants with achondroplasia.<sup>9</sup>

Safety outcomes were favourable across trials, with mild, transient injection-site reactions and brief, self-limiting blood pressure drops as the most



**Fig. 4.** Forest plot illustrating the pooled effect estimates for Vosoritide intervention in achondroplasia, depicting changes in annualised growth velocity, height Z-score, and upper-to-lower body segment ratio. Each parameter is presented with its corresponding confidence interval (CI), reflecting the overall efficacy and consistency of treatment outcomes across included studies.

common AEs.<sup>10,12</sup> No treatment-related effects on bone maturation, body proportions, or upper-to-lower body ratios were observed, indicating proportionate skeletal development. Pharmacodynamic analyses showed transient urinary cGMP rises and sustained serum CXM elevations, confirming durable biological activity at the 15 µg/kg dose.<sup>13</sup>

Caregiver-reported outcomes highlight the clinical relevance of vosoritide. In one study, 64% of caregivers (9/14) viewed height gains as beneficial for independence and daily functioning, while 71% (11/14) valued improved limb proportions for better reach, balance, and self-care, reducing reliance on assistive devices. These findings emphasise that effective therapy should target both growth and functional well-being.<sup>14</sup>

The meta-analysis shows significant improvements in annualised growth velocity and height z-scores, though the absolute annual height gain (~1.5–2.0 cm over placebo) may seem modest. However, these cumulative increases, when sustained throughout growth years, can contribute meaningfully to final adult stature. Importantly, vosoritide promotes proportional growth, enhancing limb proportions and

skeletal symmetry, which improves mobility, self-care, and psychosocial well-being.<sup>15,16</sup> Thus, its therapeutic value extends beyond statistical growth gains to supporting proportionate development and functional independence.

When compared with emerging alternatives, vosoritide remains the most validated therapeutic option. TransCon CNP, a sustained-release prodrug enabling once-weekly dosing, has shown early efficacy and good tolerability, but lacks long-term and head-to-head data.<sup>17</sup>

Nevertheless, current evidence has limitations. The included studies had small sample sizes and relatively short treatment durations, inherent to rare-disease research, restricting conclusions about adult height, limb proportionality, and reduction in surgical interventions. Age heterogeneity and open-label extensions may also have introduced bias. Long-term safety in infants and the effect on comorbidities such as sleep apnea, spinal stenosis, and cardiovascular abnormalities remain insufficiently characterised.

Integrating vosoritide into India's NPRD could markedly enhance access and enable earlier intervention

for children requiring this high-cost treatment. Future research should include long-term follow up to adult height, functional and quality-of-life outcomes, and real-world data across diverse populations, including Indian cohorts. Early intervention and combination with rehabilitative strategies may enhance outcomes. Overall, vosoritide demonstrates strong evidence for improving growth in children with achondroplasia with a favourable safety profile, though long-term multicentric studies are needed to establish its sustained benefits and cost-effectiveness.

**Author contributions:** MP: Manuscript drafting, quality assessment, study conceptualization, coordination; CP: Study screening, data extraction, manuscript writing, figures and tables preparation; AU: Study screening, data extraction; NC: Manuscript writing. All authors have read and approve the final printed version of the manuscript.

**Financial support and sponsorship:** None.

**Conflicts of Interest:** None.

**Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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**Supplementary file(s) available at:** [https://doi.org/10.25259/IJMR\\_2087\\_2025](https://doi.org/10.25259/IJMR_2087_2025)