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Consensus statement

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International consensus guidelines on the implementation and monitoring of vosoritide therapy in individuals with achondroplasia

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Abstract

Achondroplasia is the most common genetic form of short-limbed skeletal dysplasia (dwarfism). Clinical manifestations and complications can affect individuals across the lifespan, including the need for adaptations for activities of daily living, which can affect quality of life. Current international guidelines focus on symptomatic management, with little discussion regarding potential medication, as therapeutic options were limited at the time of their publication. Vosoritide is the first pharmacological, precision treatment for achondroplasia; it was approved for use in 2021, creating a need for vosoritide treatment guidelines to support clinicians. An international collaborative of leading experts and patient advocates was formed to develop this Consensus Statement. The group developed the guideline scope and topics during a hybrid meeting in November 2023; guideline statements were subsequently ratified via Delphi methodology using a predefined consensus threshold. These statements provide recommendations across the treatment pathway, from starting treatment with vosoritide through ongoing monitoring and evaluation, to stopping vosoritide and ongoing monitoring following cessation. These guidelines recommend a minimum set of requirements and a practical framework for professionals and health services worldwide regarding the use of vosoritide to treat infants, children and young people with achondroplasia. This Consensus Statement is a supplement to already established consensus guidelines for management and care of individuals with achondroplasia.

Sections

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Introduction

Achondroplasia, with an estimated prevalence of 3.72–4.60 per 100,000 births worldwide, is caused by a gain-of-function pathogenic variant in the gene that encodes fibroblast growth factor receptor 3 (*FGFR3*), which leads to impaired endochondral ossification[1–6]. A range of complications (that is, short-limbed short stature, foramen magnum stenosis, sleep apnoea and spinal canal stenosis) are associated with this condition, which can affect quality of life and influence the need for multidisciplinary care for individuals with achondroplasia[6–18].

Achondroplasia guidelines have focused on symptomatic management, with therapeutic options to increase height restricted to growth hormone therapy (where approved) and surgical limb lengthening, which has a high risk of complications[13,19–28]. Vosoritide, approved for use in 2021 (refs. 29,30), is the first pharmacological, precision treatment for achondroplasia. Vosoritide is an engineered C-type natriuretic peptide analogue that activates B-type natriuretic peptide receptor signalling, thereby inhibiting *FGFR3* downstream signalling, which leads to increased endochondral bone formation[31–38] (Fig. 1). Approval was based on phase III trial data in individuals aged ≥5 years demonstrating good tolerance and increases in annualized growth velocity and height *Z*-scores after 52 weeks of treatment versus placebo treatment[33,35]. Follow-up data showed sustained annualized growth velocity increases and continued height *Z*-score improvements versus untreated patients, without adverse effects on bone maturation after 7 years of treatment[31,36,39]. Clinical trial data published early in 2024 demonstrated height *Z*-score improvements with a mild adverse event profile in children aged 3–59 months who received vosoritide for 52 weeks[37]. Vosoritide is now approved for use from birth in Australia, Japan and the USA, and from 4 months of age in Europe[29,30,40,41].

As clinicians worldwide are now prescribing vosoritide, there is a need for treatment-specific guidelines that complement existing management guidelines[42–47]. Early real-world experience in clinical practice provided a framework for the development of these specific guidelines[48]. Australian guidelines for vosoritide have been published to support clinical rollout and to standardize the optimal use of vosoritide in the Australian context[49]. The present guidelines aim to provide practical guidance for professionals and health services worldwide on vosoritide use in individuals with achondroplasia.

Methods

Convening the steering committee

Experts were identified using an expert mapping framework developed by Mole and colleagues[50]. The expert mapping tool identified 61 professionals, of whom 53 were identified with total scores of ≥7–24 (Supplementary Table 1 and Supplementary Box 1). The tool identified the chair (R.S.) as the highest-ranking expert and informed the selection of three additional steering committee members (J.H.-F., K. Ozono and S.O.F.). Additional profiling based on the scope of the guidelines ensured a wide geographic spread and inclusion of relevant specialties for ten additional clinical members of the guideline development group (GDG). Specific criteria for selection of clinical experts included experience with skeletal dysplasia, in particular achondroplasia, and either experience

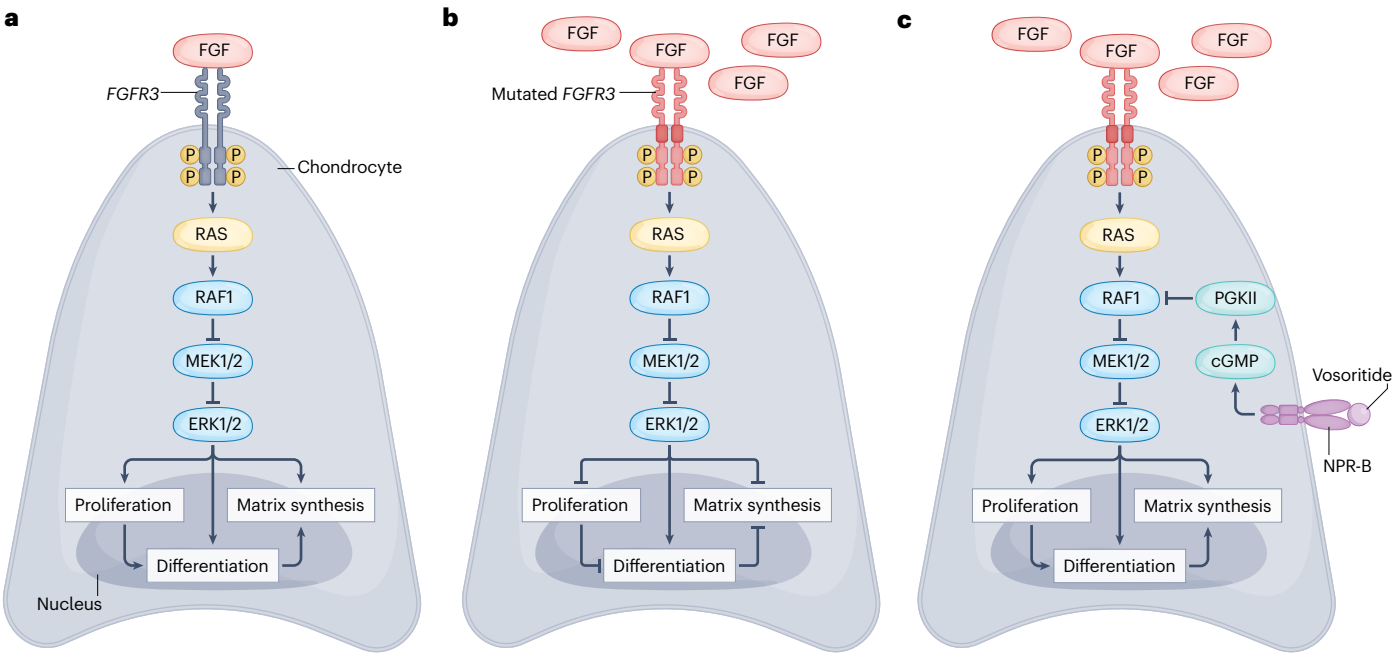

Fig. 1 | The cellular mechanism of disease in achondroplasia. a, A growth plate chondrocyte with wild-type fibroblast growth factor receptor 3 (encoded by *FGFR3*) signalling that is ligand-dependent (FGF). In this scenario, only ligand-dependent activation of the RAS–RAF1–MEK1/2–ERK1/2 pathway (otherwise known as RAS–MAPK pathway) occurs. Consequently, proliferation and differentiation of chondrocytes occurs along with matrix synthesis and bone growth. **b**, A growth plate chondrocyte with a common missense mutation in the transmembrane domain (red rectangle) of *FGFR3*. This mutation enables activation of the RAS–MAPK pathway that is both ligand-dependent and ligand-independent (FGF), with consequent excess inhibition of chondrocyte proliferation and differentiation, leading to impaired matrix synthesis and bone growth. **c**, Vosoritide, an engineered C-type natriuretic peptide analogue, activates B-type natriuretic peptide receptor (NPR-B) signalling, which inhibits *FGFR3* downstream signalling. This inhibition counteracts the effects of constitutive *FGFR3* activation and promotes endochondral bone growth by stimulating chondrocyte proliferation and differentiation. Parts **a** and **b** reproduced from ref. 46, Springer Nature Ltd.

with vosoritide in clinical practice or trials, or involvement in the care of individuals treated with vosoritide (Supplementary Boxes 2 and 3). The GDG consisted of experts from Australia, Brazil, France, Germany, Italy, Japan, Norway, the UK and the USA. The experts comprised five clinical geneticists (M.I., V.C.-D., .J.L.J., R.S. and J.H.-F.), one orthopaedic surgeon (K. Okada), one paediatrician (K. Ozono), three paediatric endocrinologists (P.B., M. Maghnie and K.M.), one paediatric endocrinologist and geneticist (N.M.), one specialist in family medicine (S.O.F.), one physiotherapist (P.I.) and one genetic counsellor (M. Menzel). To ensure the patient perspective was represented, two patient representatives from Spain (S.N.I.) and the USA (K.DeA.) completed the GDG.

R.S., the lead author, had full access to the evidence used in the study and takes responsibility for the integrity and accuracy of the content and the Delphi process. R.S., S.O.F., J.H.-F. and K. Ozono developed the concept and design and provided supervision. R.S., J.H.-F., K. Ozono, P.B., V.C.-D., K.DeA., P.I., M.I., J.L.J., M. Maghnie, M. Menzel, N.M., K.M., S.N.I., K. Okada and S.O.F. participated in the acquisition, analysis or interpretation of data. R.S., J.H.-F., K. Ozono, P.B., V.C.-D., K.DeA., P.I., M.I., J.L.J., M. Maghnie, M. Menzel, N.M., K.M., S.N.I., K. Okada and S.O.F. wrote the manuscript. R.S., J.H.-F., K. Ozono, P.B., V.C.-D., K.DeA., P.I., M.I., J.L.J., M. Maghnie, M. Menzel, N.M., K.M., S.N.I., K. Okada and S.O.F. undertook critical revision of the manuscript for important intellectual content.

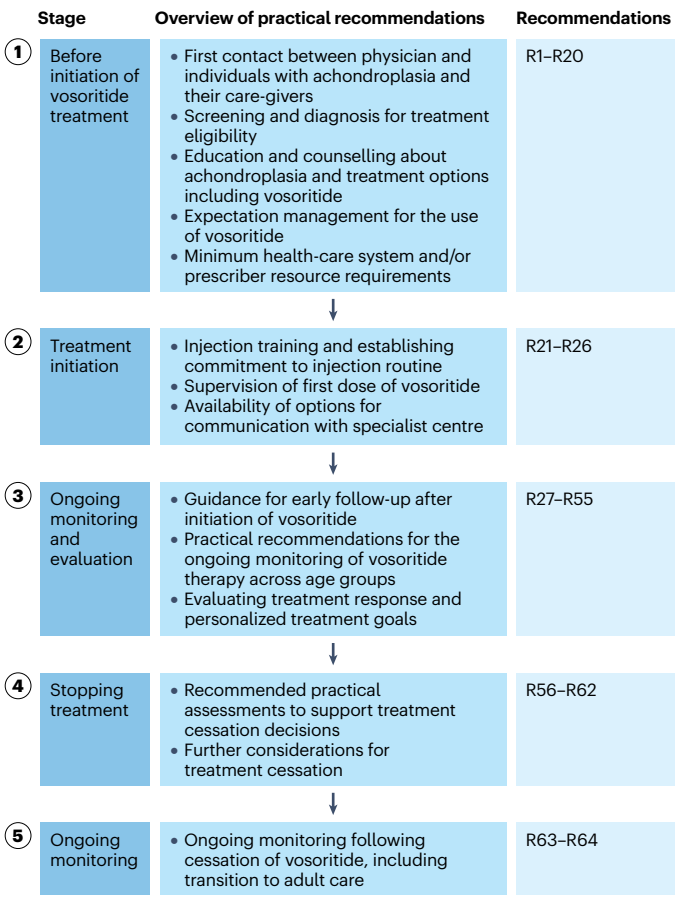

Fig. 2 | An overview of the purpose and flow of the guidelines in this Consensus Statement. These recommendations provide practical guidance for vosoritide prescribers and those involved in vosoritide treatment through the patient journey from first contact, through the implementation and evaluation of treatment with vosoritide, to ongoing monitoring following cessation of vosoritide therapy in individuals with achondroplasia.

Consensus building: statement development meeting

A targeted literature search was conducted to identify existing achondroplasia guidelines and inform the scope of this Consensus Statement. In a series of preparatory virtual meetings and correspondence, the steering committee (R.S., J.H.-F., K. Ozono and S.O.F.) defined the guideline approach and scope. The GDG attended a hybrid meeting on 18 November 2023, to develop draft consensus statements based on their expert clinical opinion and insights from patient representatives. These statements were then taken forward into the Delphi process.

Delphi questionnaire

The consensus statements were ratified using a Delphi voting process via the Within3 virtual engagement platform. Participation was anonymous to eliminate bias. The GDG members were asked to vote on all statements and were able to opt-out of statements outside of their specialty. Guidance statements were voted on using a five-point Likert scale (strongly disagree, disagree, neutral, agree and strongly agree).

Consensus was defined when >80% of the GDG either agreed or strongly agreed or either disagreed or strongly disagreed. For each final recommendation statement in these guidelines, the level of Delphi agreement and strength of recommendation are reported. Level of agreement was calculated as the percentage of the panel that voted who agreed or strongly agreed with the statement. Strength of recommendation was derived from the level of agreement, with >90% agreement classed as 'Strong recommendation' and >80% to ≤90% classed as 'Moderate recommendation'.

Recommendations and discussion

Consensus building and Delphi panel results

All members of the GDG participated fully in the guideline development meeting in which 62 statements were proposed, and all completed the subsequent Delphi panel. According to the consensus threshold, 56 of 62 statements reached consensus in round 1. All statements that reached consensus in round 1 were positive consensus (>80% agreed or strongly agreed). The six guidance statements that did not reach consensus were reviewed by the steering committee and amended based on their expert opinion for voting in round 2 of the Delphi process. An additional seven statements were suggested by the GDG and were included for voting in round 2. Of these seven, three were new statements, and four were round 1 statements that initially met consensus but were modified based on suggestions to make the initial recommendations clearer and more specific. In round 2, 12 of 13 statements reached consensus. In total, 68 guidance statements reached consensus, of which four superseded round 1 statements (refer to Supplementary Fig. 1 for visual depiction and Supplementary Box 4 and Supplementary Tables 2–7 for further details).

Guideline recommendations

The final 64 consensus statements (labelled recommendation 1 (R1), R2 and so on) are ordered by treatment pathway, which is summarized in Fig. 2. An overview of the key practical steps and considerations for health services and professionals on the implementation and monitoring of vosoritide treatment is provided in Table 1.

Note that regulatory and reimbursement requirements vary by country and must be followed where they are more stringent than these guidelines.

Table 1 | Key practical steps and considerations for initiating and monitoring treatment

Item	Actions	Key considerations
First contact and/or screening	Refer to expert centre as soon as achondroplasia diagnosis suspected	Importance of early treatment
	Genetic confirmation usually required	Awareness of underlying conditions
	Identify and manage complications	
Education and consent	Provide counselling about achondroplasia and treatment options at earliest opportunity	Age-appropriate inclusion of patients in treatment decision-making
	Discuss option of vosoritide with all eligible patients	Support for patients who decide not to pursue vosoritide
	Educate patients and care-givers on medication usage requirements and potential benefits and adverse effects prior to consent to treatment	Need for ongoing education of health-care professionals and patient advocacy groups about vosoritide as new evidence emerges
	Schedule pre-initiation visit to assess patient suitability and educate on use of vosoritide and expected outcomes	
Expectation management	Set realistic expectations prior to treatment initiation	Expectations should be revisited during treatment
		Counselling should be available for adolescents who are not eligible for treatment
Minimum resource requirements	Ensure prescriber access to expert or specialist reference centre and that follow-up plan is in place	Prescriber should either be a medical specialist experienced in the management of achondroplasia or another health-care professional in consultation with a specialist experienced in the management of achondroplasia
	Encourage patient and care-giver access to the skeletal dysplasia community	
	Ensure prescriber has appropriate resources to manage and/or coordinate the prescription process	
Injection training and first dose	Educate and train care-givers and patients on injection techniques, managing pain, hypotension, injection site reactions and the commitment to daily injections	Establishing injection as routine practice
		Importance of hydration before injection
	Supervise administration of first dose and make nursing and medical staff available for 1 h following the first dose	Multiple injection training sessions might be required to enable injection without the presence of a nurse
		Patients and care-givers should have the ability to communicate with the specialist reference centre by telephone, teleconsultation and/or e-mail
Early follow-up	Consider an initial follow-up call by a nurse around 1 week after initiation to address practical considerations (for example, injection technique, tolerance, injection site management and adverse effects)	Early follow-up should be individualized to each specific family situation
	Schedule a follow-up consultation within the first month, including discussion of medication supply management	
Monitoring of therapy	Support patients with ongoing treatment decisions and motivation	The expert centre should organize follow-up, delegating to collaborating centres and health-care professionals depending on family and centre resources
	Refer to Table 2 for ongoing monitoring recommendations by age group	
Treatment response	Discuss treatment goals with the patient and care-givers to define a personalized response target	Response to vosoritide can vary in magnitude and timing
	Investigate other comorbidities that might affect growth if a patient is not responding in the expected time frame	If poor adherence is suspected by the health-care professional (for example, due to lack of response), increasing the frequency of follow-up and assessing motivation for continuing treatment is recommended
Stopping treatment	Perform plain radiography when annual height velocity has slowed to <1.5 cm per year to check status of growth plates; if closed, stop treatment with vosoritide	Radiography could be performed every 1–2 years during puberty to confirm growth plates remain open
	Refer to recommendations 56–62 for further considerations on cessation of treatment	If a patient is undergoing surgery, the surgical team should contact the primary prescriber and/or expert centre for advice on whether temporary vosoritide treatment interruption is appropriate
Ongoing monitoring following cessation of treatment	Develop a clear transition plan for continued monitoring into adulthood following cessation of vosoritide and discuss long-term health-care management	Spinal health should continue to be monitored after cessation of vosoritide in accordance with standard of care

This table presents an overview of key practical steps for health-care professionals informed by R1–R64.

Before initiation of treatment with vosoritide

First contact (statements 1 and 2).

- **R1.** Education and resources should be available to primary care physicians to support initial contact with patients and care-givers; communication with experts is important given further emerging clinical evidence for vosoritide (strong recommendation, Delphi 100%).
- **R2.** Patients should be referred to an expert centre as soon as diagnosis is suspected to begin discussions and enable treatment to commence as early as possible (strong recommendation, Delphi 94%).

First contact by families is usually with the primary care or hospital physician. The quality and relevance of information and education about achondroplasia and vosoritide provided at this first interaction can shape treatment decisions and affect treatment success, and the importance of this session should not be underestimated. Where possible, referral to an expert centre is likely to be beneficial for the patient, as they can benefit from the experience and support of a multidisciplinary team[43,46]. However, it is recognized that expert centres will vary in availability and ease of access. Resources are available to support health-care professionals, patients and care-givers (Supplementary Boxes 5–10 and Supplementary Table 8).

Screening and diagnosis for treatment eligibility (statements 3–7).

- **R3.** Early detection, such as prenatal detection, is recommended where feasible to allow for early treatment initiation (moderate recommendation, Delphi 88%).
- **R4.** Wherever possible, treatment should be initiated as early as possible, given emerging data on the craniofacial and foramen magnum area[37] (moderate recommendation, Delphi 88%).
- **R5.** Genetic confirmation of diagnosis should be performed, according to local resources and insurer and/or reimbursement body requirements (strong recommendation, Delphi 100%).
- **R6.** In line with standard clinical care, the prescriber should be aware of any underlying conditions that could affect growth, general health and wellbeing (moderate recommendation, Delphi 81%).
- **R7.** Any complications of achondroplasia should be identified and managed (strong recommendation, Delphi 100%).

Early detection and genetic testing should be offered, where feasible, to enable early provision of education and therapeutic intervention. If genetic testing is not feasible, the clinical diagnosis can be confirmed radiologically. Assessment of patients for medical conditions that might affect growth independently of achondroplasia should be personalized based on the degree of short stature and should involve screening with a detailed history and examination, with further testing as needed.

Although expert opinion and emerging data support early (that is, in the first months of life) initiation of vosoritide treatment[37,51], the data in very young children, particularly those <1 year of age, are currently limited. A randomized, controlled, open-label study is ongoing to assess whether treatment with vosoritide in infants <1 year of age and who are at risk of requiring cervicomedullary decompression surgery is safe and can improve growth at the foramen magnum and spinal canal to alleviate stenosis[52]. It is important to balance the potential benefits of early treatment initiation with the needs of the family of a new baby with achondroplasia, for whom such information around therapy might be overwhelming. Medical management and evaluation according to standard of care should not be delayed due to starting treatment with vosoritide.

Education and consent (statements 8–15).

- **R8.** Patients and care-givers must be supported with education about achondroplasia and informed regarding medication usage requirements and adverse effects prior to providing consent to elective vosoritide treatment (strong recommendation, Delphi 100%).
- **R9.** When diagnosis is suspected, all patients and their care-givers should be offered high-quality information about vosoritide via appropriate visuals and tools and, where possible, access to unbiased resources, including individuals with achondroplasia who have chosen to pursue various management pathways (strong recommendation, Delphi 94%).
- **R10.** The option of vosoritide should be discussed with all who are eligible; however, it should be recognized and fully supported that not all patients and their care-givers will decide to pursue therapy (strong recommendation, Delphi 100%).
- **R11.** It should be acknowledged that the initial information a family receives about vosoritide from any source is important and can affect ongoing beliefs. There is a need to educate relevant health-care professionals and patient advocacy groups about vosoritide as new evidence emerges (strong recommendation, Delphi 100%).
- **R12.** Counselling about achondroplasia and treatment options must be provided by a qualified health-care professional at the earliest opportunity (strong recommendation, Delphi 100%).
- **R13.** Young patients should be included in treatment decision-making and given the opportunity to assent, express concerns and dissent (strong recommendation, Delphi 100%).
- **R14.** A visit should be scheduled with the family and patient before initiation of the treatment with the aims of assessing the suitability of the patient for vosoritide treatment and educating the patient and family on the use of vosoritide and expected outcomes (strong recommendation, Delphi 94%).
- **R15.** Patients and care-givers should be educated on the potential benefits and adverse effects of vosoritide, the need for daily injection, appropriate storage, attendance at an injection training session and the importance of long-term monitoring, and should be informed that long-term outcomes are still not known. Patients and care-givers should be informed that the safety and efficacy profile of the drug has only been established if ≥90% of the prescribed doses are given, and that the effects of irregular dosing patterns are unknown (strong recommendation, Delphi 100%).

When considering management options, care-givers might worry about whether their child, in the future, will support decisions they have made on their behalf[12]. Information for patients and care-givers should be provided in clear, accessible language and include a range of achondroplasia management options, including vosoritide and any alternatives. To remain up-to-date, there is a need for current, evidence-based education about vosoritide to be provided to relevant health-care professionals and patient advocacy groups. As new information emerges, it is important for health-care professionals and patient advocacy groups to disseminate this information to all individuals and families, irrespective of their personal stance. As part of education on potential benefits and adverse effects of vosoritide, patients and families should be informed that the effects of irregular dosing patterns are currently unknown. This educational point is of particular relevance for families who might face challenges with vosoritide supply due to the complex legal processes that some families must undertake to obtain vosoritide.

Shared decision-making is an important part of implementing youth-centred and family-centred care[53]. Patients and care-givers should be connected with communities, organizations or other patients and/or families who have experienced similar circumstances for peer support where possible. The degree of involvement of children with achondroplasia in vosoritide treatment decisions varies among families, depending on parental certainty and the child's age[54]. It is the view of the GDG that young (that is, after the age of 10 years) patients

should be included in decision-making discussions. This approach will promote their autonomy and might aid future treatment adherence. Age-appropriate written or visual materials and support from those familiar with the assent process for children should be included in these discussions.

Expectation management (statements 16 and 17).

- **R16.** Expectations must be set according to realistic personal goals prior to treatment initiation and should be revisited throughout treatment (strong recommendation, Delphi 94%).
- **R17.** Counselling for adolescents who are not eligible for treatment (due to closed growth plates or other medical factors) should be available (strong recommendation, Delphi 94%).

International expert opinion is that increased height velocity following treatment with vosoritide will continue until near adult height in individuals starting treatment before puberty, and that long-term treatment with vosoritide will probably or very probably result in clinically meaningful improvements in upper-to-lower body segment ratio in individuals starting treatment between 2 years of age and puberty[51]. A continued positive effect on growth has been shown in ongoing extension studies following 7 years of vosoritide treatment, with no waning of treatment effect over time[31,39]. With up to 3 years of follow-up, improvements in health-related quality of life have been reported among vosoritide-treated children and adolescents with achondroplasia, particularly in physical domain scores, with a more pronounced change seen in participants who had the most improvements in their achondroplasia height *Z*-score[55]. The GDG note that setting clear expectations around available information, and regularly revisiting treatment goals with the child and family are key to treatment adherence and persistence.

Minimum resource requirements (statements 18–20).

- **R18.** The prescriber must be either a medical specialist experienced in the management of achondroplasia or another health-care professional (for example, paediatrician, paediatric endocrinologist or medical geneticist) in consultation with a specialist experienced in the management of achondroplasia (strong recommendation, Delphi 94%).
- **R19.** Prior to treatment initiation, the following items must be in place: the ability to diagnose; counselling health-care professional; prescriber access to expert or specialist reference centre; and appropriate tools and plan for follow-up and revisiting continuation of therapy. The following items should also be in place: patient natural history, where practical; patient and care-giver access to community; standardized, unbiased resources for patient and care-giver; and impartial contact (or contacts) from the skeletal dysplasia community for patient and care-giver (strong recommendation, Delphi 94%).
- **R20.** The prescribing health-care professional must have the resources, including staff, required to manage and coordinate the prescription process (strong recommendation, Delphi 100%).

Prior to treatment initiation, the minimum resource requirements detailed in R19 should be in place; however, it is recognized that resources will vary between centres. In areas where patients live far away from specialists, regular prescriptions could be offered by local practitioners, and telemedicine could be used for regular check-ups by specialists.

Treatment initiation

Injection training and first dose (statements 21–26).

- **R21.** Patients and care-givers should be educated about managing pain, hypotension and injection site reactions, and should be prepared to accept the commitment of daily injections. This education should include establishing injection as routine practice (for example, after breakfast or dinner) to minimize hypotensive responses (strong recommendation, Delphi 100%).
- **R22.** This group believes that the level of risk from hypotension with vosoritide treatment is low; although it is important for the patient to be well hydrated before injection of vosoritide, measurement of blood pressure at home is not necessary (moderate recommendation, Delphi 88%).
- **R23.** Care-givers and patients, where willing and able, must be fully educated on injection techniques, including rotating injection site, by a specialist nurse, and must be trained to be able to inject without the presence of a nurse (strong recommendation, Delphi 100%).
- **R24.** Patients and families should be supervised during their first dose administration to ensure their techniques are correct and the child tolerates the injection; multiple training sessions might be required to ensure ability to inject without the presence of a nurse (strong recommendation, Delphi 100%).
- **R25.** Nursing and medical staff should be readily available for a 1-h observation period following the first dose (strong recommendation, Delphi 94%).
- **R26.** Patients and care-givers should have the ability to communicate with specialists or a specialist reference centre by telephone, teleconsultation and/or e-mail (strong recommendation, Delphi 100%).

Administering vosoritide at home can be psychologically challenging for care-givers[54], and injection training for patients and care-givers might require multiple sessions, especially if more than one family member is to be trained. It is important to ensure patients and care-givers have the option to contact a nurse or member of the team following training and initial drug administration. Older children with achondroplasia can self-administer vosoritide when they reach an age where they feel emotionally ready to do so, which can aid in their independence. This option can be discussed with families early in the treatment process and implemented at an appropriate time (generally after the age of 10 years). The observation period following the first dose might vary depending on the age of the child. Although measurement of blood pressure is not necessary, it is important that patients and care-givers can identify symptoms of hypotension.

Ongoing monitoring and evaluation

Monitoring of vosoritide therapy (statements 27–30).

- **R27.** Patients should be assessed throughout treatment and supported with ongoing treatment decisions and motivation (strong recommendation, Delphi 100%).
- **R28.** Follow-up should be organized by the expert centre and could be delegated to collaborating local centres and paediatricians as appropriate (depending on family and centre resources) (strong recommendation, Delphi 94%).

- **R29.** Additional monitoring for vosoritide should be similar to follow-up for patients who are not receiving vosoritide to maintain equity of care (moderate recommendation, Delphi 81%).
- **R30.** The socioeconomic effect on patients and care-givers must be considered when planning and implementing follow-up (moderate recommendation, Delphi 88%).

The frequency and nature of ongoing monitoring and evaluation should be tailored according to patient age. Suggested follow-up is in addition to standard of care per the international achondroplasia treatment guidelines[46]. In proposing additional follow-ups, consideration must be given to the effect on equity of care (for example, varying levels of medical attention between patients taking vosoritide and those not receiving treatment). Additional requirements for the monitoring of vosoritide should be incorporated into standard follow-up where possible to maintain equity of care and achieve a balance between providing adequate support and limiting the effect of additional appointments on family life.

Early follow-up (statements 31–33).

- **R31.** The first follow-up should be individualized to each specific family situation. The first follow-up must take place no later than 1 month after initiation and can occur via teleconsultation. An initial follow-up call by a nurse should be considered around 1 week after initiation (moderate recommendation, Delphi 81%).
- **R32.** The 1-week check-up call should focus on practical considerations (for example, injection technique, tolerance, injection site management and adverse effects) (moderate recommendation, Delphi 88%).
- **R33.** The 4-week follow-up consultation should include discussion of supply management (including local pharmacy suitability and home storage) (moderate recommendation, Delphi 81%).

Early follow-up should be individualized to the specific family situation and should provide a strong focus on well-being and emotional health, adherence issues and/or challenges with daily injections. Both the 1-week and 4-week follow-up can be completed using telehealth if face-to-face visits are not practical for the family.

Recommended ongoing monitoring across age groups (statements 34–52).

- **R34.** Frequency and nature of ongoing follow-up should be tailored according to patient age (moderate recommendation, Delphi 88%).
- **R35.** Patients 0–2 years of age should be followed up every 3 months (strong recommendation, Delphi 93%).
- **R36.** In patients 0–2 years of age, assessments should include length, weight, head circumference, and developmental and neurological assessment (strong recommendation, Delphi 100%).
- **R37.** In patients 0–2 years of age, weight and dose reviews should be conducted every 3 months. Weight could be provided by the family to reduce clinic visits (moderate recommendation, Delphi 81%).
- **R38.** Patients 3–5 years of age should be routinely followed up every 4–6 months, dependent on resources (moderate recommendation, 88%).
- **R39.** In patients 3–5 years of age, assessments should include sitting and standing height and functionality (for example, via Functional Independence Measure for Children (WeeFIM)) (moderate recommendation, Delphi 87%).
- **R40.** Ideally, the same stadiometer should be used to standardize measurement (strong recommendation, Delphi 100%).
- **R41.** Patients >5 years of age should be routinely followed up every 6 months (moderate recommendation, Delphi 88%).
- **R42.** In patients >5 years of age, assessments should include the Screening Tool for Everyday Mobility and Symptoms (STEMS[56]) and Activities Scale for Kids (ASK[57]) (moderate recommendation, Delphi 87%).
- **R43.** In patients >5 years of age, if clinical concerns are identified regarding psychosocial or quality of life aspects, consider assessing quality of life (for example, via Patient Health Questionnaire (PHQ-9)[58], Paediatric Quality of Life Inventory (PedsQL)[59] or Achondroplasia Personal Life Experience Scale (APLES)[60]) (moderate recommendation, Delphi 88%).
- **R44.** Tanner stage should be collected at all follow-up appointments from an appropriate age (strong recommendation, Delphi 100%).
- **R45.** Collection of patient-reported outcomes should be considered, if feasible (strong recommendation, Delphi 94%).
- **R46.** Patients should be monitored for adverse effects at all follow-up appointments (strong recommendation, Delphi 100%).
- **R47.** There is currently no evidence that vosoritide results in an increased rate of serious adverse effects compared with other types of non-drug treatments for achondroplasia (strong recommendation, Delphi 94%).
- **R48.** Patients should be monitored for concomitant medications at pre-initiation and all follow-up appointments (strong recommendation, Delphi 94%).
- **R49.** Sleep study is not specifically required for vosoritide follow-up but should be conducted, if clinically indicated, per standard of care (strong recommendation, Delphi 94%).
- **R50.** MRI is not routinely required for vosoritide follow-up unless otherwise clinically indicated (refer to Savarirayan et al.[46]) (strong recommendation, Delphi 100%).
- **R51.** Radiography is not routinely required before puberty for vosoritide follow-up unless otherwise clinically indicated (moderate recommendation, Delphi 87%).
- **R52.** If poor adherence is suspected by the health-care professional (for example, due to lack of response to the treatment), increasing the frequency of follow-up (for example, to every 3 months) and assessing motivation for continuing treatment is recommended (strong recommendation, Delphi 100%).

Table 2 presents a minimum set of recommended assessments for vosoritide follow-up. These guidelines are designed for international use; however, it is understood that resources might vary between countries and regions. Outcomes that are routinely monitored as part of standard of care should continue as recommended (such as foramen magnum, sleep disordered breathing, spine, leg deformities, hearing, developmental milestones and functional performance). Real-world data collection is recommended where practical, to support ongoing efforts to improve decision-making and management[61].

The frequency and nature of ongoing follow-up should be individualized according to the patient's age and condition, using a model of shared care with the local team. Increasing the frequency of reviews might be required to revisit injection training and ensure that the patient and family want to continue with treatment, particularly if

poor adherence is suspected. An assessment for new comorbidities might also be required. A community connection is an important part of ongoing supportive care for patients and families.

Treatment response (statements 53–55).

- **R53.** Response to vosoritide can vary in magnitude and timing[48] (strong recommendation, Delphi 100%).
- **R54.** Treatment goals should be holistic and individualized and might include growth (via annualized height velocity), as well as functional goals. These goals should be discussed with the patient and care-givers to define a personalized response target (strong recommendation, Delphi 100%).
- **R55.** If a patient is not responding in the expected time frame, other comorbidities that might affect growth should be investigated (strong recommendation, Delphi 94%).

The response to vosoritide treatment can vary in magnitude and timing[48]. Evidence from the vosoritide trial programme and early clinical experience suggests a response is often measurable at 1–2 years after starting the treatment[35,39]. The GDG did not reach consensus on the expected observable time frame for response to vosoritide, noting that the definition of a good or poor response to vosoritide treatment remains to be clearly defined, and might depend on the age at which treatment is initiated. Waiting too long to interpret a response might delay investigation into a poor response.

As response to vosoritide can vary, expectations should be realistic and it is important to align with patients and families as to the definition of response to treatment, prior to initiation of treatment[48]. In addition, treatment response from a functional perspective might also be difficult to gauge, especially in the short-term.

Stopping treatment with vosoritide (statements 56–62).

- **R56.** When annual height velocity has slowed to <1.5 cm per year, radiography should be performed to check the status of the growth plates; if they are closed, treatment with vosoritide should be stopped (strong recommendation, Delphi 94%).
- **R57.** During puberty, radiography should be performed every 1–2 years to confirm growth plates remain open (moderate recommendation, Delphi 81%).
- **R58.** Bone age assessments should be interpreted with caution in patients with achondroplasia (moderate recommendation, Delphi 81%).
- **R59.** Treatment can be stopped when patients reach a height they are comfortable with, based on their treatment goals (moderate recommendation, Delphi 81%).
- **R60.** Treatment can be stopped in consultation with the patient and family if desired treatment goals are not being achieved, after repeated measurements or if there is a decline in functional performance or increase in pain that is unexplained by investigation of other underlying conditions (moderate recommendation, Delphi 81%).
- **R61.** Treatment with vosoritide can be stopped if a patient is unable to tolerate the injections (strong recommendation, Delphi 100%).
- **R62.** If the patient is undergoing surgery, it is recommended that the surgical team contact the primary prescriber and/or expert centre for advice on potential temporary treatment interruption (moderate recommendation, 87%).

Table 2 | Recommended practical assessments for monitoring across age groups

Patient age (years)	Routine follow-up intervals (months)[a]	Assessments should include
0–2	3	Weight and dose reviews[b]
		Length, weight and head circumference
		Developmental and neurological assessment
		Monitoring of adverse effects[c]
		Monitoring of concomitant medications
		Patient-reported outcomes, when feasible
3–5	4–6	Sitting and standing height[d]
		Assessment of functional performance (for example, via WeeFIM)
		Monitoring of adverse effects[c]
		Monitoring of concomitant medications
		Patient-reported outcomes, when feasible
>5	6	Screening for pain and fatigue (for example, STEMS[56])
		Assessment of functional performance (for example, ASK[57])
		Tanner stage (from an appropriate age)[e]
		Monitoring of adverse effects[c]
		Monitoring of concomitant medications
		Patient-reported outcomes, when feasible
		If clinical concerns are identified regarding psychosocial and/or quality of life aspects, consider assessing quality of life (for example, via PHQ-9 (ref. 58), PedsQL[59] or APLES[60])

Table based on 14 consensus statements (R35–R48). Suggested follow-up is in addition to standard of care per the international achondroplasia treatment guidelines[46]. APLES, Achondroplasia Personal Life Experience Scale; ASK, Activities Scale for Kids; PedsQL, Paediatric Quality Of Life Inventory; PHQ-9, Patient Health Questionnaire; STEMS, Screening Tool for Everyday Mobility and Symptoms; WeeFIM, functional independence measure for children. [a]Follow-up frequency might vary depending on the standard for a particular clinic, resources available and specific needs for each patient. In the first year of treatment with vosoritide, routine follow-up at least every 3–4 months is preferred regardless of patient age. Appointments can be merged with routine standard of care per the international achondroplasia treatment guidelines. [b]After providing appropriate guidance to families, physicians might accept the weight of the child provided by families to help to manage the number of clinic visits. For younger children, shorter intervals might be required. [c]There is currently no evidence that vosoritide results in an increased rate of serious adverse effects compared with not using vosoritide (that is, receiving standard-of-care treatment). [d]Ideally the same, regularly calibrated stadiometer should be used to standardize measurement. [e]Tanner stage should be monitored by history or by examination by those appropriately trained, in accordance with standard of care for the clinic.

When approaching growth plate closure, more frequent X-rays might be warranted than advised in R57; however, some advisers prefer to use X-rays only to confirm closed growth plates when annualized growth velocity falls below 1.5 cm per year. Bone age in people with achondroplasia has not been fully characterized and very few publications have described bone age delays in children with achondroplasia. Bone age assessments can be reliable for closing of the physes but not for height prediction.

The decision to cease vosoritide can be made at any point after thorough counselling and goals discussion with the patient and

care-giver (for example, if a child no longer assents, and/or expresses a need to stop treatment for any reason). If deciding to stop treatment based on the patient-defined target height, it is important to acknowledge that patients might not achieve their desired height. Cessation of vosoritide might also be considered if a patient is not responding to the treatment or is experiencing pain that cannot be explained by underlying conditions. A decision to cease treatment based on poor tolerance of injections should only take place after suitable discussion and with provision of good support around injection administration. No data are currently available on the effect of treatment interruption.

Ongoing monitoring following cessation of treatment (statements 63 and 64).

- **R63.** Spinal health should continue to be monitored after cessation of vosoritide treatment per standard of care (strong recommendation, Delphi 100%).
- **R64.** Patients should be monitored into adulthood following cessation of treatment, with a clear transition plan from 6-monthly assessments to adult services in order to facilitate this change in their life and discuss long-term health-care management (refer to Savarirayan et al.[46]) (strong recommendation, Delphi 100%).

Baseline spine MRI is recommended where feasible to monitor spinal alignment and stenosis and for comparison purposes when and/or if symptoms such as pain, tingling or cramping, muscle weakness, decline of walking distance, bowel or urinary incontinence, or a spinal cord injury occur. Further spinal monitoring and management should be in accordance with standard care, which includes physical examination, medical history and imaging if clinically indicated[46]. It has been recognized that the care and follow-up of adults with achondroplasia can be challenging as adult services might not be readily available for the transition from paediatric care, and adults are increasingly lost to, or decline, follow-up after childhood[62]. Published in 2024, The European Achondroplasia Forum recently developed a patient-held checklist to support adults with achondroplasia and their primary care provider in managing their health[63]. As patients move into adulthood the importance of linking with others within the short statured community should be strongly emphasized. Long-term follow-up in adults via a register could be considered to assess safety following vosoritide cessation.

Strengths and limitations

The strengths of this Consensus Statement include the systematic approach to expert selection, resulting in a GDG with over 290 collective years of experience in the treatment of individuals with achondroplasia and experience in the treatment of 483 individuals with achondroplasia with vosoritide across five continents. At the time of the meeting on 18 November 2023, six of 14 clinical experts had been involved in vosoritide clinical trials for achondroplasia and eight of the 14 had prescribed vosoritide to an individual with achondroplasia in clinical practice. A holistic perspective was achieved through the inclusion of a wide range of specialties involved in the treatment of patients with achondroplasia (Supplementary Box 3), and the inclusion of patient representatives to ensure the patient view was at the centre of these guidelines. The widely accepted Delphi approach was used across multiple rounds with a predefined threshold, to assess consensus for the recommendations.

There are several limitations to this Consensus Statement. Although these guidelines are intended for international use, the requirement for the majority of the GDG to have experience with targeted achondroplasia treatment in clinical practice and/or involvement in vosoritide clinical trials meant that the geographical spread of the GDG was not entirely representative. No systematic literature review was conducted to inform these treatment guidelines owing to the availability of several reviews published in the past 5 years covering achondroplasia[5,7,13–15,17,51,64,65] and the intention to focus on practical guidance for use of vosoritide based on expert experience. Owing to the practical nature of the statements, limited published evidence was available to support individual recommendations. Long-term data in patients with achondroplasia treated with vosoritide, gained through ongoing studies, are needed to further inform the recommendations made here. These guidelines are also limited by biases that are inherent in the Delphi process, including selection of the experts, the exact definition of 'consensus' and confirmation bias regarding the selected statements and discussion around them.

Conclusions

Vosoritide has been demonstrated to increase linear growth in patients with achondroplasia. These expert guidelines recommend a minimum set of requirements and practical framework to optimize patient care and evaluate real-world outcomes of this treatment systematically, as a supplement to already established consensus guidelines[46] for management and care of individuals with achondroplasia.

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Author contributions

R.S., J.H-F., K. Ozono, P.B., V.C.-D., P.I., M.I., J.L.J., M. Maghnie, M. Menzel, N.M., K.M., K. Okada and S.O.F. contributed to all aspects of the article. K.DeA. and S.N.I. contributed to discussion of the content, and reviewed and/or edited the manuscript before submission.

Competing interests

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