nature reviews endocrinology

https://doi.org/10.1038/s41574-024-01074-9

Supplementary information

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

In the format provided by the authors and unedited

Supplementary information

Supplementary Table 1 | Expert mapping tool scoring

Method	**Weighted score**	
A search of PubMed for all relevant articles for achondroplasia was conducted on 30 September 2021, and screened for relevance to achondroplasia. Authors of each publication were traced to count publications. Scores were attributed depending on their number of publications.	Publications 5 6–9 10+	Score 2 4 5
The author's H-index provided by SCOPUS was identified and scores were attributed.	≤30 >30	3 6
Involvement at relevant patient organization events as speaker, chair, host, or founder was recorded and scored by number of events.	1–3 ≥4	6 9
Involvement at relevant scientific events as speaker, chair, or member of advisory board was recorded and scored by number of events.	2–5 6–9 ≥10	2 4 6

Supplementary Box 1 | Methods rationale

An expert-based consensus approach was chosen to develop these guidelines, with expert group selection guided by the need for clinical trial experience with vosoritide. As such, a systematic literature review was not deemed appropriate by the Steering Committee (SC) for the development of these practical guidelines.

Supplementary Box 2 | Expert mapping tool development

Experts were identified using an expert mapping framework developed by Mole et al.[1] The tool used a 4-item weighted scoring method based on relevant publication experience, author's H-index, patient organization event attendance as chair or speaker, and scientific event experience as chair or speaker.

Specific criteria for selection of clinical experts were used:

- Clinician, experienced with skeletal dysplasia, in particular achondroplasia
- Able to speak and understand English to a high level

EITHER:

- Experienced with vosoritide in clinical practice and/or involvement in vosoritide treatment clinical trials

OR:

- Expected prescriber of vosoritide for achondroplasia/involvement in care of individuals treated with vosoritide (with good knowledge of existing clinical evidence)

The final selection was based on inclusion of a suitable range of specialties and geographic variation.

Supplementary Box 3 | Convening the guideline development group

Based on the outcomes of the scoring method above, the highest scoring expert was identified and invited as chair (RS), and 18 clinical experts and 2 patient representatives were invited to the Guideline Development Group (GDG). Four clinical experts declined to participate as they were unable to attend the mandatory meeting on 18 November 2023 in New York, USA.

At the time of the meeting on 18 November 2023, 6 out of 14 clinical experts had been involved in vosoritide clinical trials for achondroplasia and 8 out of 14 had prescribed vosoritide to an individual with achondroplasia in clinical practice. The GDG had over 290 collective years of experience in managing individuals with achondroplasia and had treated 483 individuals with achondroplasia with vosoritide across 5 continents. This included involvement in setting up clinics, providing feedback about trial data, and interacting with providers to provide support when prescribing vosoritide. Patient representative experience included supporting individuals undergoing treatment with vosoritide and their families, participating in advisory committees, and involvement in the design of vosoritide clinical trials from the patient's perspective. The patient organization (ALPE)’s multidisciplinary clinic had evaluated 30 children with vosoritide and their families at the time of the meeting on 18 November 2023.

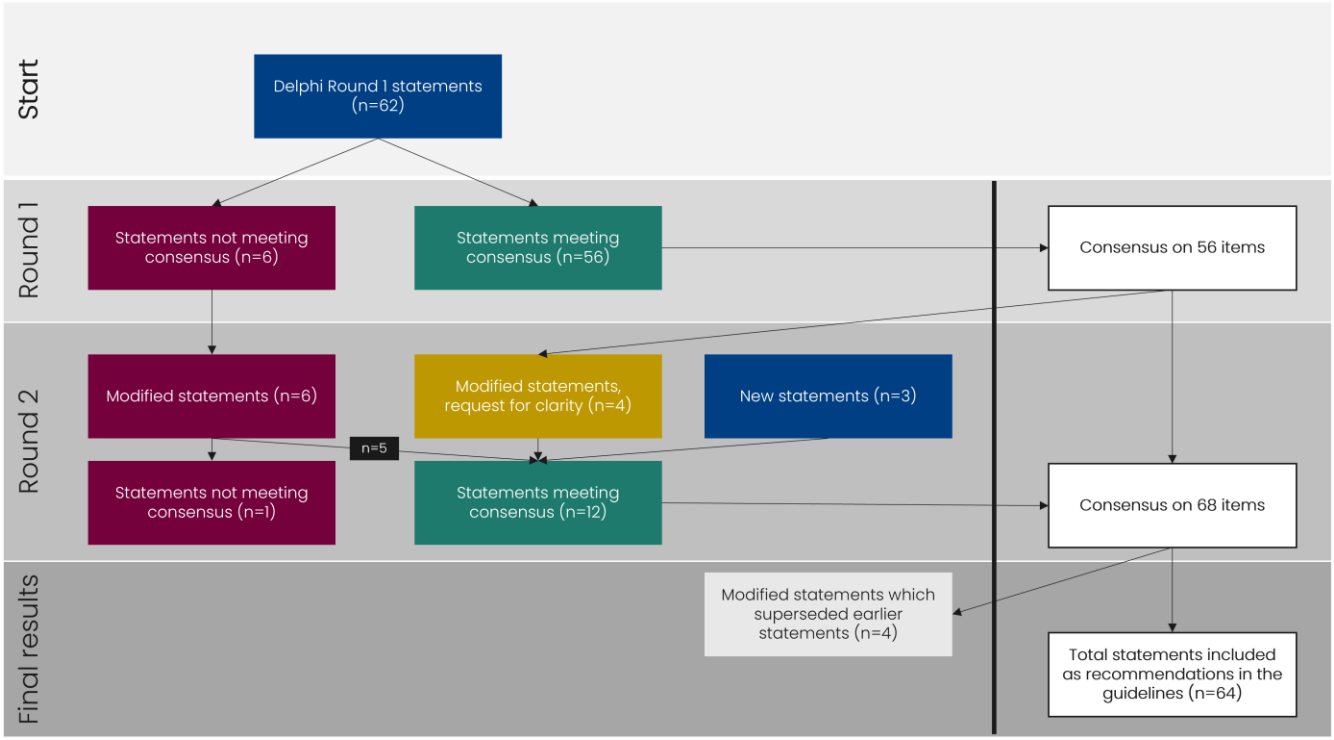
Supplementary Box 4 | Consensus building: Delphi questionnaire

The final 64 consensus statements, with percent agreement and strength of recommendation are shown in Supplementary Table 2, Supplementary Table 3 and Supplementary Table 4. The strength of recommendation is based on the percentage agreement with the statement, with >90% agreement classed as 'Strong recommendation' and >80% to ≤90% classed as 'Moderate recommendation'. Delphi panel Round 1 responses are shown in Supplementary Table 5 and Supplementary Table 6, and Round 2 responses are shown in Supplementary Table 7.

Supplementary Fig. 1 details the Delphi voting process. All statements received a vote from all 16 members of the GDG, with those voting 'unable to answer' providing rationale in the comments. For Round 1, 15 votes for 'unable to answer' were submitted out of 992 total votes. For Round 2, 1 vote for 'unable to answer' was submitted out of 208 total votes. In both rounds this was mainly due to the statement not being within the individual's area of expertise. Consensus was defined in advance of the Delphi panel as when >80% of the GDG either agreed/strongly agreed or disagreed/strongly disagreed with a denominator of at least 50% of the GDG able to vote.

Round 1 voting opened 11 December 2023, and closed 12 January 2024. Round 2 voting opened 7 February 2024, and closed 22 February 2024. A total of 320 free-text comments were received in Round 1. Comments relating to statements which did not meet consensus were used to support decision-making for updated statements for voting in Round 2. Comments relating to statements which did meet consensus were collated and either used to inform new statements for voting in Round 2 or captured to inform the body of the guideline manuscript to provide further details, context, and qualifications to the guideline recommendations. All new statements for voting in Round 2 were reviewed by the Steering Committee prior to commencing voting. A total of 52 free-text comments were received in Round 2 which were captured to inform the body of the guideline manuscript. Further revisions to the statements were made in the main manuscript during development of the guidelines publication and were approved by all authors.

Supplementary Fig. 1 | Delphi voting pathway



Supplementary Table 2 | Recommendations for starting treatment with vosoritide (statements 1–26)

Recommendation statement	% Agreement*	Strength of recommendation**
Pre-initiation of treatment		
First contact		
1. Education and resources should be available to primary care physicians to support initial contact with patients and caregivers; communication with experts is important given further emerging clinical evidence for vosoritide.	100.00	Strong
2. 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.	93.75	Strong
Screening and diagnosis for treatment eligibility		
3. Early detection, such as prenatal detection, is recommended where feasible to allow for early treatment initiation.	87.50	Moderate
4. Wherever possible, treatment should be initiated as early as possible, given emerging data on the craniofacial and foramen magnum area[2].	87.50	Moderate
5. Genetic confirmation of diagnosis should be performed, according to local resources and insurer/reimbursement body requirements.	100.00	Strong
6. In line with standard clinical care, the prescriber should be aware of any underlying conditions that could impact growth, general health, and wellbeing.	81.25	Moderate
7. Any complications of achondroplasia should be identified and managed.	100.00	Strong
Education and consent		
8. Patients and caregivers must be supported with education about achondroplasia and informed regarding medication usage requirements and side effects prior to providing consent to elective vosoritide treatment.	100.00	Strong
9. When diagnosis is suspected all patients 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.	93.75	Strong

10. The option of vosoritide should be discussed with all who are eligible; however, it should be recognised and fully supported that not all patients will decide to pursue therapy.	100.00	Strong
11. It should be acknowledged that the initial information a family receives about vosoritide from any source is important and can impact ongoing beliefs. There is a need to educate relevant healthcare professionals and patient advocacy groups about vosoritide as new evidence emerges.	100.00	Strong
12. Counselling about achondroplasia and treatment options must be provided by a qualified healthcare professional at the earliest opportunity.	100.00	Strong
13. Young patients should be included in treatment decision-making and given the opportunity to assent, express concerns, and dissent.	100.00	Strong
14. A pre-initiation of treatment visit should be scheduled with the family and patient with the aims of assessing the suitability of the patient for vosoritide treatment and to educate the patient and family on the use of vosoritide and expected outcomes.	93.75	Strong
15. Patients and caregivers should be educated on the potential benefits and side effects of vosoritide, the need for daily injection, appropriate storage, attendance at an injection training session, the importance of long-term monitoring, and informed that long-term outcomes are still not known. Patients and caregivers 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.	100.00	Strong
Expectation management		
16. Expectations must be set according to realistic personal goals prior to treatment initiation and should be revisited throughout treatment.	93.75	Strong
17. Counselling for adolescents who are not eligible for treatment (due to closed growth plates or other medical factors) should be available.	93.75	Strong
Minimum resource requirements		
18. Prescriber must be either a medical specialist experienced in the management of achondroplasia OR another healthcare professional (e.g. paediatrician, paediatric endocrinologist, medical geneticist) in consultation with a specialist experienced in the management of achondroplasia.	93.75	Strong

19. Prior to treatment initiation, the following items should be in place:	93.75	Strong

Item	Requirement level
Ability to diagnose	Must
Patient natural history, where practical	Should
Patient and caregiver access to community	Should
Standardized, unbiased resources for patient and caregiver	Should
Impartial contact(s) from the skeletal dysplasia community for patient and caregiver	Should
Counselling healthcare professional	Must
Prescriber access to expert or specialist reference centre	Must
Appropriate tools and plan for follow-up and revisiting continuation of therapy	Must

20. The prescribing healthcare professional must have the resources, including staff, required to manage and co-ordinate the prescription process.	100.00	Strong
Treatment initiation		
Injection training and first dose		
21. Patients and caregivers should be educated about managing pain, hypotension, and injection site reactions, and prepared to accept the commitment of daily injections. This education should include establishing injection as routine practice (e.g. after breakfast or dinner) to minimise hypotensive responses.	100.00	Strong
22. This group believes that the level of risk from hypotension with vosoritide treatment is low; while it is important for the patient to be well hydrated before injection of vosoritide, measurement of blood pressure at home is not necessary.	87.50	Moderate
23. Caregivers and patients, where willing and able, must be fully educated on injection techniques, including	100.00	Strong

	rotating injection site, by a specialist nurse, and must be trained to be able to inject without the presence of a nurse.		
24.	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 may be required to ensure ability to inject without the presence of a nurse.	100.00	Strong
25.	Nursing and medical staff should be readily available for a 1-hour observation period following the first dose.	93.75	Strong
26.	Patients and caregivers should have the ability to communicate with specialists or a specialist reference centre by telephone, teleconsultation, and/or email.	100.00	Strong

For specific indication/eligibility for vosoritide, please consult the label for your region.

*The percentage of the panel that voted who agreed or strongly agreed with the statement. **Derived from level of agreement, with >90% agreement classed as ‘Strong recommendation’ and >80% to ≤90% classed as ‘Moderate recommendation’.

Supplementary Table 3 | Recommendations for ongoing monitoring and evaluation of vosoritide treatment (statements 27–55)

Recommendation statement	% Agreement*	Strength of recommendation**
Monitoring of vosoritide therapy		
27. Patients should be assessed throughout treatment and supported with ongoing treatment decisions and motivation.	100.00	Strong
28. Follow-up should be organized by the expert centre and may be delegated to collaborating local centres and paediatricians as appropriate (depending on family and centre resources).	93.75	Strong
29. Additional monitoring for vosoritide should be similar to follow-up for patients who are not receiving vosoritide to maintain equity of care.	81.25	Moderate
30. The socioeconomic impact on patients and caregivers must be considered when planning and implementing follow-up.	87.50	Moderate
Early follow-up		
31. First follow-up should be individualized to each specific family situation. First follow-up must take place no later than 1 month post-initiation and can occur via teleconsultation. An initial follow-up call by a nurse should be considered around 1 week post-initiation.	81.25	Moderate
32. The 1-week check-up call should focus on practical considerations (e.g. injection technique, tolerance, injection site management, adverse events).	87.50	Moderate
33. The 4-week follow-up consultation should include discussion of supply management (including local pharmacy suitability and home storage).	81.25	Moderate
Recommended ongoing monitoring across age groups		
34. Frequency and nature of ongoing follow-up should be tailored according to patient age.	87.50	Moderate
35. Patients 0–2 years of age should be followed up every 3 months.	93.33	Strong
36. In patients 0–2 years of age, assessments should include length, weight, head circumference, and developmental and neurological assessment.	100.00	Strong

37. In patients 0–2 years of age, weight/dose reviews should be conducted every 3 months. Weight may be provided by the family to reduce clinic visits.	81.25	Moderate
38. Patients 3–5 years of age should be routinely followed up every 4-6 months, dependent on resources.	87.50	Moderate
39. In patients 3–5 years of age, assessments should include sitting and standing height and functionality (e.g. via Functional Independence Measure for Children [WeeFIM]).	86.67	Moderate
40. Ideally, the same stadiometer should be used to standardize measurement.	100.00	Strong
41. Patients over 5 years of age should be routinely followed up every 6 months.	87.50	Moderate
42. In patients over 5 years of age, assessments should include the Screening Tool for Everyday Mobility and Symptoms (STEMS[4]) and Activities Scale for Kids (ASK[5]).	86.67	Moderate
43. In patients over 5 years of age, if clinical concerns are identified regarding psychosocial/quality of life aspects, consider assessing quality of life (e.g. via Patient Health Questionnaire [PHQ-9[6]], Paediatric Quality of Life Inventory [PedsQL[7]], or Achondroplasia Personal Life Experience Scale [APLES[8]]).	87.50	Moderate
44. Tanner stage should be collected at all follow-up appointments from an appropriate age.	100.00	Strong
45. Collection of patient-reported outcomes should be considered, if feasible.	93.75	Strong
46. Patients should be monitored for adverse events at all follow-up appointments.	100.00	Strong
47. There is currently no evidence that vosoritide results in an increased rate of serious adverse events compared with untreated achondroplasia	93.75	Strong
48. Patients should be monitored for concomitant medications at pre-initiation and all follow-up appointments	93.75	Strong
49. Sleep study is not specifically required for vosoritide follow-up but should be conducted, if clinically indicated, per standard of care.	93.75	Strong
50. Magnetic resonance imaging is not routinely required for vosoritide follow-up unless otherwise clinically indicated (refer to Savarirayan et al.[9]).	100.00	Strong

51. X-rays are not routinely required pre-puberty for vosoritide follow-up unless otherwise clinically indicated.	86.67	Moderate
52. If poor adherence is suspected by the healthcare professional (e.g. due to lack of response), increasing the frequency of follow-up (e.g. to every 3 months) and assessing motivation for continuing treatment is recommended.	93.75	Strong
Treatment response		
53. Response to vosoritide can vary in magnitude and timing[10].	100.00	Strong
54. Treatment goals should be holistic and individualized and may include growth (via annualized height velocity), as well as functional goals. This should be discussed with the patient and caregivers to define a personalized response target.	100.00	Strong
55. If a patient is not responding in the expected timeframe, other co-morbidities that may impact growth should be investigated.	93.75	Strong

*The percentage of the panel that voted who agreed or strongly agreed with the statement.

**Derived from level of agreement, with >90% agreement classed as ‘Strong recommendation’ and >80% to ≤90% classed as ‘Moderate recommendation’.

Supplementary Table 4 | Recommendations for stopping treatment with vosoritide and ongoing monitoring following treatment cessation (statements 56–64)

Recommendation statement	% Agreement*	Strength of recommendation**
Stopping treatment with vosoritide		
56. When annual height velocity has slowed to <1.5 cm/year, x-rays should be conducted to check status of the growth plates; if they are closed, treatment with vosoritide should be stopped.	93.75	Strong
57. During puberty, x-rays may be conducted every 1–2 years to confirm growth plates remain open.	81.25	Moderate
58. Bone age assessments should be interpreted with caution in patients with achondroplasia.	81.25	Moderate
59. Treatment can be stopped when the patient reaches a height they are comfortable with, based on their treatment goals.	81.25	Moderate
60. Treatment may be stopped in consultation with the patient and family if desired treatment goals are not being achieved, after repeated measurements or there is a decline in functional performance or increase in pain that is unexplained by investigation of other underlying conditions.	81.25	Moderate
61. Treatment with vosoritide may be stopped if a patient is unable to tolerate the injections.	100.00	Strong
62. If the patient is undergoing surgery, it is recommended that the surgical team contact the primary prescriber/expert centre for advice on potential temporary treatment interruption.	86.67	Moderate
Ongoing monitoring following cessation of treatment		
63. Spinal health should continue to be monitored after cessation of vosoritide treatment per standard of care.	100	Strong
64. 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 healthcare management (refer to Savarirayan et al.[9]).	100	Strong

*The percentage of the panel that voted who agreed or strongly agreed with the statement. **Derived from level of agreement, with >90% agreement classed as ‘Strong recommendation’ and >80% to ≤90% classed as ‘Moderate recommendation’.

Supplementary Table 5 | Delphi panel Round 1 responses

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Unable to answer
Wherever possible, treatment should be initiated as early as possible, given emerging data on foramen magnum area[2].	**6**	**8**	**0**	**2**	**0**	**0**
Education and resources should be available to primary care physicians to support initial contact with patients and caregivers; communication with experts is important given further emerging clinical evidence for vosoritide.	**14**	**2**	**0**	**0**	**0**	**0**
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.	**12**	**3**	**1**	**0**	**0**	**0**
Early detection, such as prenatal detection, is recommended where feasible to allow for early treatment initiation.	**8**	**6**	**2**	**0**	**0**	**0**
Genetic confirmation of diagnosis should be performed, according to local resources and insurer/reimbursement body requirements.	**13**	**3**	**0**	**0**	**0**	**0**
Patients should be screened for unrelated conditions which may impact growth or treatment.	8	3	1	1	1	2
Any complications of achondroplasia should be identified and managed.	**15**	**1**	**0**	**0**	**0**	**0**
Patients and caregivers must be supported and informed prior to providing consent to elective vosoritide treatment.	**15**	**1**	**0**	**0**	**0**	**0**
The option of vosoritide should be discussed with all who are eligible; however, it should be recognized that not all patients will wish to pursue therapy.	**12**	**4**	**0**	**0**	**0**	**0**
When diagnosis is suspected all patients 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 pursued a range of different pathways.	**12**	**3**	**1**	**0**	**0**	**0**
It should be acknowledged that the first information a family receives about vosoritide from any source is important and can impact ongoing beliefs. There is a need to educate relevant healthcare professionals and patient advocacy groups about vosoritide as new evidence emerges.	**13**	**3**	**0**	**0**	**0**	**0**
Counselling must be provided by a suitably qualified healthcare professional at the earliest opportunity; this may be as early as 10 weeks gestation and if appropriate should include advice to support pregnancy decisions.	10	1	2	1	0	2

Young patients, if capable of understanding the education, should be involved in treatment decision-making.	**10**	**6**	**0**	**0**	**0**	**0**
A pre-initiation visit should be scheduled with the family and patient with the aims of assessing the suitability of the patient for vosoritide treatment and to educate the patient and family on the use of vosoritide and expected outcomes.	**13**	**2**	**0**	**1**	**0**	**0**
Patients and caregivers should be educated on the potential benefits and side effects of vosoritide, the need for daily injection, adequate storage, attendance at an injection training session, and the need for long-term monitoring. Patients and families should be informed that the safety profile of the drug has only been established if ≥90% of the prescribed doses are given, and the effects of irregular dosing patterns are unknown.	**12**	**2**	**2**	**0**	**0**	**0**
Expectations must be set according to realistic personal goals prior to treatment initiation and should be revisited throughout treatment.	**13**	**2**	**1**	**0**	**0**	**0**
Counselling for adolescents who are not eligible for treatment (due to closed growth plates) should be available.	**10**	**5**	**1**	**0**	**0**	**0**
Prescriber must be either a medical specialist experienced in the management of achondroplasia OR another healthcare professional (e.g. paediatrician, endocrinologist) in consultation with a specialist experienced in the management of achondroplasia.	**10**	**5**	**1**	**0**	**0**	**0**
Prior to treatment initiation, the following items should be in place (refer to Supplementary Table 6 below).	**7**	**8**	**0**	**1**	**0**	**0**
Prescribing healthcare professional must have the resources, including staff, required to manage and co-ordinate the prescription process.	**11**	**5**	**0**	**0**	**0**	**0**
Patients and caregivers should be educated about managing pain, hypotension, and injection site reactions, and prepared to accept the commitment of daily injections. This education should include establishing injection as routine practice (e.g. after breakfast) to minimize hypotensive responses.	**12**	**4**	**0**	**0**	**0**	**0**
Caregivers, 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.	**14**	**2**	**0**	**0**	**0**	**0**
Patients and families should be supervised during their first dose administration to ensure their techniques are correct and the child tolerates the	**14**	**2**	**0**	**0**	**0**	**0**

injection; multiple training sessions may be required to ensure ability to inject without the presence of a nurse.						
This group believes that the level of risk from hypotension with vosoritide treatment is low; while it is important for the patient to be well hydrated before injection of vosoritide, measurement of blood pressure is not normally necessary.	**6**	**8**	**1**	**1**	**0**	**0**
Nursing and medical staff should be readily available for a 1-hour observation period following the first dose.	**7**	**8**	**1**	**0**	**0**	**0**
Patients and caregivers should have the ability to communicate with specialists or a specialist reference centre by telephone and/or email.	**14**	**2**	**0**	**0**	**0**	**0**
Patients should be assessed throughout treatment and supported with ongoing treatment decisions and motivation.	**14**	**2**	**0**	**0**	**0**	**0**
Follow-up should be organized by the expert centre and may be delegated to collaborating local centres and paediatricians as appropriate (depending on family and centre resources).	**13**	**2**	**0**	**1**	**0**	**0**
Additional monitoring for vosoritide should be kept as similar as possible to follow-up for patients who are not receiving vosoritide to maintain equity of care.	**9**	**4**	**2**	**1**	**0**	**0**
The socioeconomic impact on patients and caregivers must be considered when planning and implementing follow-up.	**10**	**4**	**1**	**1**	**0**	**0**
First follow-up should be adaptable to each specific family situation. First follow-up must take place no later than 1 month post-initiation and can be via teleconsultation. An initial follow-up call by a nurse should be considered around 1 week post-initiation.	**5**	**8**	**1**	**2**	**0**	**0**
The 1-week check-up call should focus on practical considerations (e.g. injection technique, tolerance, injection site management, adverse events).	**8**	**6**	**2**	**0**	**0**	**0**
The 4-week follow-up consultation should include discussion of supply management (including local pharmacy suitability and home storage).	**7**	**6**	**3**	**0**	**0**	**0**
Frequency and nature of ongoing follow-up should be tailored according to patient age.	**10**	**4**	**1**	**1**	**0**	**0**
Tanner stage should be collected at all follow-up appointments.	**7**	**8**	**0**	**0**	**0**	**1**
Patients 0–2 years of age should be followed up every 3 months.	**7**	**7**	**1**	**0**	**0**	**1**
In patients 0–2 years of age, assessments should include length, weight, head circumference, and developmental and neurological assessment.	**11**	**4**	**0**	**0**	**0**	**1**

In patients 0–2 years of age, weight/dose reviews should be conducted every 3 months. Weight may be provided by the family to reduce clinic visits.	**5**	**8**	**2**	**1**	**0**	**0**
Patients 3–5 years of age should be routinely followed up every 6 months.	9	3	3	0	0	1
In patients 3–5 years of age, assessments should include sitting and standing height and functionality (e.g. via Functional Independence Measure for Children [WeeFIM]).	**11**	**2**	**2**	**0**	**0**	**1**
Ideally, the same stadiometer should be used to standardize measurement.	**11**	**5**	**0**	**0**	**0**	**0**
Patients over 5 years of age should be routinely followed up every 6 months.	**10**	**4**	**2**	**0**	**0**	**0**
In patients over 5 years of age, assessments should include the Screening Tool for Everyday Mobility and Symptoms (STEMS) and Activities Scale for Kids (ASK).	**6**	**7**	**2**	**0**	**0**	**1**
In patients over 5 years of age, if clinical concerns are identified regarding psychosocial/quality of life aspects, consider assessing quality of life (e.g. via Patient Health Questionnaire [PHQ-9], Paediatric Quality of Life Inventory [PedsQL], or Achondroplasia Personal Life Experience Scale [APLES]).	**7**	**7**	**1**	**1**	**0**	**0**
A sleep study should be conducted, if clinically indicated per standard of care.	**11**	**4**	**0**	**1**	**0**	**0**
Magnetic resonance imaging is not routinely required for vosoritide follow-up unless otherwise clinically indicated (refer to Savarirayan R et al.[9])	**7**	**8**	**0**	**0**	**0**	**1**
X-rays are not routinely required pre-puberty for vosoritide follow-up unless otherwise clinically indicated.	**7**	**6**	**1**	**0**	**1**	**1**
If poor adherence is suspected by the healthcare professional (e.g. due to lack of response), increasing the frequency of follow-up (e.g. every 3 months) and assessing motivation for continuing treatment is recommended.	**10**	**5**	**1**	**0**	**0**	**0**
Collection of patient-reported outcomes may be considered, where feasible.	**10**	**4**	**1**	**1**	**0**	**0**
Response to vosoritide can vary in magnitude and timing[10].	**12**	**4**	**0**	**0**	**0**	**0**
Treatment goals should be holistic and individualized and may include growth (via Annualized Growth Velocity) as well as functional targets; this should be discussed with the patient and caregivers to define a personalized response target.	**10**	**6**	**0**	**0**	**0**	**0**
Growth response for an individual patient is typically observable after 1–2 years of treatment.[10]	2	7	3	3	0	1
If a patient is not responding in the expected timeframe, other confounding	**8**	**7**	**1**	**0**	**0**	**0**

conditions should be investigated (e.g. thyroid, celiac, cancer, Crohn's disease, ulcerative colitis, scoliosis).						
When annual growth velocity has slowed to <1.5 cm/year, x-rays should be conducted to check the status of lower limb growth plates; if they are closed, treatment should be stopped.	7	5	2	2	0	0
During puberty, x-rays may be conducted every 1–2 years to confirm growth plates remain open.	**7**	**6**	**1**	**2**	**0**	**0**
Bone age assessments should be interpreted with caution in patients with achondroplasia.	**9**	**4**	**3**	**0**	**0**	**0**
Treatment can be stopped when the patient reaches a height they are comfortable with, based on their treatment goals.	**8**	**5**	**1**	**2**	**0**	**0**
Treatment may be stopped if the desired treatment goals are not being achieved, after repeated measurements (e.g. if the growth target is not achieved after 2 consecutive 6-monthly visits, or there is a decline in pain/function) and after investigation of other underlying conditions.	**8**	**5**	**2**	**1**	**0**	**0**
Treatment may be stopped if a patient is unable to tolerate the injections.	**10**	**6**	**0**	**0**	**0**	**0**
If the patient is undergoing surgery, it is recommended to contact the primary prescriber/expert centre for recommendation on temporary treatment interruption.	**6**	**7**	**2**	**0**	**0**	**1**
Spinal canal should be continued to be monitored after cessation of treatment.	4	7	2	2	0	1
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 healthcare management (refer to Savarirayan R et al.[9])	**12**	**4**	**0**	**0**	**0**	**0**

Statements meeting consensus are shown in **bold.** Consensus was defined as when >80% of the Guideline Development Group (GDG) either agreed/strongly agreed or disagreed/strongly disagreed with a denominator of at least 50% of the GDG able to vote.

Supplementary Table 6 | Items which should be in place prior to vosoritide treatment initiation

Item	Strength of recommendation
Ability to diagnose	Must
Patient natural history, where practical	Should
Patient and caregiver access to community	Should
Standardized, unbiased resources for patient and caregiver	Should
Impartial contact(s) from the skeletal dysplasia community for patient and caregiver	Should
Counselling healthcare professional	Must
Prescriber access to expert or specialist reference centre	Must
Appropriate tools and plan for follow-up and revisiting continuation of therapy	Must
Long-term multi-disciplinary care	Must

Supplementary Table 7 | Delphi panel Round 2 responses

Statement	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Unable to Answer
In line with standard clinical care, the prescriber should be aware of any underlying conditions that could impact growth, general health, and well-being.	**8**	**5**	**2**	**1**	**0**	**0**
***Patients and caregivers must be supported with education about achondroplasia and informed regarding medication requirements and side effects prior to providing consent to elective vosoritide treatment.**	**13**	**3**	**0**	**0**	**0**	**0**
***The option of vosoritide should be discussed with all who are eligible; however, it should be recognized and fully supported that not all patients will wish to pursue therapy.**	**14**	**2**	**0**	**0**	**0**	**0**
Counselling about achondroplasia and treatment options must be provided by a suitably qualified healthcare professional at the earliest opportunity.	**8**	**8**	**0**	**0**	**0**	**0**
***Patients and caregivers should be educated on the potential benefits and side effects of vosoritide, the need for daily injection, appropriate storage, attendance at an injection training session, the importance of long-term monitoring, and informed that long-term outcomes are still not known.**	**10**	**6**	**0**	**0**	**0**	**0**
Patients 3–5 years of age should be routinely followed up every 4-6 months, dependent on resources.	**4**	**10**	**1**	**1**	**0**	**0**
***Collection of patient-reported outcomes should be considered, if feasible.**	**10**	**5**	**1**	**0**	**0**	**0**
Patients should be monitored for adverse events at all follow-up appointments.	**13**	**3**	**0**	**0**	**0**	**0**
There is currently no evidence that vosoritide results in an increased rate of serious adverse events compared with untreated achondroplasia.	**9**	**6**	**1**	**0**	**0**	**0**
Patients should be monitored for concomitant medications at pre-initiation and all follow-up appointments	**12**	**3**	**1**	**0**	**0**	**0**
While growth response is variable, for an individual patient it is likely to be observable by up to 2 years of treatment[10]**.**	3	9	1	3	0	0
When annual growth velocity has slowed to <1.5 cm/year, x-rays should be conducted to check status of the growth plates; if they are closed, treatment with vosoritide should be stopped.	**7**	**8**	**1**	**0**	**0**	**0**
Spinal health should continue to be monitored after cessation of vosoritide treatment per standard of care.	**9**	**6**	**0**	**0**	**0**	**1**

Statements meeting consensus are shown in **bold.** Consensus was defined as when >80% of the Guideline Development Group (GDG) either agreed/strongly agreed or disagreed/strongly disagreed with a denominator of at least 50% of the GDG able to vote.

*Denotes modified statements which superseded statements meeting consensus in Round 1.

Supplementary Box 5 | Resources

A list of VOXZOGO® (vosoritide) resources from BioMarin, as well as home administration education including demonstration, explanation, discussion, and tips for families, are included below.

Resources may vary by country, please contact your local BioMarin representative for access.

Supplementary Table 8 | VOXZOGO® resources from BioMarin

Resource
FOR HEALTHCARE PROFESSIONALS
VOXZOGO® Injection Training Kit – training and demonstration kit which includes: • Ten empty demonstration vials • Ten prefilled syringes of Diluent for BMN 111, 0.5 mL • Ten individual diluent needles with safety device • Ten individual single-dose administration syringes with safety device
Inject-Ed Injection Training Pad (fake skin)
VOXZOGO® Demonstration Injections (pack of 10)
VOXZOGO® Dosing & Administration Guide
VOXZOGO® Injection Video
VOXZOGO® Online Dosing Calculator
VOXZOGO® Product Information
FOR PATIENTS/CAREGIVERS
“In the Know about Achondroplasia”
myVOXZOGO® app
VOXZOGO® Helpline
VOXZOGO® Injection Calendar (laminated) (also included in patient starter kit)
VOXZOGO® Patient Administration Guide
VOXZOGO® Patient Resource Flyer (Contains information on how to access the myVOXZOGO® app, VOXZOGO® helpline, injection video, and “In the Know about Achondroplasia” webpage) (also included in patient starter kit)
VOXZOGO® Patient Starter Kit (1 kit per new patient) BioMarin cooler bag containing: • Sharps container – 1 unit • Alcohol wipes – 30 pieces • “Superheroes” band-aids – 1 box of 20 • Laminated injection calendar – 1 per kit • VOXZOGO® Patient Resource Flyer
VOXZOGO® Consumer Product information

VOXZOGO® (vosoritide) home administration education for families

Supplementary Box 6 | VOXZOGO® (vosoritide) home administration education for families – Demonstration

1. Explain each piece of equipment required for reconstitution and administration (vial, DTS syringe, Easy-Point needle, Vanish-Point syringe, alcohol wipes, sharps container) to parents/caregivers.

    - The vial has the medication in it in a powder form. It needs to be mixed with the provided sterile water prior to administration.
    - The sterile water comes in pre-prepared syringes (called DTS syringes) with the correct amount of water.
    - An Easy-Point needle is attached to the DTS syringe to allow the water to be injected into the vial, wiping the top of the vial with an alcohol wipe first to ensure no bacteria or contamination occurs.
    - Once the powder is dissolved, a Vanish-Point syringe is used to draw up and administer the dose.
    - A sharps container is used to safely store used needles – these can be acquired and disposed of at most pharmacies.

2. Demonstrate the reconstitution and administration (into the skin pad) of VOXZOGO® (vosoritide) for families slowly, talking through each step.

3. Demonstrate the reconstitution and administration (into the skin pad) a second time, this time asking parent/caregivers to follow along. Perform each step and allow them to copy, providing feedback on their technique as you go.

4. Provide the family with an opportunity to ask questions throughout and at the completion of the demonstration.

This guidance is adapted from Tofts et al[3].

Supplementary Box 7 | VOXZOGO® (vosoritide) home administration education for families – Explanation

Cover the following training points (if not already covered throughout the demonstration):

- Child should have an age-appropriate drink/light snack around 30 minutes prior to injection – this is to prevent potential side effects that could be caused if a drop in blood pressure occurs.
- If kept refrigerated, allow it to come to room temperature for at least 30 minutes prior to injection. Note: VOXZOGO can be kept at room temperature (under 30°C) for up to 90 days. Advise families that the medication should be refrigerated if room temperature is above 30°C and not to put unused medication back in the fridge once it is removed.
- Once the water has been added, families have up to 3 hours to administer the dose.
- Injection should be given at roughly the same time every day. The minimum gap between doses is 12 hours.

This guidance is adapted from Tofts et al[3].

Supplementary Box 8 | VOXZOGO® (vosoritide) home administration education for families – Discussion

- Discuss injection sites. Advise caregivers to avoid moles, scars, birthmarks, or areas where the skin is tender, bruised, red, or hard, and to avoid using the same injection site 2 days in a row (e.g. alternate left/right side even if the child has a preferred body part).
- Teach families to check that the vial is not damaged prior to use and to ensure that the contents are clear and not discoloured or cloudy, and that no particles can be seen after reconstitution.
- Discuss potential serious and less serious side effects and the action to take with each (ensure that families know the emergency number 000, as well as for a local contact).
- Discuss what to do if the needle does not retract as it should (remove from skin and then retract).
- Provide education regarding not recapping needles.

This guidance is adapted from Tofts et al[3].

Supplementary Box 9 | VOXZOGO® (vosoritide) home administration education for families – Other tips for families

- In busy households it is possible parents may not realize if a dose has already been given. To avoid errors, a calendar to tick off after each day's dose can help ensure the dose is given every day and not given twice by accident. Having a regular routine will also help ensure the injection is given every day (e.g. always given after breakfast or before bed).
- Some children may be nervous around receiving injections, which may be a result of pain. Ways to reduce pain include ice/buzzy bee (more effective in older children) and numbing cream (can be effective in younger children and older children). Note: numbing cream takes approximately 45 minutes to take effect.
- Older children have reported the injections hurt less when they are still. Encourage older children to find a position they are comfortable in to receive the injection, and to practice deep breathing or utilize a distraction (e.g. TV or phone) while the injection is administered.
- Younger children may need some help staying still during the injection. It is important that they are in a position they feel safe in. A good way to approach this is to have 1 person hold the child sitting upright in their lap, hugging their arms, and placing their leg over the child's leg to help keep them still while not making them feel vulnerable or overly restrained during the injection.
- Some families have utilized reward systems for young children who struggle with injections, which may be effective.
- Other aspects that may impact child experience include time of day, number of parents/helpers present, distraction, injection site, anticipation (some warning but not too drawn out), discussing injections and their purpose with children, giving the child control when able to (e.g. choosing injection site), and involving the child where possible (e.g. put retracted needle in sharps bin, help get equipment out in advance, etc.).
- A periodic refresh of education should be provided, particularly for those who became autonomous.

This guidance is adapted from Tofts et al[3].

Other tips for families:

Supplementary Box 10 | VOXZOGO® (vosoritide) storage at home

- VOXZOGO® (vosoritide) can be kept at room temperature for up to 90 days.
- If ambient temperature exceeds 30°C, VOXZOGO (vosoritide) should be refrigerated in a domestic refrigerator.
- Once VOXZOGO® (vosoritide) has been taken out of the refrigerator, it should not be put back in.
- Ensure families are aware of the space needed, especially if they may need to refrigerate the drug.
    - Each box measures 190 (L) x 143 (W) x 119 (H) mm
    - Each box contains 10 days' worth of VOXZOGO® (vosoritide)
- If storage space in domestic refrigerator is a challenge, we recommend asking a local pharmacy if they can help.

This guidance is adapted from Tofts et al[3].

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