This congress review was created in October 2022. In November 2023, the EMA approved the expansion of the indication for vosoritide to patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing. Prescribing information and updated safety profile can be found at https://hcp.biomarin.com/en-gb/achondroplasia/expert/prescribing-information/.

ACHONDROPLASIA.EXPERT CONGRESS REVIEWS ESPE 2022

Welcome to the ESPE 2022 congress review.

The 60th annual meeting of the European Society for Paediatric Endocrinology took place 15–17 September in Rome, Italy. Over 3,000 delegates attended for a huge programme on diseases of childhood, including dedicated sessions on bone, growth, and mineral metabolism.

We have chosen a selection of abstracts with a focus on achondroplasia and a few other topics of interest in the wider field of skeletal dysplasia. These include new analyses of appropriate patient-reported outcomes to use in children with achondroplasia, and examination of differences in everyday management.

Also summarised is a sponsored symposium giving more detail on some of the early-use, real-world cohorts of patients receiving vosoritide▼ in routine practice across Europe.

We hope you will enjoy the selection of presentations summarised for you here.

The Achondroplasia Team

MORE INSIDE

REAL-WORLD DATA FOR VOSORITIDE

Early results in children with achondroplasia

▶ CLICK TO FIND OUT MORE

THE PATIENT PERSPECTIVE

Identifying disease-specific PROs

▶ JUMP TO THE DATA

EVOLVING MANAGEMENT

Treatment in the age of precision therapies

▶ GET THE SUMMARY HERE

Oral abstracts can be found in full here. Access the iposters here.

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VOSORITIDE: REAL-WORLD DATA

Vosoritide, an analogue of C-type natriuretic peptide, has been developed for the treatment of short stature in children with achondroplasia, and was approved by the EMA in August 2021.

Palm *et al.* presented epidemiological data characterising the current practice of multidisciplinary treatment in Portugal, Austria, and Germany. Routine medical history and clinical data were obtained from 575 children with achondroplasia under the age of 17. Since October 2021, vosoritide had been started in 164 children (29%). Of these, the majority (49%) are 2–6 years of age. Across the whole achondroplasia group, 19% had received cranial decompression surgery and 8% had undergone limb lengthening. To facilitate further data collection, an achondroplasia-specific list of items has been inserted in CrescNet – a web-based registry. The group will continue to collect prospective data for longitudinal evaluation of safety and treatment responses. ▸ [P1-223]

Real-world experience with vosoritide was also shared in a poster from Cormier-Daire *et al.* Vosoritide was made available in France in June 2021 via an early access programme. Prioritisation of the oldest children with achondroplasia was proposed, with enrolment focusing on those aged 5 years and older with open epiphyses. After treatment initiation and parent education, follow-up includes visits at Months 1, 3, and 6, and at 6-monthly intervals thereafter. Data are systematically collected to evaluate treatment compliance, AEs, and growth. To date, data are available for 29 patients from 6 centres across France. At baseline, 52% were female with a mean age of 9 years. The mean height was 106.9 cm, with height z-scores ranging between –3.9 and –7.7 in males and –3.4 and –6.0 in females. The duration of treatment ranged from just under 1 month to approximately 11 months, over which time 7 patients missed a total of 13 doses, but no patients discontinued treatment. In total, there were 17 AEs reported among 9 patients; the majority were mild and included injection-site reactions and vomiting, with injection-site papules being the most common (6 events). There were no serious AEs related to vosoritide, and no AEs led to permanent treatment discontinuation (please see table on page 9). The authors concluded that the overall safety profile of vosoritide over almost 12 months in a real-world setting was consistent with that observed in clinical trials. Ongoing monitoring and data collection from this early access programme will be useful to establish the ongoing real-world safety and effectiveness of vosoritide. ▸ [P1-508]

PATIENT-REPORTED OUTCOMES

Individuals with achondroplasia experience medical, emotional, and functional detriments during their lifetime. However, there are currently no validated achondroplasia-specific patient- or clinician-reported outcome measures.

In a session on growth and syndromes, Mathias *et al.* shared results of a detailed review of generic PRO and CRO measures, work which was undertaken in order to select relevant tools for further evaluation in a qualitative study. Based on the available literature, five PROs and one CRO were selected for further analysis, looking at how well the concepts map to common symptoms such as pain, ear infections, and low stamina or tiring easily. The measures were also examined for their ability to capture important impacts of achondroplasia, such as difficulty reaching objects and toileting. Of the six tools analysed, the QoLISSY, PedsQL, Pain-NRS, and WeeFIM were identified for further evaluation in a qualitative study of children with achondroplasia and their parents. ▸ [P1-118]

Results from the group's qualitative analysis were also shared at the meeting in a second poster. This research and mapping exercise combined concept elicitation and cognitive debriefing interviews in 26 participants via an online system that allowed screen sharing. Data from the interviews were used to map important concepts to the QoLISSY, PedsQL, Pain-NRS, and WeeFIM measures. The findings showed that pain was the most common symptom for both children and their parents (88%/83%), followed by feeling hot or sweaty (88%/78%). Overall, 50% of both children and parents reported difficulties with concentrating and remembering. Other common complications included sleep apnoea (13%/50%), speech issues (63%/50%), ear infections (50%/78%), and balance problems (75%/56%). The most common impacts were difficulty reaching objects (88%/78%), toileting (25%/63%) and bathing (38%/56%). Mapping confirmed that the QoLISSY, PedsQL, Pain-NRS, and WeeFIM tools cover the most important concepts. WeeFIM – the only CRO examined – contains important concepts not included in the three PROs such as difficulty bathing, dressing, and toileting. All participants said that PedsQL and QoLISSY were easy to complete, and over 90% thought that the items were relevant. Although the PedsQL was considered by 67% of respondents to be easier to understand, 61% said the content of the QoLISSY was more relevant. Most participants (79%) recommended inclusion of both measures. Pain-NRS was considered clear (88%), relevant (88%), and easy to complete (81%). The authors conclude that this comprehensive assessment provides important information on achondroplasia-related medical challenges and impacts from the perspective of both the child and the parent. Results suggest the PedsQL, QoLISSY, and Pain-NRS – in conjunction with the clinician-administered WeeFIM – map well to important concepts identified during interviews, and all measures were clear, relevant and content valid to children and parents of children with achondroplasia. ▸ [P1-327]

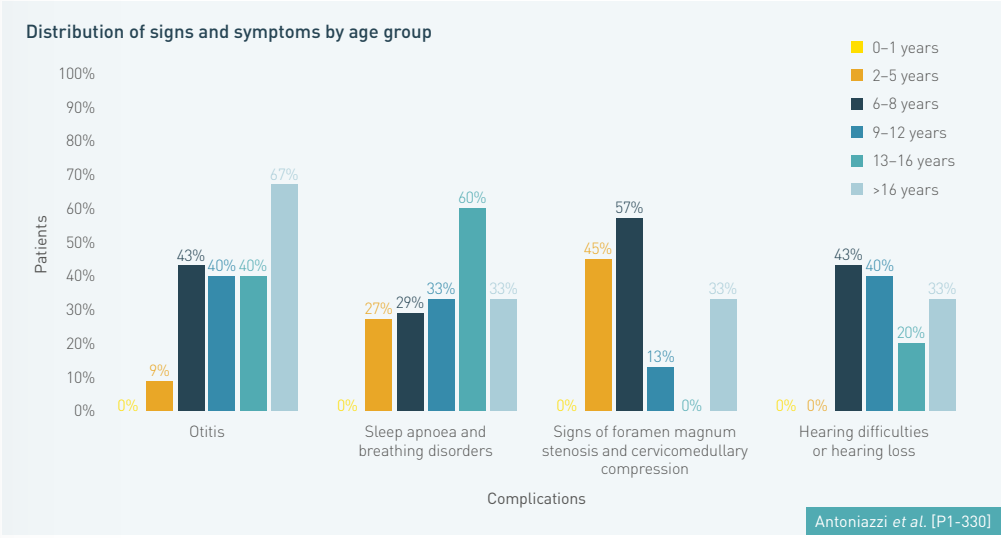
COMPLICATIONS & NATURAL HISTORY

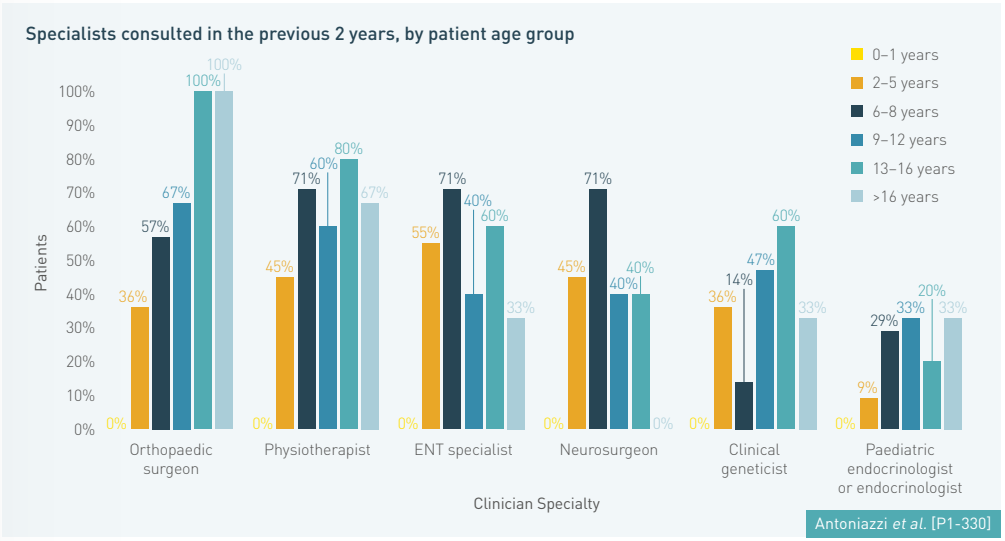
Achondroplasia is associated with a variety of complications across the lifespan. Understanding these is important to provide holistic care and management.

Despite a European consensus on principles for the management of achondroplasia providing a basis for optimal care, differences in clinical approach still exist – not only between countries, but also within local and regional contexts. As for other rare diseases, data and literature supporting best management practices in achondroplasia are often limited, specifically at the single country level. Antoniazzi *et al.* structured two online-surveys for 493 clinicians and 42 parents/caregivers of patients with achondroplasia. Overall, 39% of parents/caregivers reported the greatest impact of achondroplasia-related complications was during the ages of 2–5 years. The routine care provided to subjects with significant complications was performed by the reference centre in two-thirds of cases, with others receiving routine care by a specialist near their place of residence. The frequency of reference centre visits differed by patient age, and around 40% of subjects were required to travel a considerable distance (over 200 km) to access routine care, which may represent a barrier to adequate management. The results revealed agreement between the two groups on the need for improvement in a number of areas, such as reinforcing psychological support, more structured multidisciplinary teams, and for better follow-up and transition to adult care. Clinicians also highlighted the need for more active involvement of territorial services throughout the patient journey, while patients recognised issues in terms of access to care.

The project provides important insight into the real-world management of achondroplasia in Italy for the first time, and has the potential to help improve patient management and patient outcomes in this condition. ▸[P1-330]

Cebeci *et al.* presented a case report on SIADH as a presenting feature of foramen magnum stenosis – a severe complication in infancy that can be associated with cervicomedullary compression and sudden death. A 2-month-old boy with prenatally diagnosed achondroplasia was referred due to disordered breathing and altered consciousness. On physical examination, the patient was apathic, pale, hypotonic, and hypothermic, with typical features of achondroplasia. Shallow breathing with nasal flaring and suprasternal retractions and deep sighing was compatible with central apnoea, and blood gas analysis revealed respiratory acidosis. The patient was intubated, and laboratory investigations revealed severe hyponatremia and hypochloridaemia with normal glucose and urea levels, but high urinary sodium-output. The diagnosis of SIADH was made based on low serum osmolality in the presence of high urine osmolality and treatment was started. An emergency CT showed a high-grade stenosis at the cranio-cervical junction, and subsequent MRI demonstrated myelocompression (AFMS 4b). The patient underwent decompression surgery the next day. Prompt improvement of laboratory



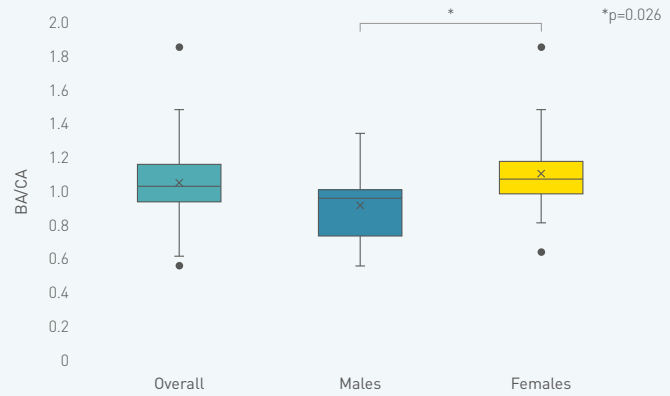


parameters was observed after operation. Spontaneous breathing after extubation was sufficient; however, only reduced spontaneous motor activity of the extremities was observed in the course, assumed due to a high-level spinal injury. This case highlights the need for clinicians to be aware of SIADH as a presenting sign of foramen magnum stenosis in children with achondroplasia. Other symptoms include feeding difficulties, respiratory distress, seizures, apnoea, and movement asymmetry. Further discussion is

needed regarding improved family education and timing of screening and neuroimaging recommendations, especially in children who did not receive polysomnography. ▸[P1-24]

Bone age is commonly used in paediatrics to define skeletal maturity for medical and non-medical purposes. Normal range is represented by 2 SDs above and below the mean. However, bone age in achondroplasia has not been fully characterised, and calculation is challenging. Previous publications have described delays in bone age in children with achondroplasia; one study showed a delay of 1.4 years for males and 1.2 years for females. In this poster, Savarirayan *et al.* described bone age at baseline in a group of children participating in PROPEL2 – a Phase 2 dose-finding study evaluating the preliminary safety and efficacy of infigratinib in achondroplasia. Left-hand radiographs from 37 children were evaluated for bone age by a single reader. Bone age in relation to chronological age was expressed as BA/CA, BA-CA overall, and by sex. Results showed mean bone age was 8.2 (P=0.1 versus chronological age). BA/CA was 1.06, and BA-CA was 0.37 years. Mean BA/CA was 1.12 in females and 0.93 in males, a statistically significant difference (P=0.026). Overall, 6 children (16.2%; 5 female, 1 male) had bone age greater than +2 SDs for age and sex, indicating an advanced bone age compared with chronological age. In contrast, 4 children (10.8%; 1 female, 3 male) had delayed bone age compared with chronological age. The group concluded that this analysis did not confirm any delay in bone age in pre-pubertal children with achondroplasia. Bone age in females was more advanced than in males, but within the expected variability for the age group. This work suggests that bone age estimation in children with achondroplasia can be employed for the same purposes as in children without skeletal dysplasia. ▸[P1-306]

BA/CA in participants



The lower and upper bounds of the rectangles represent the first and third quartiles, the horizontal line represents the median, the whiskers extend to the highest and lowest values within 1.5-times the interquartile range, and data beyond the end of the whiskers are outliers and are plotted as points. The X represents the mean.

Savarirayan *et al.* [P1-306]

GENE SEQUENCING

Most children with short stature remain without an etiologic diagnosis after extensive clinical and laboratory evaluation and are classified as idiopathic short stature.

Andrade *et al.* set out to determine the diagnostic yield of a multigene gene analysis in 102 children classified as having idiopathic short stature. Customised target panel sequencing was developed, including all genes already implicated in isolated short stature phenotypes. Rare and deleterious single nucleotide or copy number variants were assessed by bioinformatic tools. Findings identified 20 heterozygous pathogenic (P) or likely pathogenic (LP) genetic variants in 17 patients (diagnostic yield: 16.7%). Three patients had more than one P/LP genetic alteration. Most of the findings were in genes associated with the growth plate development such as *IHH*, *SHOX*, *FGFR3*, *NPR2*, *ACAN*, and *COL2A1* – or those involved in the RAS/MAPK pathway. The diagnostic yield was higher among children with severe short stature (P=0.034), but there was no significant difference in the rate of positive genetic diagnosis observed regarding familial short stature (P=0.129), or presence of mild body disproportion (P=0.116). No patient had clinical findings to guide a candidate gene approach. The authors conclude that a multigene sequencing approach is able to determine a genetic aetiology of short stature in up to one in six children, therefore removing the term idiopathic from their clinical classification. These findings are important, since knowing the genetic basis of short stature can allow precise genetic counselling. This is particularly relevant for children harbouring variants in the RAS-MAPK pathway, and with the potential to trigger development of specific treatment protocols. ▸[P1-111]

EVOLVING MANAGEMENT

This BioMarin-sponsored symposium looked at the management of achondroplasia in the age of precision therapies. The session was chaired by Professor Mohamad Maghnie.

Dr Melita Irving opened the session with updates from the vosoritide clinical programme. Vosoritide is a targeted therapy for achondroplasia, which works to counteract the effects of constitutively active FGFR3, enhancing endochondral bone growth.[1] It was approved in Europe in August 2021 for patients at least 2 years of age whose epiphyses are not closed.[2]

There was a significant cumulative height gain versus natural history controls over 5 years in the Phase 2 study, with a cumulative additional height gain over untreated patients of +9.08 cm.[2] Significant cumulative height gain was also seen in Phase 3, with +3.34 gain over 2 years, alongside significantly increased AGV and improvements in height Z-scores.[2–4] Emerging clinical trial data in younger patients show a comparable impact of vosoritide treatment on height Z-scores for patients ≥2 to <5 years of age.[5]

The Phase 3 study showed a generally good tolerability, with comparable incidence of side effects versus placebo and consistent results with Year 1 and 2. The most common adverse reactions to vosoritide were injection-site reactions.[2–4]

The vosoritide clinical trials (111-202/205, 111-301/302, and 111-206) have shown a consistent safety profile, with comparable incidence of side effects versus placebo across ages in patients with achondroplasia aged ≥2 years whose epiphyses are not closed.[3–6]

Professor Valérie Cormier-Daire and Professor Klaus Mohnike presented early clinical experience with vosoritide in real-world clinical practice. First, Professor Cormier-Daire covered the data from France, where an early use cohort has been in place since June 2021; these patients transitioned to an Approved Authorized Early Access 2 programme in December 2021. Patients ≥5 years with open epiphyses were prioritised for inclusion. As of August 2022, 48 patients from 6 centres have been enrolled, and 46 have initiated vosoritide – with a cumulative exposure of 9,334 days. Overall, the safety profile over almost 12 months was consistent with that observed in clinical trials.[3,4,6]

France: Early use cohort safety data

	n (%) patients (N=46)	Total number of AEs
Any AE	9 (19.6%)	17
Injection site reactions	8 (17.4%)	15
Skin and subcutaneous tissue disorders	1 (2.2%)	1
Gastrointestinal disorders	1 (2.2%)	1

Cormier-Daire V *et al.* [P1-508]

Finally, Professor Mohnike gave an overview of the early experience in Germany, Austria, and Portugal – where there has been collaboration between centres to collect epidemiological data characterising the current practice of multidisciplinary treatment. Overall, 15 different institutions reported medical and auxological data that were obtained routinely as standard of care, and 210 children with achondroplasia aged <17 years were included in the analysis. Since October 2021, 118 of these patients received vosoritide, which allowed comparison of treated and untreated patients. So far, all patients have continued on treatment, and no significant AEs have been reported. Future analyses will look at effectiveness measures, including AGV and change in Z-score. Ongoing collection of data

Vosoritide clinical trial programme across different ages[7–16]

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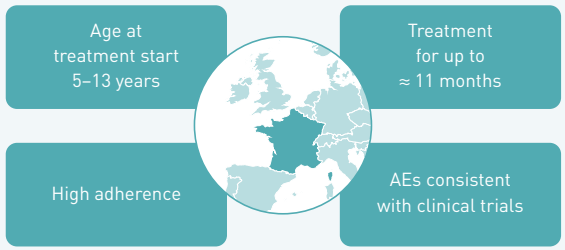
Key takeaways: Early experience with vosoritide

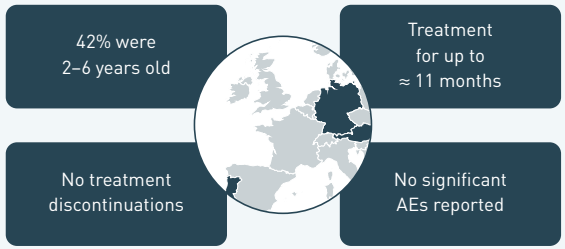
46 patients

are currently being treated with vosoritide in real life clinical practice in France since 27 September 2021, in the framework of the ATU



118 patients

are currently being treated with vosoritide in Germany, Austria and Portugal in real life clinical practice, according to EMA indication



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from clinical practice is key to establish long-term safety and effectiveness of vosoritide in the real world, and sharing these early experiences with vosoritide is essential for best practice evaluation and developing standards and guidelines for patient care.

These early experiences highlight some common practices that are essential for successful therapy initiation. From a patient and family perspective, there is a need to establish readiness of treatment, and to ensure an appropriate level of caregiver information and training, with readily available support from the healthcare team. Alongside this, there is a need to ensure site preparation, with a well-connected multidisciplinary team, regular routine follow-ups, and well-planned logistics and storage arrangements for pharmacies and families.

LIST OF ABBREVIATIONS

AFMS – achondroplasia foramen magnum score
AGV – annualised growth velocity
cGMP – cyclic guanosine monophosphate
CRO – clinician-reported outcome
CT – computed tomography
ENT – ear, nose, and throat
ERK1 – extracellular signal-regulated kinase 1
EMA – European Medicines Agency
FGFR3 – fibroblast growth factor receptor 3
MAPK – mitogen-activated protein kinase
MRI – magnetic resonance imaging
Pain-NRS – pain numeric rating scale
PedsQL – Pediatric Quality of Life Inventory
PRO – patient-reported outcome
QoLISSY Brief – Quality of Life in Short Stature Youth
SD – standard deviation
SIADH – syndrome of inappropriate antidiuretic hormone secretion
WeeFIM – Pediatric Functional Independence Measure

REFERENCES

1. Lorget F, *et al.* Am J Hum Genet 2012; 91:1108–14.
2. VOXZOGO® (vosoritide) Summary of Product Characteristics.
3. Savarirayan R, *et al.* Lancet 2020;396:684–92.
4. Savarirayan R, *et al.* Genet Med 2021; 23:2443–7.
5. Savarirayan R, *et al.* Poster presented at ENDO 2022.
6. Savarirayan R, *et al.* N Engl J Med 2019; 381:25–35
7. https://clinicaltrials.gov NCT01603095
8. https://clinicaltrials.gov NCT02055157
9. https://clinicaltrials.gov NCT02724228
10. https://clinicaltrials.gov NCT03197766
11. https://clinicaltrials.gov NCT03424018
12. https://clinicaltrials.gov NCT03583697
13. https://clinicaltrials.gov NCT03989947
14. https://clinicaltrials.gov NCT04554940
15. https://clinicaltrials.gov NCT03872531 (LISA)
16. https://clinicaltrials.gov NCT03449368 (LIAISE)