# ACHONDROPLASIA.EXPERT CONGRESS REVIEWS ESPE 2024

## Welcome to the ESPE 2024 congress review

The 62nd Annual Meeting of the European Society for Paediatric Endocrinology (ESPE) took place in Liverpool, UK, from 16th–18th November 2024. The event brought together leading experts in paediatric endocrinology to exchange knowledge and advance the care of children with various endocrine disorders, including achondroplasia (ACH). As the understanding and treatment of ACH continues to evolve, addressing the complex needs of patients remains a key priority.

This congress review highlights recent advancements and ongoing research in the treatment of ACH, with presentations, symposia, abstracts, and posters from this year's congress. Topics include real-world vosoritide▼ data, emerging therapeutic options, bone and body composition, and the impact of healthcare resources and current outcome measures on patient monitoring.

We hope this review provides valuable insights into how the ACH community can contribute to addressing the global challenges in the management of this rare genetic condition.

*The Achondroplasia Team*

**MORE INSIDE ...** Symposia and panel discussions ▶ PAGE 12

### REAL-WORLD DATA ON VOSORITIDE▼

Including multiple single-centre studies from various global regions

▶ FIND OUT MORE

### EMERGING THERAPIES FOR CHILDREN WITH ACH

Explore the latest infigratinib data from PROPEL-2

▶ FIND OUT MORE

### UPDATES IN PATIENT MANAGEMENT

Gain insight into the impact of ACH on healthcare resources

▶ FIND OUT MORE

Abstracts can be found here

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Treatments mentioned in this document may not be approved for use in your country. Please consult local licensing authorities for further information.

VOXZOGO® is a C-type natriuretic peptide (CNP) analogue indicated to increase linear growth in paediatric patients with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualised growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). The latest API for VOXZOGO® can be found on the achondroplasia.expert website, under the Prescribing Information tab. Or click here.

Some links in this document are "external links" to websites over which BioMarin has no control and for which BioMarin assumes no responsibility. When visitors choose to follow a link to any external website, they are subject to the cookie, privacy, and legal policies of the external website. Compliance with applicable data protection and accessibility requirements of external websites linked to from this website falls outside the control of BioMarin and is the explicit responsibility of the external website.

For healthcare professionals only. Achondroplasia.expert is organised and funded by BioMarin.

BIOMARIN


Developed and funded by BioMarin. EUCAN-VOX-00806 12/24

Achondroplasia .expert

# LATEST REAL-WORLD DATA ON VOSORITIDE

**Vosoritide is a C-type natriuretic peptide (CNP) analogue indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.[1] The following presentations and posters highlighted the latest real-world data for vosoritide and compared the results to clinical trial data.**

The CrescNet registry is a European initiative that tracks the growth and development of children with ACH. Mohnike *et al.* utilised CrescNet to gather detailed data on clinical outcomes including growth measurements, medical complications, treatments, and quality-of-life assessments in children with ACH.

Across the ACH module, 480 individuals with ACH were included in the registry from 30 centres across eight European countries, with the majority residing in Germany. Of those enrolled, 236 were treated with vosoritide only and 19 received vosoritide alongside limb lengthening procedures. The mean (SD) age at treatment start in the vosoritide-only group was 6.02 (3.63) years and 52% were male. The mean (SD) observation period was 6.56 (4.16) years, average (SD) height Z-score was 0.08 (1.12), and average (SD) arm span Z-score was -0.09 (1.05).

Among participants who received vosoritide for 12 months (n=143), there was a mean (SD) height increase of 6.36 (2.13) cm, with a modest Z-score improvement of 0.7 (1.13). Among participants treated for 24 months (n=73, 41 males, 32 females), the height increase was 11.86 (2.45) cm, with a Z-score improvement of 1.15 (1.15). These real-world results align with findings from clinical trials,[2–4] demonstrating the potential of vosoritide to improve growth outcomes in children with ACH. It should be noted that there is no data currently available on the effects of vosoritide treatment in combination with limb lengthening procedures. CrescNet's expansion to more European countries will provide a broader understanding of the ACH population as well as the impact of vosoritide in a real-world setting. ▶[FC2.6]

Cormier-Daire *et al.* assessed the real-world effectiveness of vosoritide in children with achondroplasia using 18-month follow-up data from an early access (EA) cohort in France. Annualised growth velocity (AGV) was calculated and effectiveness parameters of mean height, Z-score, and ACH Z-score were collected.

Within the EA program, vosoritide was initiated in ACH patients aged ≥5 years (mean 8.6 [5–13]) with open epiphyses, who were followed up at Months 1, 3, 6, and every 6 months thereafter. In total, 62 patients were enrolled, of which 57 started vosoritide within the EA program and 16 completed a mean of ≥18 (SD 1) months of treatment with a mean exposure of 18.34 (SD 1.06) months. The key findings are summarised in the table below; female patients showed greater improvements in all parameters compared with males.

**Change in height-related measurements after ≥18±1 months vosoritide treatment**

| Parameter Mean (SD) | Overall (N=16) | Males (n=4) | Females (n=12) |
|---|---|---|---|
| Age at treatment initiation, years | 9.52 (1.48) | 8.84 (1.49) | 9.75 (1.47) |
| Height increase from baseline, cm | 8.84 (1.53) | 7.50 (1.37) | 9.28 (1.34) |
| CDC Z-score improvement from baseline | 0.43 (0.57) | 0.38 (0.34) | 0.45 (0.63) |
| ACH Z-score improvement from baseline | 0.56 (0.28) | 0.30 (0.30) | 0.64 (0.23) |
| AGV, cm/year | 5.76 (1.07) | 4.94 (0.93) | 6.03 (1.0) |

Cormier-Daire *et al.* [P2-56]

AGV is defined as (change in height between baseline and final visit)/(time between visits)*365.25.

Figure reproduced with permission from Professor Valérie Cormier-Daire

The authors reported that vosoritide treatment in real-world conditions showed continued effectiveness after approximately 18 months. Further data on the long-term effectiveness and safety of vosoritide for these patients will continue through ongoing studies such as ACORN,[5] a European post-authorisation safety study. ▶[P2-56]

Based on data in the CrescNet registry from 28 European centres, Wechsung *et al.* reported changes in height and weight (n=217, 104 females) and sitting height:height ratio (n=119, 56 females) after 2 years of vosoritide treatment. SDS values were calculated using the Lambda Mu and Sigma (LMS) method with ACH-specific reference data,[6] and treatment response was defined according to Δheight SDS: no (<0.0), moderate (0.0–0.5), and good (>0.5) response. Linear models for Δheight SDS and Δsitting height ratio from baseline were derived.

Mean (SD) age at baseline (n=217) was 6.02 (3.63) years; 44% of participants were aged 0–5 years, 25% 5–8 years, and 31% >8 years. Of those completing 1 year of vosoritide treatment (n=143), 9.2%, 49%, and 42% displayed a non, moderate, and good response, respectively. At Year 2 (n=73), 4.3%, 19%, and 77% of patients displayed a non, moderate, and good response, respectively. Linear models highlighted multiple factors with a positive influence on treatment response (p<0.001): treatment duration (p=0.243); baseline age and male sex (aged 0–5 years, p=0.208; aged 5–8 years, p=0.125; aged >8 years, p=0.174); sitting height:height ratio >p75 (p=0.114).

The majority of children treated with vosoritide responded well to treatment, and young age at baseline, male sex, and sitting height ratio SDS positively correlated with growth. ▶[T20]

Further data on real-world experiences of vosoritide therapy in children with ACH was presented in a prospective study by Kahveci *et al,* who assessed changes in annual growth rate and anthropometric parameters as primary outcomes. Patients with ACH (N=14, 8 males, mean (SD) age of 7.98 (3.94) years) were treated with vosoritide

at a dose of 15 µg/kg once daily (QD) for a median [range] duration of 0.76 [0–1.31] years. A total of eight patients completed 9 months of treatment, and 11 completed 6 months. A statistically significant improvement in AGV SDS was reported, with median [range] AGV-SDS changing from -1.92 [-3.87–0.36] pre-treatment to -0.68 [-2.17–0.98] post-treatment (p=0.0029). No significant difference in upper/lower segment SDS and arm span-height was observed, suggesting that vosoritide-induced growth was proportional and maintained the typical body proportions for children with ACH. ▸[P1-265]

Real-world data on the use of vosoritide in the Middle east and North Africa (MENA) was presented by Amin *et al.* in a single-centre experience assessing safety, efficacy, and practical considerations. The study enrolled 11 participants aged 1.6–14 years, with genetically confirmed ACH, to receive vosoritide (15 µg/kg subcutaneous QD), with follow-up visits at Months 1, 3, and 6, and every 6 months thereafter. The follow-up interval was increased to every 3 months for better monitoring of primary outcomes, including height and growth velocity change from baseline, as well as observation of side effects.

Preliminary statistical analysis (9/11 patients) showed a significant effect of vosoritide on height increase (p=0.040); two patients were excluded due to short treatment duration (2 months). AGV increased by an average [range] of 2.5 [1–5] cm/year from baseline. Compliance significantly impacted growth velocity results, with the prevalence of non-compliance being attributed to the burden of daily injections. Although all patients experienced self-limiting side effects such as injection site redness, no serious adverse events (SAEs) were noted. ▸[P2-37]

A prospective observational study from Leonardi *et al.* investigated vosoritide 15 µg/kg subcutaneous QD in children with ACH up to 15 months (N=12), comparing auxological parameters of total height, sitting height, arm span, and growth velocity to baseline values.

Preliminary results showed a significant increase in growth velocity compared to baseline (average increase of 81% at Month 3; 76% at Month 6; 71% at Month 9; 83% at Month 12; 87% at Month 15). Height Z-scores improved at all time points, with a significant improvement at Month 12 (-4.17 SDS; p>0.05), however, the most statistically significant increase was observed at Month 6 (p<0.001). Sitting height and arm span showed improvements at 6 months (increase of 3.4%, and 5.5% respectively) and observed growth was proportional. Vosoritide displayed a good safety profile with no SAEs or significant changes in laboratory parameters. High treatment compliance and good treatment experience were indicated via a caregiver questionnaire, with the majority reporting positive impacts on the child's quality of life (QoL) and 89% of responders reporting no missed doses. The authors suggest early and prolonged treatment intervention with vosoritide may enhance skeletal growth and overall clinical outcomes. ▸[P1-264]

Adachi *et al.* retrospectively evaluated the efficacy and safety of vosoritide in 16 children with ACH over 16 months of treatment at Tokyo University Hospital, Japan. The median [range] age at treatment initiation was 29 [1–106] months, and patients were prepubertal. Three patients switched from growth hormone (GH) therapy to vosoritide, and four patients were postoperative for foramen magnum stenosis (FMS) or hydrocephalus.

Height SD (n=13) and AGV SD (n=10) were calculated for patients treated with vosoritide for ≥6 months, based on previously reported ACH patient data. Height SD values and arm span:height ratio improved during the treatment period, however values for AGV and upper:lower body segment ratio showed no significant improvement.

Of patients with reduced AGV SD (n=5), three switched from GH therapy and two had previous surgery. One patient discontinued vosoritide due to compensated shock following their first dose. Non-mild side effects were observed in four patients and presented within 30 minutes of administration; compensated shock (3-month-old, leading to discontinuation of vosoritide), pallor and vomiting (3-month-old), pallor of the face (~6-year-old), and vomiting after influenza (5-year-old). These newly reported improvements in arm span:height ratio with vosoritide contribute toward further understanding the benefits of this therapy. ▸[P1-18]

In a single-centre retrospective study Abali *et al.* assessed growth response to vosoritide in children with ACH who were monitored by a specialised multidisciplinary team (MDT) in Turkey. Participants visited the MDT every 3 months for monitoring of QoL, comorbidities, anthropometric measurements, body proportions, and AEs.

Of participants with >0.25 Z-score gain/year (n=13, 61.5% female), the mean (SD) age at treatment onset was 5.8 (3.0) years and 100% were at Tanner stage 1. Mean height Z-score was -5.1 (0.8) and BMI Z-score at onset was 1.8 (0.9). Among patients who completed 6 months treatment (n=22), mean (SD) [range] AGV was 6.3 (2.2) [2.5–10.8] cm, with a median height gain of +0.28 SDS. At Month 12 (n=14), median growth velocity was 5.5 (1.2) [3.7–7.8] cm/year, median height gain was +0.20 SDS/year. No SAEs or treatment-emergent adverse events (TEAEs) were observed in any of the patients. ▸[P2-51]

# ESTABLISHED, EMERGING, AND NOVEL THERAPEUTIC OPTIONS FOR THE TREATMENT OF ACH

**Vosoritide is the only commercially available medical therapy for the treatment of achondroplasia. The following presentations and posters highlighted some of the latest vosoritide data alongside new and emerging therapies, which may further expand the treatment options available for the management of ACH.**

Angelelli *et al.* longitudinally assessed body composition and bone markers in children with ACH during treatment with vosoritide. Patients (N=29, 15 females) were evaluated over 12 months using dual-energy x-ray absorptiometry (DXA), measuring a range of parameters including lumbar spine (LS) and total body less head (TBLH) measurements of bone mineral content and density (BMC, BMD), as well as bone mineral apparent density (BMAD). Pubertal status based on Tanner staging, bone alkaline phosphatase (bALP), and C-terminal telopeptide (CTx) were measured at each time point.

The median (range) age at baseline was 8.7 years (6.4–10.1). At baseline, five patients (three female) were pubertal; seven (five female) had entered puberty by Month 12. Height SDS increased (p=0.016), while weight stayed relatively unchanged by Month 12 (p=0.022). Height SDS increased comparably in males and prepubertal females, whereas weight SDS increased only in prepubertal males (p=0.015). Bone parameters at the TBLH site improved, (BMD-TBLH at baseline (n=28): 0.48 [0.43–0.56] g/cm$^2$; at Month 6 (n=25): 0.50 [0.43–0.54] g/cm$^2$; at Month 12 (n=28): 0.54 [0.47–0.60] g/cm$^2$; p<0.0001), whereas those at the LS site remained relatively stable (BMD-LS at baseline (n=28): 0.56 [0.52–0.63] g/cm$^2$; at Month 6 (n=25): 0.56 [0.51–0.61] g/cm$^2$; at Month 12 (n=28): 0.64 [0.56–0.68] g/cm$^2$; p<0.0001). Total body fat increased, while fat-free mass decreased.

Overall, an increase in bALP was observed (p=0.002) and CTx increased specifically in the acute phase but decreased after 12 months. These preliminary data show that vosoritide treatment is associated with increased TBLH and LS bone densitometric DXA parameters in children with ACH. ▸ [RFC2.1]

Infigratinib is a fibroblast growth factor receptor 3 (FGFR3) inhibitor currently under development as a treatment option for children with ACH, designed to target overactive FGFR3 signalling. Irving *et al.* reported improved body proportionality, with 18-month results from the Phase 2 PROPEL-2 study. The study consisted of a dose-escalation phase (five ascending dose cohorts, 0.016 mg/kg QD to 0.25 mg/kg QD), followed by a 12-month extended treatment period. Safety was assessed across all cohorts, and annualised height velocity (AHV), height Z-score and body proportion ratio were analysed up to 18 months. Efficacy results were presented for Cohort 5 (0.25 mg/kg QD).

Of the children enrolled, (N=72, 58.3% female, mean age (SD) [range] of 7.5 (2.2) [3.1–11.5] years), 67 completed 18 months of treatment. The most common TEAEs were infections and infestations; all children experienced ≥1 TEAE, none experienced ocular or hyperphosphatemic events, and no SAEs or TEAEs led to treatment discontinuation. Cohort 5 showed a statistically significant increase in AHV; (mean (SD)) at Month 6 (+3.38 (2.70) cm/year, p=0.0012, n=12), Month 12 (+2.51 (2.21) cm/year, p=0.0037, n=11), and Month 18 (+2.50 (1.91) cm/year, p=0.0015, n=11). In children with positive AHV changes from baseline at Month 18 (10/11), 73% experienced an AHV increase of >25%. Month 18 mean (SD) change from baseline in height Z-score was +0.54 (0.28) (p<0.0001), relative to an untreated ACH population. Infigratinib was well tolerated and a statistically significant improvement in upper:lower body segment ratio was observed, with a mean (SD) change from baseline of -0.12 (0.09) (p=0.0012) at Month 18. Further safety and efficacy of infigratinib 0.25 mg/kg QD will be evaluated in the Phase 3 PROPEL-3 study. ▸ [FC15.4]

Han *et al.* presented promising selectivity and efficacy of the preclinical FGFR3 inhibitor GSC000829 as a potential oral treatment for ACH in a preclinical murine model. The pharmacology of GSC000829 was characterised, and a strong inhibition towards FGFR3 and significantly improved selectivity over FGFR1 and FGFR4 was observed. The authors identified an improved safety window compared with other pan-FGFR inhibitors using toxicology studies. *Ex vivo*, GSC000829 effectively reversed FGF-induced femur growth arrest and promoted chondrocyte development.

FGFR3-mutated mice with ACH treated with GSC000829 for 14 days demonstrated significant elongation in overall body length and an improvement in growth plate architecture alongside favourable physicochemical and pharmacokinetic properties and preclinical toxicity profile. This therapy is currently undergoing investigational new drug (IND)-enabling studies and is scheduled to enter clinical development early in 2025. ▸ [FC2.1]

# FACTORS AFFECTING THE MANAGEMENT OF PATIENTS WITH ACH

## The treatment of ACH requires multidisciplinary care. However, many healthcare models are fragmented and make comprehensive patient monitoring difficult. These sessions revealed the scope of this issue and highlighted ongoing work in addressing patient management.

The VISTA study from Pimenta *et al.* aimed to comprehensively monitor real-world treatment outcomes for individuals with ACH using a patient-centred, virtual, and decentralised approach. To overcome the limited data source provided by United States (US) electronic health records (EHRs) VISTA collected data directly from patients, both untreated and treated with vosoritide, to evaluate the real-world effectiveness of the therapy.

From February 2023 to January 2024 20 children with ACH (50% males, median age 4.2 years) were enrolled through the PicnicHealth digital platform, which aggregates EHR data from various healthcare providers. Of those enrolled, 55% received vosoritide treatment. Data was available for all domains of interest including comorbidities, surgeries, and anthropometric measures. The median rate of standing height measurements

**EAF survey responses: Physical measures**

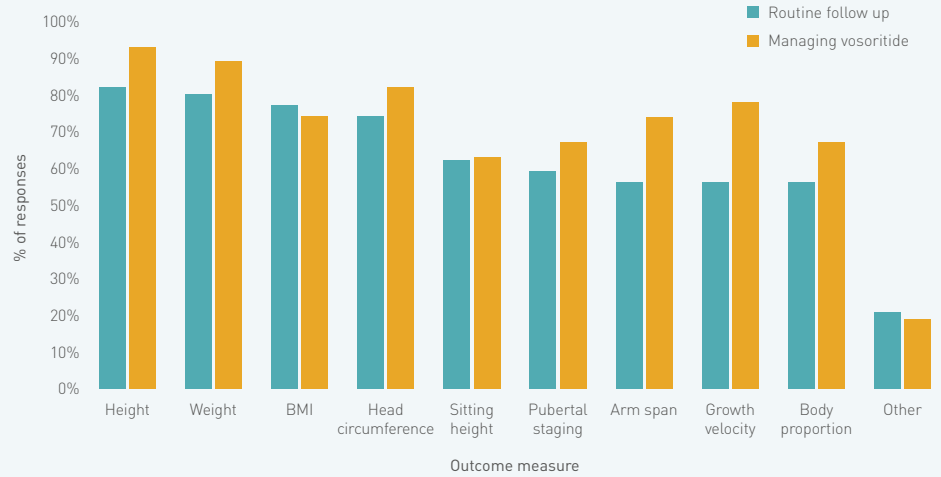


Figure reproduced with permission from Dr Melita Irving.

Irving *et al.* [P2-172]

**EAF survey responses: Medical history**

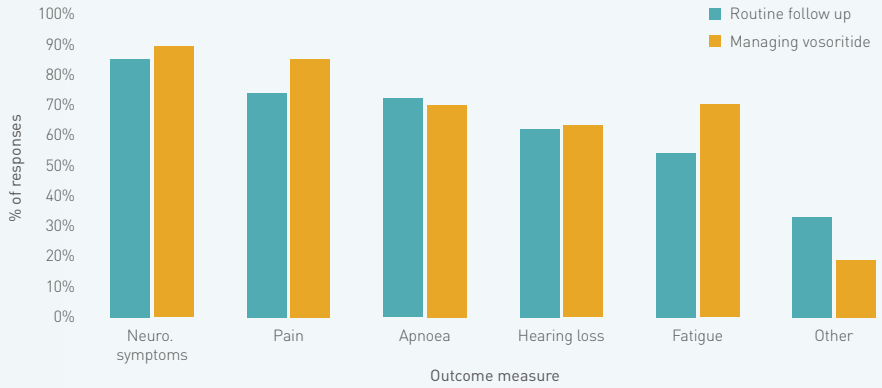


Figure reproduced with permission from Dr Melita Irving.

Irving *et al.* [P2-172]

**EAF survey responses: Quality of life**


Figure reproduced with permission from Dr Melita Irving.

Irving *et al.* [P2-172]

was six measurements per year. Most participants (90%) completed questionnaires on medication adherence and clinical trial participation, while patient-reported outcomes measurement information (PROMIS) and paediatric quality of life (PedsQL) assessments were completed by a majority of parents and eligible children.

The pilot phase highlighted that each child had a median of 22 healthcare providers from eight different care sites, with a median of 5.8 visits per year. The most common specialists visited were geneticists (95%), paediatric orthopaedists (90%), and otolaryngologists (75%). Adherence to vosoritide was high, with 82% of treated

participants reporting no missed doses in the prior month. The results confirmed the feasibility and value of this patient-centred approach, providing insight into the healthcare resource use and treatment outcomes for individuals with ACH. As VISTA expands, it will continue to gather critical data on health-related quality of life (HRQoL), surgical interventions, and comorbidities. ▸ [P1-118]

Irving *et al.* reviewed existing health surveillance measures in a new era of ACH management, assessing both their applicability to clinical practice and the impact of targeted medical therapy. Health status monitoring was assessed via online questionnaire and focused on routine clinical practice and in determining response to vosoritide, the only currently licensed medical treatment for ACH. The questionnaire was distributed to European Achondroplasia Forum (EAF) registrants identified as healthcare professionals specialising in ACH, and the results were discussed in a 2024 online workshop.

The questionnaire was completed by 50 respondents, representing a range of specialities from 14 countries across Europe, Latin America, the Middle East, and the USA. Outcomes monitored in current practice as part of routine follow-up were overall similar to those used when monitoring children receiving vosoritide. Of respondents monitoring physical outcomes in children receiving vosoritide (n=29), 93% were monitoring height, 89% weight, 82% head circumference, 78% growth velocity, 74% arm span, 74% BMI, 67% pubertal staging, 67% body proportion, and 63% sitting height. Regarding medical history, 89% were monitoring neurological symptoms, 85% pain, 70% apnoea, 70% fatigue, and 63% hearing loss. QoL measures were also assessed; 78% were monitoring independence skills, 74% functionality, 63% psychosocial factors and 52% academic achievement. Overall, 27.5% (8/29) of respondents felt that current clinical measures were inadequate to capture response to vosoritide.

Of the survey respondents who were not monitoring children receiving vosoritide, 28% (11/39) responded that current measures did not accurately capture outcomes in routine practice, and 72% (28/39) were not contributing clinical data to a registry. The workshop was joined by 63 attendees (38 healthcare professionals, 19 industry representatives, and three patient advocacy group representatives) and highlighted the need for simplified and combined QoL measures for ongoing monitoring of response to condition-modifying treatments. A digital patient-reported outcome (PRO) tool was suggested to facilitate communication with a central registry, to address barriers to effective collection of health information in ACH. ▸ [P2-172]

Abraham *et al.* assessed the clinical and healthcare resource utilisation (HCRU) burden of ACH in children and adolescents (aged <18 years) from the USA. This retrospective study assessed patients with ≥1 inpatient claim, or ≥2 distinct claims in any other setting, with ACH International Classification of Diseases (ICD)-10 diagnosis codes in Optum's de-identified Clinformatics® Data Mart Database (01-Oct-2015 to 01-Oct-2023). All-cause HCRU (outpatient, emergency room (ER), inpatient, intensive care unit (ICU), and non-ICU inpatient visits) was assessed in ACH patients (N=241) and compared against controls (N=1205, matched 1:5 on age, sex, and index date). Adult cohort (≥18 years at index) results were included for comparison.

The mean (SD) age was 7.9 (5.4) years and 53.1% were female in both ACH and control cohorts; 54.4% and 48.2% were white, respectively. Mean (SD) follow-up was 40.3 (24.4) months in ACH patients vs 41.5 (24.0) months in controls and all paediatric patients were commercially insured. Follow-up skeletal comorbidity rate was significantly higher in ACH patients vs controls across multiple domains (62.7% vs 4.1%; p<0.01). HCRU encounters were higher in ACH patients vs controls (p<0.01), with more frequent outpatient visits (incidence rate ratio (IRR) [95% CI]: 2.10 [2.05–2.15]), ER visits (IRR [95% CI]: 1.47 [1.27–1.69]), inpatient admissions (IRR [95% CI]: 3.46 [2.94–4.08]), and pharmacy fills (IRR [95% CI]: 1.97 [1.91–2.02]). Results were similar when comparing adult ACH patients to controls.

Mean total healthcare costs were significantly higher in patients with ACH vs controls ($31,388 vs $4,164 per patient-year (PPY); p<0.01), primarily due to increased inpatient admission ($12,232 vs $1,170 PPY; p<0.01) and pharmacy costs ($8,452 vs $565 PPY; p<0.01). ACH incurs a substantial clinical and healthcare resource burden in children and adolescents receiving care in US clinical practice, and this burden remains considerable in adults. The impact of disease-modifying therapies on these outcomes remains to be determined. ▸ [P1-267]

To assess the scale of health and life risks associated with children with ACH, Wrobel *et al.* collected patient data (N=72) from nine paediatric endocrinology reference centres in Poland. Of the cases assessed, 100% presented with short stature, rhizomelia, lumbar hyperlordosis, kyphosis of the thoracolumbar junction and spinal stenosis (L1-L4 segments).

FMS was associated with neurological problems including hydrocephalus and spinal canal stenosis, resulting in nerve compression, cervical myelopathy, and brainstem compression which can cause breathing difficulties such as central sleep apnoea; consequently increasing the risk of sudden death. Patients with ACH were found to be predisposed to obesity and impaired middle ear function. The proportion of patients with bone and neurological defects as well as ear, nose, and throat (ENT) complications were recorded. The percentage of patients with FMS, hydrocephalus, and spinal stenosis confirmed by magnetic resonance imaging (MRI) and/or computed tomography (CT) was 11%, 17%, and 3%, respectively. For ENT complications, obstructive sleep apnoea (15.3%), respiratory infections requiring hospitalisation (23.6%), non-invasive ventilation (4.2%), recurrent middle ear infections (29.2%), conditions after adenoidectomy/tonsillectomy (23.6%), and myringotomy (11.1%) were reported.

The authors concluded that many children with achondroplasia are underdiagnosed, and emphasised the importance of careful observation, diagnosis and treatment with vosoritide according to existing guidelines. ▸ [P1-255]

FMS is a severe complication of ACH in infants and young children. It can be asymptomatic or can cause cervical-medullary compression (CMC), with patients experiencing hydrocephalus, hypotonia or hypertonia, central sleep apnoea, or sudden death. Hatziagapiou *et al.* retrospectively assessed craniovertebral junction (CVJ) abnormalities using achondroplasia foramen magnum score (AFMS) with MRI scans, as well as sleep-disordered breathing using cardiorespiratory sleep studies (CRS) in patients with ACH.

Of the patients assessed (N=10, 7 males, 3 females), the age at first appointment was between 40 days and 14.5 years. ACH was caused by a *de novo* FGFR3 p.Gly380Arg (c.1138G>A) gain-of-function variant in 80% of individuals; the remaining 20% were two siblings who inherited the same p.Gly380Arg variant from their affected mother. The mean (SD) age at first brain and cervical spine MRI was 3.32 (2.65) years, and mean (SD) age at FMS diagnosis was 4.66 (3.31) years. Three patients were categorised AFMS3 with cord compression (mean age 2.53 ± 0.8 years) which was associated with mild apnoea-hypopnea (2.2–3.3 episodes/hour), and one patient was diagnosed with AFMS4 at the age of 14.58 years. AFMS3/4 were associated with abnormal speech and gross motor developmental milestones. AFMS0 was associated with normal CRS results; one infant (aged 7 months) exhibited mild apnoea-hypopnea (1.7 episodes/hour). AFMS0/1 was not strongly associated with developmental milestones. Snoring or sleep apnoea were subjectively reported in six patients, and CRS screening revealed abnormal breathing during sleep in four patients. The authors concluded that clinical manifestations of FMS severity do not necessarily correlate with AFMS. Early MRI surveillance should be included in ACH follow-up as patients could benefit from early intervention such as cervicomedullary decompression. ▸ [P1-266]

# SYMPOSIA AND PANEL DISCUSSIONS

## Industry-sponsored symposia and panel discussions brought together experts to explore the evolving landscape of ACH management.

In the *Future hope for skeletal disorders* symposium, Svein Fredwall outlined the health risks associated with ACH and provided an update on the current international and European consensus recommendations for follow-up and management.

In infants, the most severe medical complications are FMS which can compress the cervical cord and lead to neurological issues or sudden death (decompression surgery in ~20% of patients), central and obstructive sleep apnoea (50–70% of patients), and thoracolumbar kyphosis (10–15% of patients). The AFMS score has been devised to classify patients from minor FMS (AFMS0/1) to those requiring neurological decompression surgery (AFMS4, ~20% of patients). AFMS3 patients were reported to be particularly difficult to manage due to their unpredictability. Other complications present in a proportion of ACH infants include spinal stenosis (10–20%), tibial bowing (40–50%), recurrent upper airway infections/chronic otitis media (70–90%), and impaired hearing (25–40%). A predisposition for obesity, chronic pain, and delay in developmental motor milestones are present in the majority of children with ACH and have an impact on participation and psychosocial health.

Adults also exhibit complications such as symptomatic spinal stenosis (>70–80%), chronic pain (70%), obstructive sleep apnoea (60%), impaired hearing (40–50%), hypertension (50%), obesity, and impaired HRQoL and mental health. Spinal stenosis is often caused by a congenital narrow spinal canal and other spine deformities, resulting in walking-induced neurogenic claudication, bladder or bowel symptoms, and pathological reflexes.

The implications for clinical practice were detailed and international consensus guidelines identified 136 recommendations for the treatment of ACH, highlighting the need for pro-active, multidisciplinary, lifelong care of both medical and psychosocial factors. The guidelines outline three key sections: diagnosis, genetic counselling, and pregnancy; multidisciplinary management across a patient's life span; and thematic management by specialty area. Management of FMS in infants was highlighted, alongside ACH-specific growth charts, developmental milestones, and adult-specific recommendations to address the most prevalent complications observed in patients with ACH.

Following the approval of vosoritide, a team of 16 experts and two patient advocacy groups (PAGs) have developed 64 consensus statements for its use in individuals with ACH. These practical recommendations follow vosoritide treatment through pre-initiation, treatment start, ongoing monitoring and evaluation, stopping treatment, and follow-up monitoring. There was an emphasis on early referral and treatment initiation, realistic expectations, and organised follow-up by an MDT in an expert centre. ▸ [S7.3]

Achondroplasia .expert

## LIST OF ABBREVIATIONS

ACH – achondroplasia

AE – adverse event

AGV – annualised growth velocity

AHV – annualised height velocity

bALP – bone alkaline phosphatase

BMC – bone mineral content

BMD – bone mineral density

BMI – body mass index

CDC – Centres for Disease Control

CMC – cervical-medullary compression

CNP – C-type natriuretic peptide

CRS – cardiorespiratory sleep studies

CT – computed tomography

CTx – C-terminal telopeptide

CVJ – craniovertebral junction

DXA – dual-energy x-ray absorptiometry

EA – Early access

EAF – European Achondroplasia Forum

EHR – electronic health record

ENT – ear, nose, and throat

ER – emergency room

ESPE – European Society for Paediatric Endocrinology

FGFR3 – fibroblast growth factor receptor 3

FMS – foramen magnum stenosis

GH – growth hormone

HCRU – clinical and healthcare resource utilisation

HRQoL – health-related quality of life

HV – height velocity

ICD – International Classification of Diseases

ICU – intensive care unit

IND – investigational new drug

IRR – incidence rate ratio

LMS – Lambda Mu and Sigma

LS – lumbar spine

MDT – multidisciplinary team

MENA – Middle East and North Africa

MRI – magnetic resonance imaging

PAG – patient advocacy group

PedsQL – paediatric quality of life

PPY – per patient-year

PRO – patient-reported outcome

PROMIS – patient-reported outcomes measurement information

QD – once daily

QoL – quality of life

SAE – serious adverse event

SD – standard deviation

SDS – standard deviation score

TBLH – total body less head

TEAE – treatment-emergent adverse event

## REFERENCES


1. Vosoritide European Summary of Product Characteristics
2. Savarirayan R *et al.* N Engl J Med 2019;381:25–35
3. Savarirayan R *et al.* Lancet 2020;396:684–692
4. Savarirayan R *et al.* Genet Med 2024;26:101274
5. Pimenta J *et al.* GIM Open 2023;1:100366
6. Merker A *et al.* Am J Med Genet A 2018;176:1723–34


BIOMARIN