ACHONDROPLASIA.EXPERT CONGRESS REVIEWS ACMG 2025

Welcome to the ACMG 2025 congress review

The 31st American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting took place in Los Angeles, USA, 18th–22nd March 2025, and was attended by approximately 3000 specialists in genetic conditions such as achondroplasia (ACH).

This congress review includes a symposium summary on the cause, natural history and complications of ACH, and the perspective of people with ACH and their caregivers. The abstract summaries include the latest data on medical therapies for the treatment of ACH, an investigation of suspected genetic causes of skeletal dysplasia, and an exploration of the value of sleep studies in ACH.

We hope this review provides you with valuable insights into the latest developments in ACH.

The Achondroplasia Team

Abstracts can be found **here**

A DEEPER LOOK INTO ACHONDROPLASIA

Dr Legare explores the cause, complications, and care of ACH

▶ FIND OUT MORE

LATEST DATA ON ACH MEDICAL THERAPIES

Findings from clinical trials and the real world on medical therapies for ACH

▶ FIND OUT MORE

CAUSE AND EFFECTS OF SKELETAL DYSPLASIA

Classification of genetic variants and polysomnography (PSG) evaluation

▶ FIND OUT MORE

VOXZOGO® (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. The latest EMA SmPC for VOXZOGO® can be found by clicking **here**. The latest aPI for VOXZOGO® can be found on the achondroplasia.expert website, or by clicking **here**.

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A DEEPER LOOK INTO ACHONDROPLASIA

A summary of the symposium led by Dr Janet Legare on the underlying cause and pathophysiology of impaired bone growth in achondroplasia (ACH), natural history and complications to look out for in clinical practice, and understanding the patient and caregiver perspective on the condition.

The BioMarin-sponsored session focused on providing education on ACH, with the objectives of reviewing its underlying cause and pathophysiology, natural history, and the caregiver's perspective.

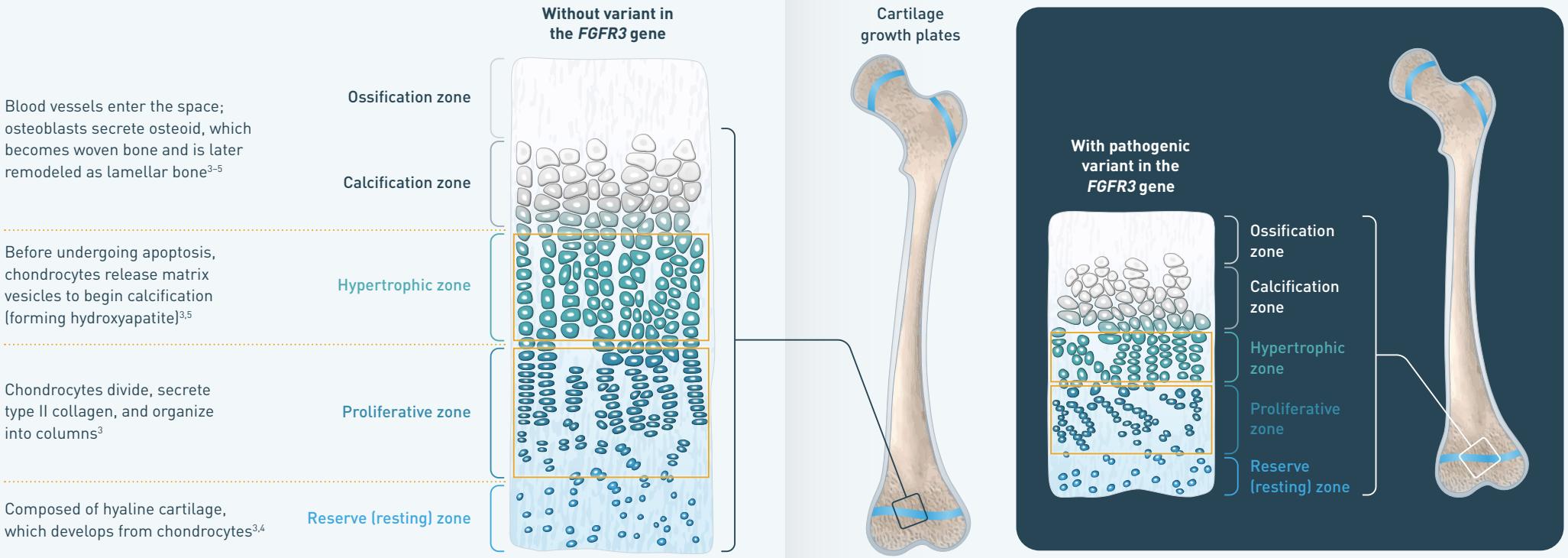
Dr Janet Legare explained the role of fibroblast growth factor receptor 3 (FGFR3) signalling and naturally occurring C-type natriuretic peptide (CNP), with the balance of the two ensuring that bones do not grow too long, or too short.

In ACH, the *FGFR3* variant is a gain-of-function mutation, inhibiting bone growth at a rate that CNP cannot match.

The characteristics of ACH include short stature, disproportionality, frontal bossing, limited elbow extension, *genu varum*, trident hand, hyperlordosis, and midface hypoplasia. Radiographic features include short pedicles, narrow interpedicular distance, square-shaped pelvis, and rhizomelic shortening. The timing and diagnosis of ACH can be variable, although prenatal diagnosis is becoming more common, particularly in people with an affected parent. Using the correct ACH-specific charts for height, weight, and body mass index (BMI) is key to effective monitoring and to enable appropriate referrals.

Dr Legare shared the common sequelae of ACH across the life stages and the importance of anticipatory care to address complications such as foramen magnum stenosis, sleep-disordered breathing (SDB), thoracolumbar kyphosis, otitis media, spinal stenosis, *genu varum*, chronic pain and the impact of ACH on quality of life.

Overactive FGFR3 signaling in individuals with achondroplasia impacts proliferation and hypertrophy of chondrocytes[1,2]



Legare J. BioMarin symposium

Dr Legare used videos featuring the mother of a child with ACH who explained the multiple specialists involved in care and the importance of patient groups for support and information.

She closed the session by highlighting the importance of the lexicon used when talking to patients and their families to ensure effective communication and care.

Communicating with caregivers and patients

Instead of saying ...	Say ...
Achon	**Achondroplasia**
The "M" word or dwarf	**Individual with achondroplasia or their name**
Disease or disorder	**Condition**
Mutation	**Change in the gene or variant**
Being different or height impairment	**Short stature**
Normal stature	**Average stature**
Differing bone growth or abnormal bone growth or stunted bone growth	**Impaired bone growth**

Legare J. BioMarin symposium

LATEST DATA ON ACH MEDICAL THERAPIES

Vosoritide is a CNP analogue for the treatment of ACH in patients 4 months of age or older whose epiphyses are not closed.[6] Infigratinib* is an orally bioavailable FGFR1–3 selective tyrosine kinase inhibitor in development for patients with ACH.[7] The following abstract summaries highlight the latest clinical-trial and real-world data on these medical therapies.

Lourenco *et al.* gathered data from Brazilian patients with ACH treated with vosoritide. Data were from a single centre for rare diseases across a 3-year period. All available medical records, including anthropometry, surgery, polysomnography (PSG), and imaging were analysed.

Data from 18 patients (60% girls, mean age 4.5 years) pre- and post-treatment were compared. Increased growth velocity was seen in all patients; the greatest improvement was seen in participants who started therapy <3 years old. No patients who started therapy <2 years old developed foramen magnum stenosis or recurrent ear/upper airway infections. All patients showed improvement in hypotonia. Sleep studies indicated small improvements, particularly in patients who started vosoritide <3 years old. The youngest patient to start therapy was a 16-month-old girl, who also showed the greatest change in growth curve and facial bone structure. A total of 10 mild adverse events (AEs) were reported: there were no serious adverse events (SAEs) or injection-site reactions.

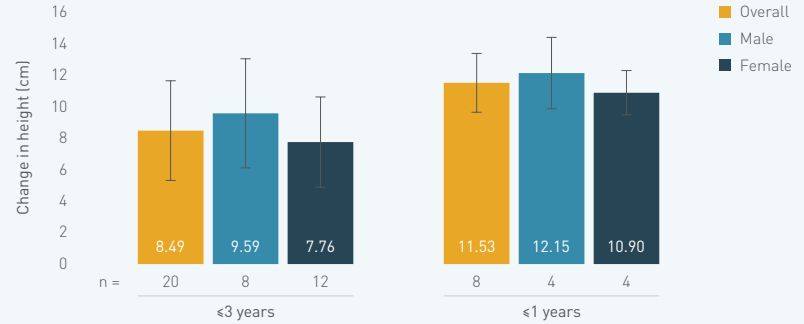
In addition to improving growth velocity in this cohort of patients, vosoritide resulted in greater changes in facial volume, facial sinus volume and great aperture area. Greatest improvements were seen in patients who started treatment <3 years old. Vosoritide reduced the risk of recurrent respiratory infections and reduced risk of death in infancy due to apnoea in patients with ACH. ▶ [P156]

Vosoritide was approved for the treatment of ACH from birth in Japan in 2022. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) required a survey evaluating the long-term safety and effectiveness of vosoritide in children with ACH as a condition of approval (111-604). Data were collected from the start of treatment in August 2022, and participants will be followed until treatment termination or August 2031 (survey end), whichever comes first.

The current data cut was made on 25th August 2024, with data from 212 participants from all regions of Japan available for analysis. Among the participants, 63 (29.7%) were ⩽3 years old at treatment initiation, with a mean (standard deviation [SD]; min, max) age at treatment initiation of 15.4 (11.3; 0, 36) months. Of the children ⩽3 years old, 30 (47.6%) started therapy ⩽1 year old (minimum age of enrolment 1 month). Mean (SD; min, max) height/length Centres for Disease Control and Prevention (CDC) z-score was -3.75 (1.44; -7.0, -0.6) at treatment

*Infigratinib is not approved for use in the EU

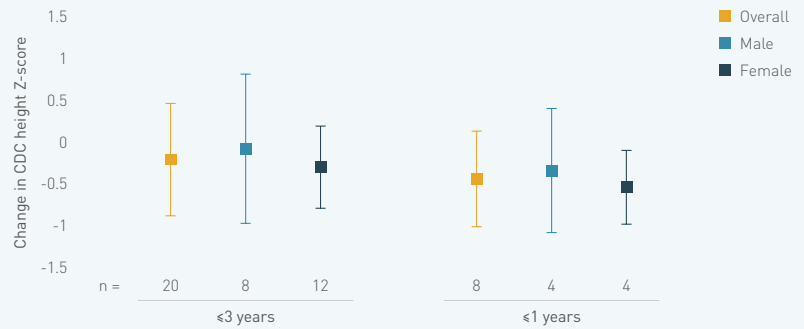
Change in height from treatment initiation



Data are presented as mean ± SD.

Michigami T, *et al.* [P208]

Change in height Z-score from treatment initiation



Data are presented as mean ± SD.

Michigami T, *et al.* [P208]

initiation in children ≤3 years old and -3.03 (-1.36; -6.0, -0.6) in children ≤1 year old. Most children ≤3 years old were boys (55.6%).

All 63 children ≤3 years old were available for safety analysis. A single SAE unrelated to vosoritide was reported (respiratory syncytial virus infection in a child ≤1 year old at initiation). No adverse drug reactions, bone- or joint-related safety events, or safety events associated with reductions in blood pressure were reported. A total of 11 ACH-related surgical procedures were reported in 10 (15.9%) children ≤3 years old at initiation: six foramen magnum decompressions (FMDs, four of which were reported in children ≤1 year), two adenoidectomies (AD), two myringotomy tube surgeries, and one hydrocephalus-related surgery.

Data for 20 children ≤3 years old were available for effectiveness analysis (eight of whom were ≤1 year at initiation). Participants increased in height after 12 months of treatment, with greatest height gains in children ≤1 year old (+8.49 cm in children ≤3 years, +11.53 cm in children ≤1 year). Mean height z-score remained stable after 12 months of treatment in a population which would expect to see a decrease in height z-score.

The cumulative mean (SD) duration of treatment exposure was 17.97 (4.76) months for children ≤3 years old and 16.00 (5.48) months for children ≤1 year old. There were no reported dose interruptions, and one non-safety-related discontinuation was reported.

The real-world safety profile of vosoritide in children with ACH ≤3 years old was acceptable in Japan, with high treatment adherence. The benefits of early intervention demonstrated in these real-world data are consistent with data from the 111-206 clinical trial. ▸ [P208]

The PROPEL 2 study was conducted to identify the dose of infigratinib* for further study and to evaluate preliminary evidence of efficacy. All 72 participants completed ≥6 months of growth assessments in the PROPEL study prior to enrolment in PROPEL 2. Most participants were girls (58.3%) with a mean (SD, range) age of 7.5 (2.2, 3.1–11.5) years. There were five ascending dose cohorts in the 6-month dose-escalation stage ranging from 0.016 mg/kg/day to 0.25 mg/kg/day. A 12-month extended treatment period followed. Annualised height velocity (AHV), height z-score, and body proportion were analysed for up to 18 months. Safety data are available for all five cohorts and efficacy data are available for the 0.25 mg/kg/day cohort.

Of the participants, 67 (93.1%) completed 18 months of treatment. All participants experienced at least one treatment-emergent adverse event (TEAE). No grade 3 TEAEs, ocular AEs, hyperphosphatemia, or accelerated progression of bone age was reported. No SAEs and TEAEs led to treatment discontinuation. The most common AE (occurring in ≥10% of participants) was nasopharyngitis, which occurred in 29 (40.3%) participants.

Of the 13 participants in the 0.25 mg/kg/day cohort, 11 completed the study. The two participants who discontinued the study withdrew consent due to personal reasons. No adverse changes in bone age or bone mineral density were reported at Month 18. A significant increase in AHV was observed in the 0.25 mg/kg/day cohort, with a mean (SD) change from baseline at Month 6 of +3.38 (2.70) cm/year (p=0.0012, n=12), which persisted to 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). Most (73%) participants with improved AHV from baseline experienced a >25% increase in AHV at Month 18. Mean (SD) change from baseline in height z-score was +0.54 (0.28) (p<0.0001) at Month 18 relative to an untreated ACH population. A significant (p=0.0012) improvement in upper: lower body segment ratio was observed, with mean (SD) change from baseline of -0.12 (0.09) at Month 18.

Oral infigratinib was well-tolerated for up to 18 months. Daily doses of 0.25 mg/kg/day resulted in sustained increases in AHV and improvement in body proportionality. These data suggest oral infigratinib may provide meaningful benefits to children with ACH. The safety and efficacy of oral infigratinib at the 0.25 mg/kg/day dose is being evaluated in the Phase 3, randomised, placebo-controlled study, PROPEL 3. ▸ [O13]

*Infigratinib is not approved for use in the EU

CAUSE AND EFFECTS OF SKELETAL DYSPLASIA

ACH is caused by a pathogenic variant in the gene encoding *FGFR3,* which impairs the endochondral ossification of the growing skeleton.[8] Sleep studies and neuroimaging are performed in infants with ACH but interpretation of sleep studies is challenging.[9] These abstract summaries review the classification of *FGFR3* variants and value of PSG data in determining surgical needs.

Volz *et al.* aimed to demonstrate the impact of a collaborative approach to reclassifying *FGFR3* variants of uncertain significance (VUSs). The project consisted of several steps, including: gathering clinical data associated with *FGFR3* VUSs via the 'Discover Dysplasias' programme from December 2019 to April 2024; assessing data from external sources to identify frequency, phenotypic correlations, and potential pathogenicity of *FGFR3* VUSs; data reviews from a clinical perspective by clinician researchers with expertise in skeletal dysplasia and genetic testing; and an objective review of all available evidence.

A total of 168 *FGFR3* VUSs were reviewed, including 119 unique nucleotide variants. As of 15th November 2024, 53 clinicians were contacted and 20 clinician interviews had been conducted. Data from ClinVar, UK Biobank (UKBB), and gnomAD were reviewed. Clinician interviews included patient chart review and discussion of family history, which provided clear phenotypic evidence to support potential variant reclassification. Certain VUSs were identified to potentially impact patient care, including p.Val555Leu (four patients, two nucleotide variants), p.Ser249Phe (two patients, one nucleotide variant), and p.Asp758Asn (eight patients, one nucleotide variant).

Collection and analysis of clinical and laboratory data are required to facilitate variant classification (in addition to publicly available sources). Further multidisciplinary work and collaboration across healthcare systems can improve variant classification. Functional assays can also provide crucial missing evidence to support variant classification. ▸[P213]

Legare *et al.* sought to clarify the natural history of PSG indices over the first 2 years in infants with ACH with and without surgery (AD and cervicomedullary decompression (CMD)) and compare indices after surgery to assess the utility of interventions. Retrospective data from the CLARITY ACH research electronic data capture (REDCap) database were reviewed. PSG data were limited to those performed from 2008 onwards because standardised scoring was published by the American Academy of Sleep Medicine in 2007. Limiting the timeframe ensured consistency and comparability of scoring. PSG data including obstructive apnoea hypopnea index (OAHI) and central apnoea index (CAI), as well as instances of AD surgery and CMD surgery were evaluated. PSGs from surgically naïve (SN) patients were assessed over time using two separate generalised linear mixed models (LMMs).

To assess the influence of surgery, LMMs were limited to pre- and post-operative PSGs.

Overall, 172 PSGs from 86 infants were reviewed. In SN children, OAHI decreased in the first year of life but then increased in the second year, while CAI remained unchanged over the first 2 years. OAHI was 0.93 units higher and CAI was 0.58 units lower in PSGs from pre-operative patients than in SN patients, but neither difference was significant (p=0.763 and p=0.157 respectively).

There was a nonsignificant decrease in OAHI after surgery in patients who underwent AD and/or tonsillectomy (change in OAHI -5.6, 95% confidence interval (CI): -16.4 to 5.2). When analysis was limited to patients who underwent AD alone a significant drop in OAHI was found (change in OAHI -14.1, 95%CI: -23.5 to -4.7). When adjusted for age, there was no significant difference in OAHI after CMD surgery (change in OAHI 1.2, 95%CI: -10.3 to 12.8). CAI decreased significantly in patients who underwent CMD independent of the patient's age (change in CAI -3.3, 95%CI: -5.1 to -1.5).

Due to the variability in OAHI and CAI in children with ACH, these metrics alone are not reliable benchmarks for determining the need for surgery. Further interpretation of sleep study findings in children with ACH are needed in the context of age, particularly for obstructive indices. Improvement in OAHI after AD and the improvement in CAI after CMD suggest the surgeries did successfully treat the respective sleep disorders. Re-evaluation of using PSGs to determine surgical risk in this population is needed. ▸[P313]

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LIST OF ABBREVIATIONS

ACH – achondroplasia

ACMG – American College of Medical Genetics and Genomics

AD – adenoidectomy

AE – adverse event

AHV – annualised height velocity

BMI – body mass index

CAI – central apnoea index

CDC – Centres for Disease Control and Prevention

CI – confidence interval

CMD – cervicomedullary decompression

CNP – C-type natriuretic peptide

FGFR3 – fibroblast growth factor receptor 3

FMD – foramen magnum decompression

LMM – linear mixed model

OAHI – obstructive apnoea hypopnea index

PMDA – Pharmaceuticals and Medical Devices Agency

PSG – polysomnography

SAE – serious adverse event

SD – standard deviation

SDB – sleep-disordered breathing

SN – surgically naïve

REDCap – research electronic data capture

TEAE – treatment-emergent adverse event

UKBB – UK Biobank

VUSs – variants of uncertain significance

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