This congress review was created in August 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 ACMG 2022

Welcome to the ACMG 2022 congress review.

The Annual Clinical Genetics Meeting took place in March 2022 with attendees from around the globe, both in person and online.

Achondroplasia was brought under the spotlight in two oral presentations; one examining the impact of birth delivery methods on surgical morbidity, the second describing new trial data on growth velocity over pubertal milestones in children with achondroplasia treated with vosoritide▼. Dr Melita Irving and colleagues introduced new data on associations between height, HRQoL and functional independence in children with achondroplasia. Additionally, Professor Ravi Savarirayan showcased top-line results from a Modified Delphi study on the impact of achondroplasia on HRQoL, and long-term effects of vosoritide.

The discussions around achondroplasia at this meeting are extremely positive for this patient population and confirms the increasing awareness and understanding within the medical community. We hope you will enjoy the selection of presentations summarised for you here.

The Achondroplasia Team

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ACHONDROPLASIA IMPACT ON HRQOL

Achondroplasia may have an impact on HRQoL and functional independence.

An abstract exploring the associations between height, HRQoL and functional independence in children with achondroplasia was presented by Dr Melita Irving. Vosoritide is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

This exploratory analysis used height Z-score, HRQoL, and functional independence data from 121 children with achondroplasia who were enrolled in the vosoritide Phase 3 trial and who had completed at least 6 months of a baseline observational growth study. Height Z-scores were assessed every 3 months, and PedsQL, QoLISSY, and WeeFIM questionnaires were completed every 6 months. The mean scores for all questionnaires were generally lower in subjects with greater height deficits (≤ -6 SDS), compared to taller subjects (height Z-score > –4 SDS). Clear linear relationships between height Z-scores and several domain scores were observed. This was particularly evident in the PedsQL Physical domain, the height-specific QoLISSY Physical domain, and the WeeFIM Self-care and Mobility domains. The authors concluded that height deficit in achondroplasia impacts HRQoL and function. These data suggest that therapies that reduce height deficits in children with achondroplasia may also improve HRQoL and functional independence. ▸[eP266]

Savarirayan *et al*. presented the results of a modified Delphi study regarding the impact of achondroplasia on HRQoL and long-term effects of vosoritide. The study aimed to elicit structured expert opinion to understand the anticipated modifying effect of vosoritide on medical complications, physical function and HRQoL, beyond the currently available follow-up of clinical trials.

Expert opinion was obtained through a modified Delphi study involving 14 clinicians from different countries and specialties, each with relevant expertise in managing achondroplasia.

The group agreed that until final height is reached, growth velocity increases will be maintained in individuals with achondroplasia who start on vosoritide between two years of age and puberty.

The majority of the panel thought that long-term treatment is "likely or very likely" to result in clinically meaningful improvements in upper-to-lower body segment ratio, that a clinically meaningful improvement is more likely if treatment is started earlier, and that starting earlier will result in a greater final height.

Over 75% agreed that the earlier long-term treatment is started, the larger the probability of a positive impact on the lifetime incidence of symptomatic spinal stenosis, kyphosis, obstructive sleep apnoea, and foramen magnum stenosis.

According to 82%, vosoritide will likely improve HRQoL throughout the life span if long-term treatment is started before puberty.

Over 70% agreed that a positive impact of vosoritide on the incidence of surgeries, on pain, work participation, and activities of daily living through lifetime, is more likely in individuals starting treatment at an earlier age.

This study provides further insight into the impact of achondroplasia on medical complications and HRQoL, and outlines an expert opinion on the anticipated long-term benefits of vosoritide.

These predictions can be used in discussing potential vosoritide outcomes with families and healthcare providers as its use becomes more prevalent. However, the authors note that careful and critical prospective data collection will be required before these assumptions can be substantiated. ▸[eP204]

Assumptions and questions related to impact of vosoritide on growth velocity, height, and body proportions reaching ≥75% panel agreement

Assumption	% Panelists[a]						% Agreement[b]
It is likely that long-term treatment with vosoritide increases growth velocity until final height is reached in individuals with achondroplasia starting treatment between 2 years of age and puberty (Tanner stage >1)	0%	0%	8%	54%	31%	8%	92%
It is likely that long-term treatment with vosoritide results in a greater final height in those starting at an earlier age than in those starting later	0%	0%	0%	54%	38%	8%	100%
A clinically meaningful positive impact of vosoritide on abnormal upper-to-lower body segment ratio is more likely in individuals with achondroplasia starting long-term treatment at an earlier age than in those starting treatment later	0%	0%	8%	54%	31%	8%	92%
Question	**% Panelists[c]**						**% Likely + Very likely[d]**
How likely do you consider long-term treatment with vosoritide to result in a clinically meaningful improvement in upper-to-lower body segment ratio in individuals with ACH starting between 2 years of age and puberty (Tanner stage >1)?	0%	0%	15%	62%	23%	0%	85%

Savarirayan *et al*. [eP204]

[a]% of panelists (N=13) voting
Strongly disagree; Disagree; Neutral; Agree; Strongly agree; Can't judge

[b]% of panelists agreeing or strongly agreeing with the assumption, excluding "can't judge" votes

[c]% of panelists (N=13) voting
Very unlikely; Unlikely; Neutral; Likely; Very likely; Can't judge

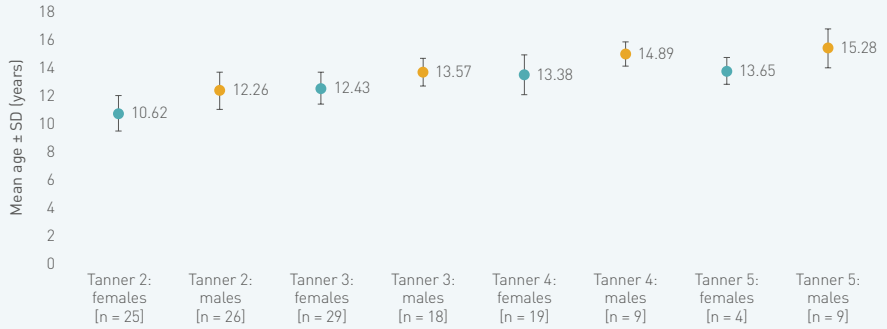
[d]% of panelists voting "likely" or "very likely", excluding "Can't judge" votes

VOSORITIDE IN CHILDREN WITH ACHONDROPLASIA

A report on the growth velocity during puberty and pubertal milestones in children with achondroplasia treated with vosoritide.

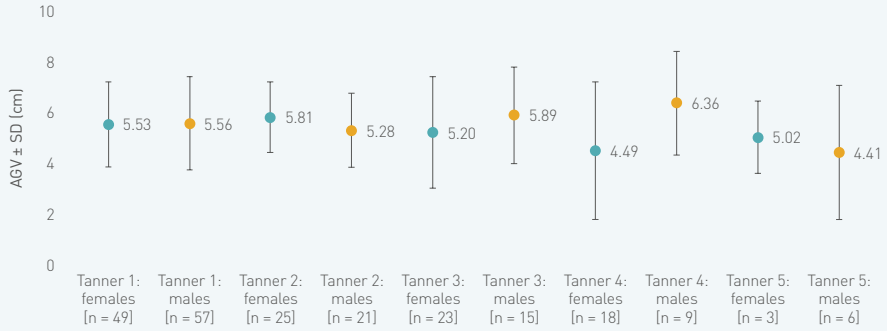
For any growth agent used in children, it is important to evaluate AGV in the context of pubertal milestone timing. Melita Irving presented data on vosoritide, a potent stimulator of endochondral bone growth for children with achondroplasia, with a focus on growth velocity and pubertal milestones. Data from BMN 111-202 and -301 were analysed to determine age and AGV at the onset of each Tanner stage.

Mean age on reaching Tanner stage



Irving *et al.* [OP021]

Corresponding AGV in cm/year at Tanner stage



Irving *et al.* [OP021]

At six monthly intervals, mean standing heights were used to assess growth and to calculate AGV as and when participants progressed from one Tanner stage to another. Of the 152 children who had received vosoritide 15 or 30 µg/kg, 82 had data available to assess their age at onset of Tanner stages 2–5, and 149 subjects had data to assess AGV at Tanner stages 1–5. Similar to previous reports, peak growth velocity occurred at Tanner 2 for females, and Tanner 4 for males. The peak growth velocity on vosoritide was 5.81 cm/year for females and 6.36 cm/year for males. It is important to note that the peak growth velocity in the general US population is 6.65 cm/year for females and 7.66 cm/year for males[1] – a 0.84 cm/year and 1.3 cm/year difference from children with achondroplasia who have been treated with vosoritide.

The authors of the study concluded that treatment with vosoritide significantly improved growth velocity in children with achondroplasia, and that this improvement persisted even during later stages of puberty. Furthermore, vosoritide did not appear to alter the onset or progression of pubertal milestones. The participants in the study will continue to be monitored, and more data will be made available as these children reach their final adult height. ▶[OP021]

PREVALENCE OF NON-SKELETAL COMPLICATIONS IN ACHONDROPLASIA

Achondroplasia results in impaired bone growth and multisystem complications. This study aimed to estimate rates of non-skeletal complications compared with general population controls.

Data from a UK matched cohort study were shared by Irving *et al.* This retrospective cohort study used the Clinical Practice Research Datalink (CPRD-GOLD) – a primary-care database of over 16 million anonymised electronic medical records from general practitioners in the UK. This study is the first to assess complications in achondroplasia compared to an appropriately matched control group from the general population. In total, 541 achondroplasia cases were index date-matched to 2,052 controls – defined as those without evidence of skeletal or growth disorders. The results showed that rates of any non-skeletal complication were significantly higher in achondroplasia cases compared to controls, with a rate ratio of 1.76 (95% CI 1.56–1.98). Significantly higher rate ratios in achondroplasia versus controls were seen in all body systems, except cardiovascular. Complications differed by ages when compared to controls. For example, among those under 18 years, rate ratios for developmental delay, enlarged tonsils and headaches were higher in achondroplasia patients. Among those aged 18 or over, rate ratios for

depression, anxiety and seizures were higher in achondroplasia patients. Regardless of age group, hearing loss, otitis media, obesity, gastrointestinal issues and musculoskeletal pain were higher in achondroplasia. The authors concluded that achondroplasia patients have significantly more non-skeletal multisystemic complications compared to the general population, and that these are present throughout the life span. ▸[eP265]

Rate ratios (95% CI) for non-skeletal complications

Body system	Rate Ratio, RR (95% CIs)	Specific complications			
		Statistically significantly higher RR in ACH compared to controls		No difference in RR between ACH cases and controls	Condition included in body system but <5 events*
Any Non-skeletal	1.76 (1.56–1.98)				
Developmental	8.84 (4.18–18.72)	Developmental delay Speech delay	8.80 (3.02–25.68) 7.61 (3.03–19.13)	–	Motor delay
Neurological	7.56 (4.24–13.50)	Seizures Hydrocephalus/ ventriculomegaly	4.01 (1.52–10.58) Cases only	Dementia	Craniocervical stenosis Failure to thrive Subdural haematoma
Respiratory	4.15 (2.51–6.88)	Apnoea/sleep disordered breathing	25.81 (10.0–66.60)	Sleep disorder	–
ENT	2.98 (2.43–3.65)	Enlarged tonsils Hearing loss/ deafness Otitis media	3.34 (1.26–8.86) 3.50 (2.50–4.89) 3.11 (2.45–3.94)	Sinusitis Voice abnormality	Middle ear dysfunction Tracheomalacia Bronchomalacia
Metabolic	1.65 (1.24–2.18)	Obesity	2.59 (2.26–2.97)	Diabetes Hyperlipidaemia	–
Mental Health	1.62 (1.21–2.17)	ADD/ADHD/ adjustment disorder Depression/anxiety Self-harm/ suicidal ideation	3.44 (1.13–10.51) 1.51 (1.09–2.08) 3.71 (1.17–11.77)	Substance abuse	'Other' mental health
Cardiovascular	1.17 (0.92–1.49)	–		Chest pain/angina Coronary disease Hypertension Myocardial infarction Stroke	–
Other	1.76 (1.52–2.03)	Gastrointestinal issues Pain-musculoskeletal	1.66 (1.31–2.09) 1.84 (1.58–2.15)	Headache Sexual health/ gynaecological issues	–

Irving *et al.* [eP265]

* Due to database requirements, data for cases or controls which have less than 5 events are not permitted to be reported.

PRENATAL CONSIDERATIONS IN ACHONDROPLASIA

Pregnancy presents a unique challenge for both mothers and foetuses with achondroplasia.

The optimal delivery for foetuses with achondroplasia whose mothers are of average height has not yet been established. It has traditionally been suggested that vaginal delivery is not feasible for babies with achondroplasia due to foetal macrocephaly, and that the compressive forces of vaginal delivery may contribute to cervical spinal complications. Brar *et al.* gave an oral presentation on the impact of route of delivery on surgical morbidity in foetuses with achondroplasia, sharing data from a multi-centre retrospective study. The study aimed to assess the prevalence of different routes of delivery in 694 foetuses with achondroplasia, to describe indications for caesarean section and to determine whether the route of delivery impacts subsequent surgical morbidity.

There was no difference in the odds of having one or more achondroplasia-related surgeries if delivered by caesarean section versus vaginally. The authors concluded that – in light of recent global efforts to decrease caesarean section rates – these data suggest it is reasonable for foetuses with achondroplasia born to mothers of average stature to undergo vaginal labour in the absence of routine obstetric contraindications. ▸[OP048]

GENETIC TESTING IN SKELETAL DYSPLASIA

More than 400 skeletal dysplasias have been described. Accurate prenatal diagnosis is critical for appropriate counselling, pregnancy management, and expected postnatal outcomes.

MacCarrick *et al.* described a sponsored program that provides a no-charge skeletal dysplasia gene panel to patients in the US, with the goal of facilitating accurate and timely diagnoses. Eligible patients must have one or more of the following characteristics: skeletal abnormalities, dysmorphic facial features, or other signs suggestive of skeletal dysplasia, short stature or disproportionate growth. To date, 2,641 patients have been tested, with initial symptom onset noted prenatally for 10%, and at birth for 19%. For the remaining 71% with first symptoms after birth, the median age at onset was 5 years. A molecular diagnosis was established for 678 patients (68 genes); the most common genes were *FGFR3* (20%), *COL2A1* (14%), *ALPL* (11%), *COL1A1* (8%), *COMP* (6%),

RUNX2 (4%), *COL1A2* (3%), *LMX1B* (2%), *SLC26A2* (2%), and *FBN1* (2%). Molecular diagnoses for *FGFR3*-related conditions were identified in 141 patients, of which 93 were associated with achondroplasia, and 35 with hypochondroplasia. These data demonstrate the clinical utility of gene panel testing in identifying the aetiology of skeletal dysplasia, which could facilitate earlier implementation of disease-specific management. ▸[eP409]

Exome analysis of pre and postnatal cases referred with skeletal dysplasia was examined by Haworth *et al*. The development of therapeutics for skeletal dysplasia – such as vosoritide and infigratinib for children with achondroplasia, and asfotase alpha for hypophosphatasia – has highlighted the need to provide accurate and timely diagnosis to inform early intervention. The authors described phenotypic and genomic findings from 60 cases referred to a clinical genetics service in the UK. This cohort represents 6.9% of all cases referred for exome sequencing, although referrals for achondroplasia are not included. Overall, molecular diagnosis was obtained in 51.6% of cases, with higher diagnostic yield in pre- rather than post- natal cases (64% versus 40%). Causal variants were identified in 29 different genes, illustrative of the heterogeneity of these conditions, and only *SLC26A2* and *COL1A2* were identified in more than one case. The molecular diagnosis was not always concordant with the suspected clinical diagnosis, particularly for prenatal cases, highlighting the challenges of diagnosis in this setting. The authors note that the results confirm the advantages of undertaking analysis of all genes known to be associated with skeletal dysplasia, rather than a more restrictive targeted approach. ▸[eP360]

Tran *et al*. presented an abstract on the role of clinical exome sequencing in genetic diagnosing of skeletal dysplasia detected by prenatal ultrasound in Vietnam. This study aimed to comprehensively characterise the molecular genetic landscape in 98 unselected cases suspected of skeletal dysplasia through prenatal screening, particularly novel variants as well as foetal phenotypes. The predominant sign of skeletal dysplasia on ultrasound is short and/or bowing long bones. Other findings include bipedal varus, aplasia/dysplasia of nasal bones, absence of limb bones, deformities in metacarpal bones and part of the distal phalanx, fixed joints of wrist and knee, digit malformation, bilateral rocker-bottom feet, osteogenesis imperfecta, skull bone anomalies, and spina bifida. In this study, 97% of foetuses had normal copy number variants (CNV) and the remaining individuals had CNV anomalies. Among cases with normal CNV, further analysis revealed 49% harboured a variety of SNV and over 57% of these were categorised as "pathogenic and likely pathogenic". A total of 50 variants in 23 different genes associated with skeletal dysplasia were identified, including 21 novel variants, 13 of which are variants of uncertain significance. Remarkably, most variants were frequently located in *FGFR3*, *FLNB*, *COG4*, *COL10A1*, *COL1A2*, and *COL2A1* – of which the common phenotype is short and/or bowing long bones. The authors highlight that molecular findings are crucial to guide medical treatment and management and to inform assessment of risk for familial recurrence. Multiple novel variants reported in this study will substantially expand the genetic archive of genes associated with skeletal dysplasia, but more research is needed to uncover the pathogenicity of novel variants. ▸[eP471]

Narang *et al*. presented a case of suspected campomelic dysplasia, which remains a diagnostic dilemma despite thorough genetic evaluation. At 20 weeks, the foetus was growth restricted (<10th percentile) with all shortened long bones. Markers of lethality of skeletal dysplasia included a cardiothoracic ratio of 53% (normal <50%), and femur length. These findings prompted a diagnostic genetic work up, all of which were returned normal. Sonographic surveillance showed findings concerning for skeletal dysplasia, including bilateral proximal femoral diaphyseal bowing/fractures, left clubfoot, 11 total ribs, and micrognathia. A foetal MRI at 32 weeks demonstrated normal brain structure, short femurs, normal lung volumes, unilateral talipes, and micrognathia. Prenatal exome sequencing was negative for pathogenic or likely pathogenic variants associated with the prenatal phenotype. At birth, the female infant was normocephalic with age-appropriate fontanelles. There was micrognathia with intermittent airway obstruction and evidence of Pierre Robin sequence. The spine was straight without lesions, both femurs were shortened with clubbing of the left foot. All fingers and toes appeared normal. A skeletal survey revealed 12 ossified rib pairs, hip dislocation, lateral bowing/angulation of the mid femoral diaphyses, as well as club feet bilaterally. No fractures were identified. With exception of hip abduction, she had appropriate movement of her extremities. Postnatal expanded genome sequencing revealed no pathogenic, likely pathogenic or variants of uncertain significance. Optical Mapping showed several genomic insertion, deletion, inversion, duplication, and translocation events involving multiple genes. However, none of the reported genomic events were a good fit with the infant's phenotype. This case illustrates challenges associated with prenatal diagnosis of suspected skeletal dysplasia. ▸[eP460]

Diagnosis of Severe Skeletal Dysplasia was also highlighted by Sergi *et al*. in their case of a compound MYH3 VUS heterozygote after negative exome sequencing. The patient was a female born with multiple congenital anomalies and respiratory failure requiring intubation. Her parents chose compassionate care only and signed a DNR, but decided to pursue genetic evaluation. The patient had many distinct physical exam features including kyphoscoliosis, bilateral club feet, severe arthrogryposis, vertebral anomalies, cleft palate, sacral tuft (concerning for spina bifida occulta), multiple pterygia, redundant neck skin (concerning for presence of a cystic hygroma), large metopic fontanelle, forward sloping shoulders, and a broad chest. Imaging and echocardiogram revealed a horseshoe kidney, undetermined gonadal differentiation, very large patent ductus arteriosis, atrial septal defect, severe tricuspid regurgitation, peg teeth, and respiratory failure secondary to restrictive lung disease. Rapid trio exome sequencing was presented as an option for genetic evaluation of skeletal dysplasia. Though initial results were negative – reporting only carrier status and variants of unknown significance – further investigation revealed a low coverage region of *MYH3* containing a second likely pathogenic variant. These *MYH3* variants coupled with her severe phenotype provided the diagnosis of autosomal recessive spondylocarpotarsal synostosis syndrome. Based on this, the parents were appropriately counselled for recurrence risks in future pregnancies. ▸[eP240]

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LIST OF ABBREVIATIONS

AGV – annualised growth velocity

CNV – copy number variant

QoL – quality of life

HRQoL – Health-related quality of life

PedsQL – Pediatric Quality of Life Inventory

SD – standard deviation

SNV – single nucleotide variant

QoLISSY – Quality of Life in Short Stature Youth

VUS – variants of uncertain significance

WeeFIM – Pediatric Functional Independence Measure

REFERENCES

1. Kelly A, *et al.* Age-based reference ranges for annual height velocity in US children. *J Clin Endocrinol Metab* 2014;99(6):2104–12.

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