ACHONDROPLASIA.EXPERT CONGRESS REVIEWS ICCBH 2024

Welcome to the ICCBH 2024 congress review

The 11th *International Conference on Children's Bone Health* took place in Salzburg, Austria, from 22–25 June 2024 and was attended by 470 delegates from over 45 countries.

In this congress review, we have highlighted the key abstracts from ICCBH, focusing on the clinical data on vosoritide▼ and other therapies in development for achondroplasia; as well as multidisciplinary management; and the importance of following up infants with spinal cord compression rated AFMS3. There is also a brief summary of the ISCBH ERN BOND workshop.

We hope you find this summary of the congress useful.

The Achondroplasia Team

VOSORITIDE CLINICAL DATA

Latest data on vosoritide in achondroplasia

▶ FIND OUT MORE

THERAPIES IN DEVELOPMENT

Data on achondroplasia therapies in development

▶ FIND OUT MORE

MULTIDISCIPLINARY MANAGEMENT

Assessing multidisciplinary clinics in Glasgow

▶ FIND OUT MORE

The abstracts can be found on the ICCBH 2024 congress website.

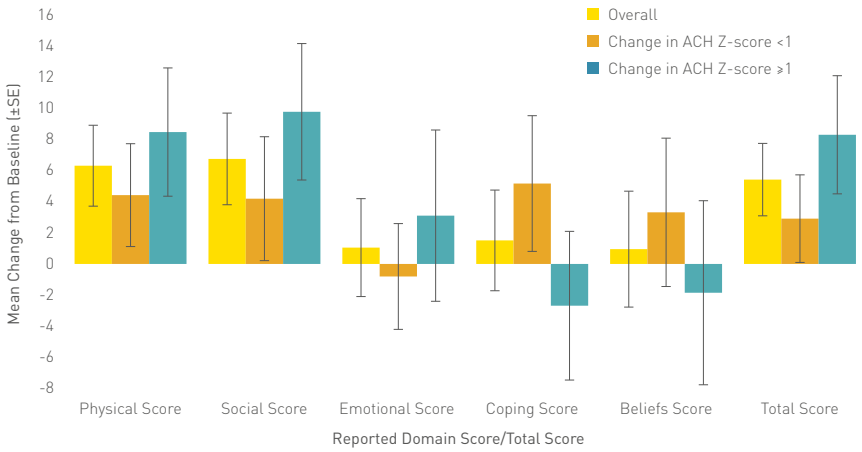
VOSORITIDE CLINICAL DATA

Full summaries of the oral presentations and posters below are included in our ACMG 2024 congress review here

Persistent growth-promoting effects of vosoritide in children with achondroplasia is accompanied by improvement in physical aspects of quality of life (Savarirayan *et al.*) [OC 4.3]

- Data from a Phase 3 OLE trial (111-301/302) demonstrating efficacy of vosoritide in promoting growth in children with ACH; QoLISSY questionnaire used to explore effects of vosoritide on HRQoL
- After 3 years, self-reported mean (SD) change from baseline was 6.3 (20.2) in physical domain score; in children with ≥1SD increase in ACH height z-score, mean change in physical domain score was 8.5 (21.8)
- After 3 years of vosoritide there was improvement in QoLISSY physical domain scores, particularly in children with a pronounced change in height z-score over time

Mean change from baseline in self-reported QoLISSY scores at Year 3 in the treated population



Overall	60	59	59	58	59	58
Change in ACH Z-score <1	32	32	31	31	32	31
Change in ACH Z-score ≥1	28	27	28	27	27	27

Savarirayan R, *et al.* [OC 4.3]

Persistence of growth promoting effects in infants and toddlers with achondroplasia: Results from a Phase 2 extension study with vosoritide

(Savarirayan *et al.*) [P78]

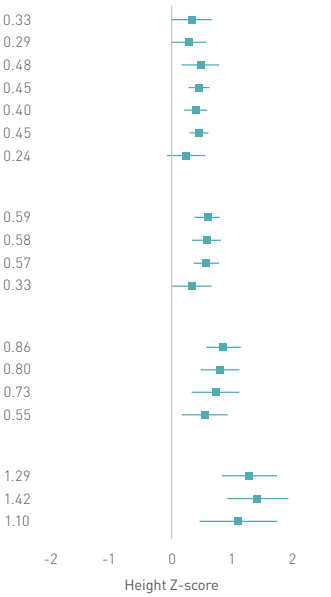
- Data from a Phase 2 extension study (111-208) exploring safety, tolerability and effect of vosoritide on height/body length in children with ACH aged 0 to <5 years*
- Results demonstrated consistent and durable treatment effect of vosoritide on growth up to 4 years, with no worsening in body proportions over time and no treatment-limiting AEs or new safety issues observed

**Vosoritide is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The youngest patient treated was 4.5 months of age.*

Height Z-score consistently increased over time in treated children vs controls

Children ≥ 2 years at start of treatment

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference	Treatment difference (95% CI) Vosoritide minus comparator
1 year					
Study 111-206 (FAS randomized)	111-206 placebo	15	16	0.33	
Study 111-206 (FAS)	111-206 placebo	19	16	0.29	
Study 111-206 (FAS randomized)	AchNH longitudinal	15	124	0.48	
Study 111-206/111-208	AchNH longitudinal	34	198	0.45	
Study 111-206/111-208	AchNH cross-sectional	34	761/701	0.40	
Study 111-206/111-208	Obs/Pbo longitudinal	34	72	0.45	
Study 111-206/111-208	Obs/Pbo cross-sectional	34	77/134	0.24	
2 year					
Study 111-206/111-208	AchNH longitudinal	30	146	0.59	
Study 111-206/111-208	AchNH cross-sectional	30	725/614	0.58	
Study 111-206/111-208	Obs/Pbo longitudinal	30	55	0.57	
Study 111-206/111-208	Obs/Pbo cross-sectional	30	80/163	0.33	
3 year					
Study 111-206/111-208	AchNH longitudinal	22	107	0.86	
Study 111-206/111-208	AchNH cross-sectional	22	672/484	0.80	
Study 111-206/111-208	Obs/Pbo longitudinal	22	21	0.73	
Study 111-206/111-208	Obs/Pbo cross-sectional	22	80/167	0.55	
4 year					
Study 111-206/111-208	AchNH longitudinal	8	30	1.29	
Study 111-206/111-208	AchNH cross-sectional	9	444/254	1.42	
Study 111-206/111-208	Obs/Pbo cross-sectional	9	79/109	1.10	



Consistent and sustained treatment effect with mean height Z-score gain > 1 SDS after 4 years

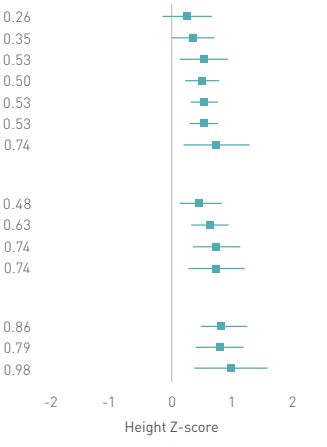
AchNH reference derived from CLARITY

Savarirayan R, *et al.* [P78]

Height Z-score consistently increased over time in treated children vs controls

Children < 2 years at start of treatment

Timepoint Studies	Comparator	Number of subjects Vosoritide	Number of subjects Comparator	Treatment difference	Treatment difference (95% CI) Vosoritide minus comparator
1 year					
Study 111-206 (FAS randomized)	111-206 placebo	17	16	0.26	
Study 111-206 (FAS)	111-206 placebo	24	16	0.35	
Study 111-206 (FAS randomized)	AchNH longitudinal	16	216	0.53	
Study 111-206/111-208	AchNH longitudinal	32	287	0.50	
Study 111-206/111-208	AchNH cross-sectional	32	788/716	0.53	
Study 111-206/111-208	Obs/Pbo longitudinal	32	31	0.53	
Study 111-206/111-208	Obs/Pbo cross-sectional	28	49/56	0.74	
2 year					
Study 111-206/111-208	AchNH longitudinal	25	223	0.48	
Study 111-206/111-208	AchNH cross-sectional	25	767/638	0.63	
Study 111-206/111-208	Obs/Pbo longitudinal	25	20	0.74	
Study 111-206/111-208	Obs/Pbo cross-sectional	25	55/64	0.74	
3 year					
Study 111-206/111-208	AchNH longitudinal	14	150	0.86	
Study 111-206/111-208	AchNH cross-sectional	14	715/509	0.79	
Study 111-206/111-208	Obs/Pbo cross-sectional	14	61/85	0.98	



Consistent and sustained treatment effect with mean height Z-score gain > 0.79 SDS over 3 years

AchNH reference derived from CLARITY

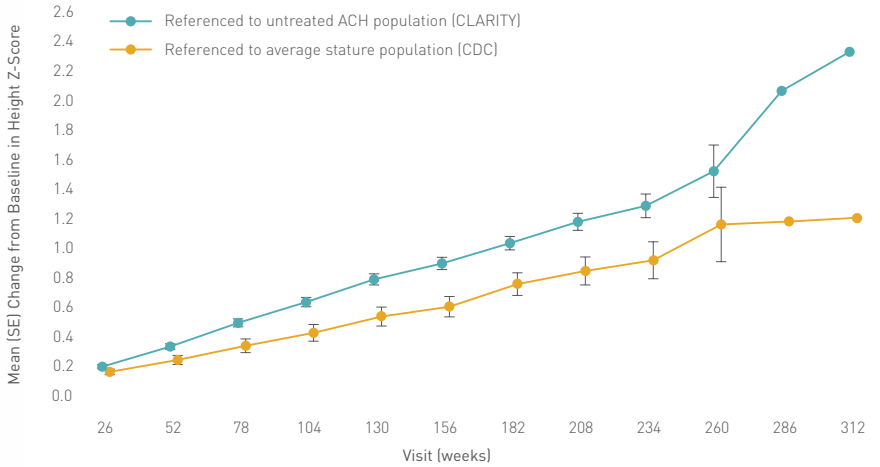
Savarirayan R, *et al.* [P78]

Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 4 years: Update from Phase 3 extension study

(Savarirayan *et al.*) [P79]

- Data from a Phase 3 OLE trial (111-301/302) initiated to investigate long-term safety and efficacy of vosoritide in children with ACH
- Over 4 years, mean AGV was consistently higher vs. age-matched untreated children with achondroplasia and was comparable to that of average stature children prior to puberty
- Durability of treatment effect was demonstrated with a consistent increase in height z-score, when referenced to both untreated ACH population, and to an average stature population
- Additional height gain of 5.75 cm (95% CI 4.93, 6.57) over 3 years for treated children vs untreated ACH age- and sex-matched controls
- Body proportionality continued to improve over time, with marked changes in girls aged <11 years and boys <12 years
- Long term treatment with vosoritide was not associated with serious or treatment-limiting adverse events

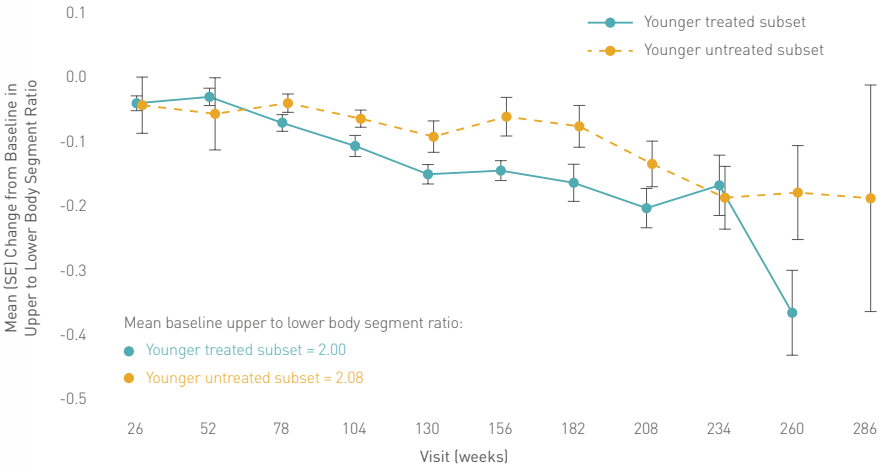
Consistent increase in height z-score over time



Ref ACH untreated	111	111	109	112	109	111	91	53	35	9	1	1
Ref Average stature	111	111	109	112	109	111	90	53	35	9	1	1

Savarirayan R, *et al.* [P79]

Change in upper to lower body segment ratio in a subset of children under 11(F)/12(M) years old*



Younger treated subset	78	69	60	57	51	47	42	22	14	3	0
Younger untreated subset	212	163	135	84	55	33	24	19	11	7	2

*Assessments beyond these ages are excluded from analysis given any treatment is unlikely to impact proportionality.

Savarirayan R, *et al.* [P79]

Does vosoritide treatment affect bone strength in children with achondroplasia?

A total of 103 hand/wrist radiographs from 30 children with ACH between the ages of 7.8 and 16 years were deidentified. Data were collected from hand films at Weeks 104, 156, 208 and 260 on treatment with vosoritide from the Phase 2 OLE 111-205. Second metacarpal length and midshaft width, cortical thickness, robustness and cortical area (correlating with strength) were measured and compared to 378 radiographs from 114 average-stature controls between the ages of 6–16 years.

Individuals treated with vosoritide were found to have longer metacarpals and increased cortical area and thickness at weeks 208 and 260 compared with week 104 ($p<0.05$). No significant changes in relative cortical area and robustness occurred at any time, with no differences being seen between males and females. Children with ACH had higher robustness and cortical area throughout treatment versus the controls ($p<0.001$).

This study showed that an additional 2–3 years vosoritide treatment is associated with increased bone length and cortical area compared with the initial timepoint (Week 104), without adversely affecting bone strength. Further studies are needed to confirm these findings in a comparative study of treated and untreated children with ACH. [P151]

Vosoritide therapy in children with achondroplasia: Early experience in an Italian cohort

A total of 38 participants, aged ≥2 to <14 years, started vosoritide between December 2022 and February 2024 at the Paediatric Endocrinology Unit, IRCCS Giannina Gaslini, Genoa, Italy. Height SDS, sitting height SDS, head circumference SDS, weight SDS, upper and lower segment ratio, TS, and AEs were assessed at treatment initiation, 3, 6, and 12 months. A total of 8 participants were excluded due to difficulties in obtaining accurate measurements or short follow-up.

Over a >6 month follow up was available for 30 participants; 14 males (46.7%) and 16 females (53.3%), with a median age at baseline of 8.9 years (1st–3rd quartiles: 7.1–10.1 years). At treatment initiation 26 patients (86.7%) were in TS I–I/II and 4 (13.3%) were in TS II–II/III, weight SDS median value was -0.11 (1^{st}–3^{rd} quartiles -1.40;0.76) and height SDS was -0.43 (-1.17;0.31).

AEs were transient ISRs, with no participants opting for treatment discontinuation. No cardiac abnormalities were reported.

A significant increase in height and weight SDS was reported, with the upper and lower segment ratio remaining stable after 6 months of treatment with vosoritide. Further follow-up is needed to assess vosoritide's impact on QoL and cardiometabolic effects. [P88]

Growth response to vosoritide in achondroplasia – Real world experience from a tertiary centre in the UAE

Children treated with vosoritide were assessed for linear growth response. Height SDS was measured and compared with the general population. Linear height SDS was also measured before treatment, at 6 months, and at 12 months.

Of 8 patients receiving vosoritide at the centre, 5 received vosoritide for over 6 months. Vosoritide showed a beneficial effect on growth, with height SDS increases ranging from 0.24 to 0.87 SDS in the first year. 1 patient had a poor response and is being investigated for growth hormone deficiency.

Treatment with vosoritide produced positive growth responses in line with clinical trial data, apart from the 1 case under investigation. While initial results are promising, long-term outcomes are yet to be determined. [P197]

Design and objectives of the Acorn study: A non-interventional study evaluating long-term safety in achondroplasia children treated with vosoritide

The Acorn study is a European multicentre, non-interventional, post-authorisation study, that is the first treatment-based registry for ACH conducted with the aim of monitoring the long-term safety of vosoritide in real-world use. The recruitment goal is approximately 380 patients across 8–10 European countries. Participants will be recruited into 2 cohorts: 1. Incident users aged ≥4 months to ≤8 years, defined as those who either recently started, or plan to start treatment with vosoritide, and 2. Prevalent users who initiated treatment as part of the French expanded access programme or vosoritide open-label clinical trials.

The primary objective is to evaluate long-term safety of vosoritide including bone-related adverse events, such as spinal canal disorders, fractures and slipped capital femoral epiphyses, and immunogenicity. Secondary objectives will include evaluating the long-term impact on disease-related outcomes, and changes in anthropometric measures.

The study period is 10 years from the date of first patient enrolled. Patients who complete (reach adult height) or discontinue treatment will be followed up 2 years later. Almost all vosoritide-treated children aged ≥4 months to ≤8 years will be eligible for the study.

Recruitment began in April 2023, with 66 participants from 15 sites across 7 countries enrolled to date. Acorn will provide critical insights into vosoritide's long-term safety, effectiveness, and contextual use among other interventions. [P91]

THERAPIES IN DEVELOPMENT

TransCon CNP (navepegritide) improves physical functioning and well-being in children with achondroplasia (ACH) in the ACcomplisH trial

Savarirayan *et al.* present the 1-year analysis from ACcomplisH, a Phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial of once-weekly TransCon CNP versus placebo in children with ACH.

Pre-pubertal children with ACH between the ages of 2 and 10 years old were randomised 3:1 to receive TransCon CNP across 4 dose-escalation cohorts for 52 weeks, after which participants could continue to receive TransCon CNP in an OLE. HRQoL assessments at 52 weeks compared the results of participants receiving 100 µg/kg/week with results from the pooled placebo group during the randomised period.

A total of 57 participants were enrolled and 100% continued into the OLE. Significant improvements were observed for the Daily Living Functioning (p=0.047) and Emotional Well-Being (p=0.045) domains of the ACH Child Experience Measure-Impact assessment and SF-10 Physical Summary in participants ≥5 years old (p=0.002). Growth in the full trial population on TransCon CNP 100 µg/kg/week for 52 weeks was consistent with results from this cohort during the randomised period. No new safety signals and no treatment-related SAEs were reported; most TEAEs were Grade 1–2 and no TEAEs led to treatment modification or death.

These results suggest that once-weekly TransCon CNP offers clinical benefits with a favourable safety profile and supports the continued development of TransCon CNP for the treatment of ACH. [OC 4.2]

TYRA-300 demonstrates significant increases in bone length and foramen magnum area in a mouse model of FGFR3-related skeletal dysplasia

TYRA-300 is an oral, highly selective FGFR3 tyrosine kinase inhibitor that is currently undergoing assessment in the phase 1/2 clinical trial, SURF301 (Study in Untreated and Resistant FGFR3+ Advanced Solid Tumours). To explore the effectiveness of TYRA-300 in FGFR3-related chondroplasias, a daily dose of 1.2 mg/kg was administered for 15 days in the $Fgfr3^{Y367C/+}$ mouse model.

TYRA-300 resulted in a significant increase in body length in $Fgfr3^{Y367C/+}$ mice by 17.9% compared with control (p<0.0001). Increases were also seen in femur (+22.6%) and tibia (+33.0%) lengths and in the L4–L6 vertebrae (+23.5%; p<0.0001). Foramen magnum area in TYRA-300 treated mice increased by 15.08% versus control (p<0.0001) on mCT analysis. Furthermore, TYRA-300 treatment was also observed to restore the hypertrophic zone and secondary ossification centre within the epiphyses, improve the trabecular bone structure and increase chondrocyte differentiation.

These data indicate FGFR3 inhibition with TYRA-300 leads to increased bone length and foramen magnum area in this preclinical model. [OC 4.4]

MULTIDISCIPLINARY MANAGEMENT

Achondroplasia multidisciplinary team clinic evaluation

An ACH MDT in Glasgow was established to provide coordinated care from paediatric specialists in the fields of endocrinology, neurology, ENT, respiratory, clinical genetics, orthopaedic surgery and occupational therapy. Zwierzchowska *et al.* undertook a survey-based study to analyse the perspectives of clinicians and patients' families on the clinic's efficacy.

For this study, 2 surveys were designed: an 8-question survey for clinicians and a 15-question survey for the patients' families. Both surveys included close- and open-ended questions, assessing satisfaction with the clinics and their organisation, effectiveness of communication with the clinics and general feedback.

A total of 7 families and 8 clinicians responded to the survey. 100% of clinicians and 71% of families preferred the MDT clinics over separate appointments. Respondents generally agreed on the effectiveness and clarity of communication and management plans, with only 1 family reporting difficulty understanding these aspects. Suggestions were made to include more specialists in clinical psychology, dentistry and dietetics in the clinics. Other suggestions included increasing clinic frequency, improving room organisation, and offering clinics closer to patients' residences.

Overall, there was strong satisfaction and appreciation for the MDT clinics, with emphasis on possible areas of improvement to provide holistic and accessible care. These findings emphasise the importance of ongoing efforts to improve the clinics and the importance of the clinics' existence, prompting consideration for the establishment of more clinics in future. [P135]

MONITORING AFMS3 AND EVALUATING PAIN

Natural history of spinal cord compression stage AFMS3 in infants with achondroplasia: Retrospective cohort study

The Achondroplasia Foramen Magnum Score (AFMS; 0–4) is used to classify the severity of FMS to inform neurosurgical management. Well children with AFMS3 are not immediately referred for neurosurgery, but undergo routine repeat MRIs after 12 months. As the natural history of children with AFMS3 is unclear, a review of the follow-up MRIs of infants with ACH with AFMS3 was carried out by Cheung *et al.* to understand the progression of FMS.

This retrospective cohort study from 2 tertiary centres included infants with ACH and AFMS3 on initial MRI who subsequently underwent repeat MRI or proceeded straight to neurosurgery. A total of 22 infants were included in this study with a mean age (SD) in months of 6.23 (±3.82) at baseline and 17.95 (±7.68) at follow up.

From the cohort, 5 participants (22.7%) showed no change at follow-up MRI, 8 (36.2%) improved to AFMS2 or AFMS1, and 9 (40.9%) progressed to AFMS4. Of those who progressed to AFMS 4, 1 participant (4.5%) had neurosurgery without repeat MRI.

MRI screening for FMS in infants with ACH is essential and follow up MRI in children with AFMS3 should be carried out, as over 40% progressed and required intervention. Follow up MRIs should be conducted every 6 months to detect changes earlier in this at-risk cohort. [P150]

Pain and biopsychosocial impact in children with skeletal dysplasias

Participants up to age 18 years with confirmed or suspected skeletal dysplasias were recruited from the multidisciplinary clinic in Eastern Ontario, Ottawa, Canada. Parents and caregivers completed validated questionnaires during clinic visits assessing their child's pain, HRQoL, fatigue, pain interference, symptoms of depression and anxiety, sleep, peer relationships, and physical function. Participants aged ≥6 years also completed a 2-legged jump as part of the physical-function assessment. Descriptive statistics were used for analysis and associations were identified using Pearson's correlations.

A total of 32 participants (41% female) with a mean age of 11.8 years (SD 4.1) were included. Diagnoses included achondroplasia (28%), osteogenesis imperfecta (16%), juvenile osteoporosis (9%), and other skeletal dysplasias (47%). Results showed that 63% of parents and caregivers reported that their child experienced pain, with median current pain and worst pain in the previous week being 2.1 (0.2–9.8) and 5.0 (0.2–100), respectively. Current pain was associated with pain interference (r=0.73, p<0.0001), HRQoL (r=-0.56, p<0.0001), peer relationships (r=-0.51, p=0.004), fatigue (r=0.45. p=0.01), and depressive symptoms (r=0.38.p=0.03). Worst pain the previous week was associated with pain interference (r=0.72, p<0.0001), HRQoL (r=-0.65, p<0.0001), fatigue (r=0.53, p=0.002), peer relationships (r=-0.52, p=0.002), and weight-adjusted single 2-legged jump score (r=-0.49, p=0.05).

Pain is prevalent in children with skeletal dysplasias and is shown to be linked to increased pain interference, fatigue, and depressive symptoms, as well as decreased HRQoL, peer relationships, and muscle power. Further exploration of these biopsychosocial outcomes is needed to determine appropriate targets of future intervention to treat pain in children with skeletal dysplasias. [P168]

ISCBH ERN BOND ACHONDROPLASIA SESSION

This year the ISCBH ERN BOND session included a debate titled *Should leg lengthening be recommended for everyone with achondroplasia?* Professor Mohamad Maghnie presented the argument *Leg lengthening should be recommended to all individuals with achondroplasia,* and Chair of BKMF, Mrs Patricia Carl-Innig presented the case against. A round-table discussion was led by Dr Simone Riganti and moderated by Professor Deborah Eastwood. As in previous years, the group will develop a publication as the output from the workshop.

LIST OF ABBREVIATIONS

ACH – achondroplasia
AE – adverse event
AFMS – achondroplasia foramen magnum score
AGV – annual growth velocity
BKMF – Federal Association of People of Short Stature and their Families (Bundesverband Kleinwüchsige Menschen und ihre Familien e.V.)
CNP – C-natriuretic peptide
ENT – ear, nose and throat
FGFR3 – fibroblast growth factor receptor 3
FMS – foramen magnum stenosis
HRQoL – health-related quality of life
IRCCS – Institute of Scientific Hospitalisation and Care (Istituto di Ricovero e Cura a Carattere Scientifico)
ISR – injection-site reaction
mCT – micro computed tomography
MDT – multidisciplinary team
MRI – magnetic resonance imaging
OLE – open-label extension
QoL – quality of life
QoLLISY – quality of life in short stature youth
SAE – serious adverse event
SD – standard deviation
SDS – standard deviation score
TEAE – treatment emergent adverse event
TS – Tanner stage

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