
From October to November 2021,
48 achondroplasia patients
aged 2 to 15 years started
vosoritide treatment at
Freiburg University Hospital

UNIVERSITÄTS KLINIKUM FREIBURG

Disclosures

Outside of the current work, I have also received travel and honoraria from BioMarin International Ltd.

Advances in Achondroplasia
Frankfurt, 21st April 2023

UNIVERSITÄTS KLINIKUM FREIBURG

Early Experience of Vosoritide in Clinical Practice

1.) Requirements and practicalities around training patients and caregivers to administer vosoritide

2.) Clinical capacity and infrastructure requirements (MDT)

3.) Key clinical investigations required prior to initiation of treatment

4.) Key parameters to measure during follow-up

5.) Clinical case: vosoritide therapy and monitoring in toddlers

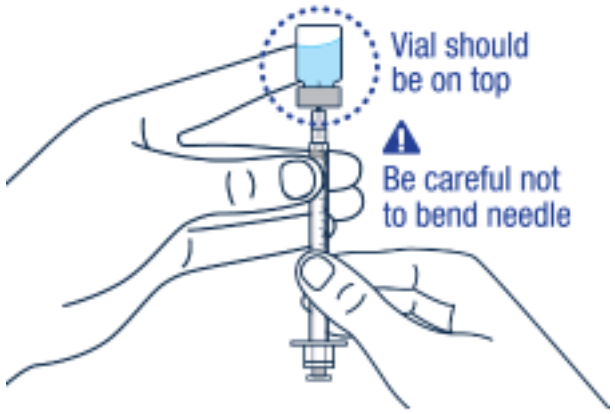
6.) Real world data: safety and efficacy in 59 patients

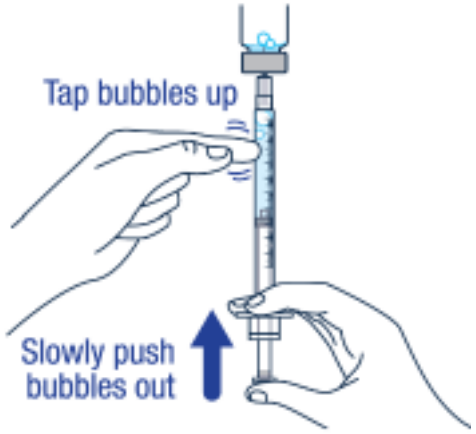
1.) Requirements and practicalities around training patients and caregivers to administer vosoritide: fighting with hardware

UNIVERSITÄTS KLINIKUM FREIBURG

Frequent handling problems:

- **Bending of the needle**
- **Loss of syringe while eliminating bubbles**





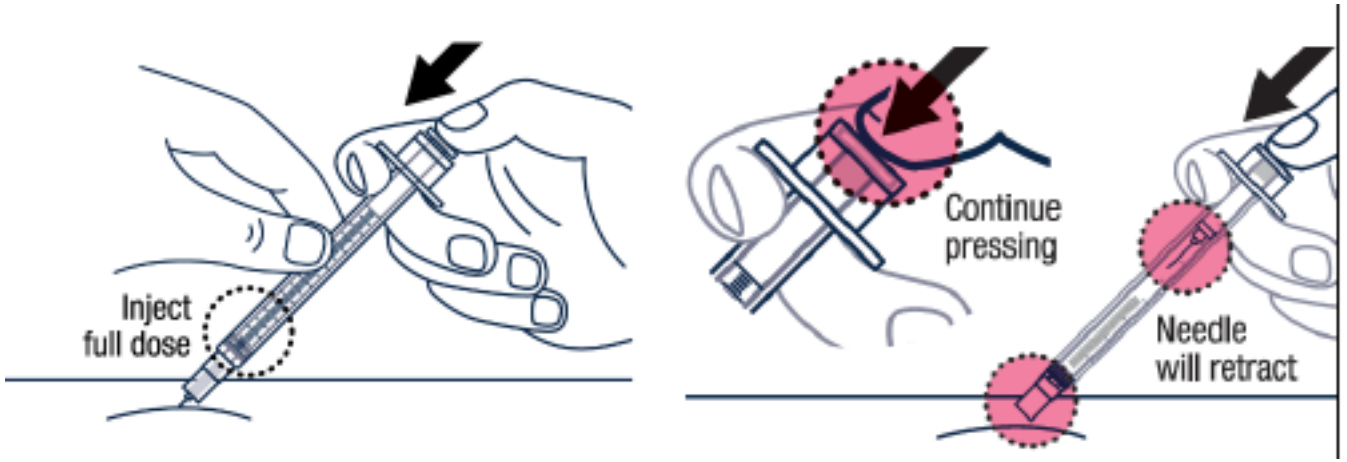
► Minimum 2 rounds of patients/caregivers training are required:
1.) Demonstration (may take place online) 2.) Practical handling training

1.) Requirements and practicalities around training patients and caregivers to administer vosoritide

UNIVERSITÄTS KLINIKUM FREIBURG

Frequent complications:

- **Needles do not retract easily**



► Additional syringes have to be provided. Support of families by nurse service (n=2/56), especially for those with younger children.

1.) Requirements and practicalities around training patients and caregivers to administer vosoritide

UNIVERSITÄTS KLINIKUM FREIBURG

Frequent complications:

- **Limited number of injection sites in your**

⚠

Do not inject through clothes.

Do not inject into skin that is swollen, sore, bruised, red, hard, or scarred.

The following sites are recommended for injection:

- **Thighs** or
- **Abdomen** (2 inches from belly button) or
- **Buttocks**
- Healthcare providers and caregivers may also inject VOXZOGO into the **back of the upper arms.**

► Self support/interconnecting of families on therapy (to allow children on therapy to interact), strategies to facilitate acceptance for different ages

UNIVERSITÄTS KLINIKUM FREIBURG

x 3 = lasts 1 month

ınd storage of large

1.) Requirements and practicalities around training patients and caregivers to administer vosoritide

UNIVERSITÄTS KLINIKUM FREIBURG

Logistics, part 2:

Currently N=56: 12 x 56 = 672 prescriptions per year. Be prepared…

Private healthcare requires additional paperwork.

Due to high costs (1.200 Euro/dose), German health insurance only allows the vosoritide prescription for a month (i.e. 36.000 Euro)

1.) Requirements and practicalities around training patients and caregivers to administer vosoritide: Year 1 (4–5 visits in 12 months)

UNIVERSITÄTS KLINIKUM FREIBURG

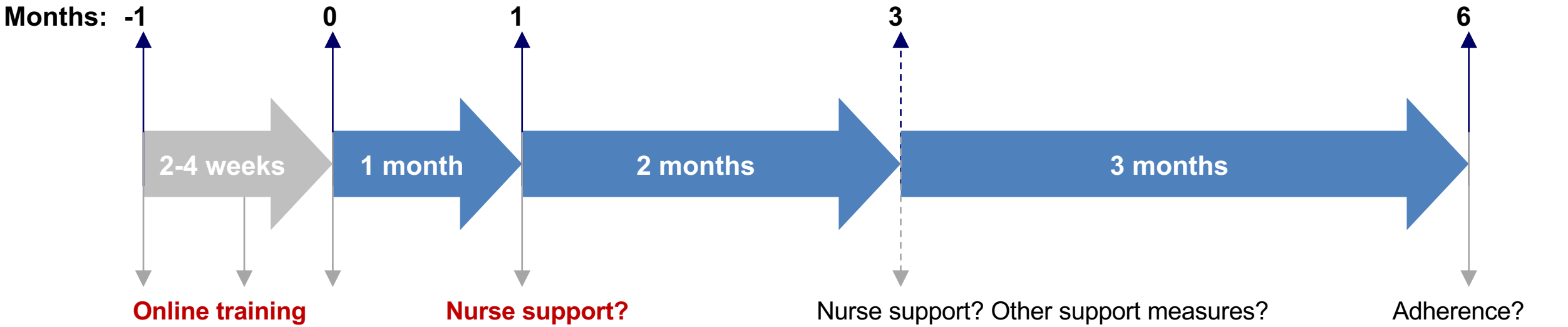
Pre-initiation visit
- Baseline lab,
- 1st vosoritide prescription

Initiation
- Baseline auxology
- bone age

1st follow-up
Local reactions
cGMP levels

Optional follow-up
- Auxology
- Optional lab

2nd follow-up
- Auxology (growth velocity)
- Lab



1st practical instruction, training kits

1st supervised application

2nd supervised application

(3rd supervised application)

3rd supervised application

2.) Clinical capacity and infrastructure requirements – „must have“

ERSITÄTS
KUM FREIBURG

2.) Clinical capacity and infrastructure requirements - „must have easy access to“

UNIVERSITÄTS KLINIKUM FREIBURG

3. Pediatric neurology:
- Electrophysiology, physiotherapy, social workers

4. Pediatric pulmonology (cardiology):
- Sleep laboratory, home mechanical ventilation (CPAP)

5. Pediatric HEENT/audiology:
- Brainstem evoked potentials, tympanometry

6. Pediatric orthopedics:
- Experience with hemiepiphyseodesis in skeletal dysplasias

7. Pediatric neurosurgery:
- Experience with spinal decompression/laminectomy

2.) Clinical capacity and infrastructure requirements

UNIVERSITÄTS KLINIKUM FREIBURG

8. Time!

► Minimum 1 hour for patients/caregivers are required for practical training.

► Minimum 1 hour for patients/caregivers are required for pre-initiation/initiation visits.

► Additional time for administrative tasks has to be taken into account.

ired prior to

UNIVERSITÄTS KLINIKUM FREIBURG

WARNUNG: Das chronologische Alter ist außerhalb des für die Befundung zulässigen Bereichs.

Knochenalterbestimmung [1]

Chronologisches Alter (CA)/ Geschlecht

2 Jahre 6 Monate
(30 Monate) / W

Knochenalter

1 Jahre 7 Monate
(19 Monate)

Natürliche Standardabweichung (SD) [2]

5.37 Monate

Status (basiert auf 2SD) [2]

NORMAL

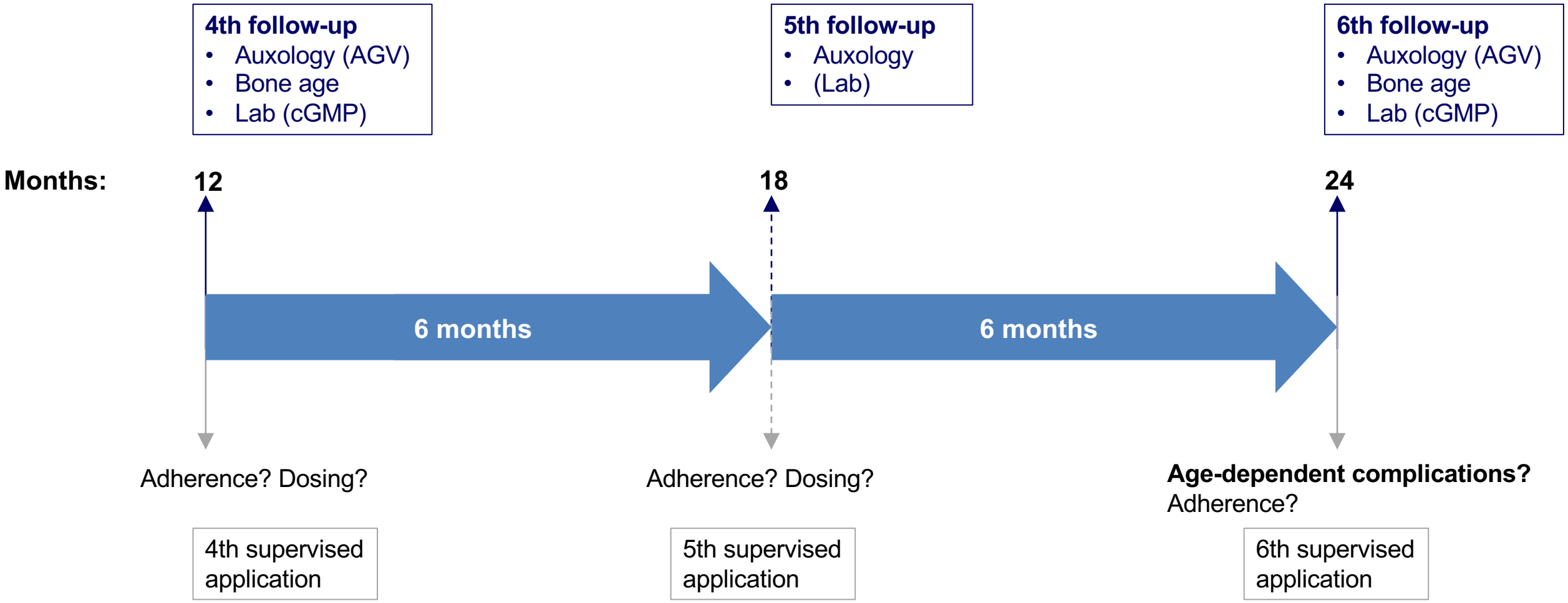
1J 7.3M CA - 2SD | CA - 1SD | 2J 6M CA | CA + 1SD | 3J 4.7M CA + 2SD

Prospektive Endgrößenbestimmung [3]

Wachstumspotenzial

Berechnung nicht möglich: Knochenalter außerhalb des Referenzbereiches. [3].

4.) Key parameters to measure during follow-up: **Year 2** (2–3 visits in 12 months)



4.) Key parameters to measure during follow-up

UNIVERSITÄTS KLINIKUM FREIBURG

First follow-up (1 months of vosoritide):

- Therapy-related complications, supervision of application, correct dosing

Second follow-up (6 months of vosoritide):

- Auxology, annualized growth velocity, lab, dosing

Third follow-up (1 year of vosoritide):

- Auxology, annualized growth velocity, lab, dosing, **bone age**

►Bi-annual or 3 monthly visits, depending on age/secondary complications

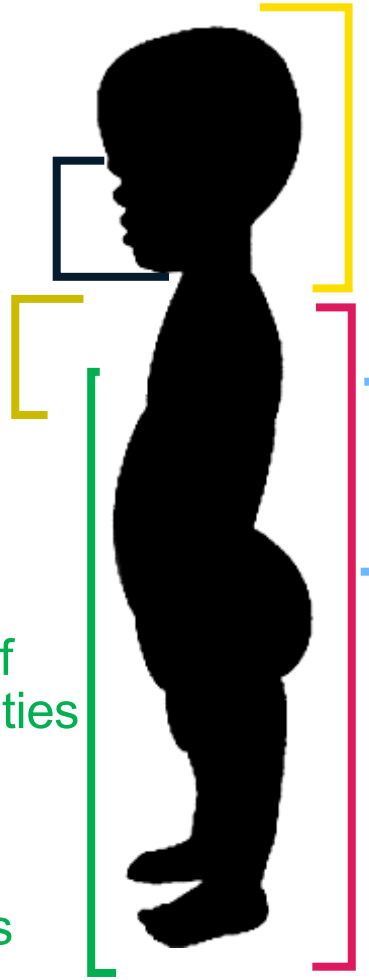
- Standardized assessment of diagnostic findings under vosoritide (e.g. classification of foramen magnum stenosis, axis deviation etc)

Multi-System Comorbidities Associated With Achondroplasia [1-3]

EAR, NOSE, AND THROAT
- Recurrent otitis media
- Hearing loss
- Dental malocclusion

CARDIOPULMONARY COMPLICATIONS
- Sleep-disordered breathing
- Cardiovascular disease

EXTREMITIES
- Rhizomelic shortening of upper and lower extremities
- Trident hand
- Radial head subluxation
- Genu varum
- Lateral discoid meniscus
- Hip flexion contractures
- Elbow contractures



NERVOUS SYSTEM
- Cervicomedullary compression
- Craniocervical junction anomalies

BACK
- Spinal stenosis
- Thoracolumbar kyphosis
- Lumbar hyperlordosis

Metabolic
- Obesity

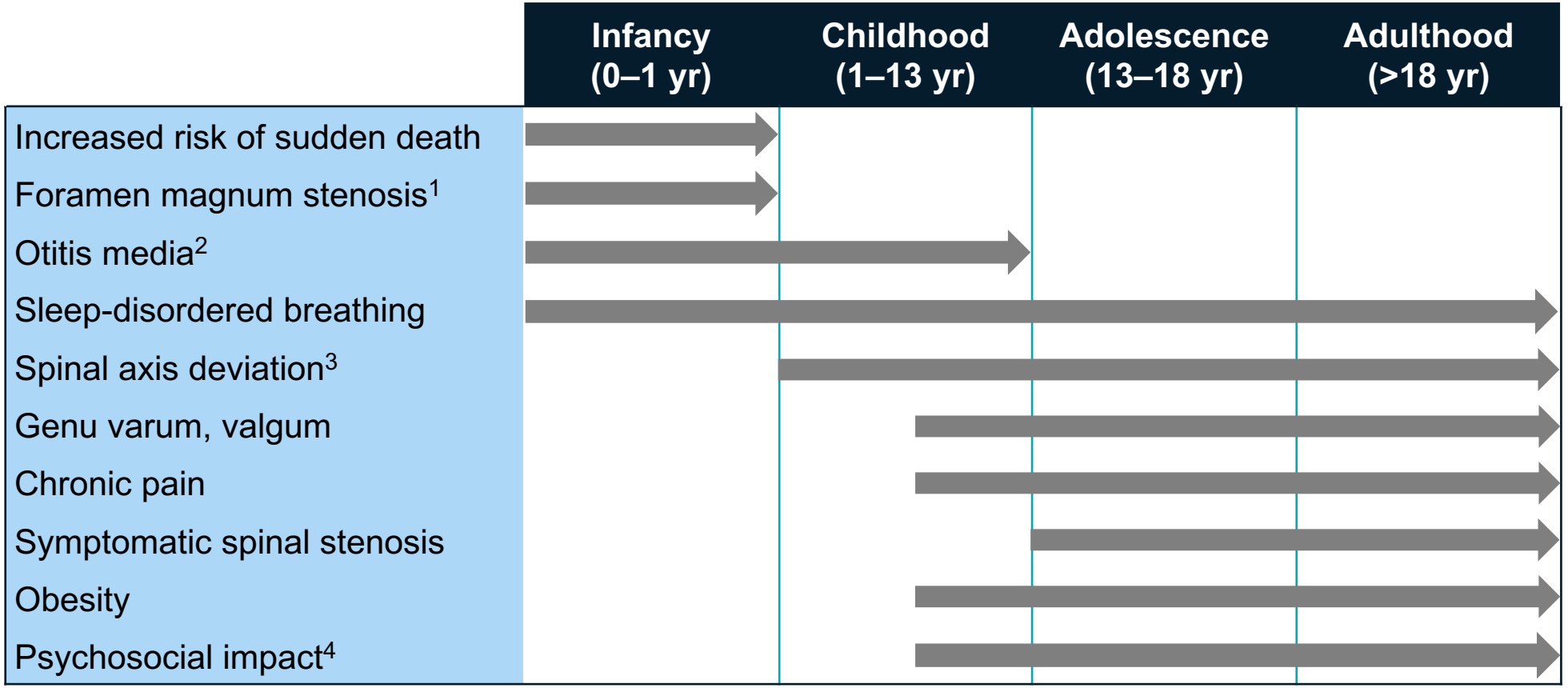
[1]Ireland PJ, et al. Appl Clin Genet. 2014;7:117-125. [2]Hunter AGW, et al. J Med Genet. 1998;35:705-712.[3]Horton WA, et al. Lancet. 2007;370:162-172.

4.) Key parameters to measure during follow-up

UNIVERSITÄTS KLINIKUM FREIBURG

Age-dependent secondary complications

Complications of achondroplasia beyond growth across life stages*



*non-exhaustive list; Adapted from Hoover-Fong J, et al. Bone 2021;146:115872; 1. Hecht JT, et al. Am J Med Genet 1989;32:528-35; 2. Wright MJ, et al. Arch Dis Child 2012;97:129-34; 3. Kopits SE. Basic Life Sci 1988;48:241-55; 4. Yonko EA, et al. Am J Med Genet A 2021;185:695-701.

Age-specific prevention schemes – consensus?

- For each child (re)assess his/her current status and discuss it with parents
- Is it the best time to start therapy?
- Manage expectations regarding improvement of each complication
- Special attention for children newly referred to your team

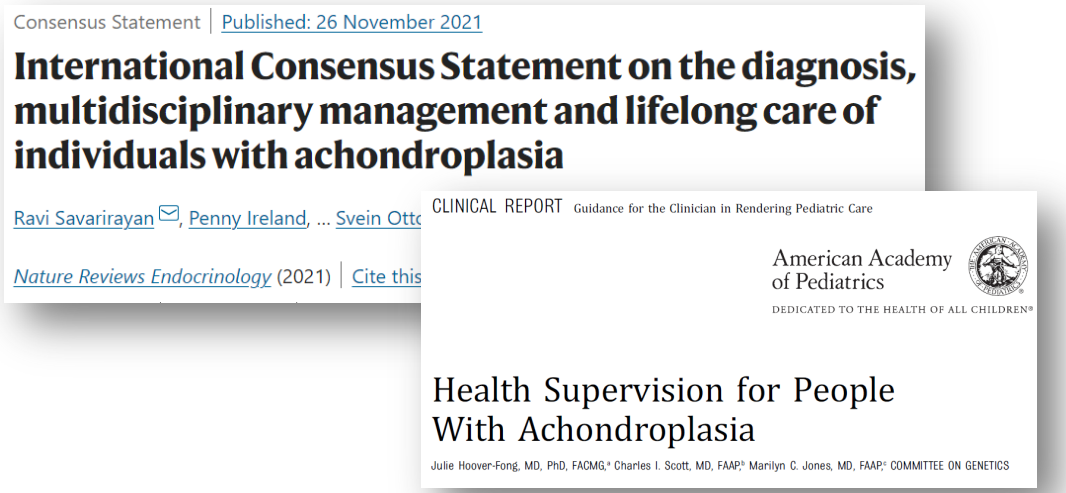


TABLE 1 Health Supervision for People With Achondroplasia

	Prepregnancy and Short-Stature Parents	Prenatal and Short- and Average-Stature Parents	Birth to 1 mo	1 mo to 1 y	1–5 y	5–13 y	13–21 y	Adult
Diagnosis								
Physical examination	X	X of fetus	X	X	—	—	—	—
Imaging	X radiographs	X ultrasonography of fetus	X	—	—	—	—	—
Molecular testing	X	X of fetus	X	—	—	—	—	X
Genetic counseling								
Review natural history	X of potential offspring	X	X	X	X	X	X	X
Recurrence risk and genetics	X	X	X	X	X	X	X	X
Delivery mode and location	X	X	—	—	—	—	—	X
Support group(s), family support	X	X	X	X	X	X	X	X
Desired pregnancy?	—	X	X	—	—	—	—	X
Medical evaluation								
Growth (height or length, weight, occipitofrontal circumference)	—	X	X	X	X	X	X	X
Physical examination	—	—	X	X	X	X	X	X
Neurologic examination	—	—	X	X	X	X	X	X
Development	—	—	X	X	X	X	—	—
Neuroimaging	—	—	X	X if new diagnosis	X as indicated	X as indicated	X as indicated	X as indicated
Polysomnography	—	—	X	X if new diagnosis	X as indicated	X as indicated	X as indicated	X as indicated
Hearing assessment	—	—	X	X	X	X	X	X
Radiography for kyphosis, genu varus, bowing	—	—	—	X	X as indicated	X as indicated	X as indicated	X as indicated
Anticipation or guidance								
Warning signs of severe complications	—	—	X	X	X	X	X	X
Car seats	—	X for hospital discharge	X	X	X	X	—	—
Achondroplasia-specific development	—	—	X	X	X	—	X	—
Jugular bulb dehiscence warning	—	—	—	X	X	X	X	X
Supplemental security income inclusion	—	—	—	X	X	X	X	X
Accommodations	—	—	—	—	X	X	X	X
Obesity, exercise, diet	—	—	—	—	X	X	X	X
Driving	—	—	—	—	—	—	X	X
College	—	—	—	—	—	—	X	X
Job training	—	—	—	—	—	—	X	X

Savarirayan R et al. *Nat Rev Endocrinol.* 2021; 18: 173–189. Hoover-Fong J et al. *Pediatrics.* 2022;145(6):e20201010.

4.) Key parameters to measure during follow-up

UNIVERSITÄTS KLINIKUM FREIBURG

Multidisciplinary management and vosoritide – What do we monitor when?

Therapy-related monitoring:

- Safety, supervision of application, correct dosing, efficacy

Monitoring based on the known natural history of achondroplasia:

- Known age-related complications, „regular“ multidisciplinary care schedule

►Monitoring based on the evolving knowledge of treated achondroplasia:

- „Adapted“ multidisciplinary care schedule

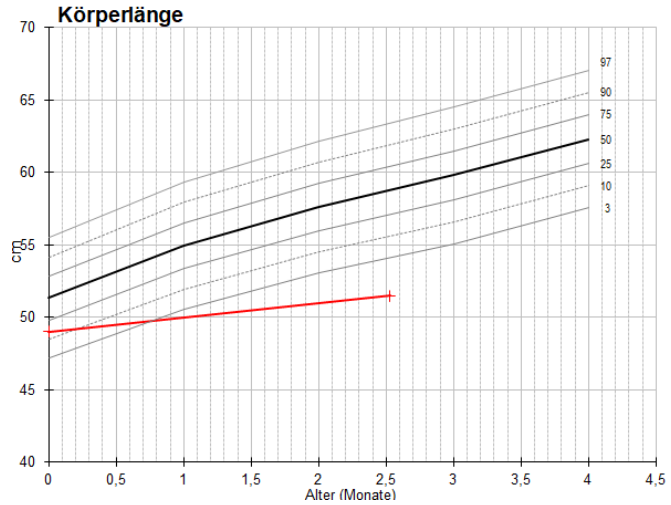
Unbiased monitoring for rare or late complications in treated children:

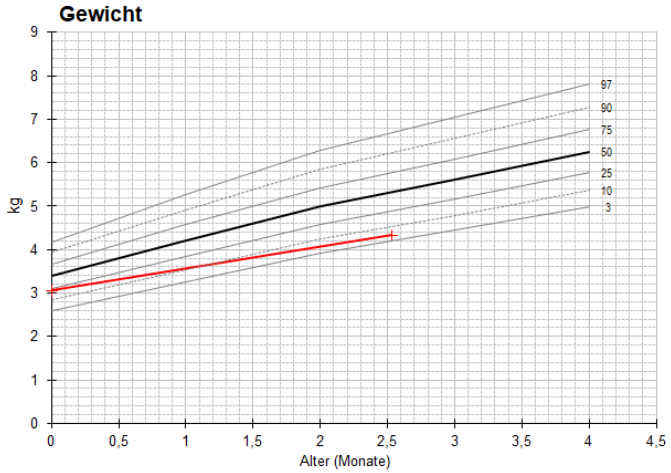
- Comprehensive clinical and laboratory investigation schedule

5.) Clinical case: vosoritide therapy and monitoring in toddlers

UNIVERSITÄTS KLINIKUM FREIBURG

2.5 months old girl, centile-crossing parameters

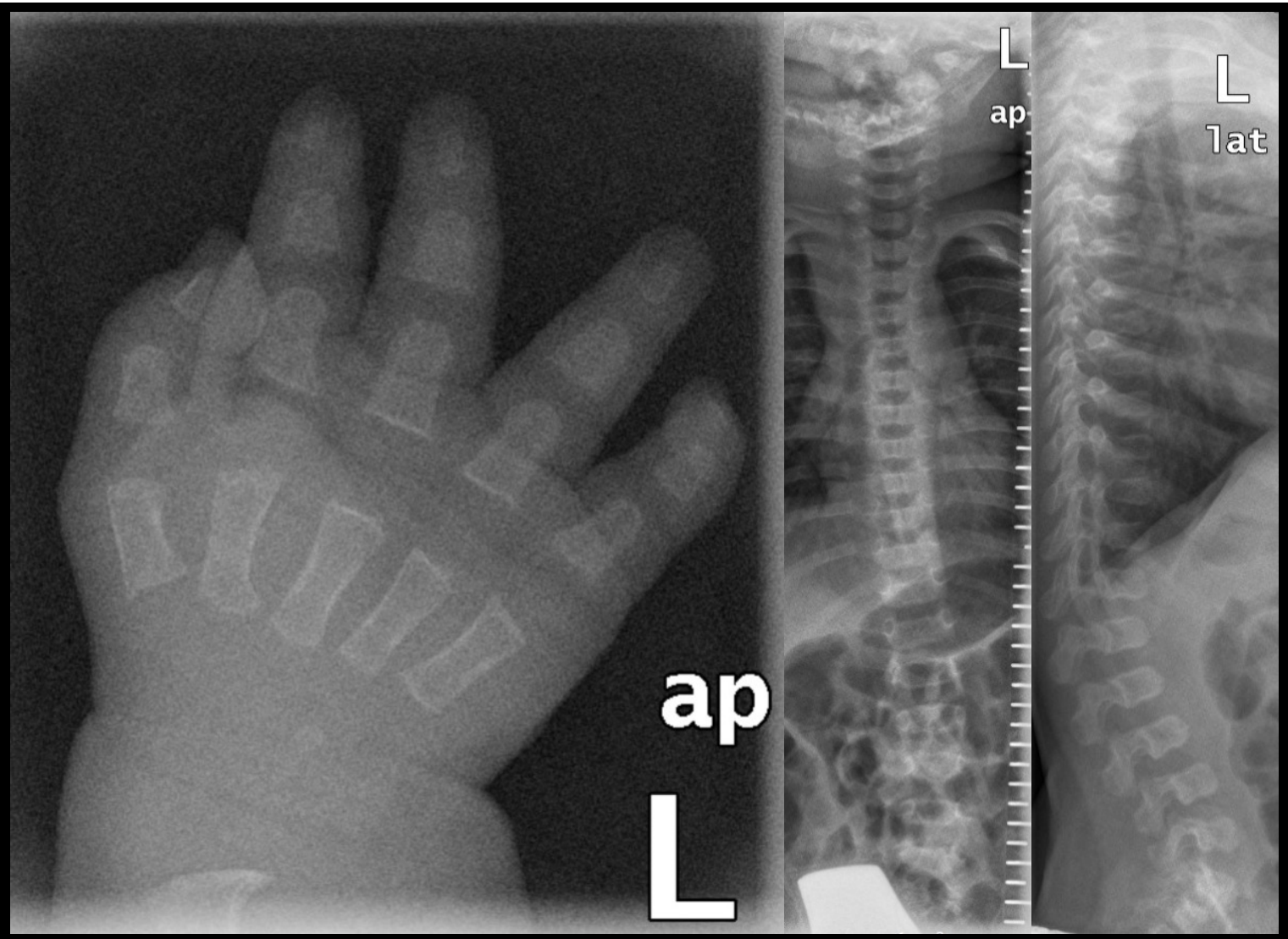




Presenter's clinical case study

5.) Clinical case: vosoritide therapy and monitoring in toddlers

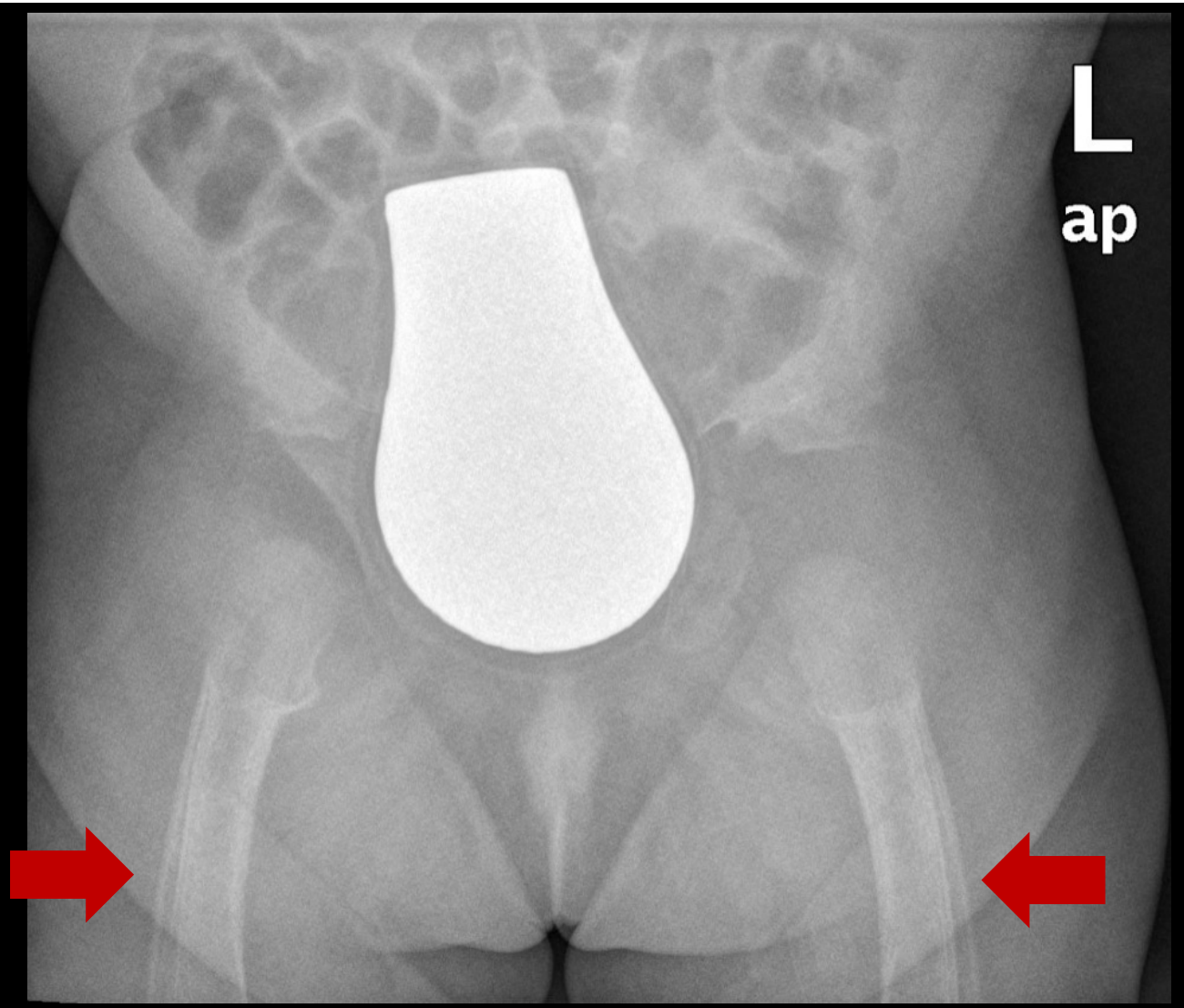
UNIVERSITÄTS KLINIKUM FREIBURG



Presenter’s clinical case study

5.) Clinical case: vosoritide therapy and monitoring in toddlers

UNIVERSITÄTS KLINIKUM FREIBURG



Presenter’s clinical case study

No health problems at 8 months!

UNIVERSITÄTS KLINIKUM FREIBURG

Auxology, 8 months – German schedule

Achondroplasie-Betreuungsplan:

Vorgeburtlich (bei Verdacht):
- Ultraschall, genetische Beratung

Bei Diagnosestellung:
- Klinischer Befund, Röntgen, Genanalyse, Beratung

2-3 Monate:
- Klinischer Befund, u.U. Schlaflabor

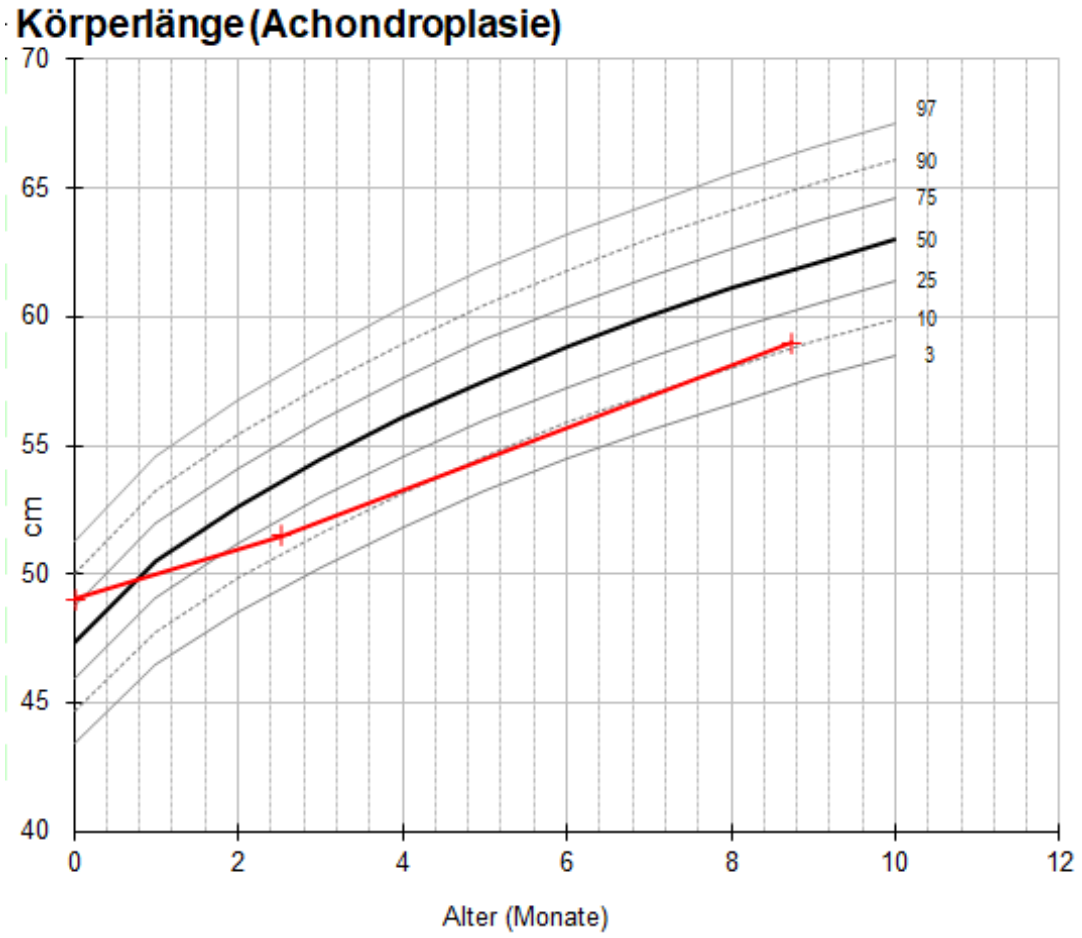
6 Monate:
- Klinischer Befund, **HNO** mit Hörtest

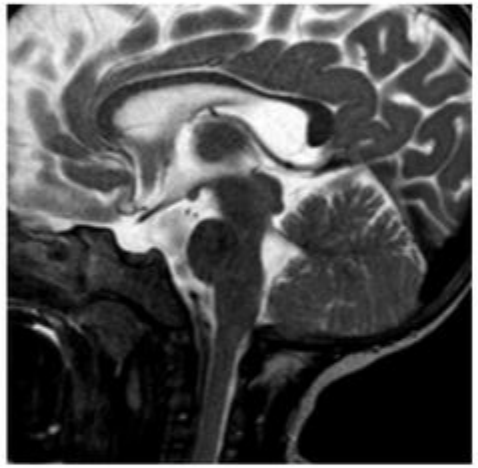
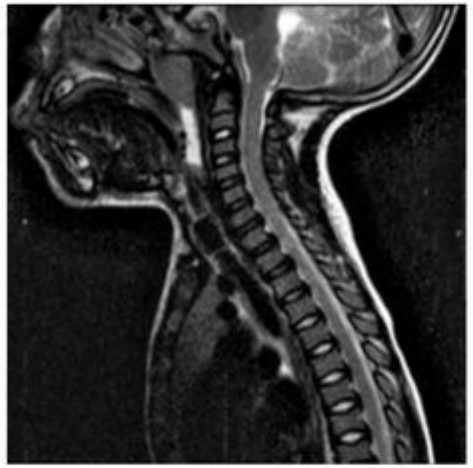
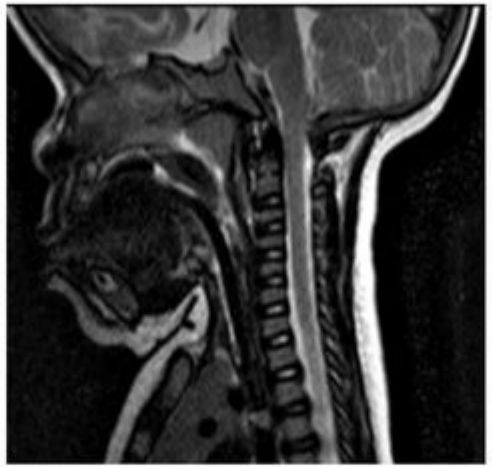
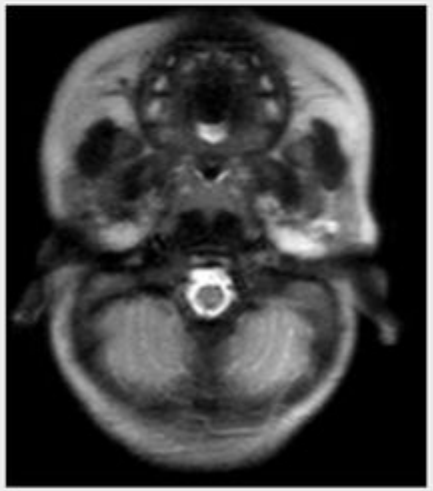
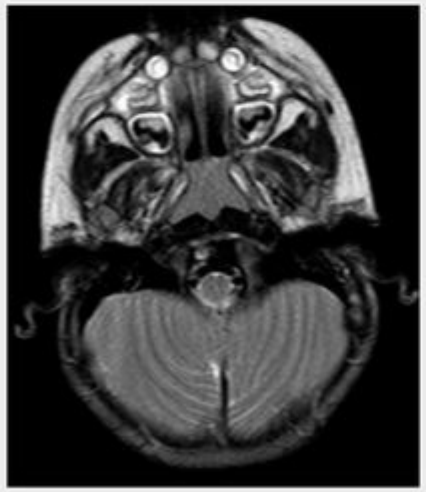
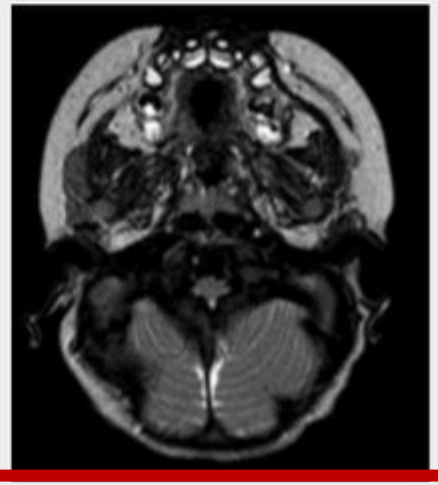
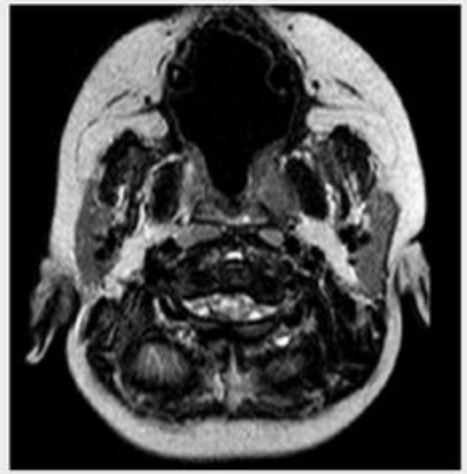
9 Monate:
- Klinischer Befund, u.U. HNO

12-18 Monate:
- Klinischer Befund, HNO, Schlaflabor, **MRT, u.U. SSEP**

2 Jahre:
- Klinischer Befund, SSEP, HNO, **Orthopädie**

Später jährlich:
- Klinischer Befund evtl. weitere neurologische bzw. zusätzliche spezielle Diagnostik, Beratung



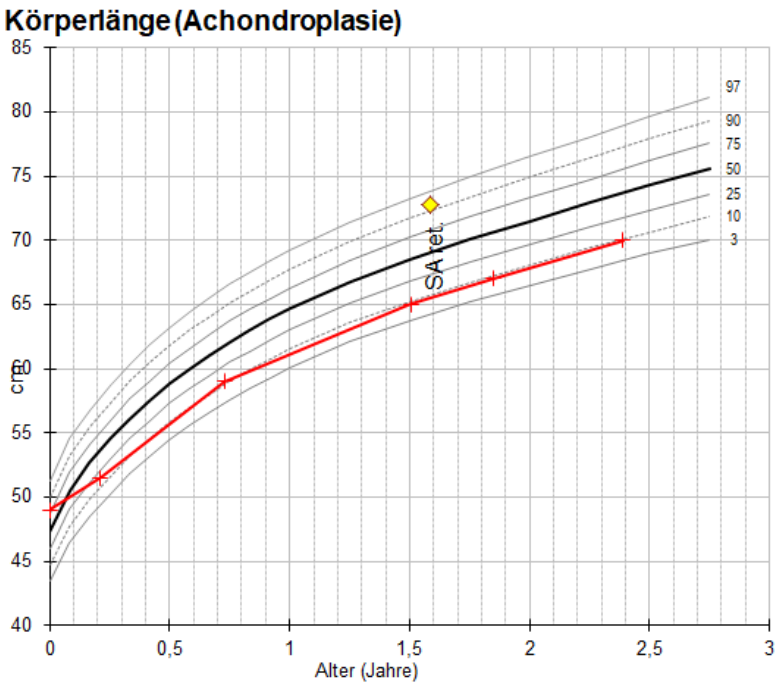
AFMS0	AFMS1	AFMS2	AFMS3	AFMS4
Normal foramen magnum	Constitutional narrowing of the foramen magnum with preserved CSF (no cord distortion)	Narrowing of the foramen magnum with loss of CSF space surrounding the cord	Loss of the CSF space with cord compression	Cord compression and signal changes (Myelomalacia)
				
				

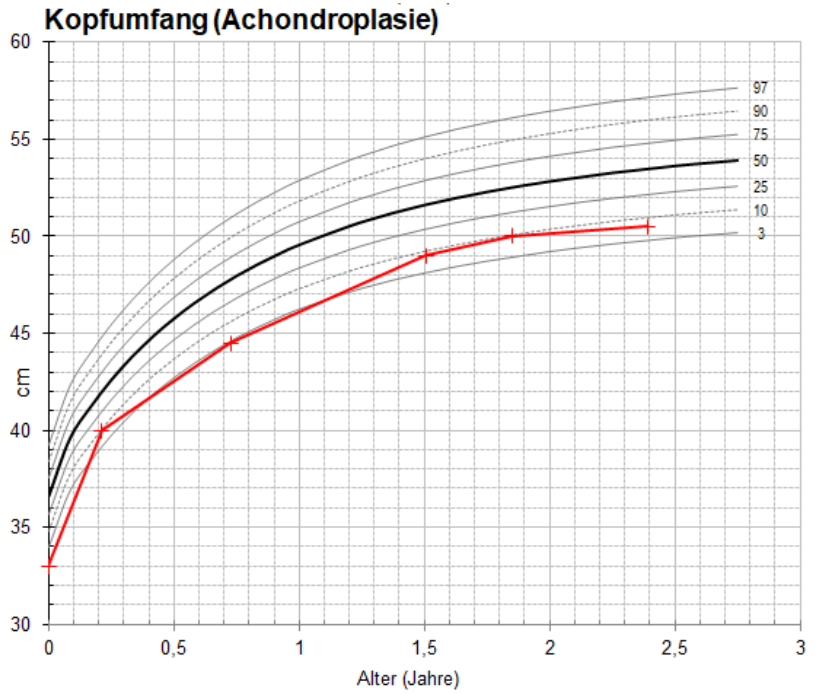
Presenter's clinical case study

Dougherty H *et al.*, 2018,
Cheung *et al.*, 2020

5.) Clinical case: vosoritide therapy and monitoring in toddlers

28 months, start of vosoritide therapy





Presenter's clinical case study

Key clinical investigations required prior to initiation of treatment

UNIVERSITÄTS KLINIKUM FREIBURG

1. Genetic confirmation of ACH
- Required for coverage by health insurance in Germany (HCH-ACH)

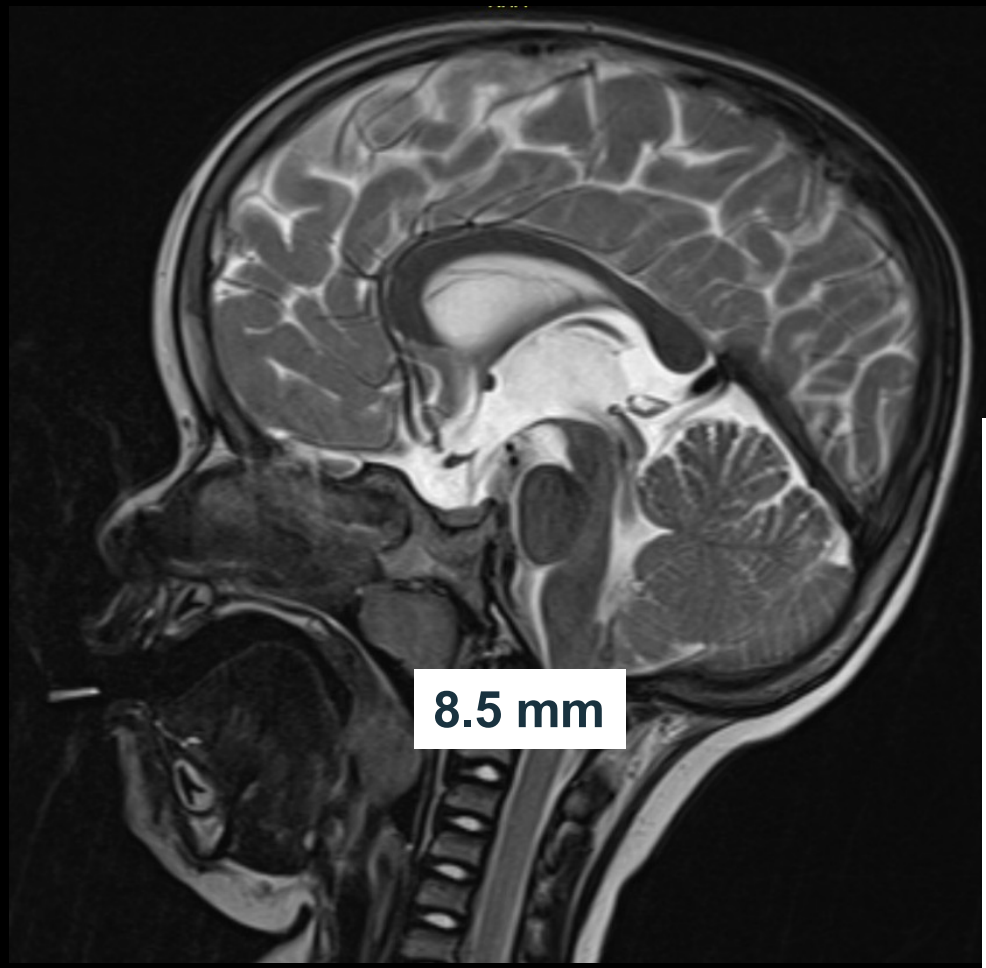
2. Comprehensive auxology (ACH centiles)
- Including sitting height, arm span, growth velocity

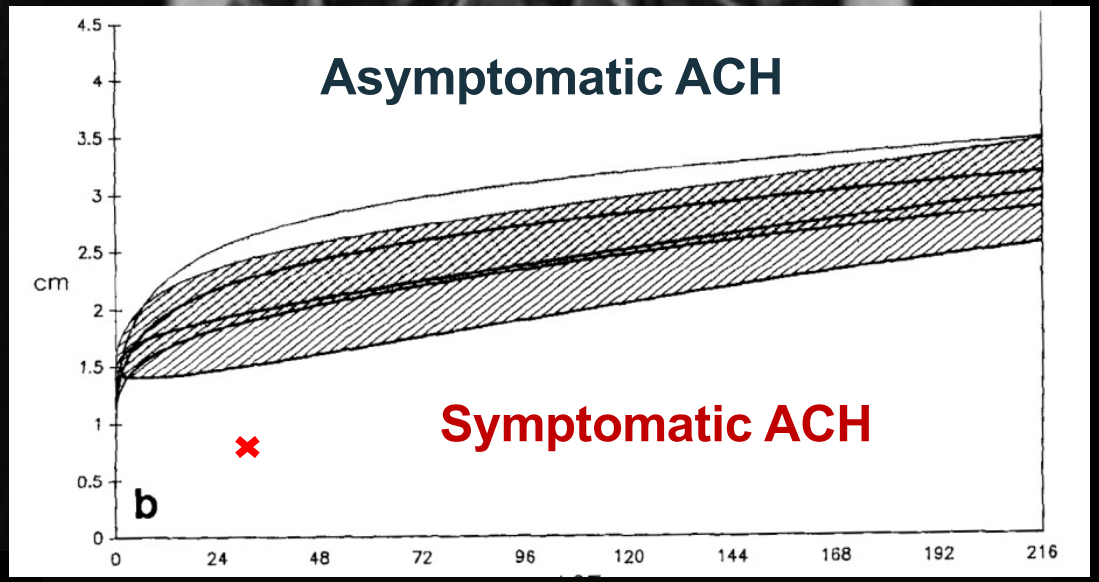
3. Bone age
- Standardized assessment, software supported (i.e. „Bone Expert“)

4. Comprehensive clinical chemistry of blood and urine
- Including hormones, vitamin D, PTH, ostase, crosslinks

5. Review of age-related complications, baseline investigations at initiation
- 2–5 years: cranial MRI; 2–5 years: cardiology if OSA; 12–15 years: spinal MRI

Imaging at 28 months: Asymptomatic ACH



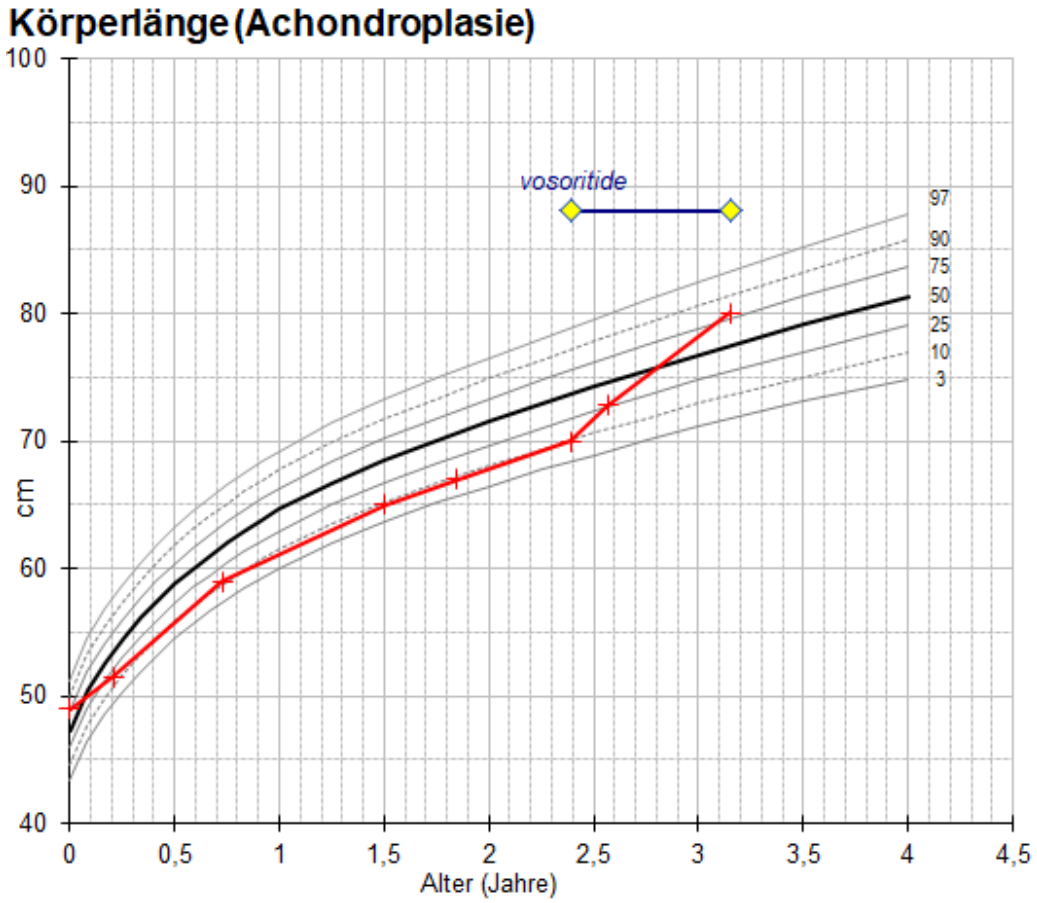


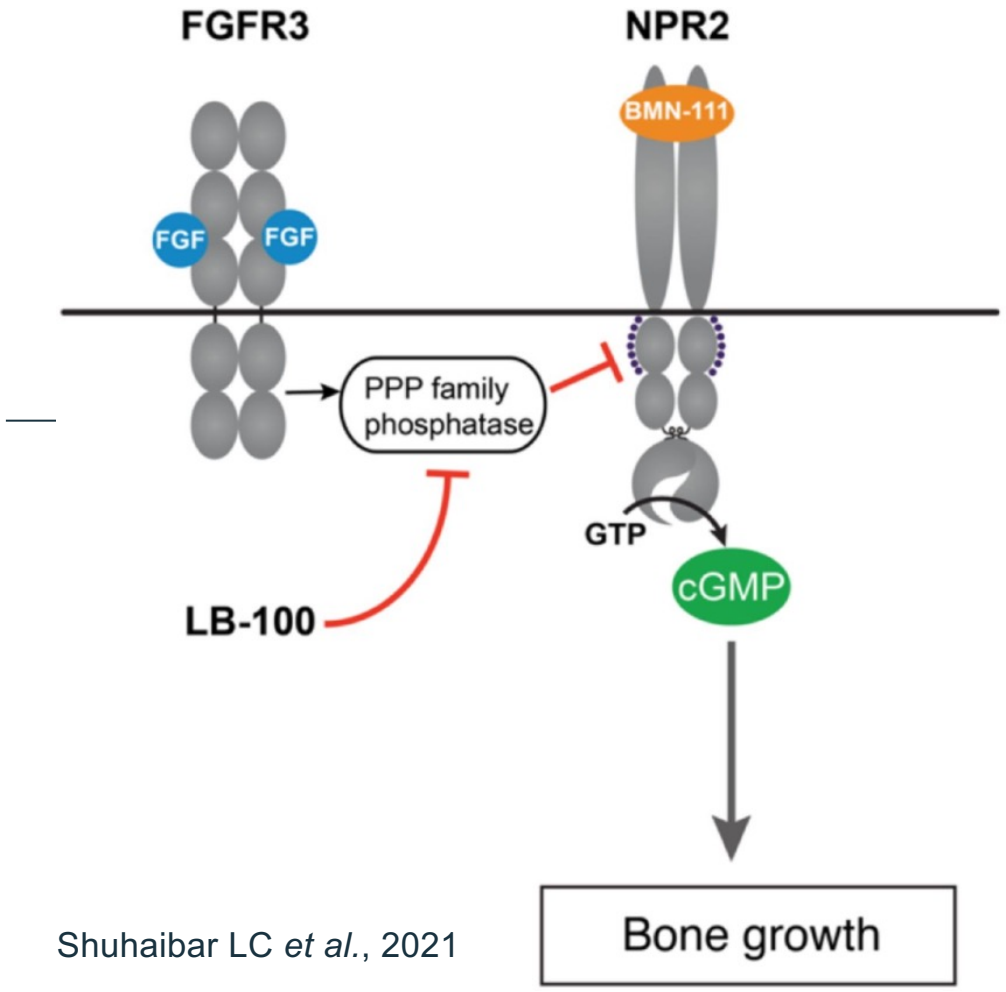
ACH, achondroplasia

Presenter‘s clinical case study

5.) Clinical case: vosoritide therapy and monitoring in toddlers

6 months of vosoritide, 34 months of age

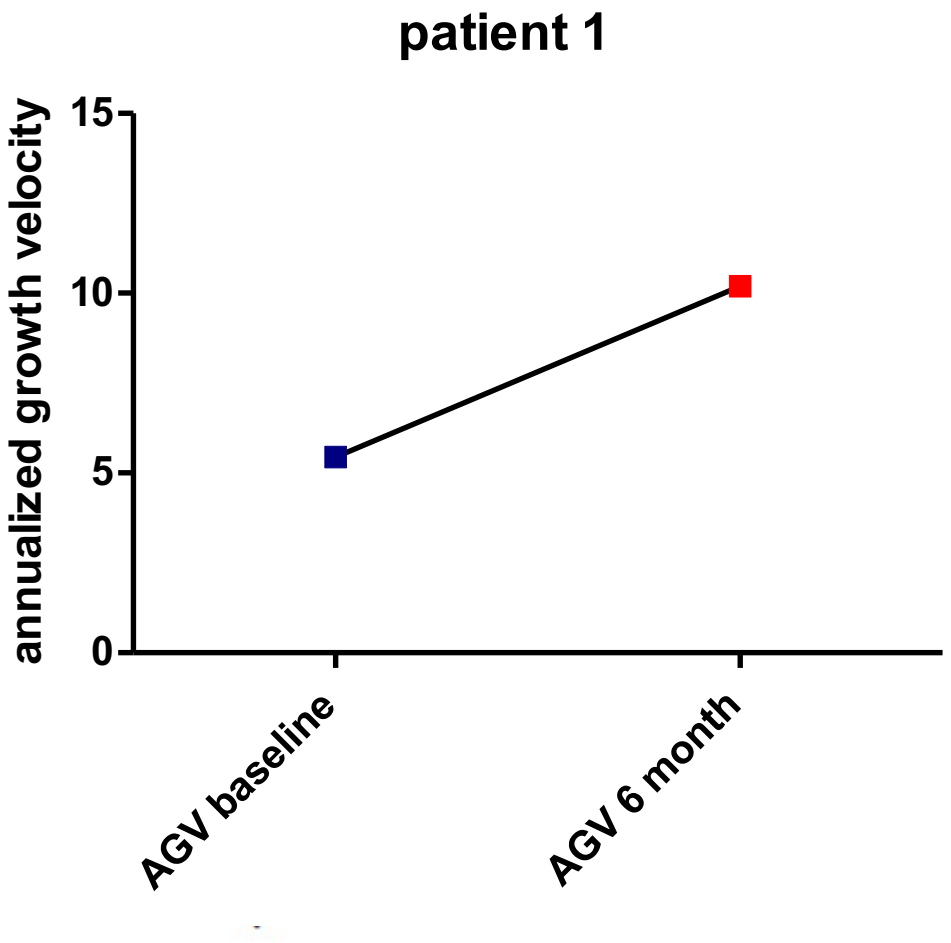


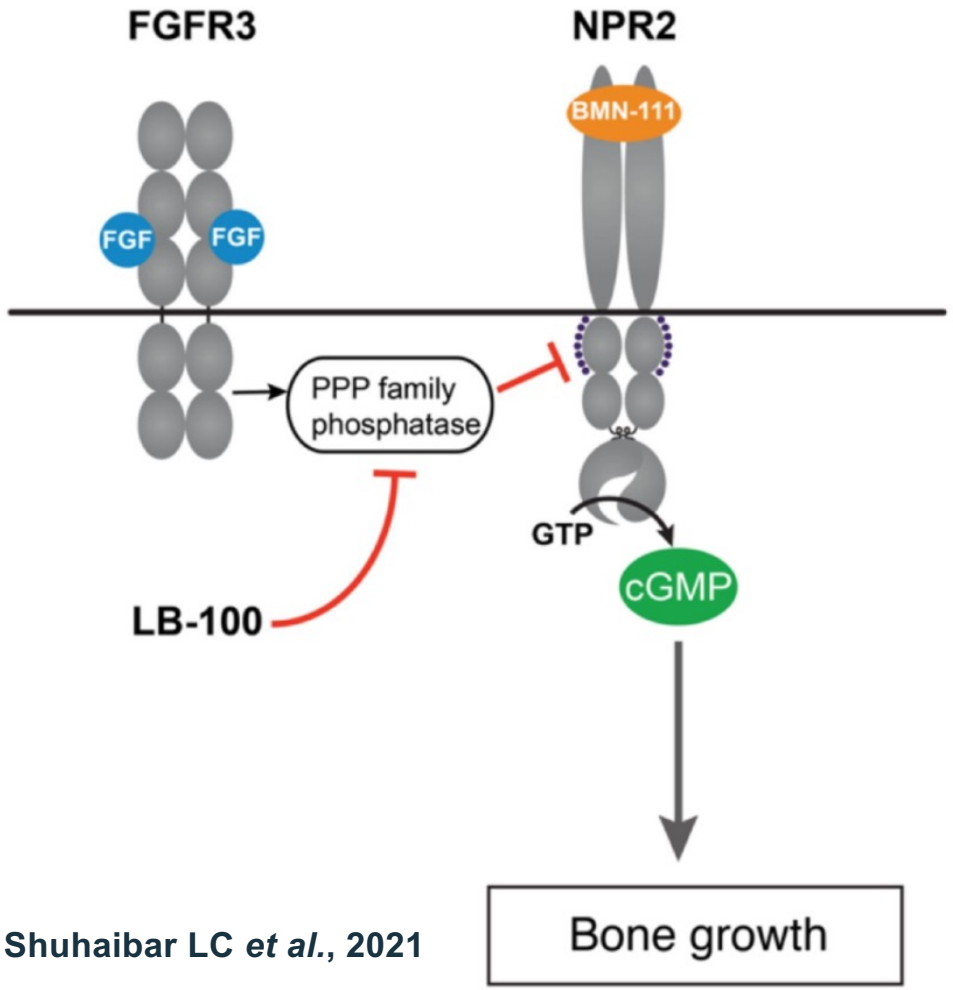


Shuhaibar LC *et al.*, 2021

ACH, achondroplasia; OFC, occipitofrontal circumference; SD, standard deviation; US/LS, upper segment to lower segment ratio; AS, arm span
Presenter's clinical case study; Shuhaibar LC et al. *JCI Insight*. 2021; 6: e141426.

6 months of vosoritide, 34 months



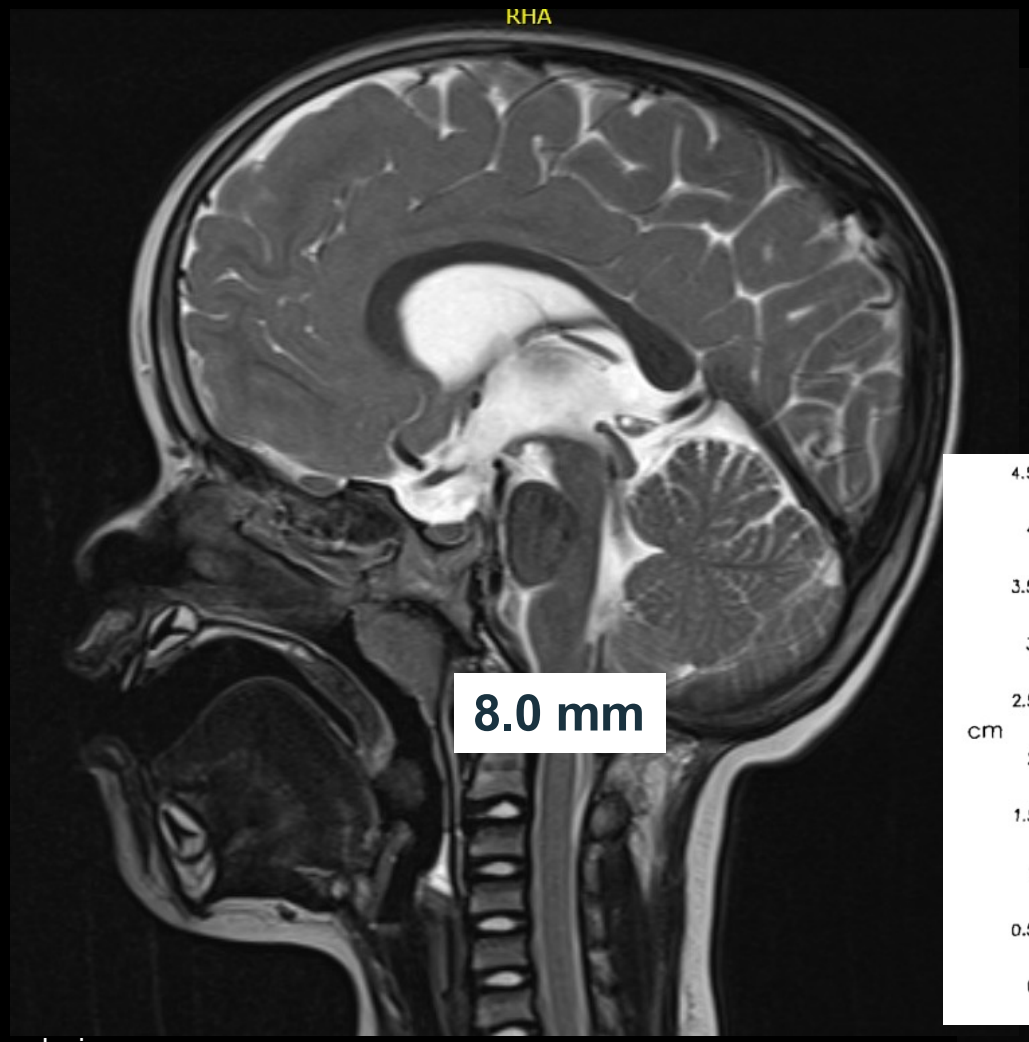


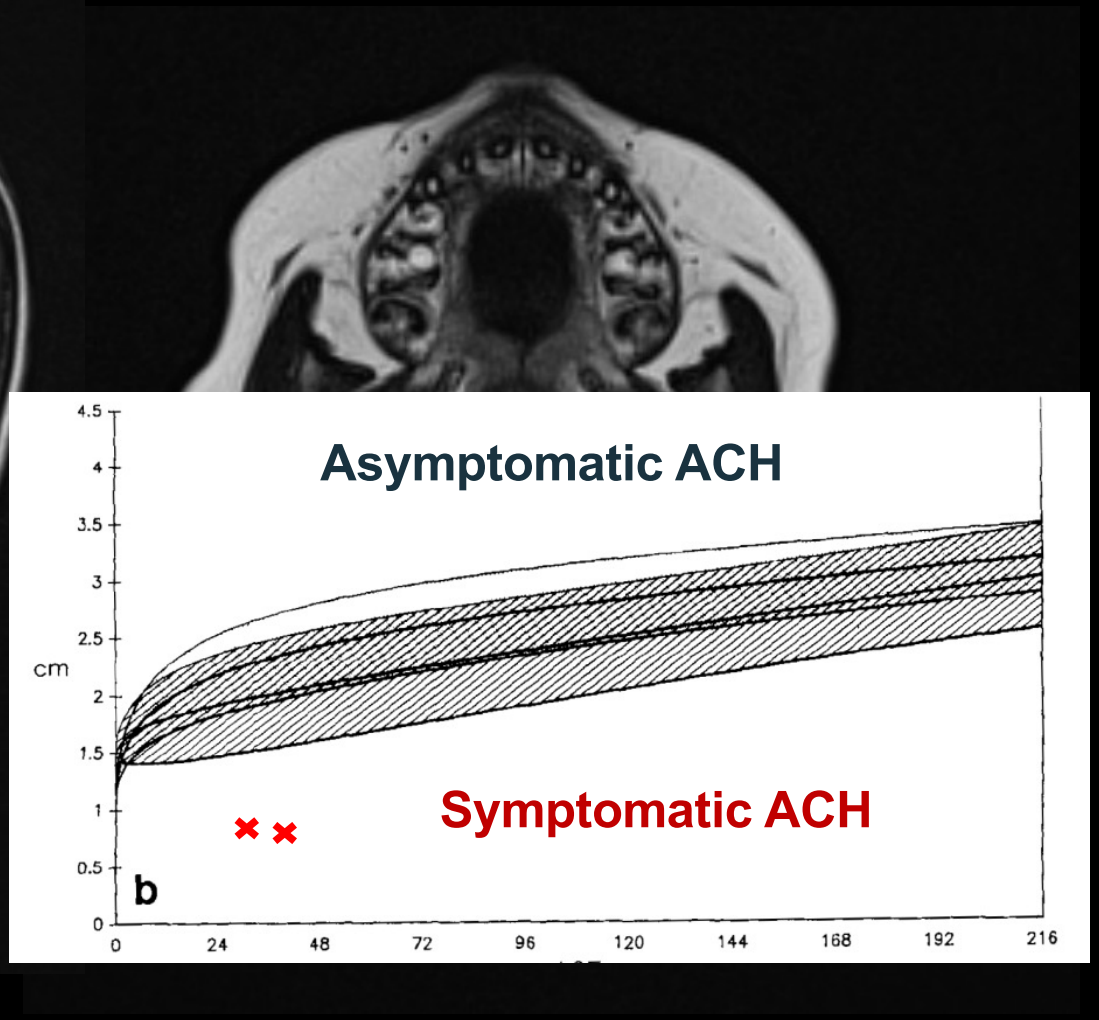
Shuhaibar LC *et al.*, 2021

AGV, annualised growth velocity; cGMP, cyclic guanosine monophosphate

Presenter's clinical case study; Shuhaibar LC et al. *JCI Insight*. 2021; 6: e141426.

Imaging at 38 months: Asymptomatic ACH, but..





ACH, achondroplasia

Presenter‘s clinical case study

5.) Clinical case: vosoritide therapy and monitoring in toddlers

UNIVERSITÄTS KLINIKUM FREIBURG

Key parameters to measure during follow-up

First follow-up (1 months of vosoritide):

- Therapy-related complications, supervision of application, correct dosing

Second follow-up (6 months of vosoritide):

- Auxology, annualized growth velocity, lab, dosing

Third follow-up (1 year of vosoritide):

- Auxology, annualized growth velocity, lab, dosing, **bone age**

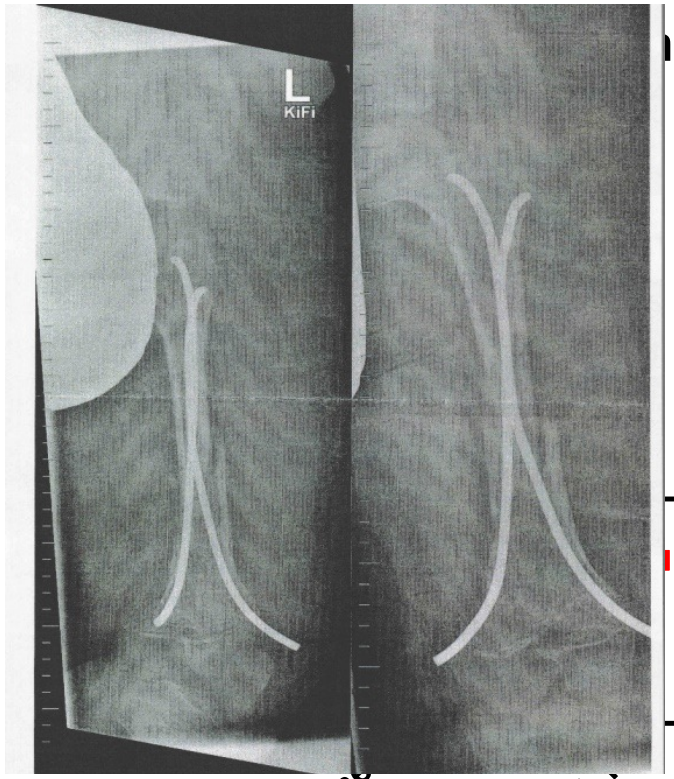
►Bi-annual or 3 monthly visits, depending on age/secondary complications

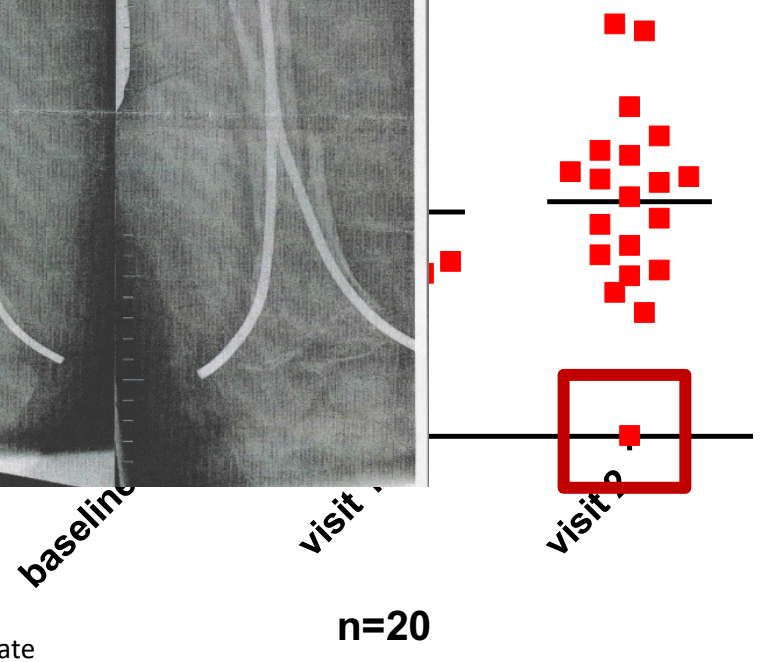
- Standardized assessment of diagnostic findings under vosoritide (e.g. classification of foramen magnum stenosis, axis deviation etc)

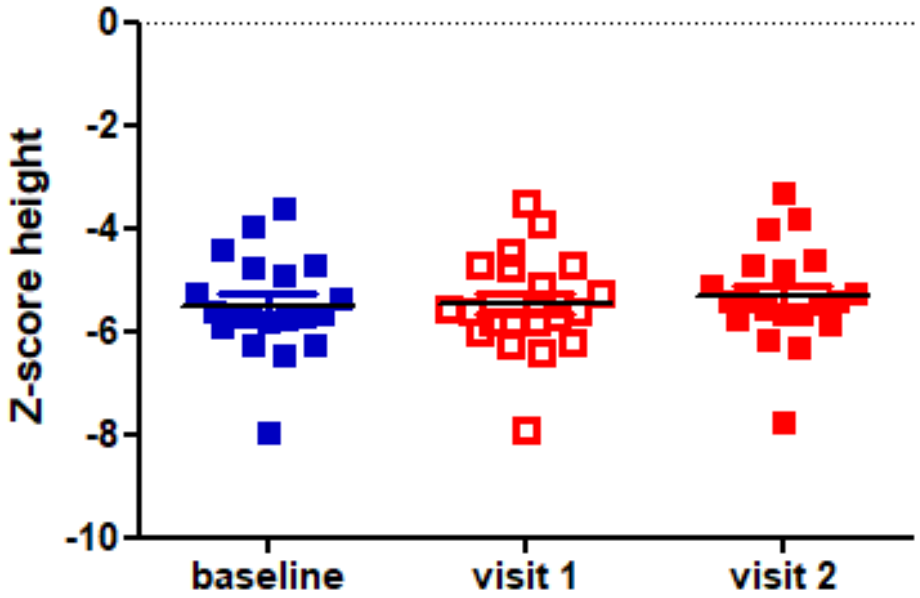
5.) Real world data: safety and efficacy (6 months)

- **Potential adverse reactions: 2 patients with fractures (tibia, femur)**

- **…ary cGMP in the first 20 patients**





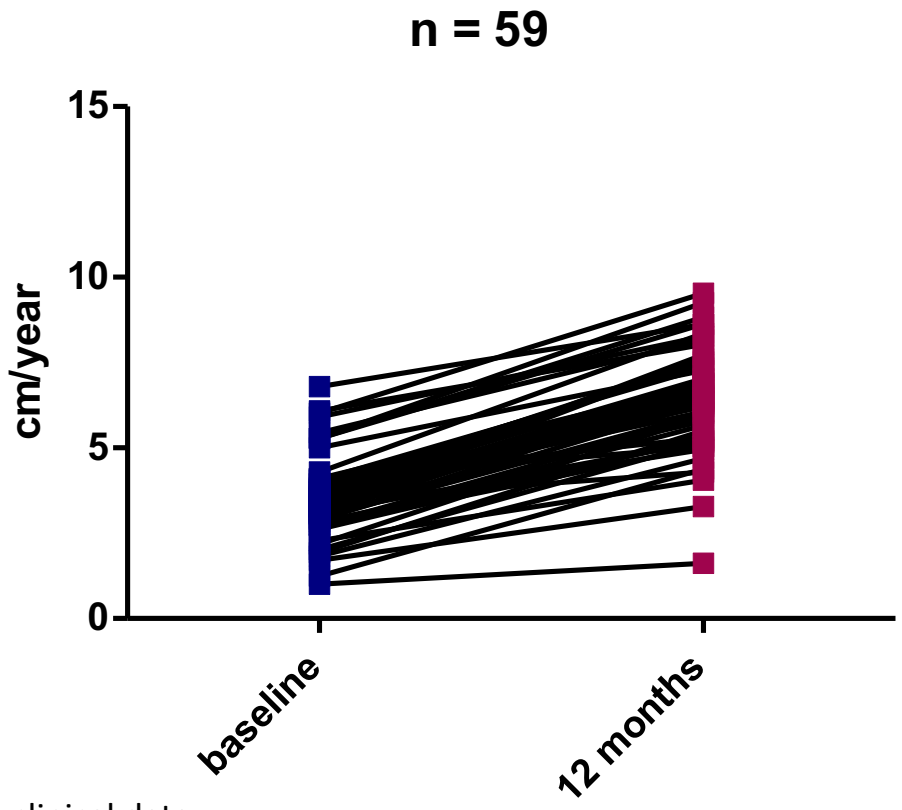


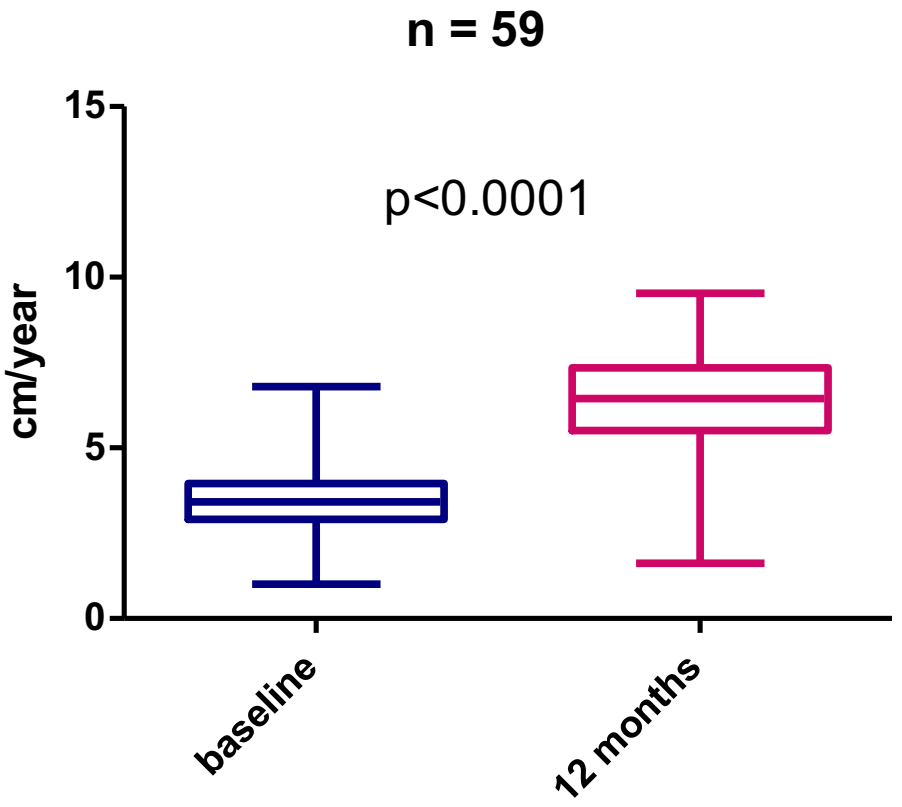
n=20

cGMP, cyclic guanosine monophosphate
Presenter's clinical data

5.) Real world data: safety and efficacy (12 months)

- **Monitoring: annualized growth velocity at 12 months**

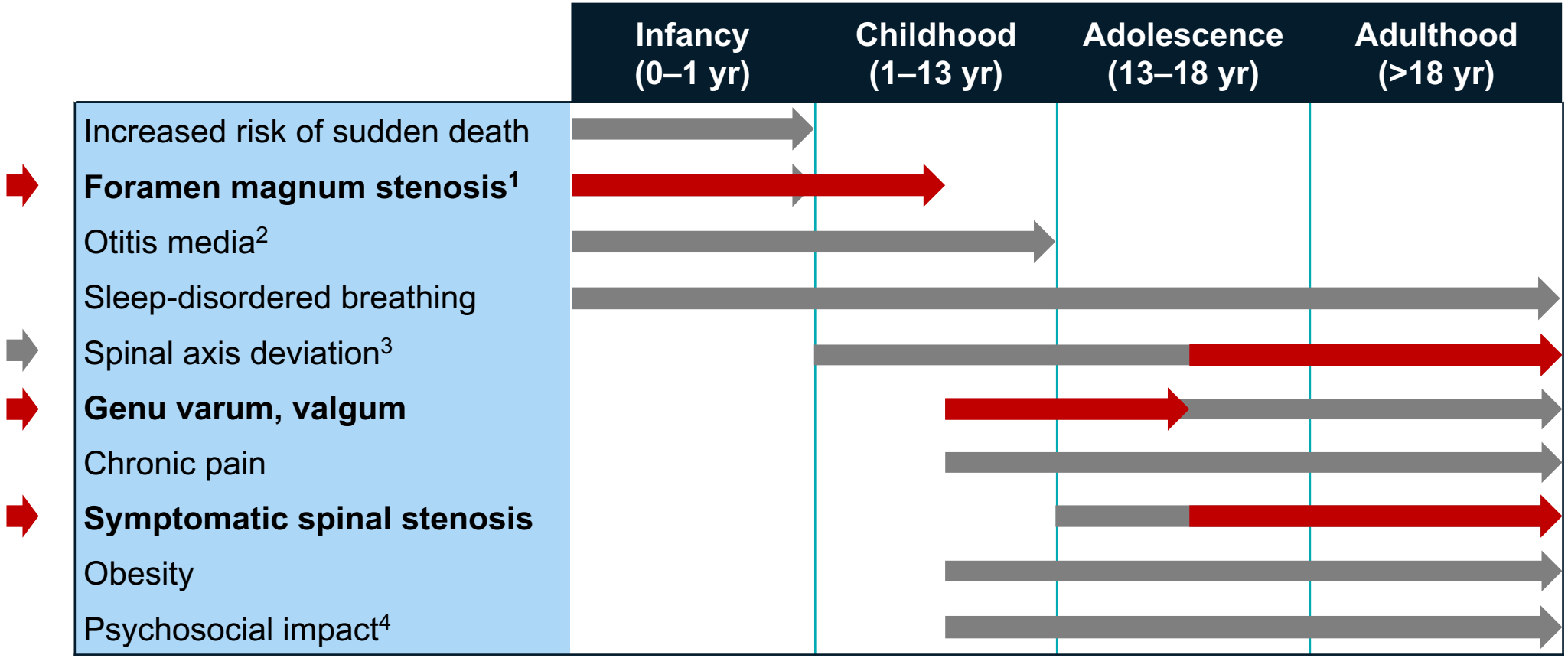




Presenter's clinical data

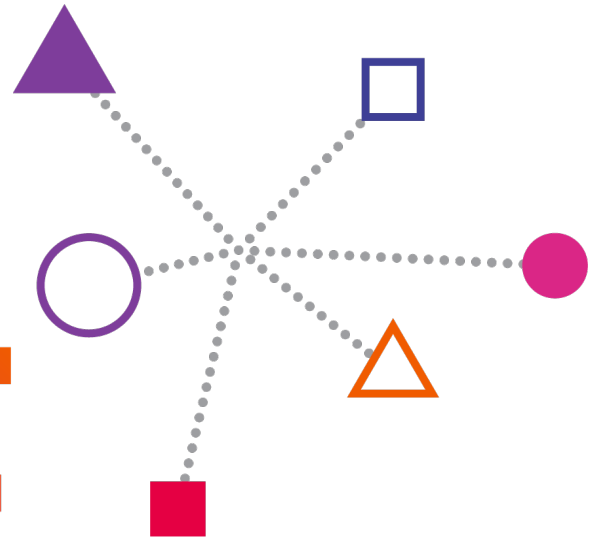
Age-dependent secondary complications and therapy

Complications of achondroplasia beyond growth across life stages*



*non-exhaustive list

Adapted from Hoover-Fong J, et al. Bone 2021;146:115872; 1. Hecht JT, et al. Am J Med Genet 1989;32:528-35; 2. Wright MJ, et al. Arch Dis Child 2012;97:129-34; 3. Kopits SE. Basic Life Sci 1988;48:241-55; 4. Yonko EA, et al. Am J Med Genet A 2021;185:695-701.



EAF

European Achondroplasia Forum