Growth and Syndromes

Vosoritide Phase 2 Extension Trial in Children with Hypochondroplasia: Three-Year Effects on Growth, Body Proportions and Collagen X Biomarker Activity

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ESPE
European Society for Paediatric Endocrinology

Disclosures

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BioMarin played no role in the design or conduct of the study, analysis of data, or preparation of the abstract or presentation.

Giulia Del Medico: Nothing to disclose

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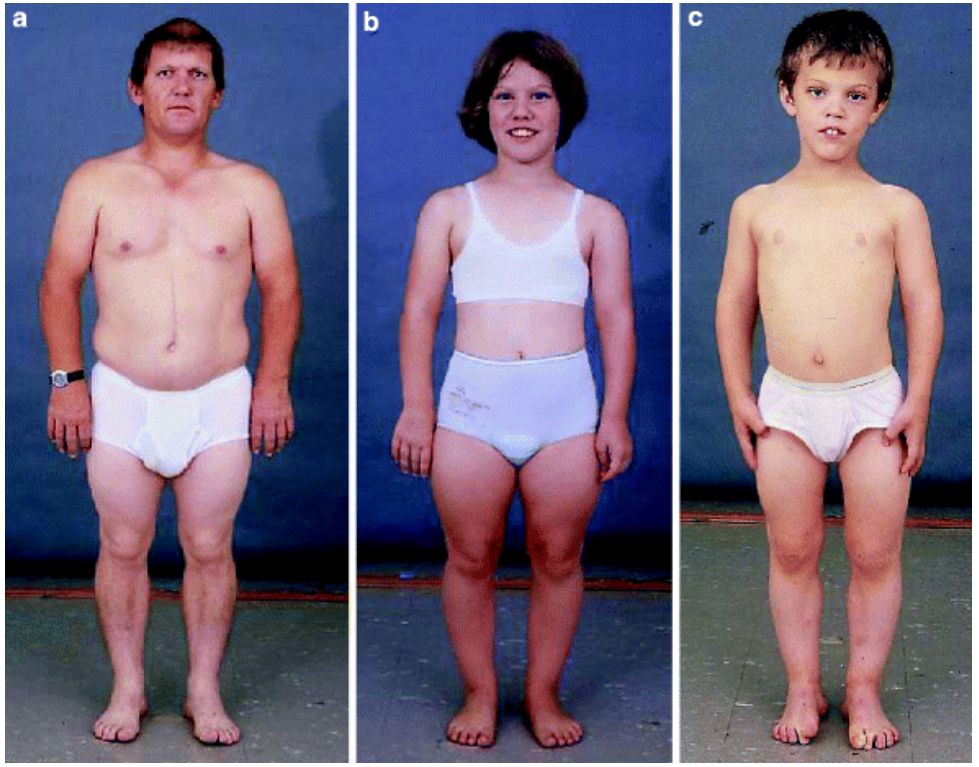
Kimberly Pitner: Nothing to disclose

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Background: HYPOCHONDROPLASIA (HCH)

- Autosomal dominant skeletal dysplasia caused by activating *FGFR3* variants
- Clinical features:
  - Disproportionate short stature
  - Relative macrocephaly
  - Limb shortening
  - Limited elbow extension
  - Lower limb bowing



Hypochondroplasia. In: Chen, H. (eds) Atlas of Genetic Diagnosis and Counseling, 2012.

No approved growth-promoting therapy currently exists for HCH

Background: Vosoritide

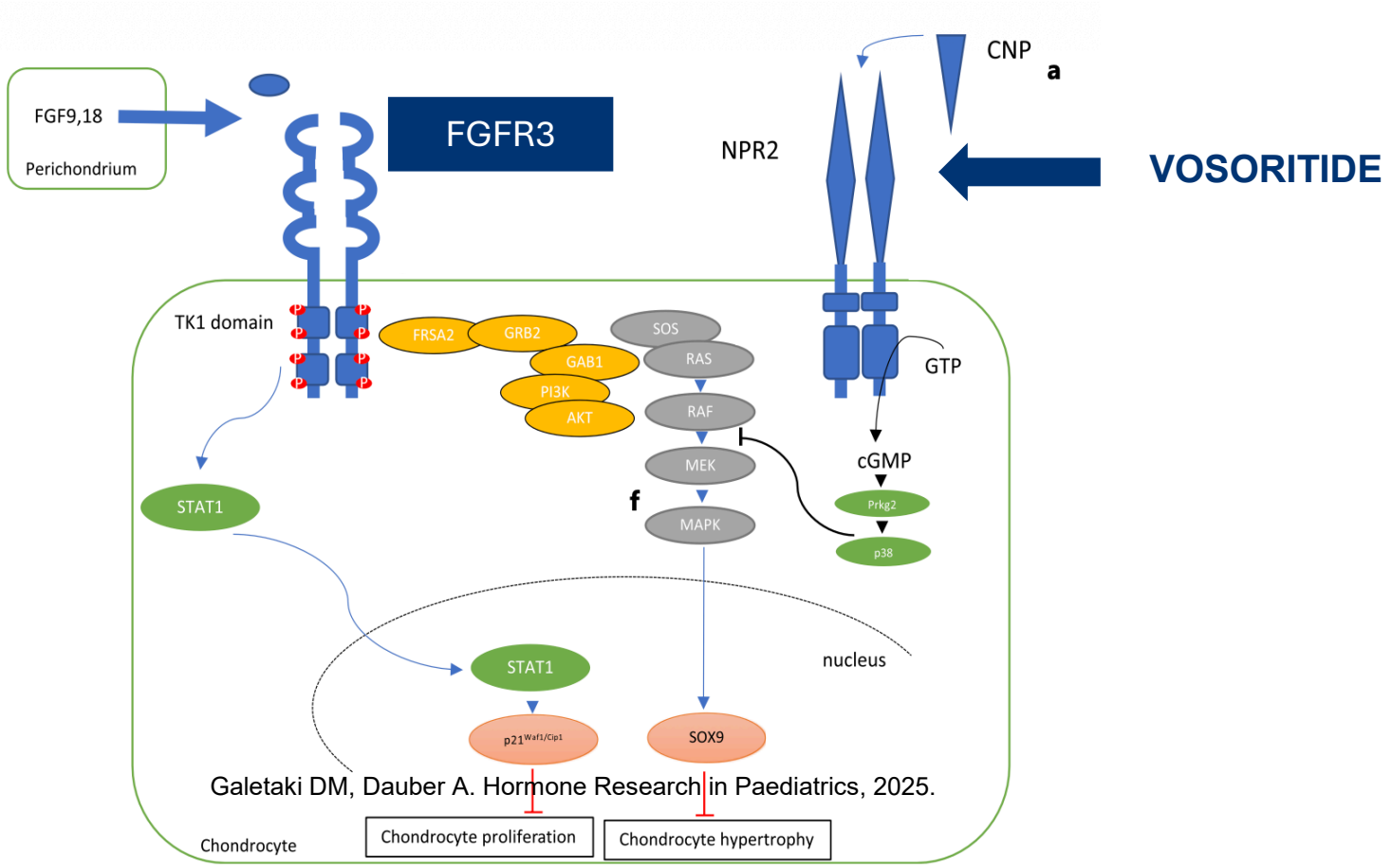
CNP analog that inhibits the FGFR3/MAPK signaling promoting endochondral growth

↓

Approved for treatment of short stature in achondroplasia (ACH)

↓

Potential therapeutic target in HCH due to shared FGFR3 pathophysiology



Galetaki DM, Dauber A. Hormone Research in Paediatrics, 2025.

Objectives

To evaluate the long-term safety and efficacy of vosoritide in children with HCH

Endpoints:

- Incidence of adverse events (AE)
- Change from baseline in absolute and age-sex standardized annualized growth velocity (AGV)
- Change from baseline in height standard deviation score (SDS)

Methods

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CORE STUDY

- **Design**: Single-arm, open-label, phase 2 trial (NCT04219007)
- **Population**:
  - Genetically confirmed HCH
  - Prepubertal
  - Age 3-11 years for males and 3-10 years for females
  - Standing height ≤ -2.25 SD (CDC growth charts)
- **Timeline**: Screening → 6-month observation period → 12 months of daily subcutaneous vosoritide (15 µg/kg/day)

EXTENSION

- **Eligibility:** Participants with **AGV increase >1.6 cm/year** during core study
- **Follow up**:
  - In-person visits every 6 months
  - Interim phone monitoring
  - Treatment continuation until growth cessation
- **Endpoints**: Unchanged compared to core study

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Previous 12-month results

- **24 children** with HCH were treated in the core study
- After 12 months of vosoritide:
  - Standing height increase: **+0.36 SD**
  - AGV increase: **+1.81 cm/year** (+2.26 SD)
  - No new safety concerns were reported

Vosoritide treatment for children with hypochondroplasia: a phase 2 trial

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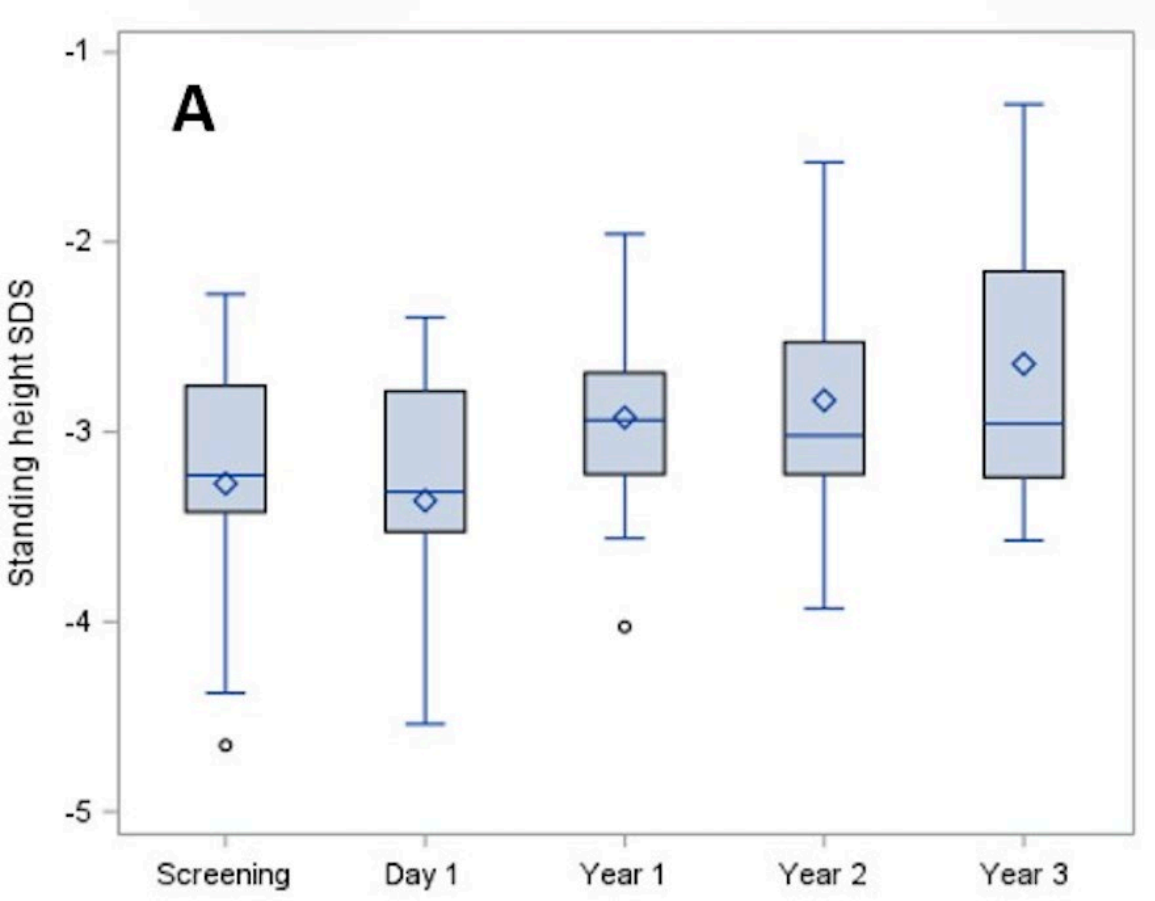
RESULTS FROM 3 YEARS IN THE EXTENSION STUDY

Participant Baseline Characteristics

Total enrolled subjects	**N = 13**
Age at screening (years)	
Mean (SD); median (IQR)	5.78 (1.13); 5.70 (1.70)
Sex	
Female	7 (53.8%)
Male	6 (46.2%)
Previously treated with growth hormone	
Yes	1 (7.7%)
No	12 (92.3%)
Genetic Variant	
Asn540Lys	11 (84.6%)
Gly342Cys	1 (7.7%)
Ser351Phe	1 (7.7%)
Standing height SDS at Screening	
SDS -2.25 to -3	4 (30.8%)
SDS -3 to -4	7 (53.8%)
SDS below -4	2 (15.4%)

Results: Standing Height

	Mean (SD) Height at Each Timepoint				
	Screening	Day 1	Year 1	Year 2	Year 3
Standing height SDS CDC	-3.27 (0.71)	**-3.36** (0.64)	-2.92 (0.57)	-2.83 (0.70)	**-2.64** (0.79)
Standing height SDS HCH-specific charts	-0.32 (0.79)	**-0.43** (0.73)	0.06 (0.77)	0.17 (0.94)	**0.40** (1.05)



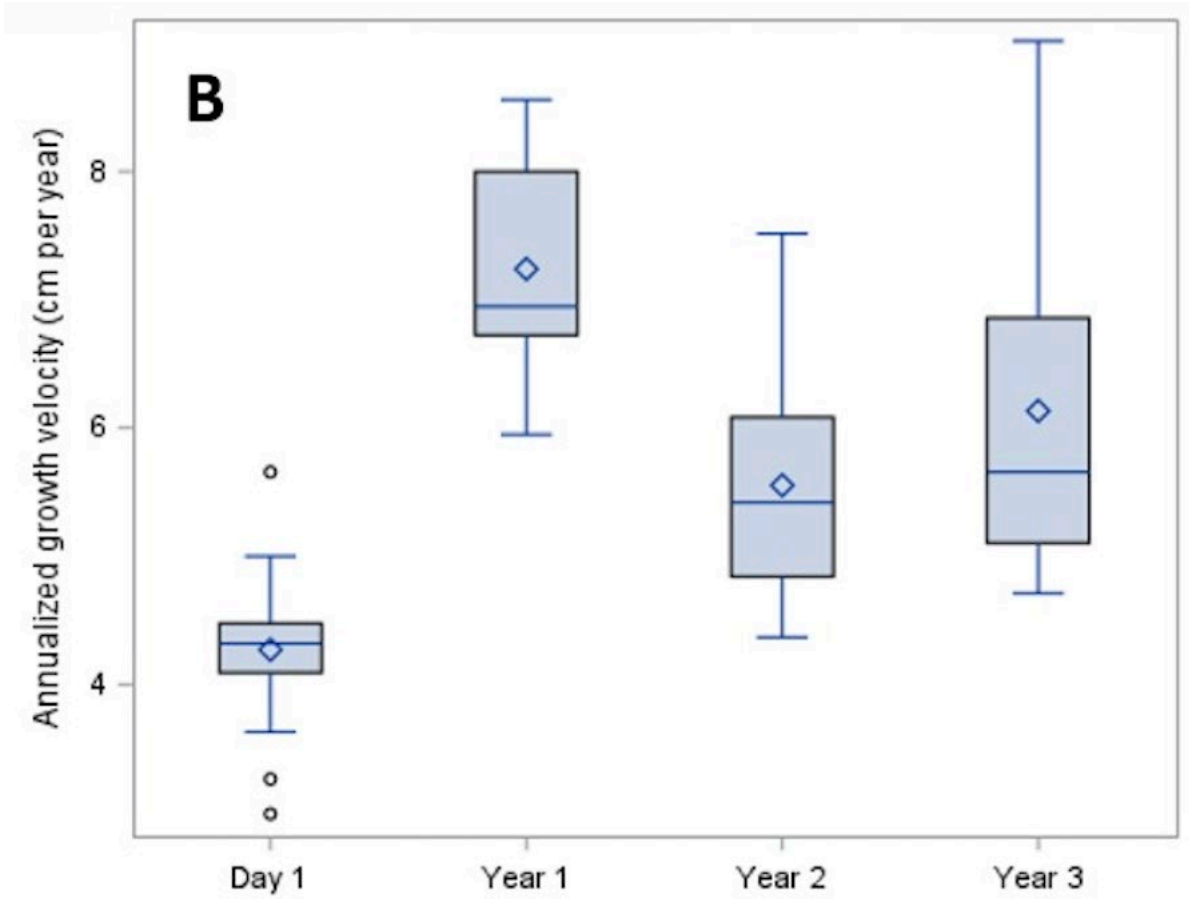
From Day 1 to Year 3:

+0.72 SDS (0.45,0.99) [<0.0001] on the CDC charts

+0.83 SDS (0.51,1.15) [0.0001] on the HCH charts

Results: AGV

	Mean (SD) AGV at Each Timepoint				
	Screening	Day 1	Year 1	Year 2	Year 3
Annualized growth velocity (cm/yr)	N/A	**4.27** (0.70)	7.24 (0.80)	5.55 (1.02)	**6.13** (1.27)
Annualized growth velocity SDS	N/A	**-2.01** (0.78)	1.56 (1.03)	-0.11 (1.41)	**0.53** (1.20)



From baseline to Year 3:

+1.86 cm/year (0.82,2.90) [0.002]

+2.54 SDS (1.52,3.56) [0.0002]

Results: Body Proportions

	Mean (SD) at Each Timepoint					
	Screening	Day 1	Year 1	Year 2	Year 3	From Day 1 to Year 3:
Sitting-to-standing height ratio (Unadjusted)	0.63 (0.03)	0.63 (0.03)	0.62 (0.03)	0.61 (0.03)	0.60 (0.03)	**-0.02** (-0.03,-0.02) [<.0001]
Sitting-to-standing height ratio (Age/Sex adjusted SDS)	6.66 (1.57)	6.74 (1.60)	6.57 (1.66)	6.23 (1.56)	5.88 (1.77)	**-0.86** (-1.22,-0.50) [0.002]
Arm span-to-height ratio (Unadjusted)	0.94 (0.04)	0.94 (0.03)	0.94 (0.04)	0.94 (0.04)	0.95 (0.04)	**+0.007** (-0.002,0.02) [0.10]
Arm span-to-height ratio (Age/Sex adjusted SDS)	-1.89 (2.17)	-2.15 (1.65)	-2.39 (1.68)	-2.36 (1.87)	-2.27 (1.74)	**-0.13** (-0.51,0.26) [0.48]

Results: Bone Age

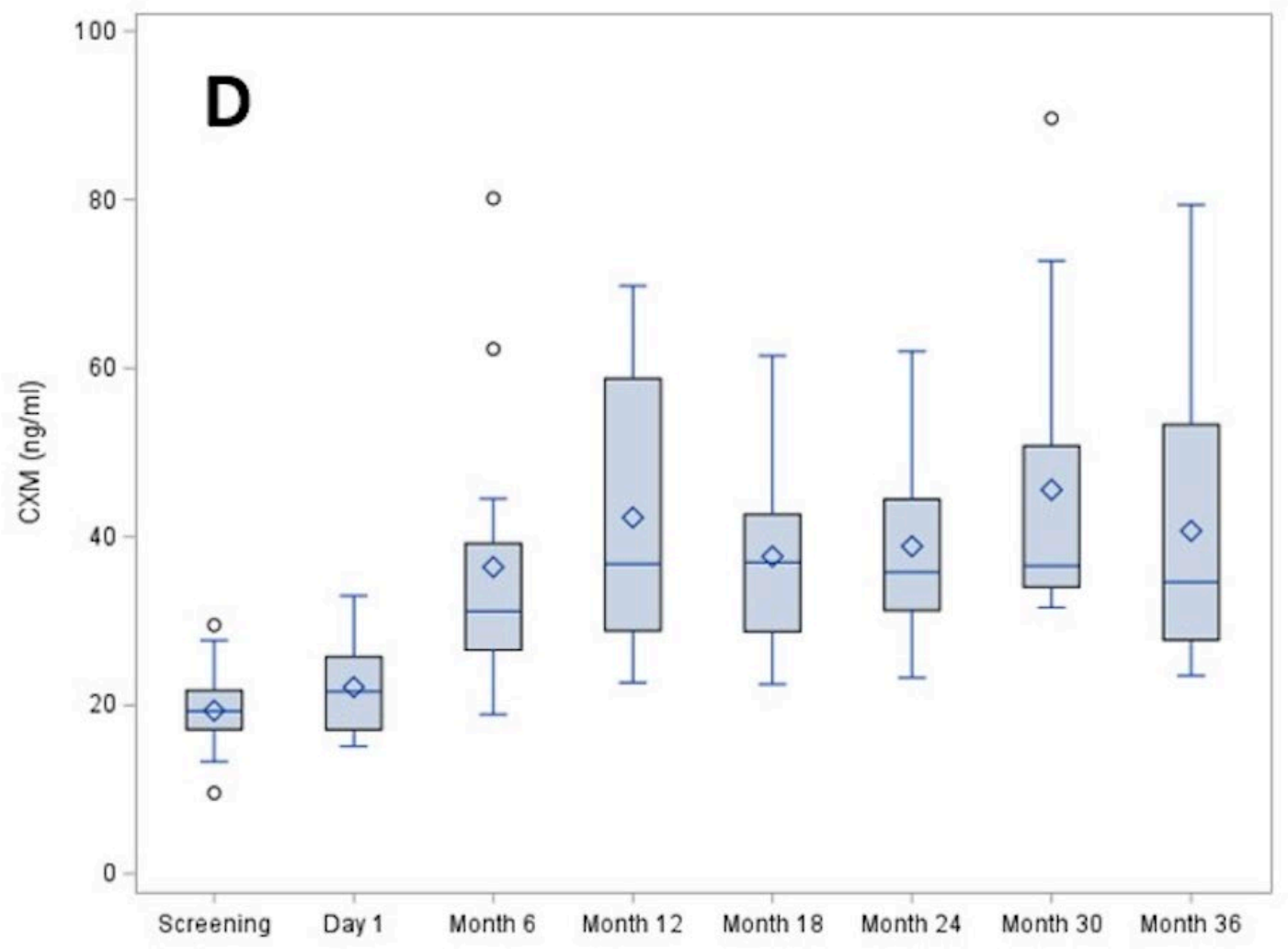
	Mean (SD) at Each Timepoint				
	Screening	Day 1	Year 1	Year 2	Year 3
Bone age (months)	N/A	61.77 (24.96)	71.60 (25.24)	87.38 (24.95)	97.82 (27.17)
Bone age to chronological age ratio	N/A	0.80 (0.15)	0.81 (0.15)	0.87 (0.13)	0.87 (0.15)

From Day 1 to Year 3:

36.05 (29.71, 42.39) [<.0001]

0.07 (0.007,0.14) [0.03]

Results: Collagen X Biomarker Levels



Results: QoLISSY Score

	Day 1 Mean (SD)	Year 3 Mean (SD)	Mean difference (95% CI)	Two-sided p-value
Physical	54.49 (20.80)	60.07 (19.74)	7.29 (-6.31, 20.89)	0.26
Social	61.54 (21.96)	66.41 (18.94)	6.51 (-9.74, 22.76)	0.40
Emotional	67.79 (20.50)	70.83 (13.21)	4.17 (-8.85, 17.18)	0.50
Coping	35.55 (19.88)	46.46 (14.24)	8.57 (-4.64, 21.79)	0.18
Belief	66.35 (25.46)	68.75 (28.20)	4.69 (-19.68, 29.06)	0.68
Treatment	N/A	49.11 (16.46)	N/A	N/A
Total (Physical, Social, Emotional)	61.27 (19.95)	65.77 (15.14)	5.99 (-7.18, 19.16)	0.35

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No significant changes were observed in the QoLISSY score

Results: Safety

Reported AE:

- Injection site reactions
  - Year 1: 76.9%
  - Years 2–3: 23.1%
- Other events
  - Traumatic fractures (n=2) → healed without complications
  - Mild scoliosis (n=2)
  - Mild genu valgum (n=2)

Overall:

- Vosoritide was well tolerated
- No treatment-related serious AE
- No treatment discontinuations

Conclusions

- Three years of vosoritide treatment increased height SDS by **+0.72 SD.**
- Body proportions showed improvement in standardized sitting height-to-standing height ratio, while arm span-to-height ratio remained overall within normal ranges.
- Bone age-to-chronological age ratio increased slightly but remained on average delayed.
- CXM levels increased from baseline to Month 6 and remained stable through Year 3.
- No significant changes were observed in the QoLISSY score.
- Vosoritide was generally well tolerated with no new safety concerns.
- Interpretation is limited by small sample size, lack of control group, and selection of initial good responders.