Vosoritide Increases Growth Velocity in Hypochondroplasia: Phase 2 Trial Results

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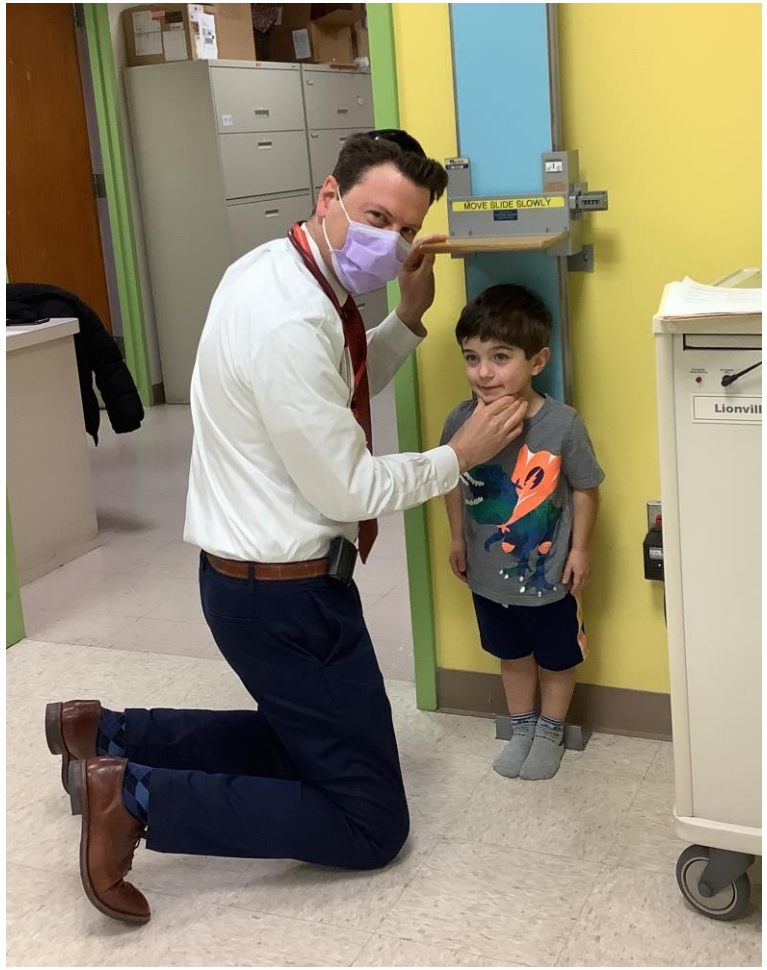
Hypochondroplasia Overview

- Autosomal dominant skeletal dysplasia
- Activating variants in *FGFR3*
  - p.Asn540Lys most common
- Prevalence estimated between 1 in 15,000-40,000
- Disproportionate short stature
- Mean adult height of ~131 cm for females and 144 cm for males[1]
- No approved therapies



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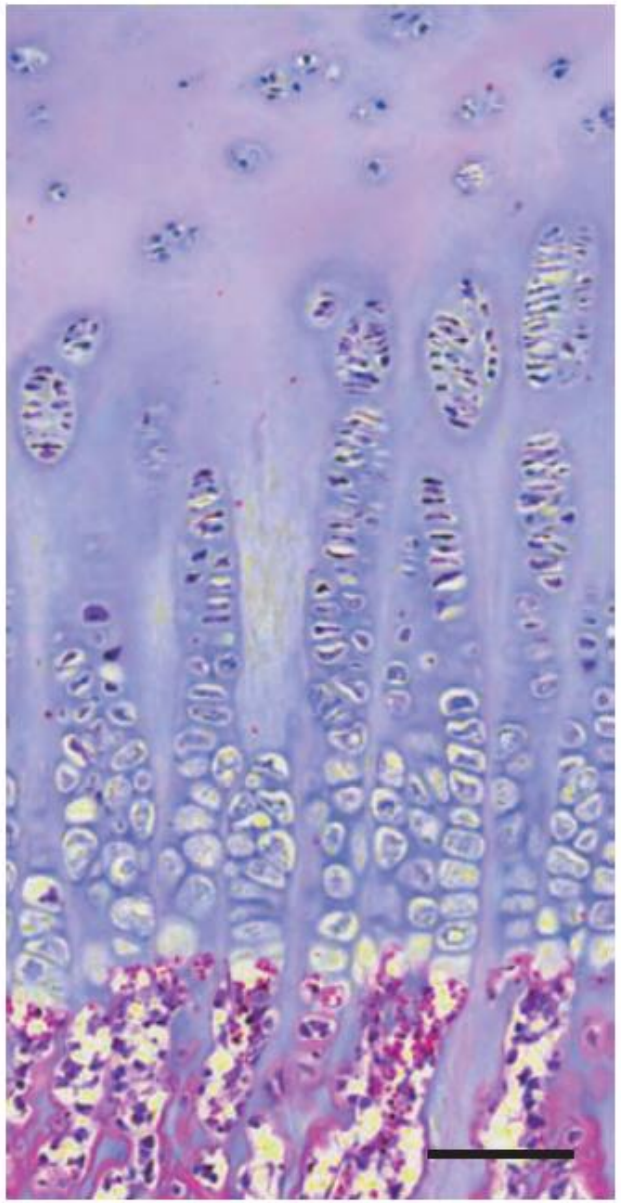
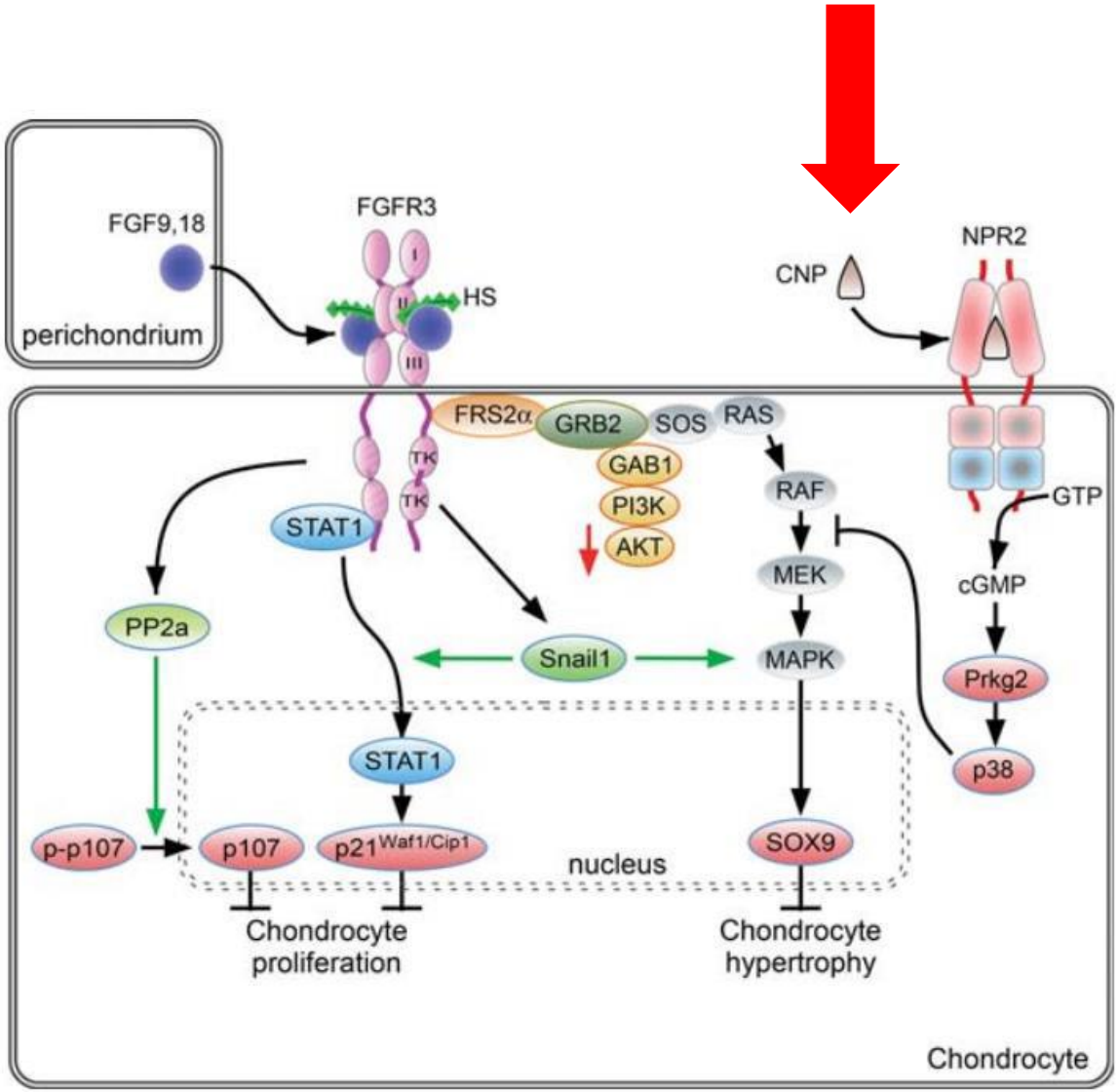
1. Arenas et al. *Journal of Pediatric Endocrinology and Metabolism*. 2018;31(11):1279-1284.





Baron J et al. Short and tall stature: a new paradigm emerges. Nature Reviews Endocrinology 2015;11(12)735-46.
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

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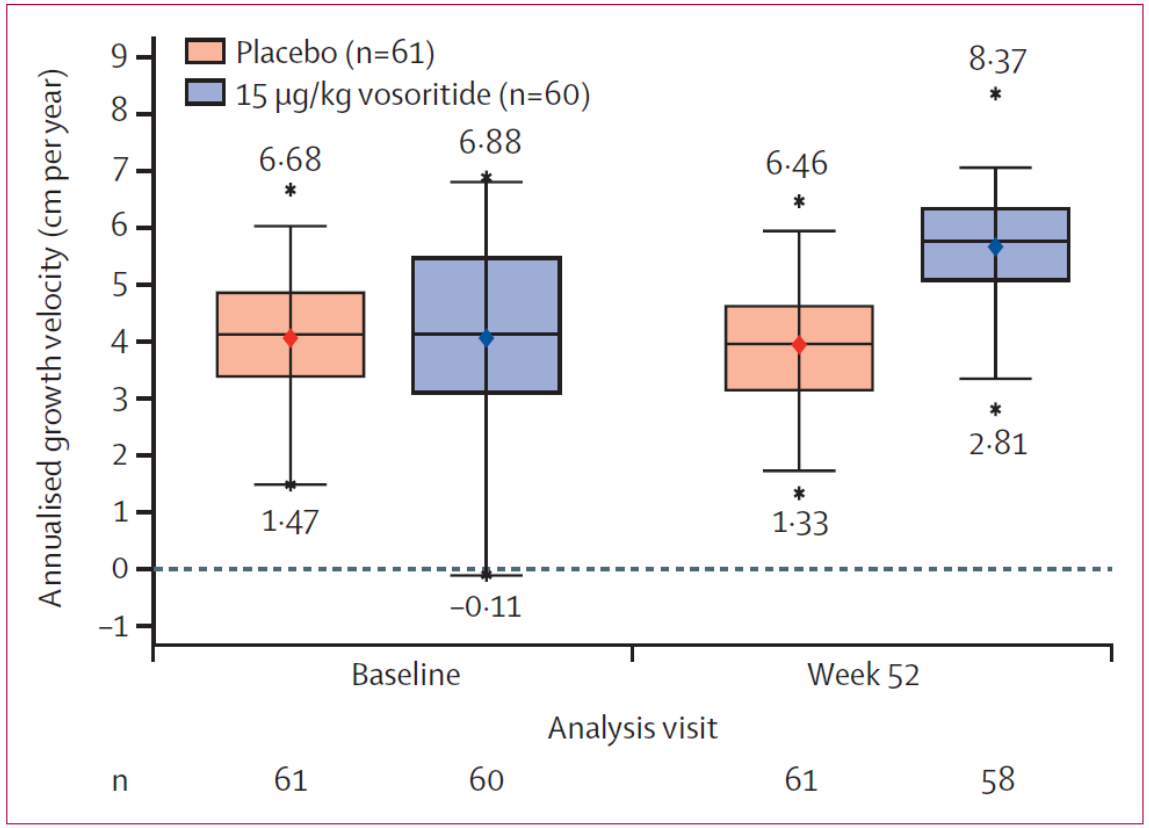
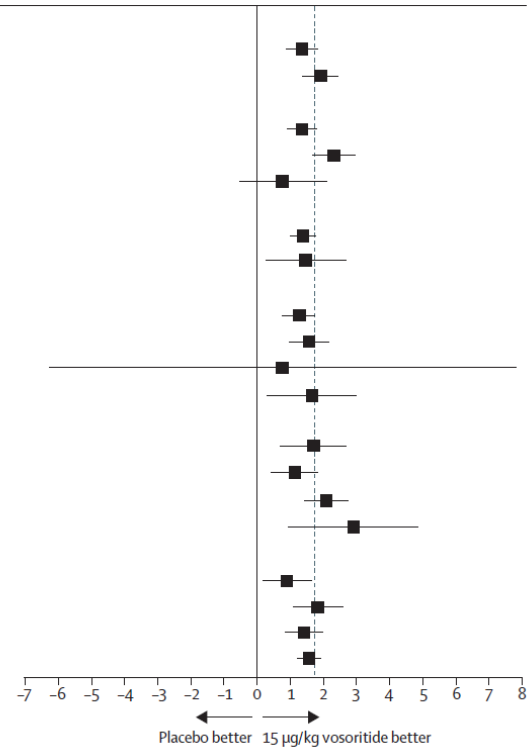
Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial



	Number of subjects (%)		LS mean change from baseline	Difference (95% CI) in least-squares mean change from baseline
	15 µg/kg vosoritide	Placebo	Difference (cm)	15 µg/kg vosoritide minus placebo
Sex				
Male	31 (51·7)	33 (54·1)	1·36	
Female	29 (48·3)	28 (45·9)	1·91	
Age group (years)				
≥5 to <8	31 (51·7)	24 (39·3)	1·35	
≥8 to <11	17 (28·3)	24 (39·3)	2·32	
≥11 to <15	12 (20·0)	13 (21·3)	0·77	
Tanner stage				
I	48 (80·0)	48 (78·7)	1·38	
>I	12 (20·0)	13 (21·3)	1·47	
Strata				
Male Tanner Stage I	28 (46·7)	28 (45·9)	1·27	
Female Tanner Stage I	20 (33·3)	20 (32·8)	1·57	
Male Tanner Stage >I	3 (5·0)	5 (8·2)	0·76	
Female Tanner Stage >I	9 (15·0)	8 (13·1)	1·65	
Height Z score category				
≤−6	15 (25·0)	10 (16·4)	1·69	
>−6 to ≤ −5	18 (30·0)	24 (39·3)	1·14	
>−5 to ≤ −4	22 (36·7)	19 (31·1)	2·09	
>−4	5 (8·3)	8 (13·1)	2·90	
Annualised growth velocity category				
≤3·5 cm/year	19 (31·7)	19 (31·1)	0·90	
>3·5 to ≤4·5 cm/year	14 (23·3)	18 (29·5)	1·84	
≥4·5 cm/year	27 (45·0)	24 (39·3)	1·42	
Overall	**60 (100·0)**	**61 (100·0)**	**1·57**	



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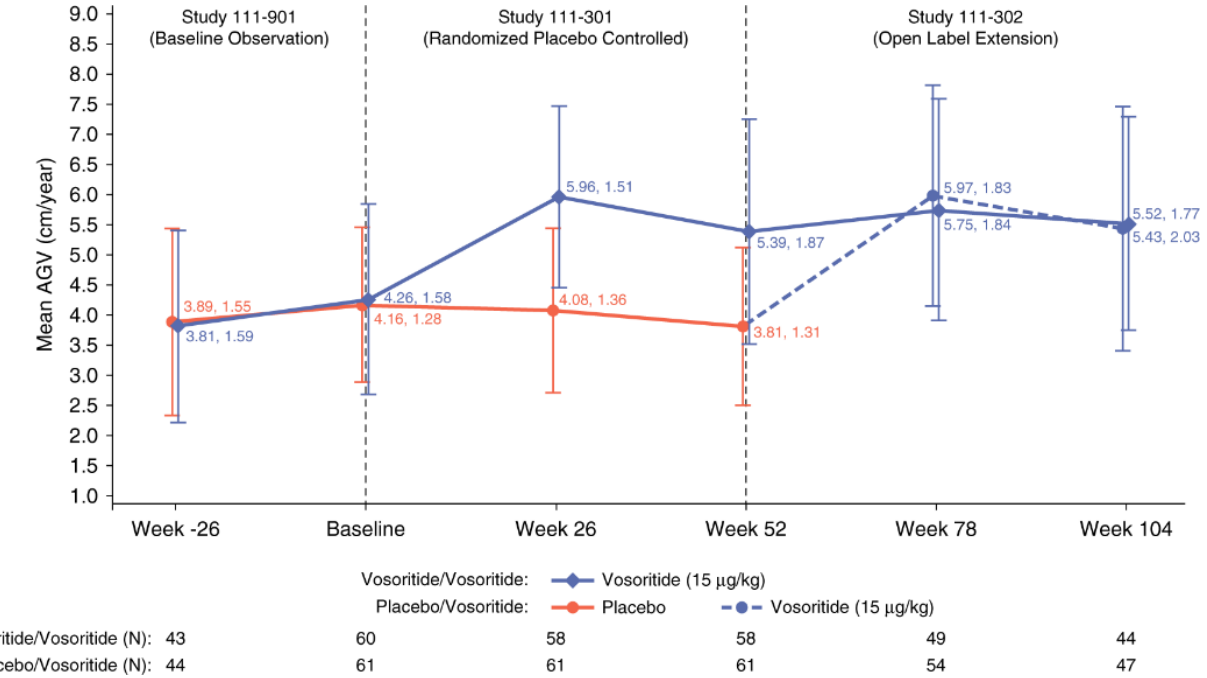
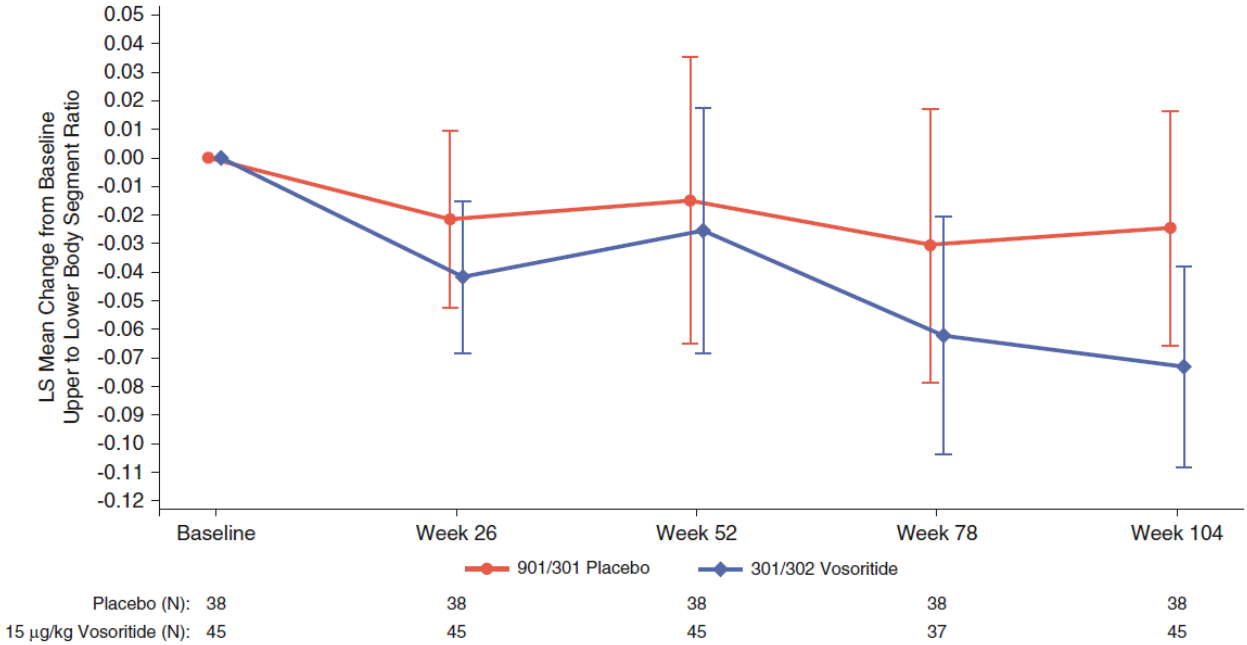
Savarirayan et al. Lancet 2020; 396:684-92.

2nd Year Results: Sustained increased in growth velocity and improvement in body proportions





Savarirayan et al. Genetics in Medicine, 2021;2:1-5.

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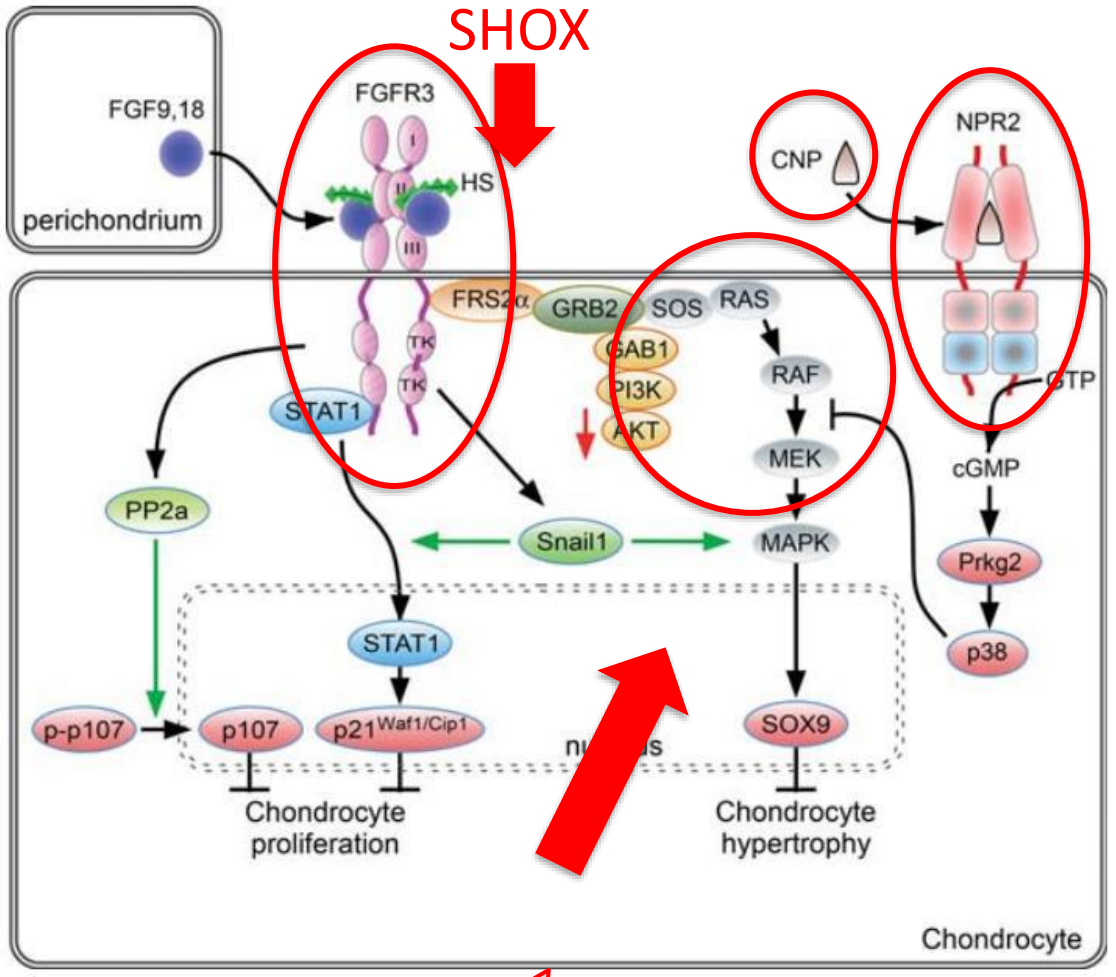
Vosoritide for Selected Genetic Causes of Short Stature

- Hypochondroplasia
- CNP Deficiency
- Heterozygous NPR2 mutation
- RASopathy
- SHOX
- Aggrecan Deficiency



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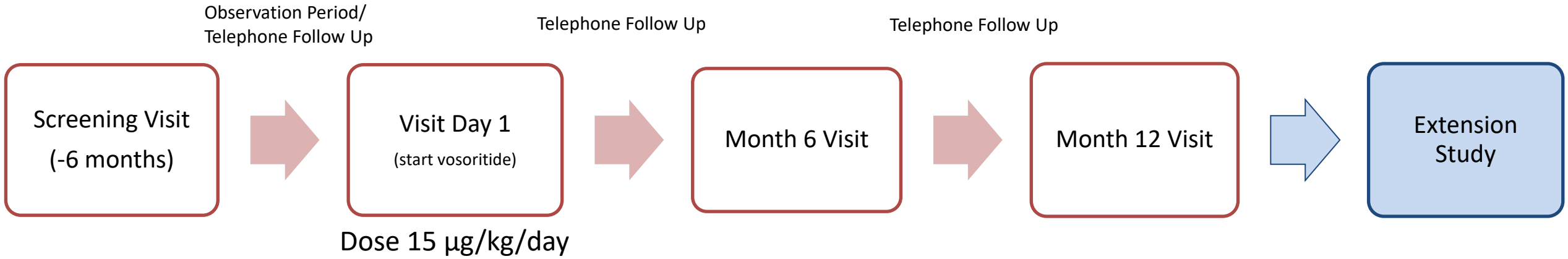
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

Inclusion Criteria and Study Design

- Age ≥3 years 0 days AND ≤10 years 364 days for males, ≤9 years 364 days for females
- Pre-pubertal
- Patient height <-2.25 SDS.
- Mutation in one of 6 categories
- Absence of growth hormone deficiency
- No concurrent treatment with GH (prior Rx is OK).
- No other significant medical history



Study Outcomes

Primary study endpoints:

- Incidence of adverse events
- Δ growth velocity at 12 months
- Δ height SDS at 12 months

Secondary study endpoints:

- Body proportions
- Δ bone age/chronological age at 12 months

The exploratory study endpoints include:

- Pharmacokinetic studies
- Pharmacodynamic markers
- Bone mineral density
- Effect on quality of life

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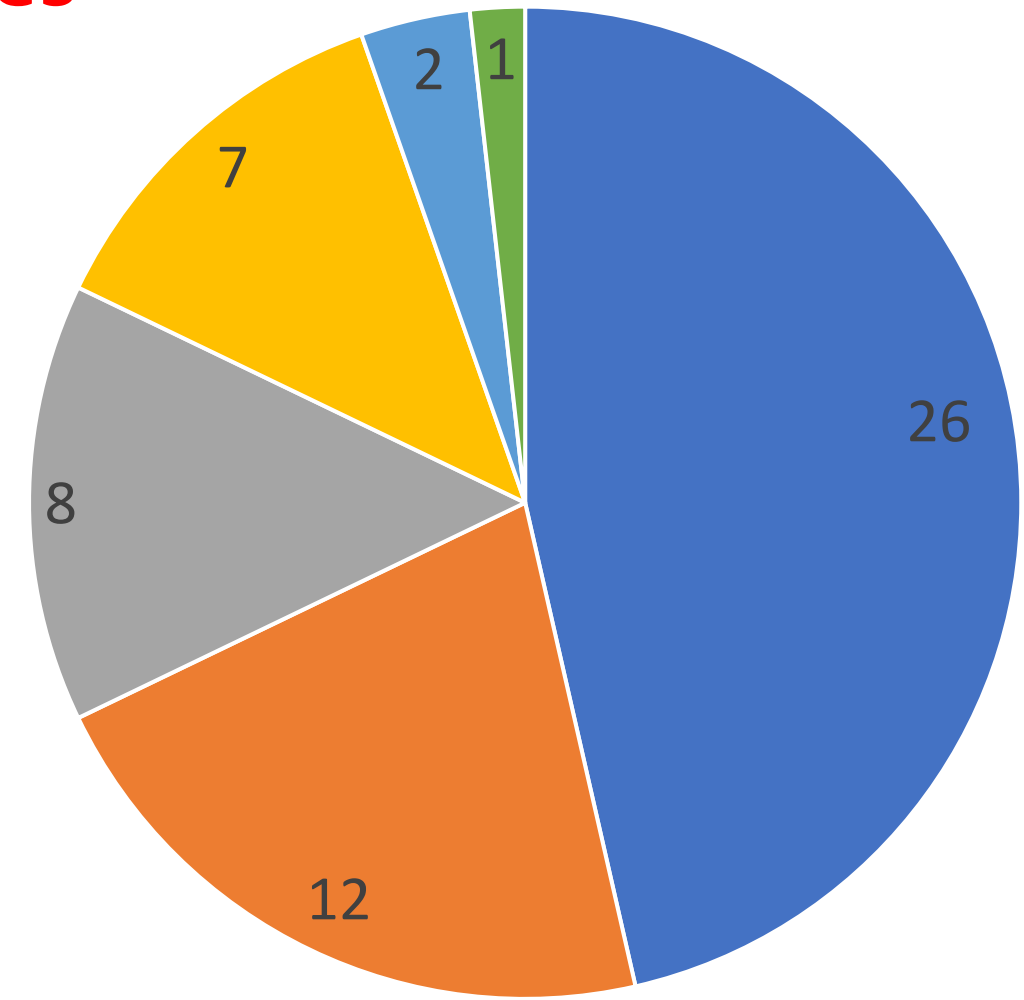
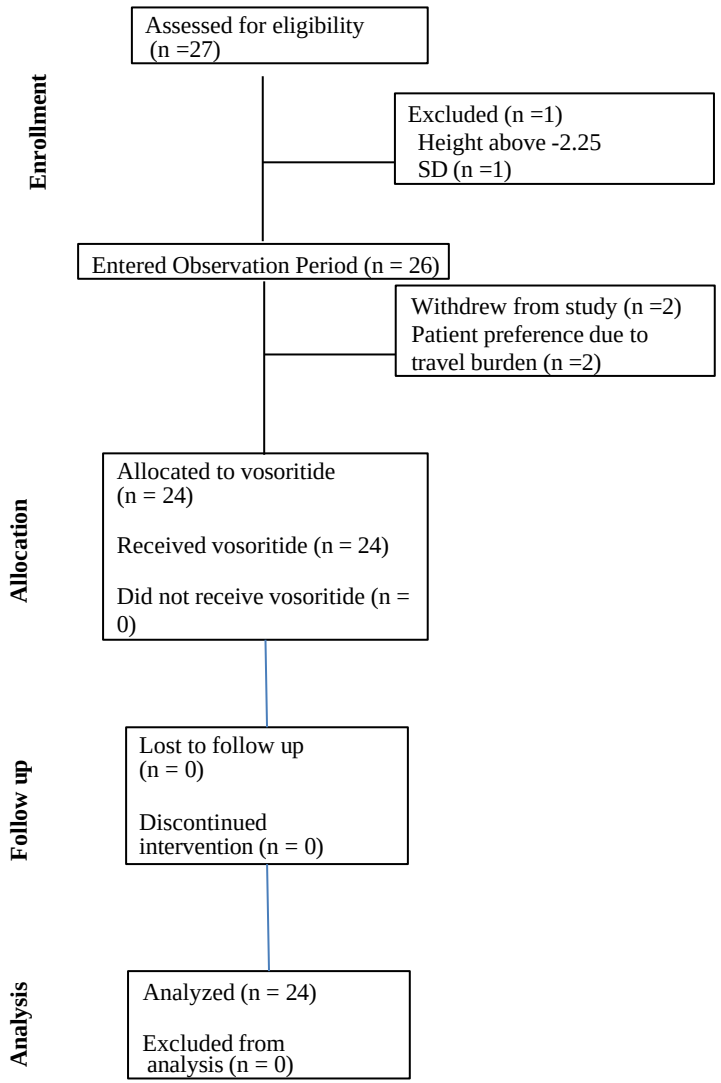
Genetic Categories



Hypochondroplasia Subjects Only



Total enrolled subjects	N=24
Age at screening (years) mean (SD); median (IQR)	5.86 (2.29); 5.55 (2.39)
Age group # (%)	
3 to <5 year	10 (41.7%)
5 to <9 year	11 (45.8%)
9 to <11 year	3 (12.5%)
Sex	
Female	12 (50%)
Male	12 (50%)
Race	
Caucasian	17 (70.8%)
Asian	4 (16.7%)
Other	3 (12.5%)
Ethnicity	
non-Hispanic/Latino	23 (95.8%)
Hispanic/Latino	1 (4.2%)
Previously treated with growth hormone	
Yes	3 (12.5%)
No	21 (87.5%)
Genetic Variant	
Asn540Lys	22 (91.7%)
Gly342Cys	1 (4.2%)
Ser351Phe	1 (4.2%)

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Safety

- 83% of subjects had injection site reactions
  - All grade 1 or 2
  - All self-resolved without intervention
- No subjects discontinued treatment due to an AE
- 1 SAE unrelated to vosoritide – viral induced ITP
- 1 episode of syncope with documented normal blood pressure
- No episodes of symptomatic hypotension

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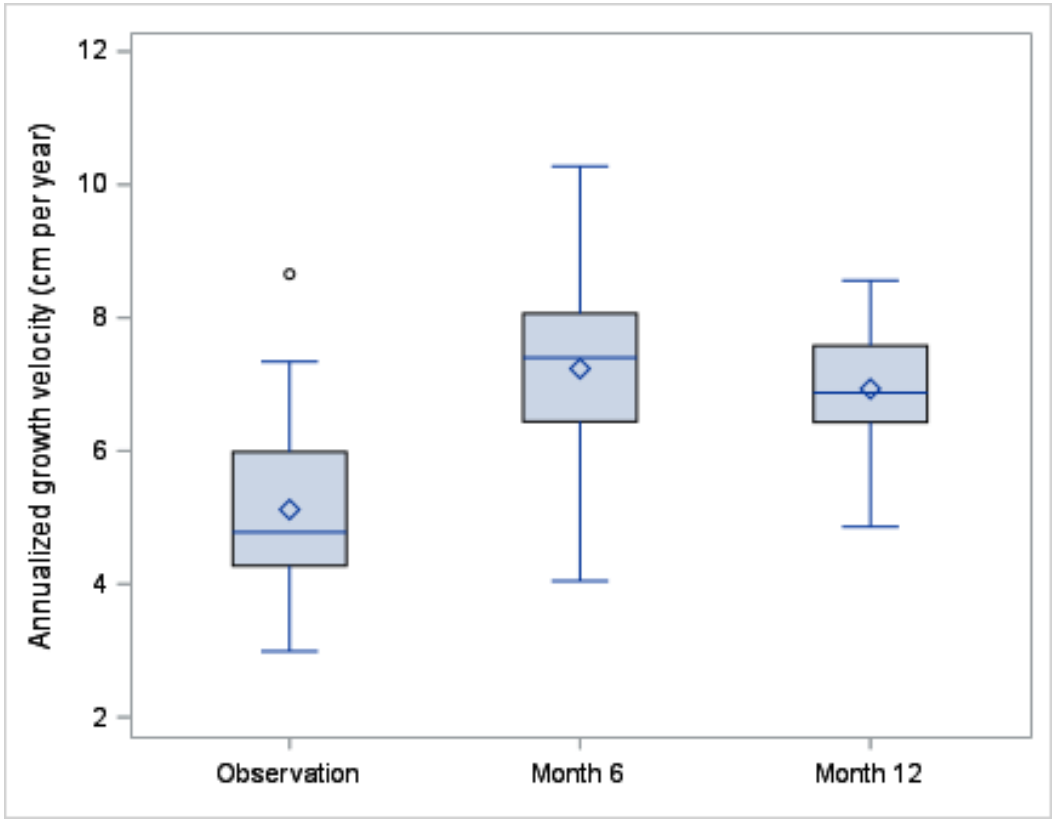
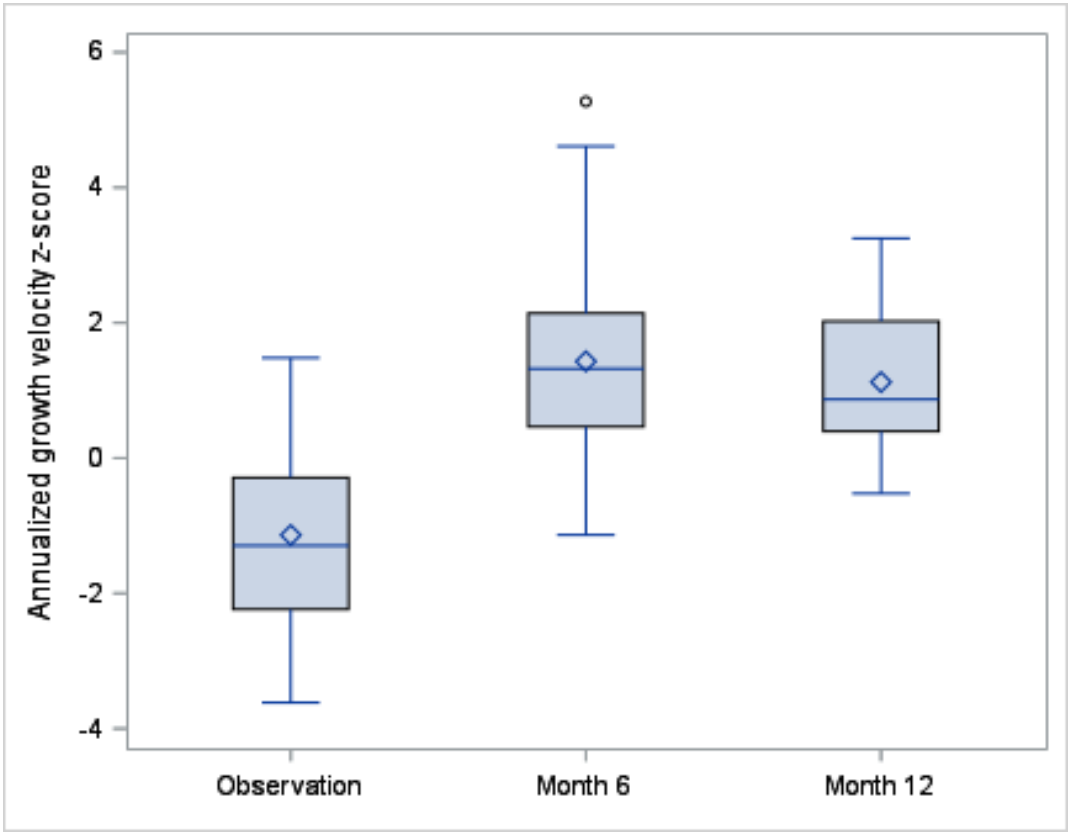
Hypochondroplasia – Growth Velocity Outcomes

Annualized Growth Velocity



Annualized Growth Velocity Z-score



1.81 cm/year increase in AGV; 2.26 SD increase in AGV Z-score

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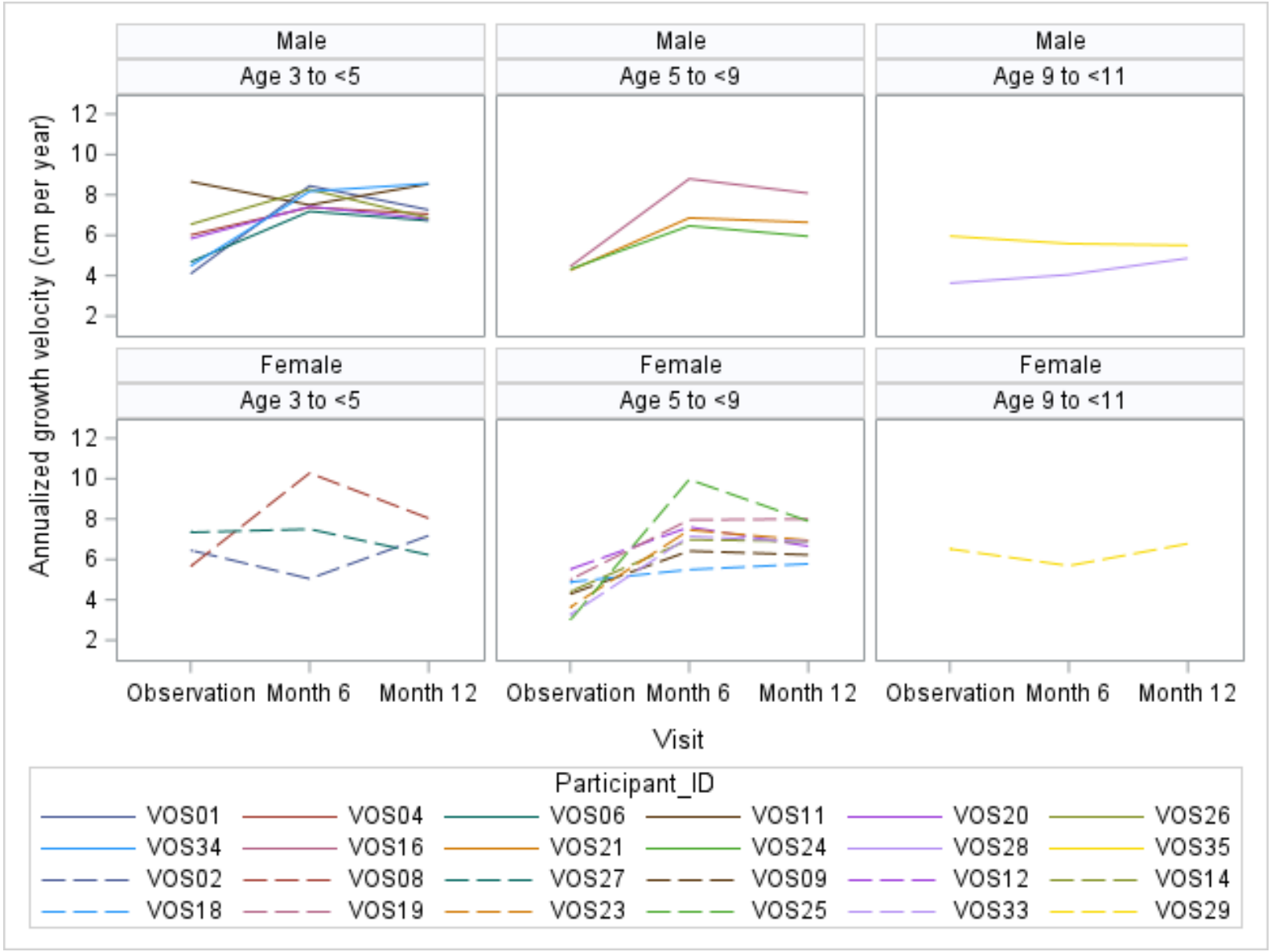
Individual Growth Velocity Curves



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Growth Velocity Subgroup Analysis

Annualized growth velocity (cm/yr)	Observation Period Mean (SD)	Treatment Period Mean (SD)	Difference Between Treatment and Observation (95% CI)	Two-sided p value
Age 3 to <5 Year (N=10)	5.97 (1.38)	7.32 (0.79)	1.35 (0.23, 2.47)	0.02
Age 5 to <9 Year (N=11)	4.27 (0.75)	6.91 (0.80)	2.63 (1.82, 3.44)	<0.0001
Age 9 to <11 Year (N=3)	5.37 (1.53)	5.71 (0.98)	0.34 (-1.76, 2.45)	0.55
GV baseline ≤ 5.0 (N=14)	4.17 (0.59)	6.91 (1.01)	2.74 (2.08, 3.40)	<0.0001
GV baseline > 5.0 (N=10)	6.45 (0.94)	6.96 (0.85)	0.52 (-0.18, 1.21)	0.13
Height SDS baseline ≤-3.5 (N=7)	4.67 (1.11)	6.64 (1.14)	1.97 (0.63, 3.31)	0.01
Height SDS baseline -3.5 to ≤3.0 (N=9)	5.17 (0.89)	6.88 (0.84)	1.72 (0.77, 2.66)	0.003
Height SDS baseline >-3.0 (N=8)	5.46 (1.95)	7.24 (0.86)	1.78 (0.07, 3.49)	0.04

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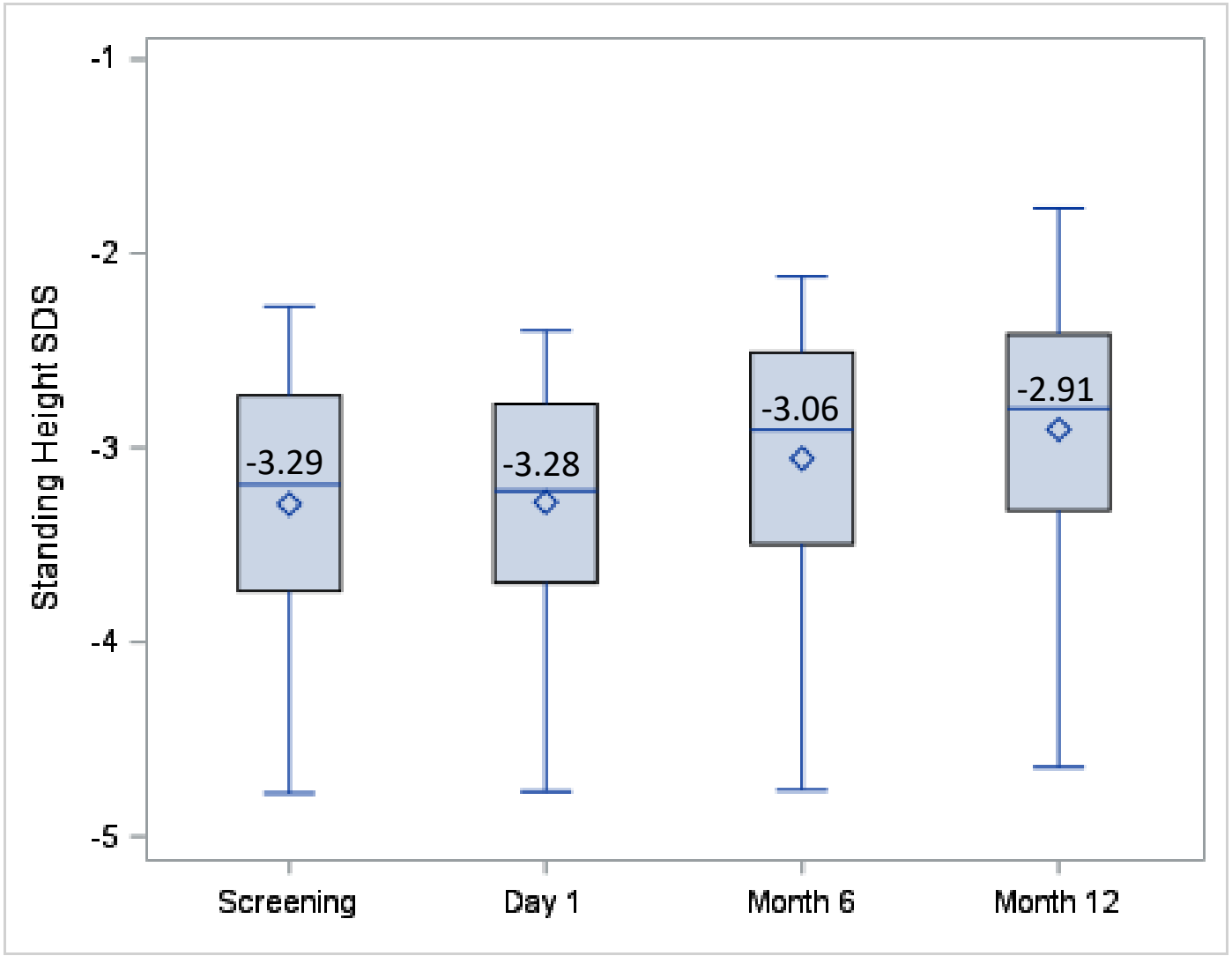
CDC Height SDS Outcomes



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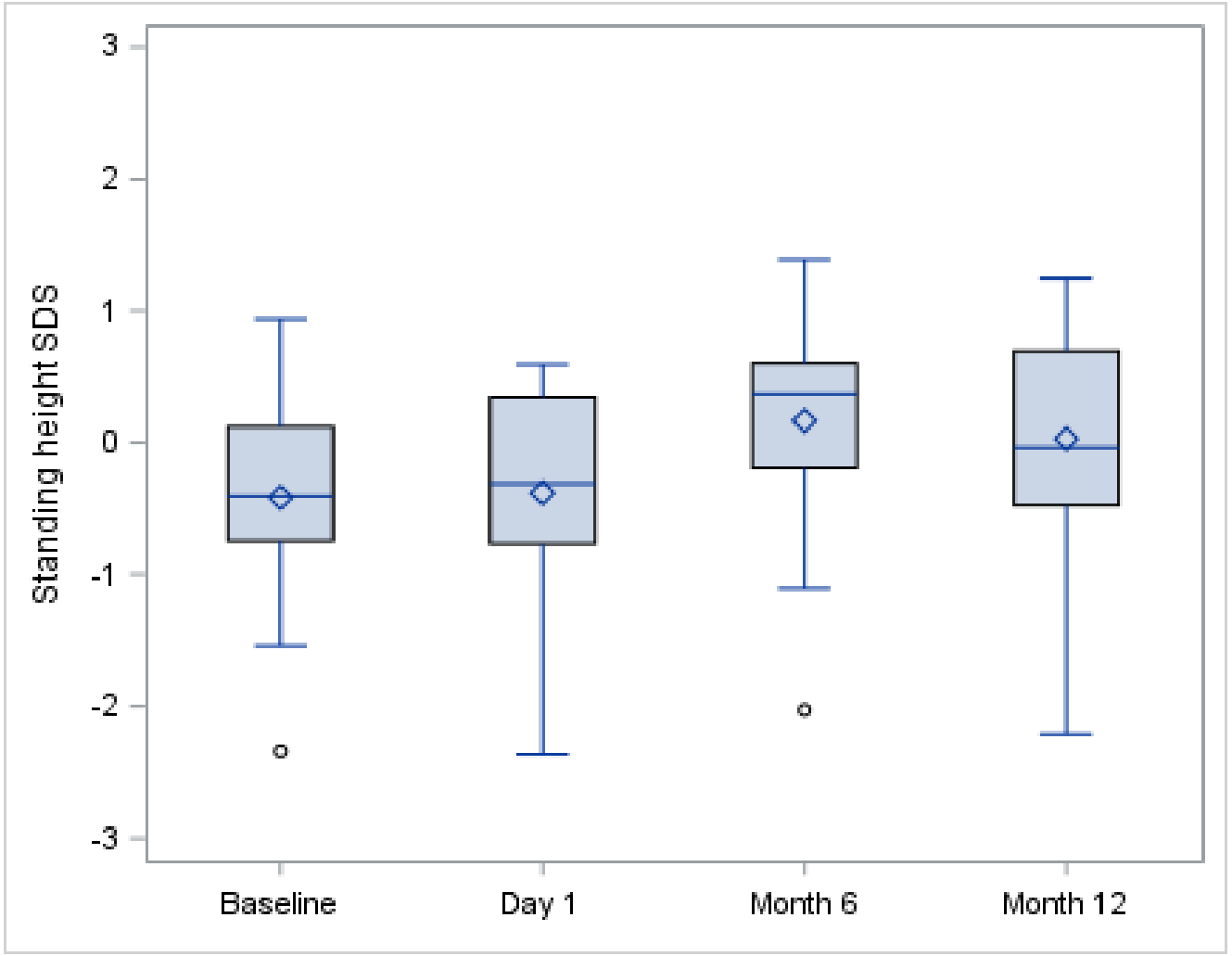
Hypochondroplasia Specific Height SDS Outcomes



0.03 SD change during observation vs 0.41 SD change during treatment

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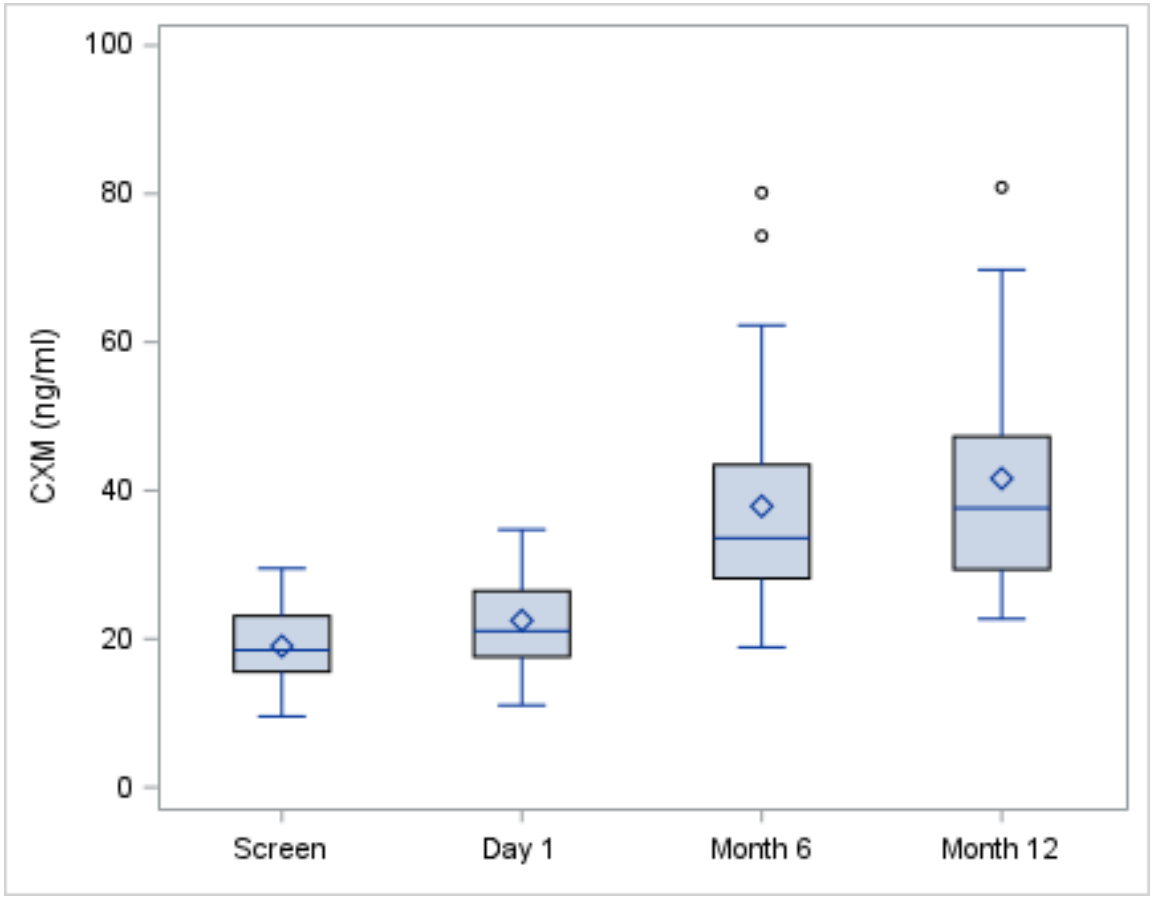
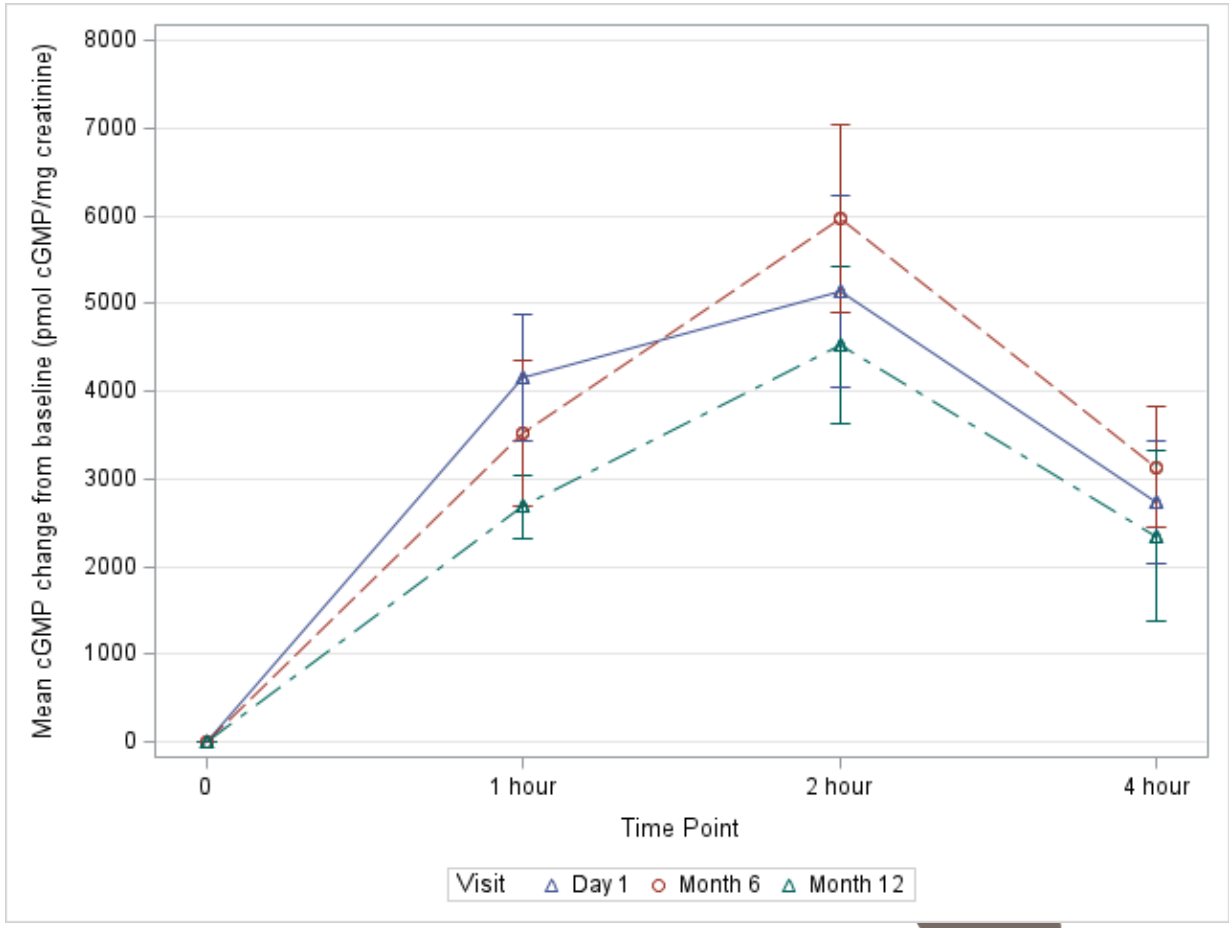
Analysis used growth charts by Cheung MS et al, AJMG Part A 2024.

Pharmacodynamic Biomarkers

Collagen X Biomarker



Urine cGMP Response



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Secondary Outcomes

- No change in bone age/chronological age
  - 0.78 at Day 1 vs 0.79 at Month 12 (p=0.67)
- Sitting height ratio showed minor decrease over 1 year of treatment but not significant when adjusted for age/sex.
- No change in arm span minus height.
- No change in parent reported quality of life.

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Conclusions

- Vosoritide increases growth velocity in children with hypochondroplasia to a similar degree as has been seen in achondroplasia.
- Safety profile was relatively benign and consistent with prior reports.
- Additional analyses are ongoing to examine factors that may predict response.
- Our data support further study of vosoritide for children with hypochondroplasia.

Acknowledgements

We would like to thank the patients and their families for their participation.

We would like to thank the staff of the clinical research center and investigational pharmacy at Children's National Hospital.

Interested in enrolling in studies? – Contact me at adauber@childrensnational.org

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