Vosoritide Increases Growth Velocity in Hypochondroplasia: Phase 2 Trial Results

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Financial Disclosure

Andrew Dauber

Discloses the following relevant relationships with ineligible companies. Any potential interests have been mitigated:

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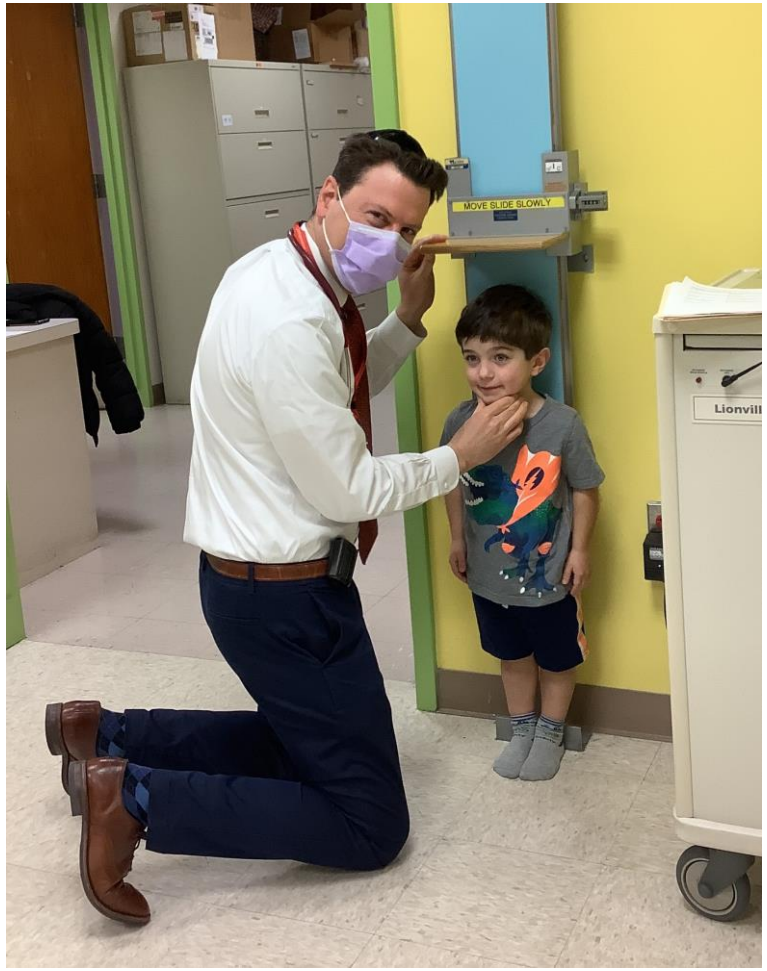
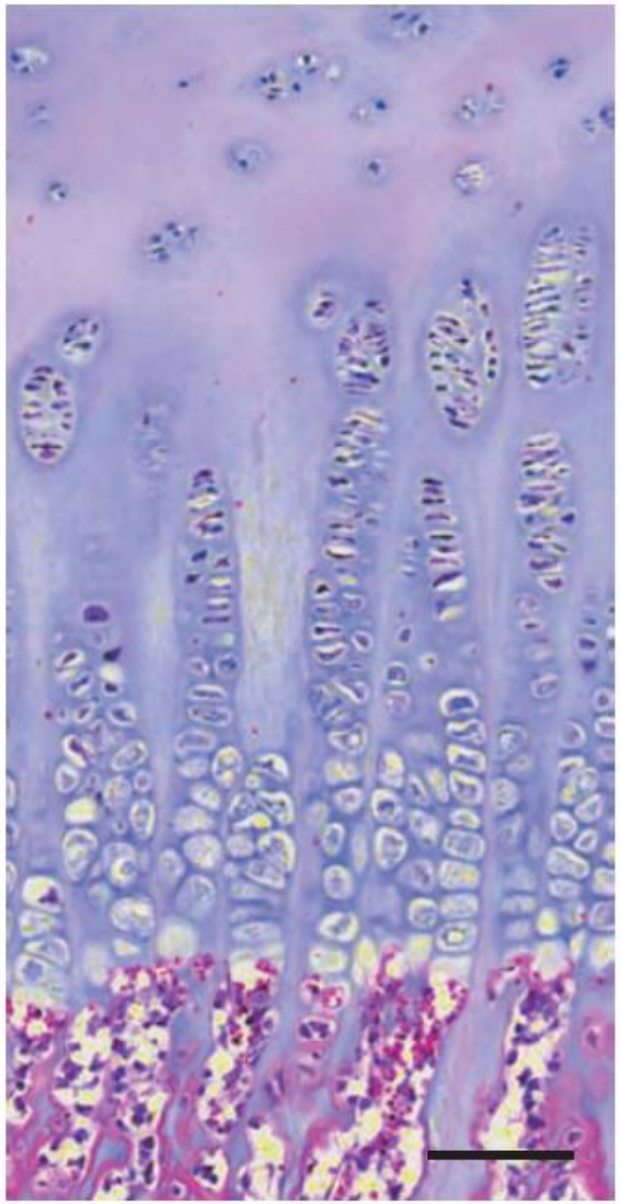
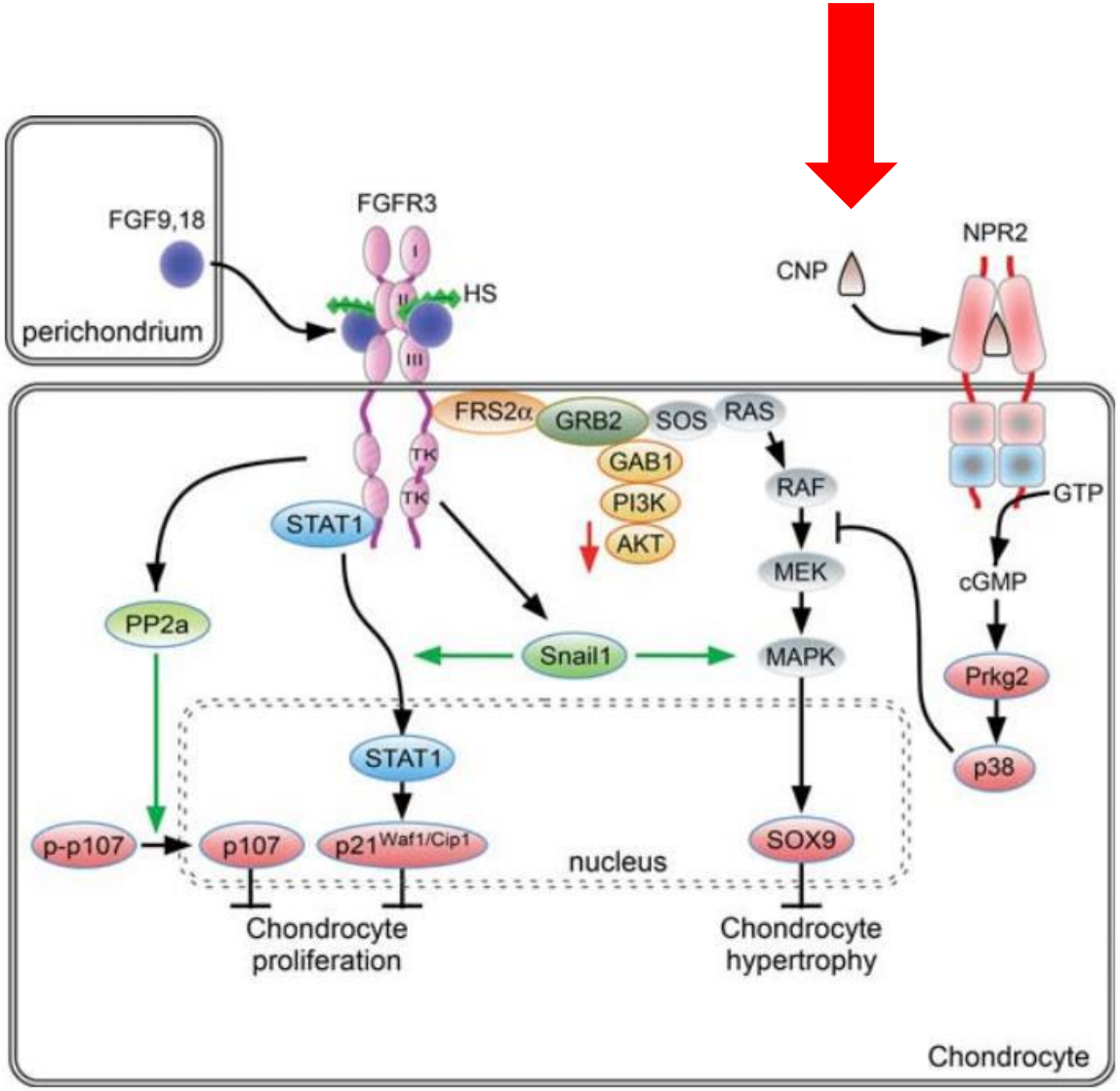
Hypochondroplasia Overview

- 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



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





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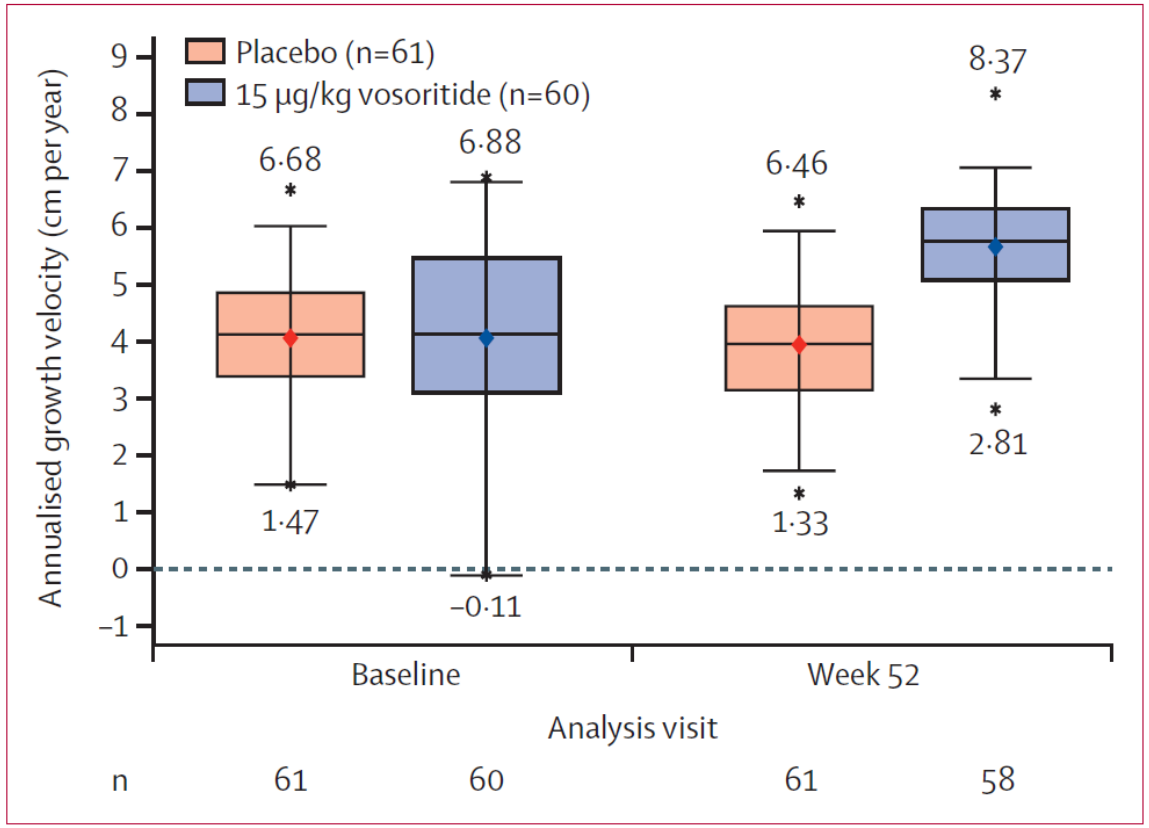
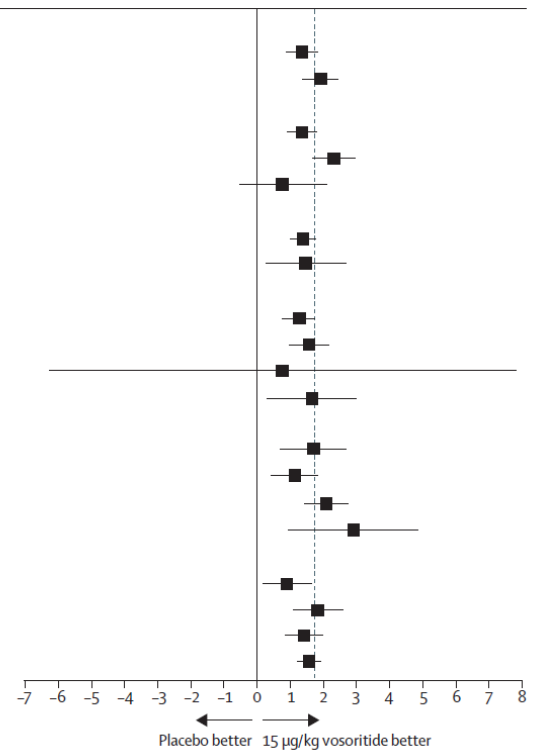
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

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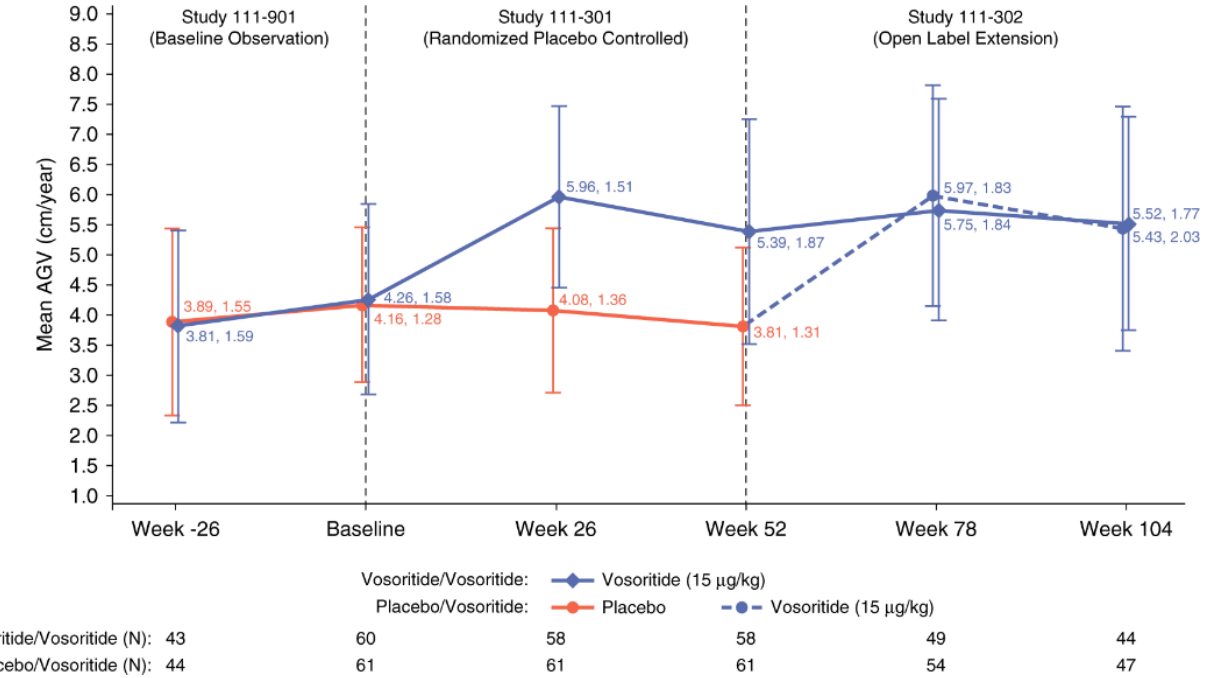
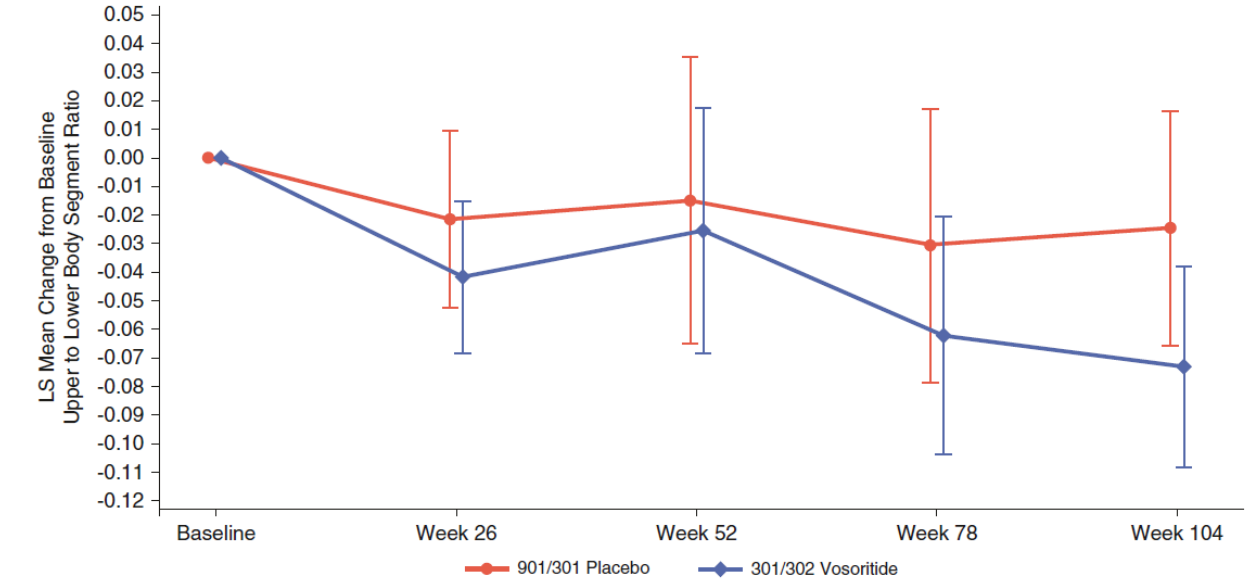
2nd Year Results: Sustained increased in growth velocity and improvement in body proportions



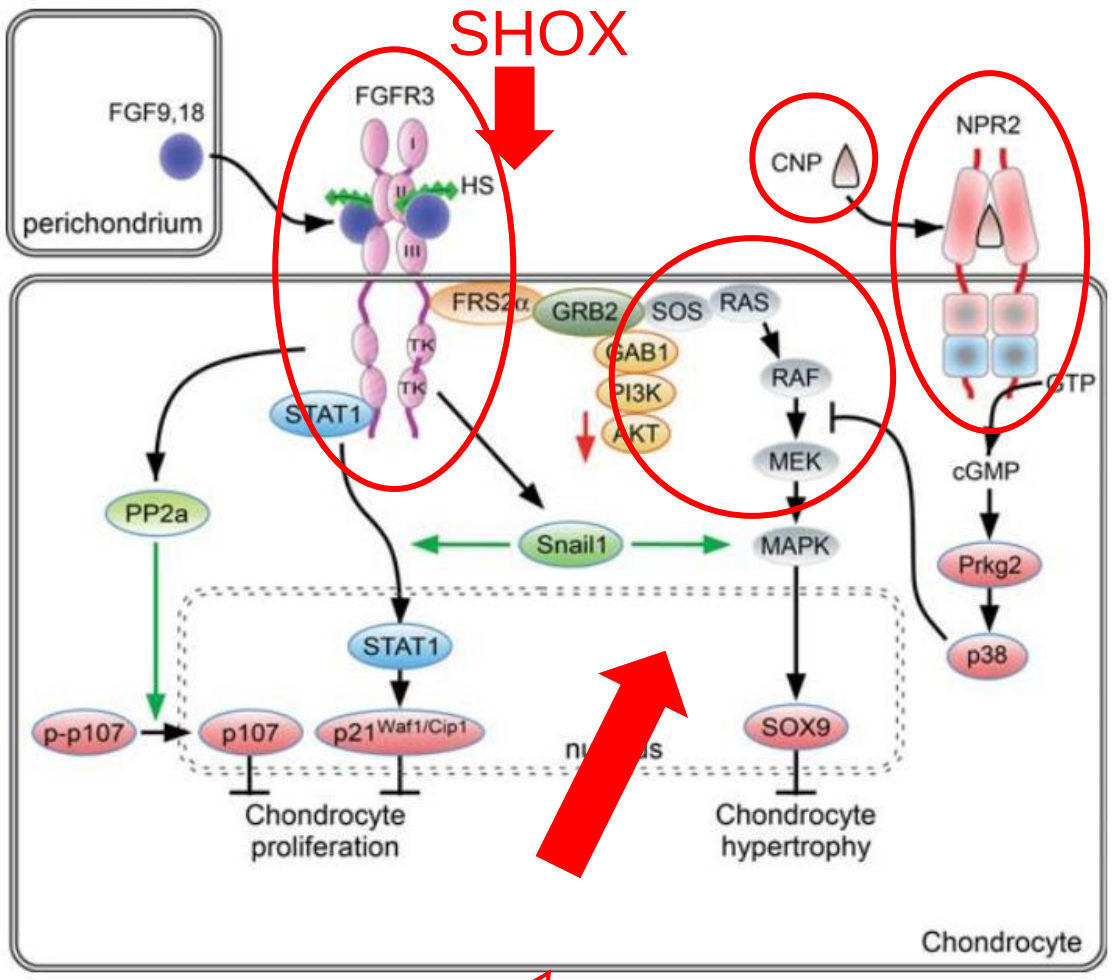
Vosoritide/Vosoritide (N):	43	60	58	58	49	44
Placebo/Vosoritide (N):	44	61	61	61	54	47



Placebo (N):	38	38	38	38	38
15 µg/kg Vosoritide (N):	45	45	45	37	45

Vosoritide for Selected Genetic Causes of Short Stature

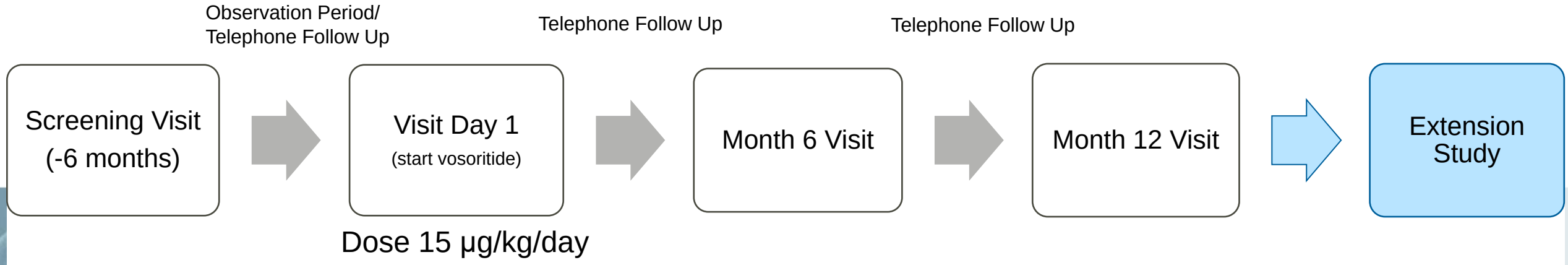
- Hypochondroplasia
- CNP Deficiency
- Heterozygous NPR2 mutation
- Rasopathy
- SHOX
- Aggrecan Deficiency



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

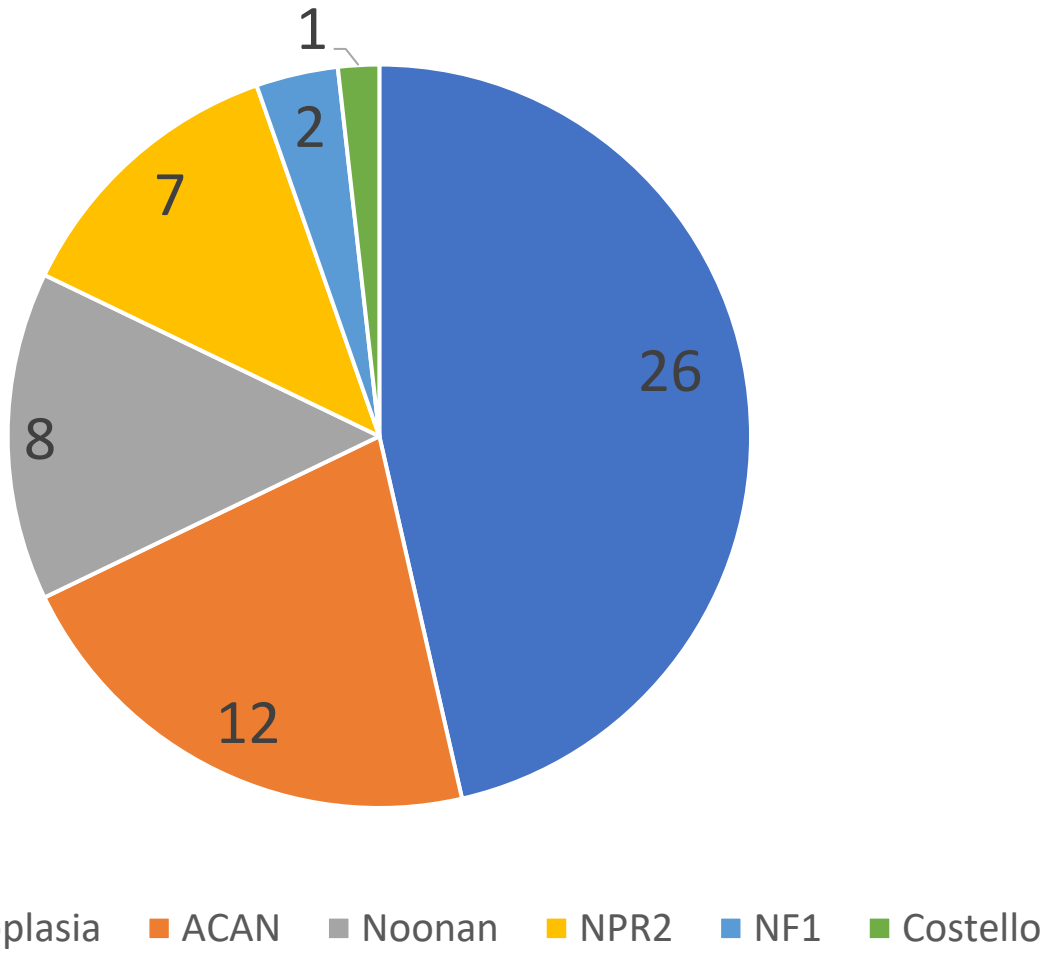
Secondary study endpoints:

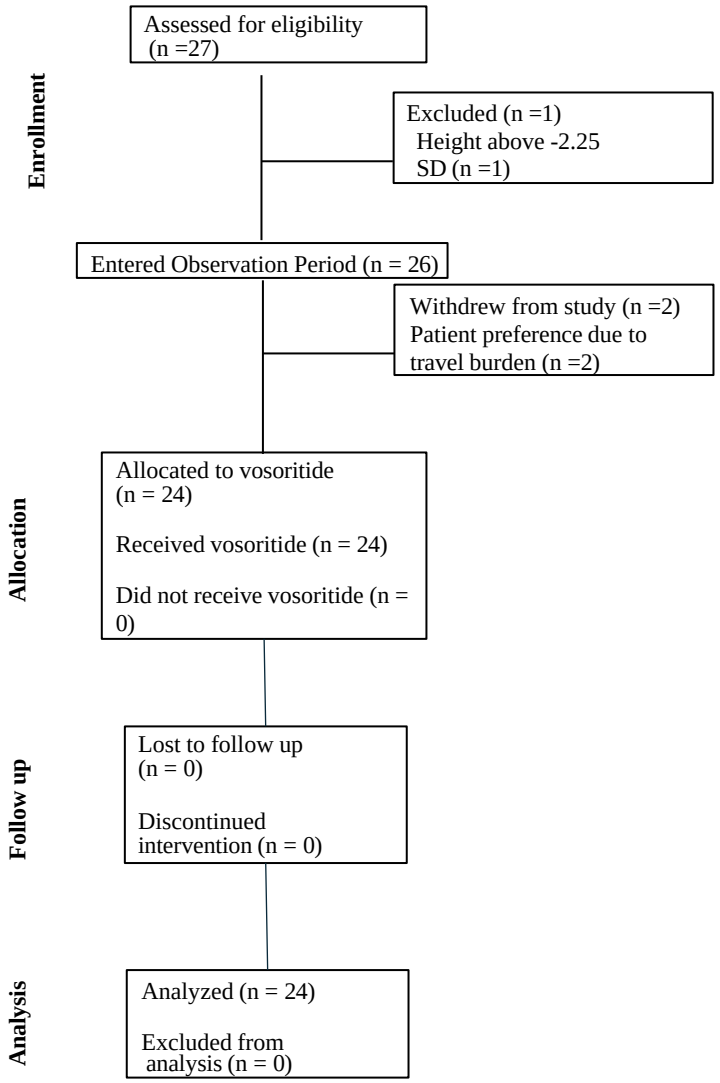
- Body proportions
- Δ bone age/chronological age at 12 months

The exploratory study endpoints include:

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

Genetic Categories





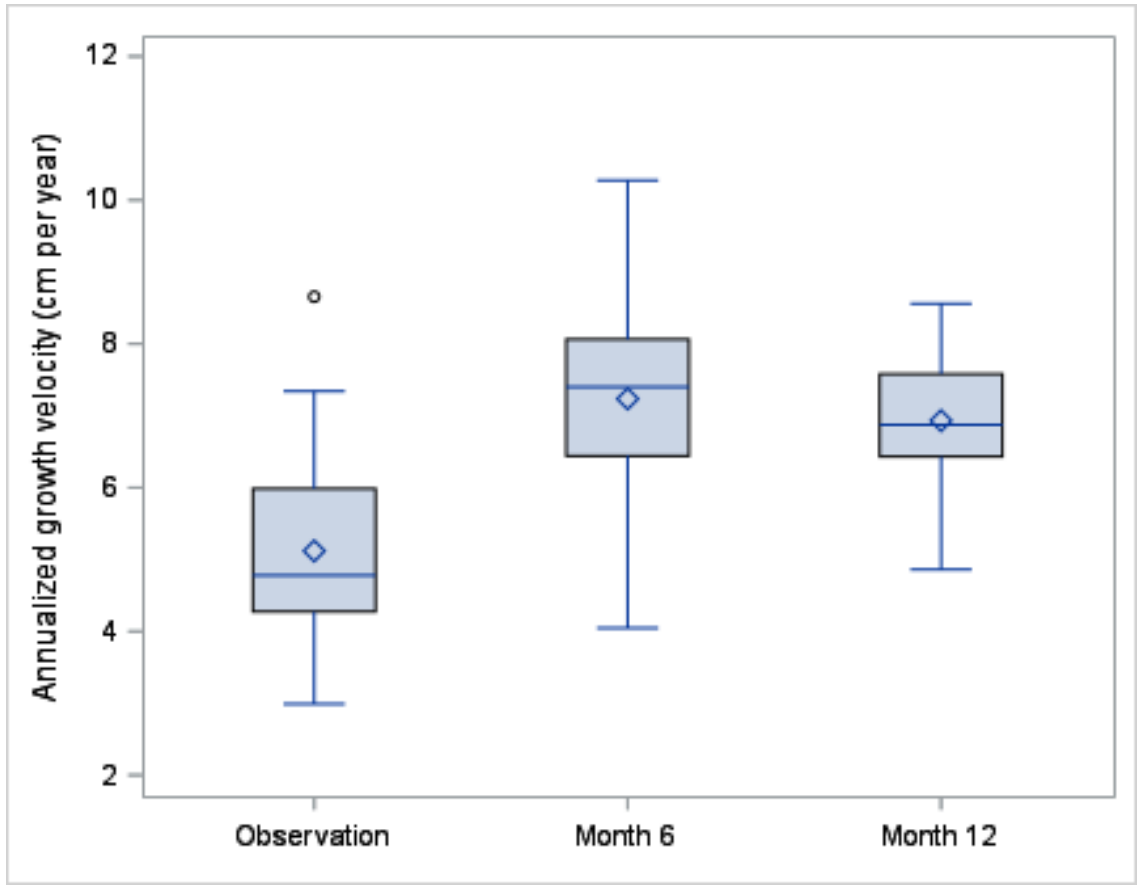
Total enrolled subjects	N=24
Age at screening (years) mean (SD); median (IQR)	5.86 (2.29); 5.55 (2.39)
Age group # (%)	
3 to <5 year	10 (41.7%)
5 to <9 year	11 (45.8%)
9 to <11 year	3 (12.5%)
Sex	
Female	12 (50%)
Male	12 (50%)
Race	
Caucasian	17 (70.8%)
Asian	4 (16.7%)
Other	3 (12.5%)
Ethnicity	
non-Hispanic/Latino	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%)

Safety

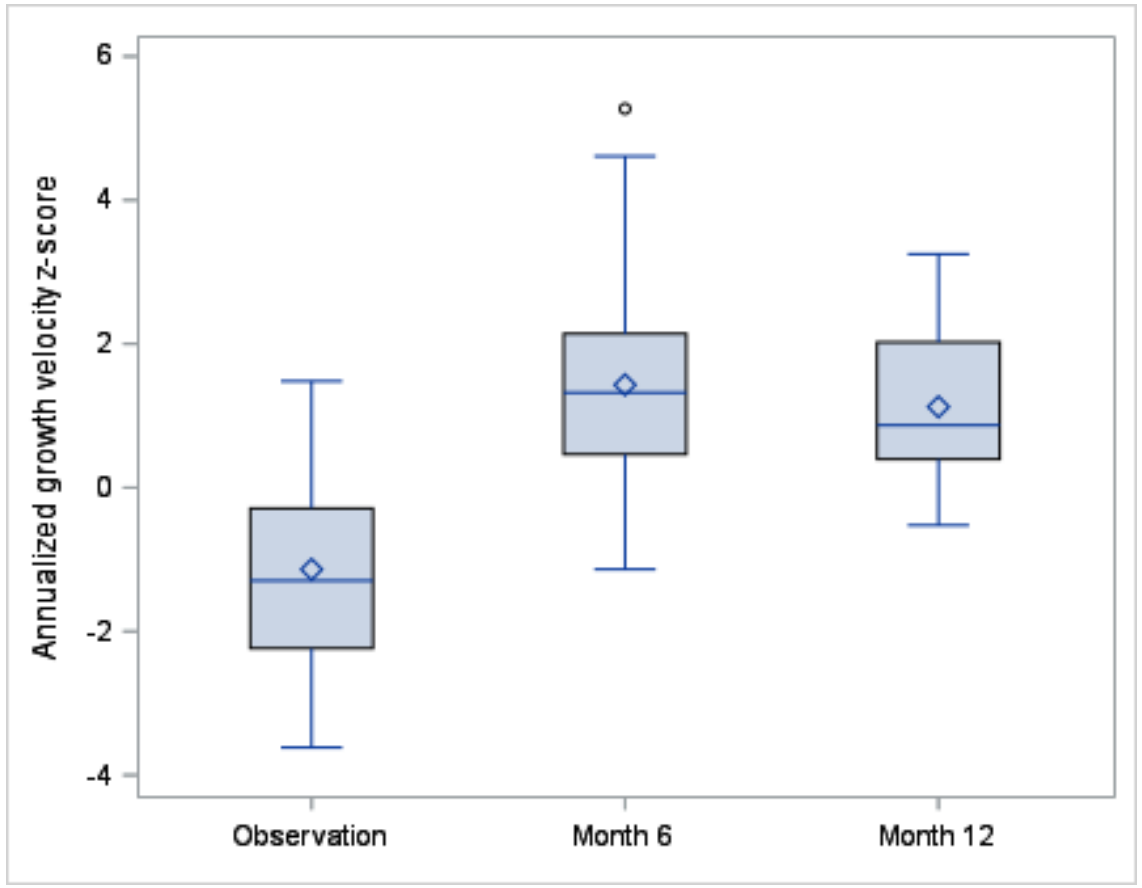
- 83% of subjects had injection site reactions
  - All grade 1 or 2
  - All self-resolved without intervention
- No subjects discontinued treatment due to an AE
- 1 SAE unrelated to vosoritide – viral induced ITP
- 1 episode of syncope with documented normal blood pressure
- No episodes of symptomatic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

Hypochondroplasia – Growth Velocity Outcomes

Annualized Growth Velocity

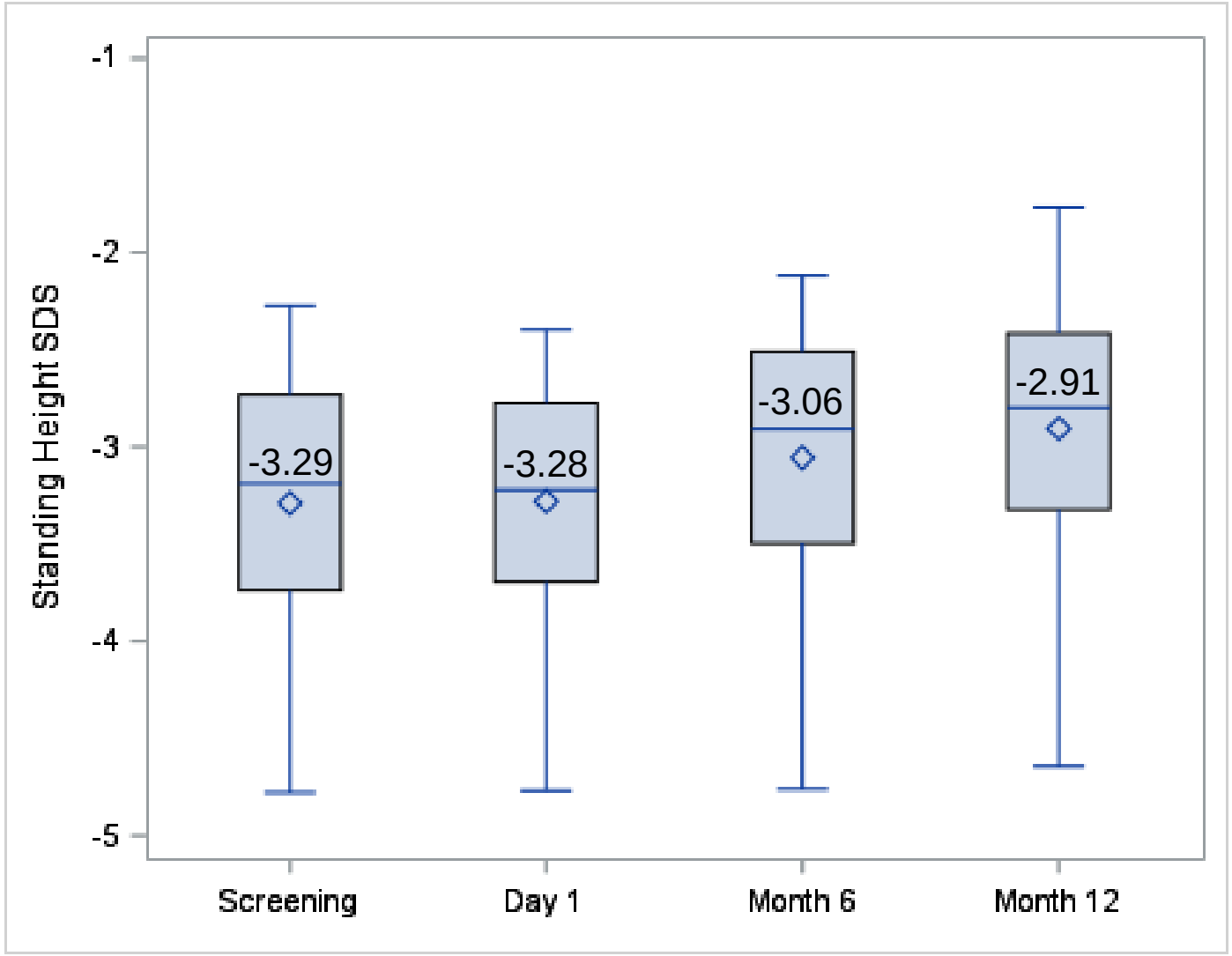


Annualized Growth Velocity Z-score



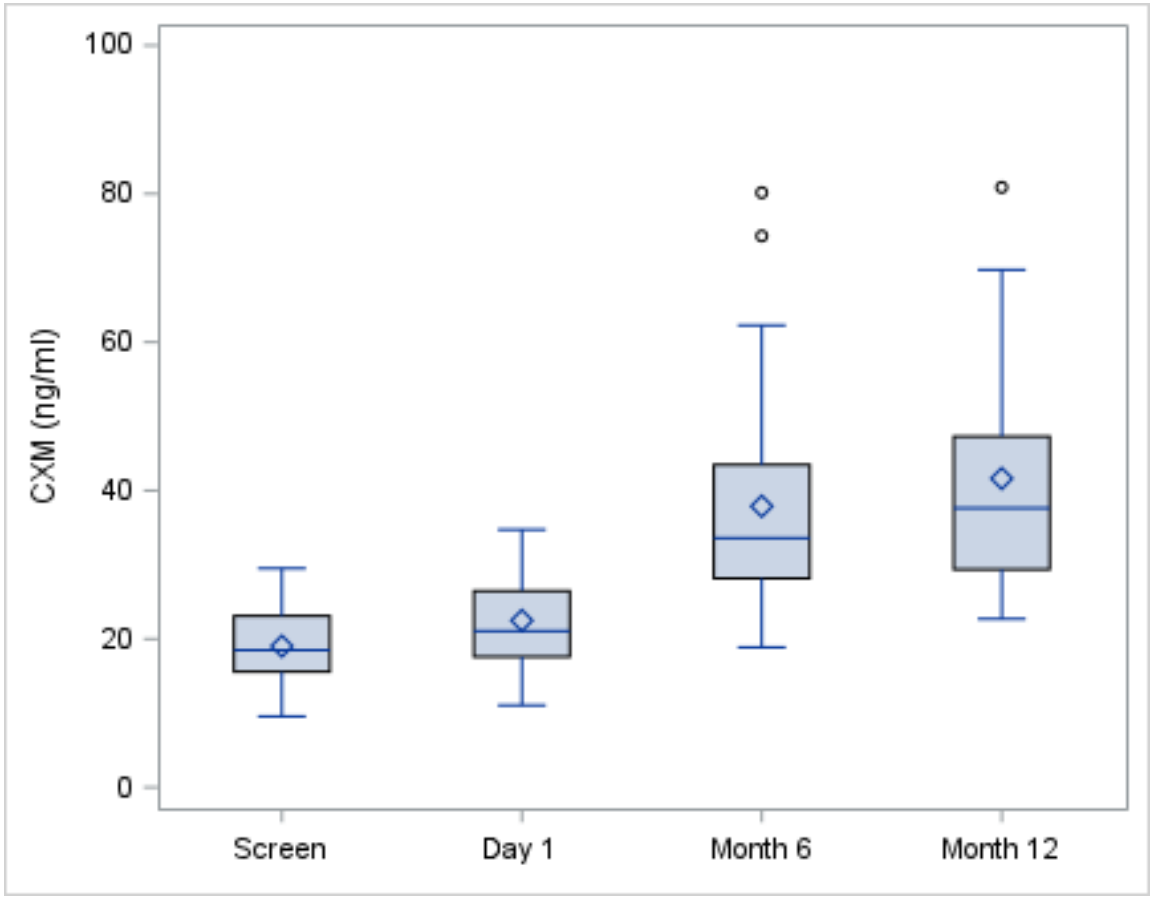
1.81 cm/year increase in AGV; 2.26 SD increase in AGV Z-score

Hypochondroplasia – Height SDS Outcomes

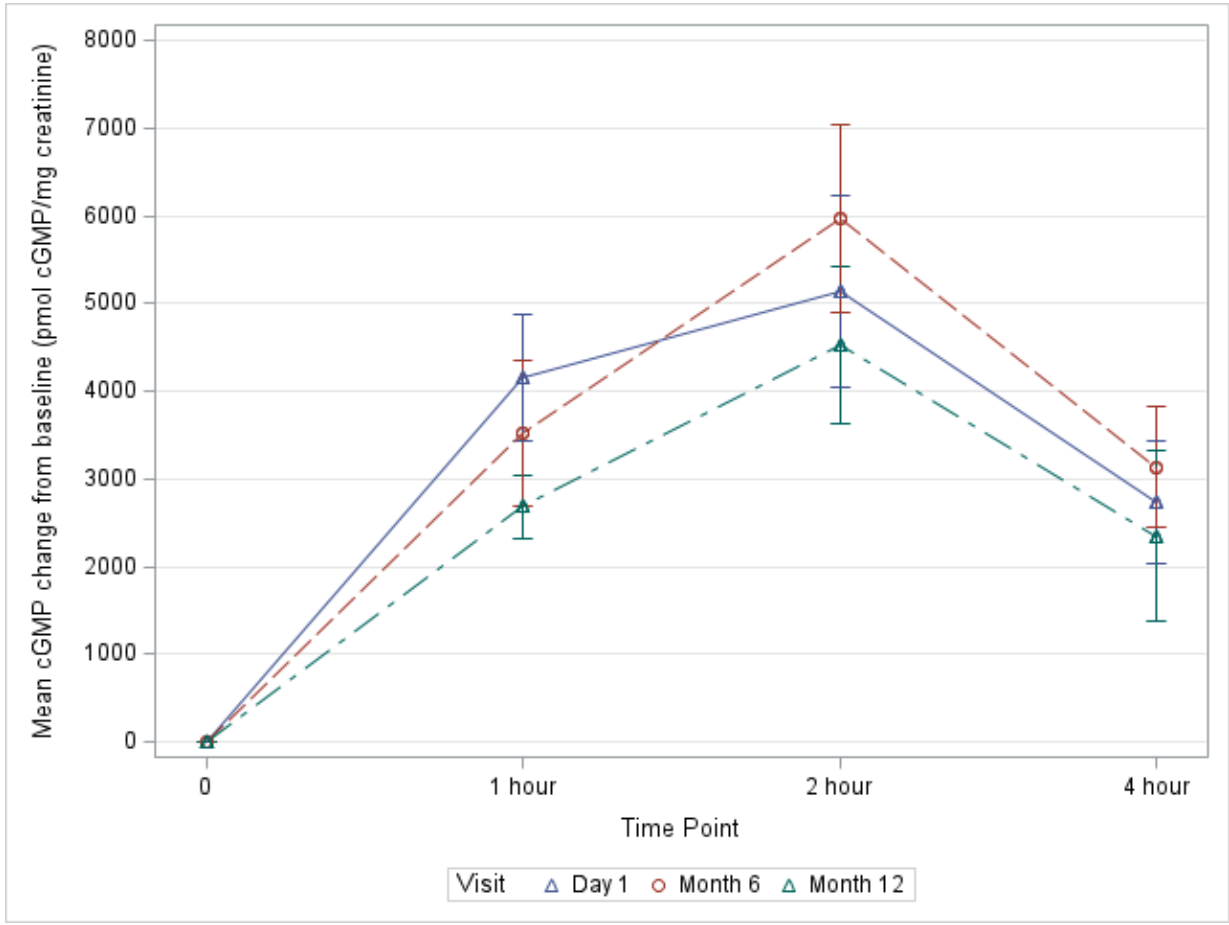


Pharmacodynamic Biomarkers

Collagen X Biomarker



Urine cGMP Response



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.

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

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.

Precision Medicine for Genetic Short Stature

- Recent major advances in knowledge of genetic mechanisms underpinning growth disorders leading to short stature
- Understanding the biology of growth expanded beyond days of using GH for Idiopathic Short Stature
- Allows for precision medicines targeted to address specific underlying pathophysiology
- Any genetic condition leading to a pathological increase in ERK1/2 phosphorylation should be responsive to vosoritide

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