Vosoritide Improves Growth in RASopathies, Aggrecan and NPR2 Deficiency: A Phase 2 Trial

Andrew Dauber MD MMSc, Anqing Zhang PhD, Niusha Shafaei MSc, Raheem Seaforth BA, Kimberly Pitner RN, Niti Dham MD MBA, Roopa Kanakatti Shankar MBBS MS, Nadia Merchant MD

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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.
- AD has served as a consultant to BioMarin, but all compensation has been paid to Children's National Hospital.

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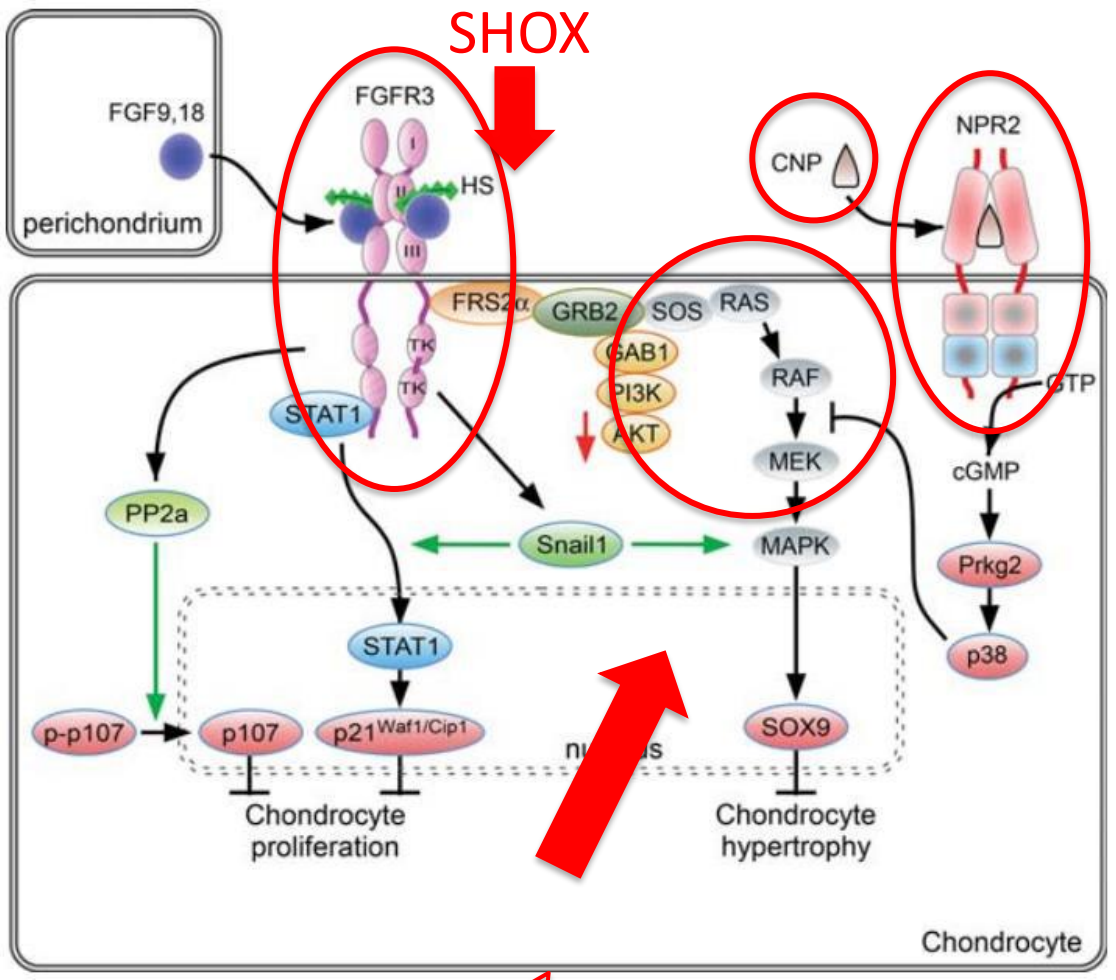
Vosoritide for Selected Genetic Causes of Short Stature

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



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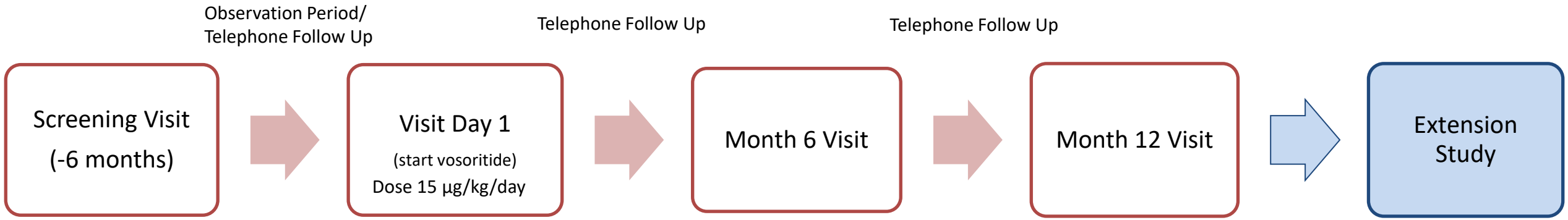
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

Phase 2 Trial of Vosoritide for Selected Genetic Causes of Short Stature Including Hypochondroplasia

- Age ≥3 years 0 days AND <11 years for males, <10 years 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



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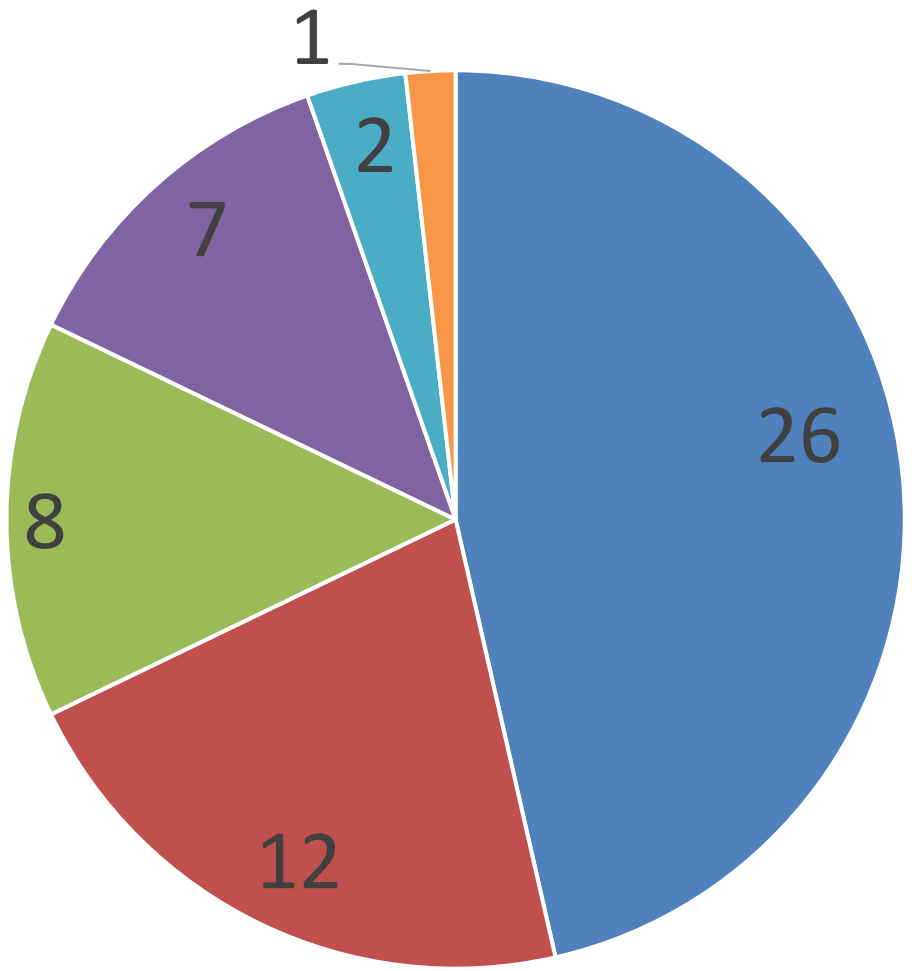
Genetic Subgroups



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Demographics and Patient Flow

Total enrolled subjects	N=30
Age at screening (years) mean (SD); median (IQR)	7.17 (2.22); 7.21 (3.01)
Age group # (%)	
3 to <5 year	6 (20%)
5 to <9 year	18 (60%)
9 to <11 year	6 (20%)
Sex	
Female	8 (26.7%)
Male	22 (73.3%)
Previously treated with growth hormone	
Yes	5 (16.7%)
No	25 (83.3%)
Height SDS at Baseline	
-2.25 to -3	19 (63.3%)
<-3 to -4	10 (33.3%)
<-4	1 (0.3%)

- 34 subjects screened
  - 4 excluded for height >-2.25 SD
- 30 subjects started on vosoritide
  - 2 subjects discontinued prior to first follow up unrelated to treatment
- 28 subjects included in the efficacy analysis
  - 5 subjects were Tanner 2 at the end of Year 1 (4 male, 1 female)

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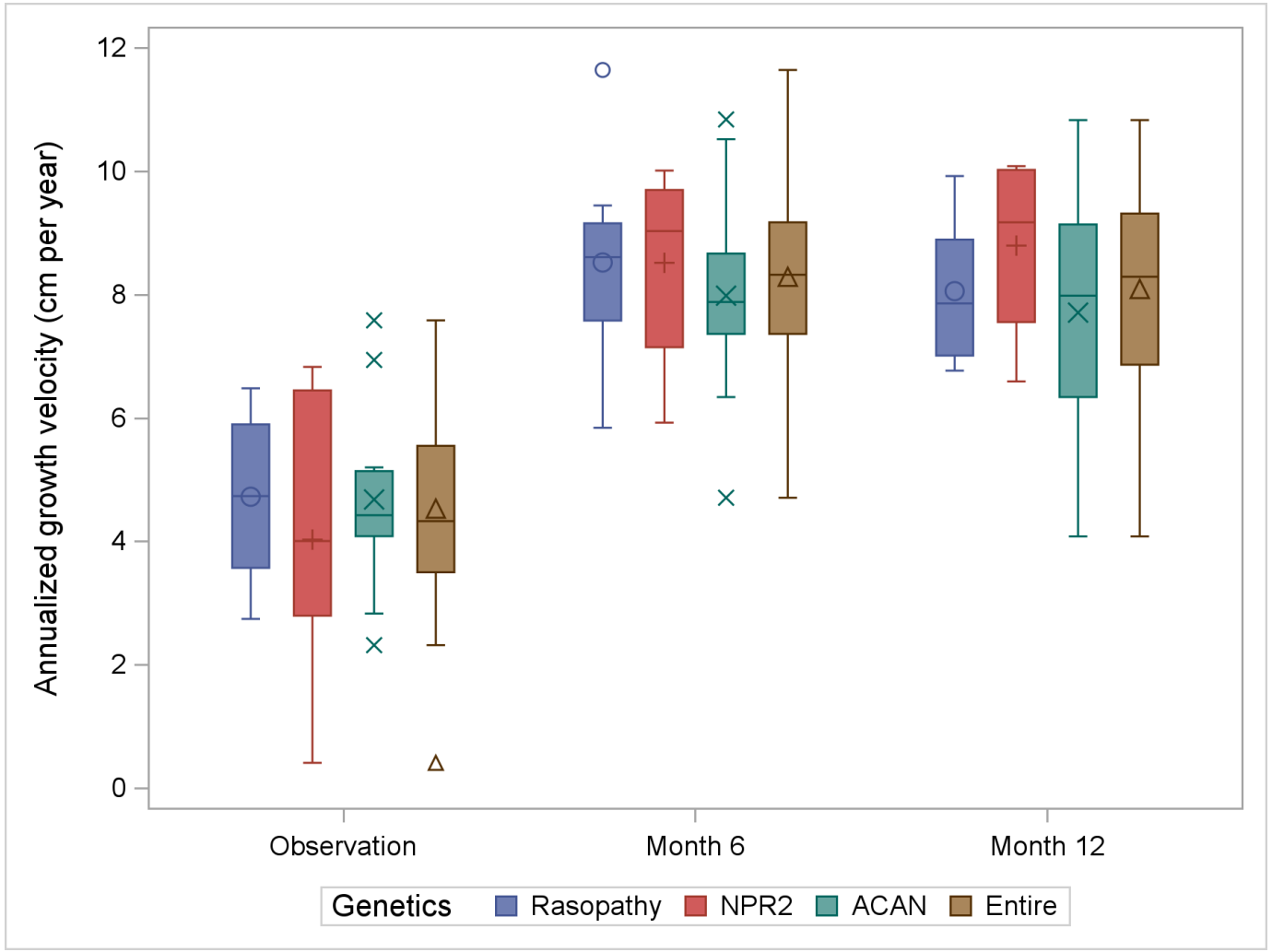
Efficacy Outcome – Growth Velocity



Cohort	Observation Period Mean (SD)	Treatment Period Mean (SD)	Difference Between Treatment and Observation (95% CI)	Two-sided p value
All subjects (N=28)	4.53 (1.61)	8.09 (1.58)	3.56 (2.69, 4.43)	<0.0001
NPR2 (N=7)	4.03 (2.19)	8.79 (1.34)	4.76 (2.19, 7.34)	0.004
RASopathy (N=9)	4.72 (1.35)	8.05 (1.10)	3.33 (2.32, 4.35)	<0.0001
ACAN (N=12)	4.68 (1.48)	7.71 (1.96)	3.03 (1.52, 4.54)	0.001

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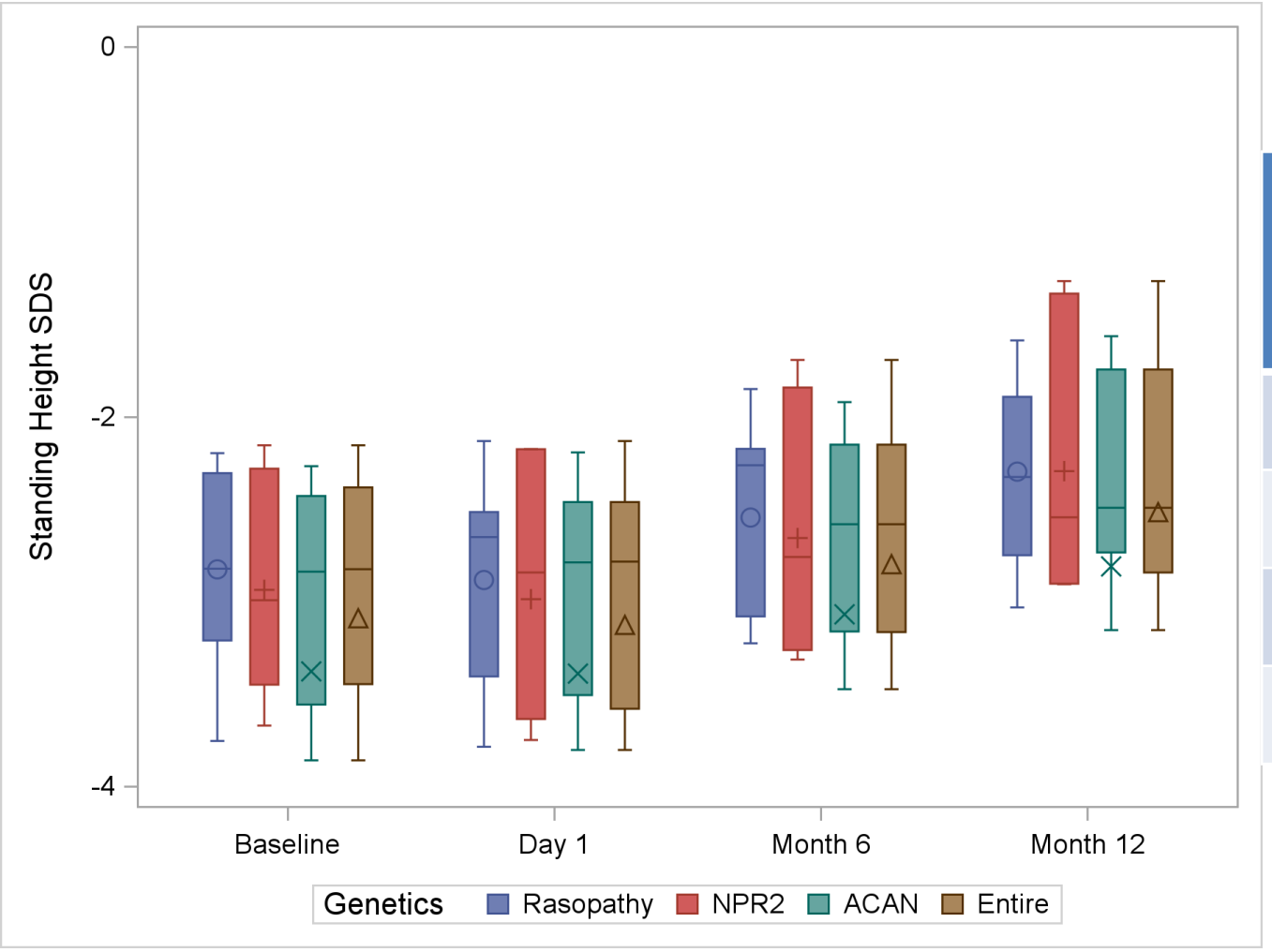
Efficacy Outcome – Height SDS



Cohort	Change in Height SDS During Observation Period (95% CI)	Change in Height SDS During Treatment Period (95% CI)	Mean Difference Between Treatment and Observation (95% CI)	Two-sided p value
All subjects (N=28)	-0.04 (-0.09, 0.02)	0.61 (0.51, 0.71)	0.65 (0.53, 0.77)	<0.0001
NPR2 (N=7)	-0.05 (-0.19, 0.09)	0.69 (0.49, 0.90)	0.74 (0.46, 1.02)	0.0006
RASopathy (N=9)	-0.06 (-0.19, 0.07)	0.59 (0.41, 0.76)	0.64 (0.51, 0.78)	<0.0001
ACAN (N=12)	-0.01 (-0.11, 0.08)	0.58 (0.37, 0.79)	0.59 (0.33, 0.85)	0.0004

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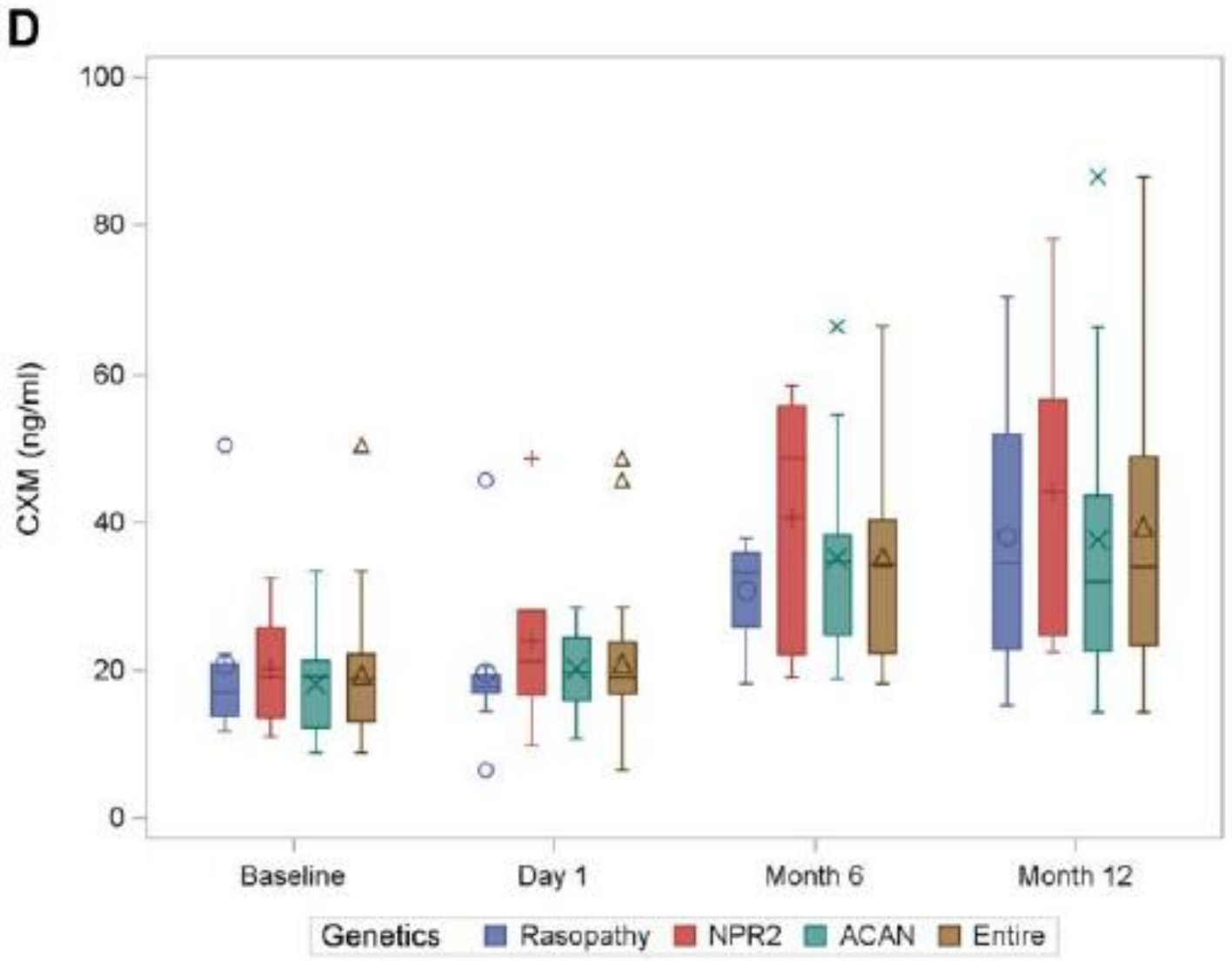
Collagen X BioMarker (CXM)



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Secondary OUtcomes

Secondary endpoints	Baseline Mean(std)	Day 1 Mean(std)	Month 12 Mean(std)	Change During Observation Period (95% CI)	Change During Treatment Period (95% CI)	Mean Difference Between Treatment and Observation (95% CI)	Two-sided p value
Bone age (years)	N/A	7.2 (2.7)	8.0 (2.8)	N/A	0.8 (0.6, 1.1)	N/A	<.0001
Bone age/ chronological age	N/A	0.94 (0.20)	0.92 (0.17)	N/A	-0.02 (-0.06, 0.01)	N/A	0.22
Sitting height ratio							
Unadjusted	0.56 (0.02)	0.56 (0.02)	0.55 (0.02)	-0.003 (-0.006, 0.001)	-0.008 (-0.01, -0.005)	-0.005 (-0.01, 0.00005)	0.05
Age/Sex adjusted	2.88 (1.01)	2.95 (0.77)	2.66 (0.92)	0.07 (-0.19, 0.34)	-0.30 (-0.52, -0.08)	-0.37 (-0.79, 0.05)	0.08
Arm span minus height							
Unadjusted	-2.61 (3.98)	-2.01 (3.47)	-3.08 (4.23)	0.60 (-0.34, 1.55)	-1.07 (-1.81, -0.33)	-1.67 (-3.0, -0.34)	0.02
Age/Sex adjusted	-0.49 (1.26)	-0.36 (1.08)	-0.83 (1.28)	0.13 (-0.20, 0.47)	-0.47 (-0.72, -0.23)	-0.61 (-1.07, -0.15)	0.01
CXM (ng/ml)	19.37 (8.98)	20.94 (9.17)	39.43 (19.37)	1.76 (-1.57, 5.08)	18.43 (11.45, 25.42)	16.28 (7.25, 25.30)	0.001

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Safety

- Well tolerated during the 1st year of treatment
- Injection site reactions in 40%
- In 1st year, no grade 3 or higher treatment-related adverse events.
- In extension phase, 5 subjects discontinued treatment due to adverse events (4 ACAN and 1 Noonan).
  - 4 of the subjects developed significant genu valgum
  - 3 of the subjects developing a slipped capital femoral epiphysis (SCFE)

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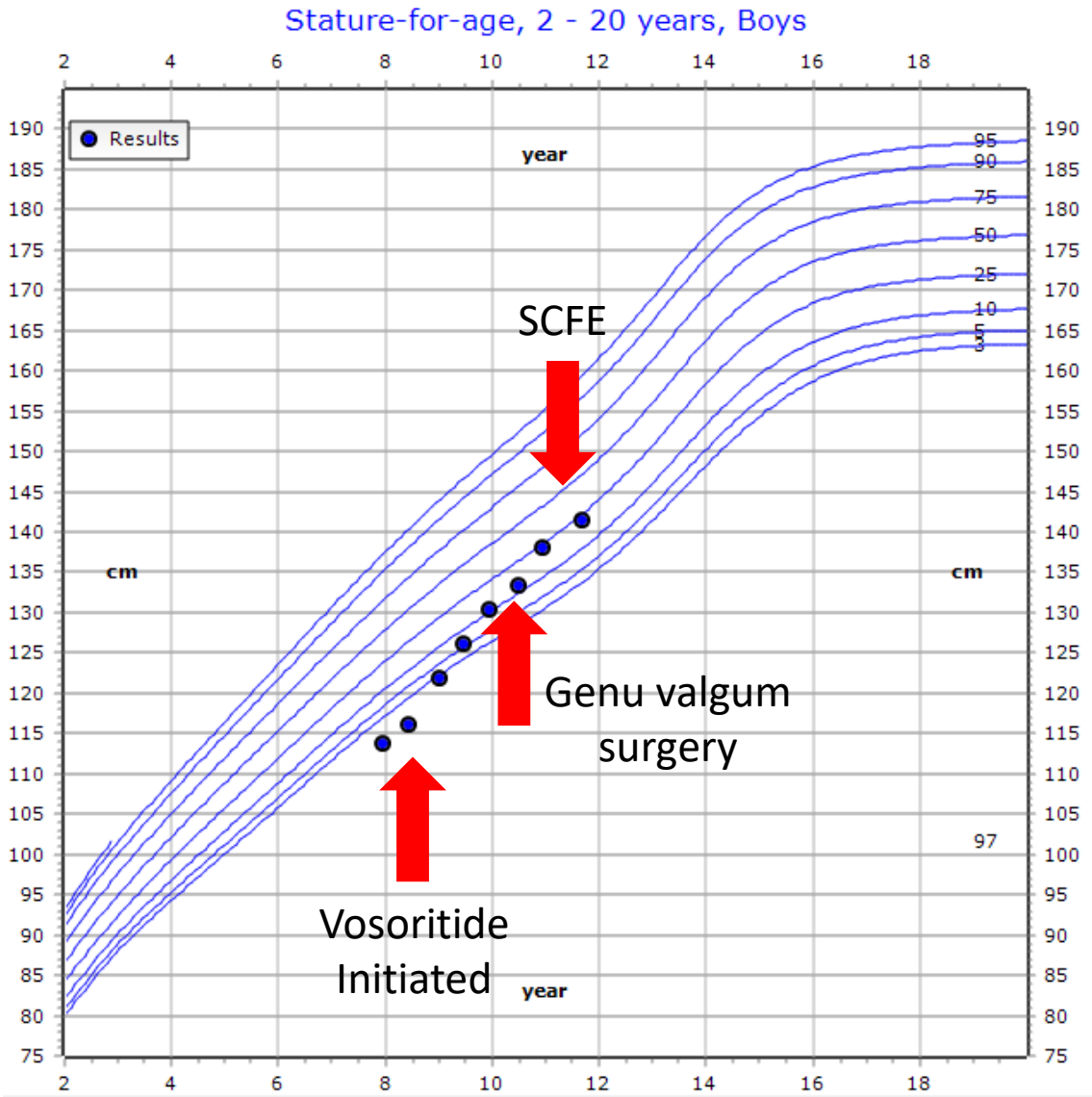
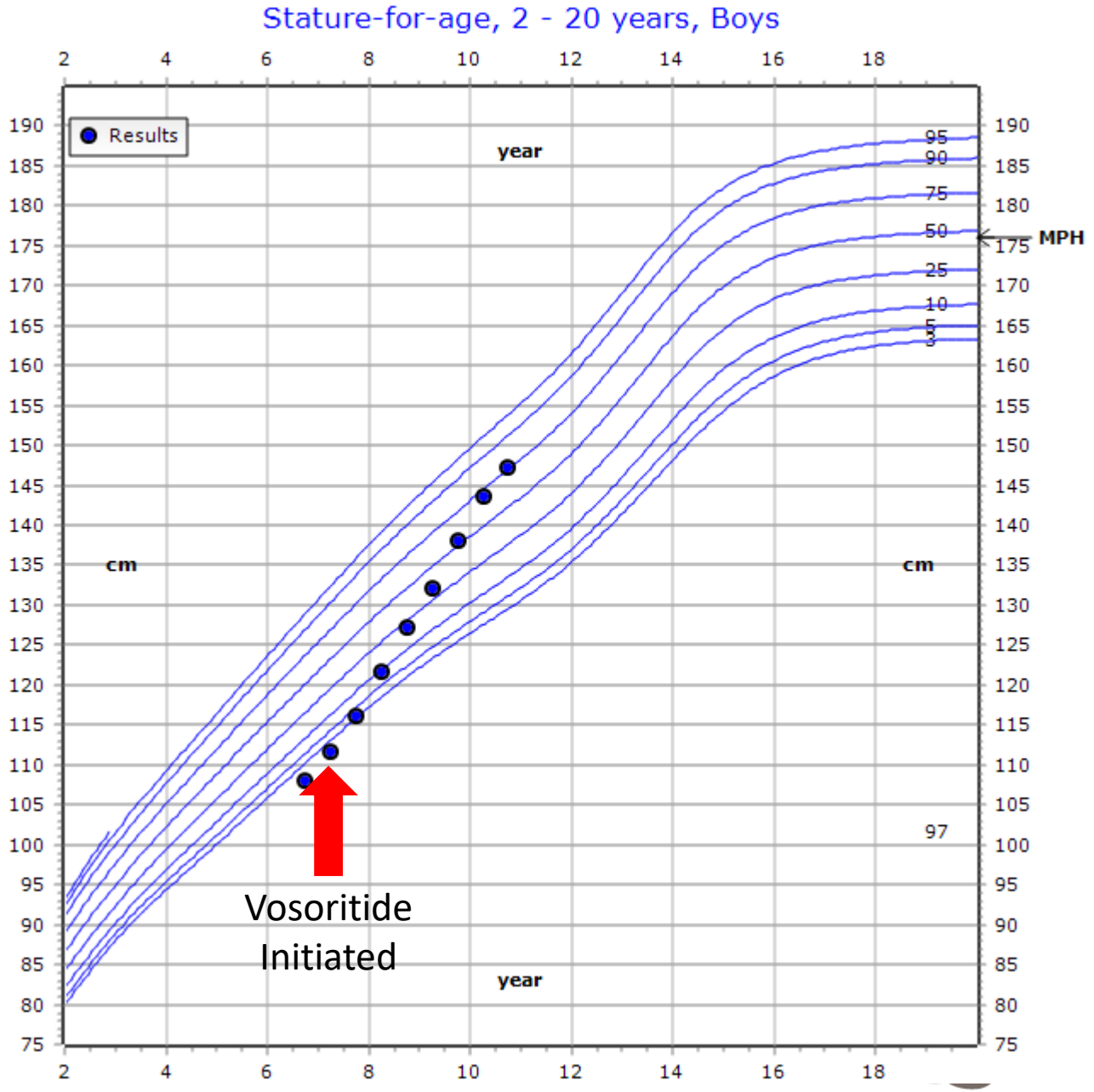
Boy with frameshift variant in ACAN on treatment for 35 months



Unpublished data, Children's National Hospital

Boy with NPR2 missense variant on treatment for 3.5 years

-Remains pre-pubertal
-No significant adverse events



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Unpublished data, Children's National Hospital

Conclusions

- Vosoritide increased growth velocity in patients with RASopathies, ACAN, and NPR2 deficiency.
- Vosoritide acts as a precision medicine for patients with disorders leading to overactivity of the RAS/MAPK pathway.
- Longer term treatment led to significant musculoskeletal adverse events in some patients (especially ACAN deficiency).

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