A Prospective Trial of Vosoritide in Selected Genetic Causes of Short Stature

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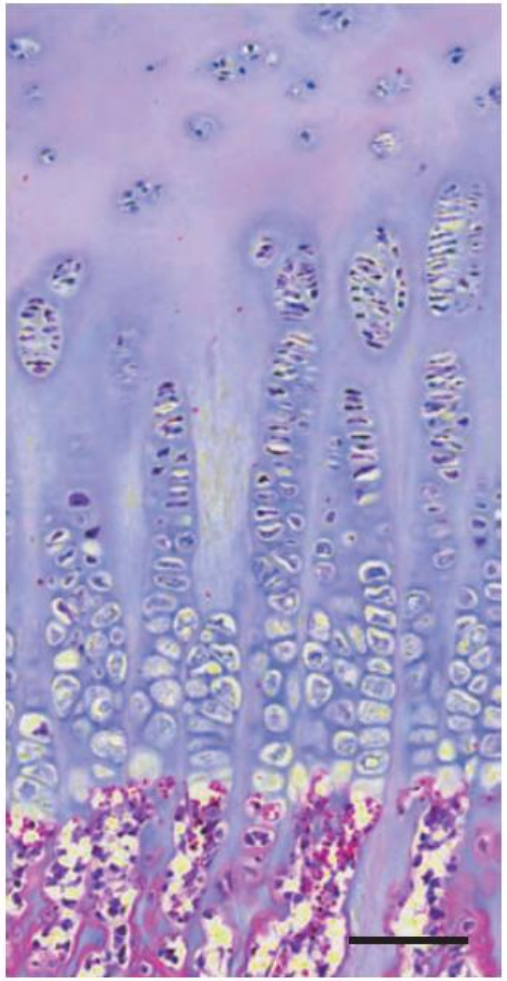
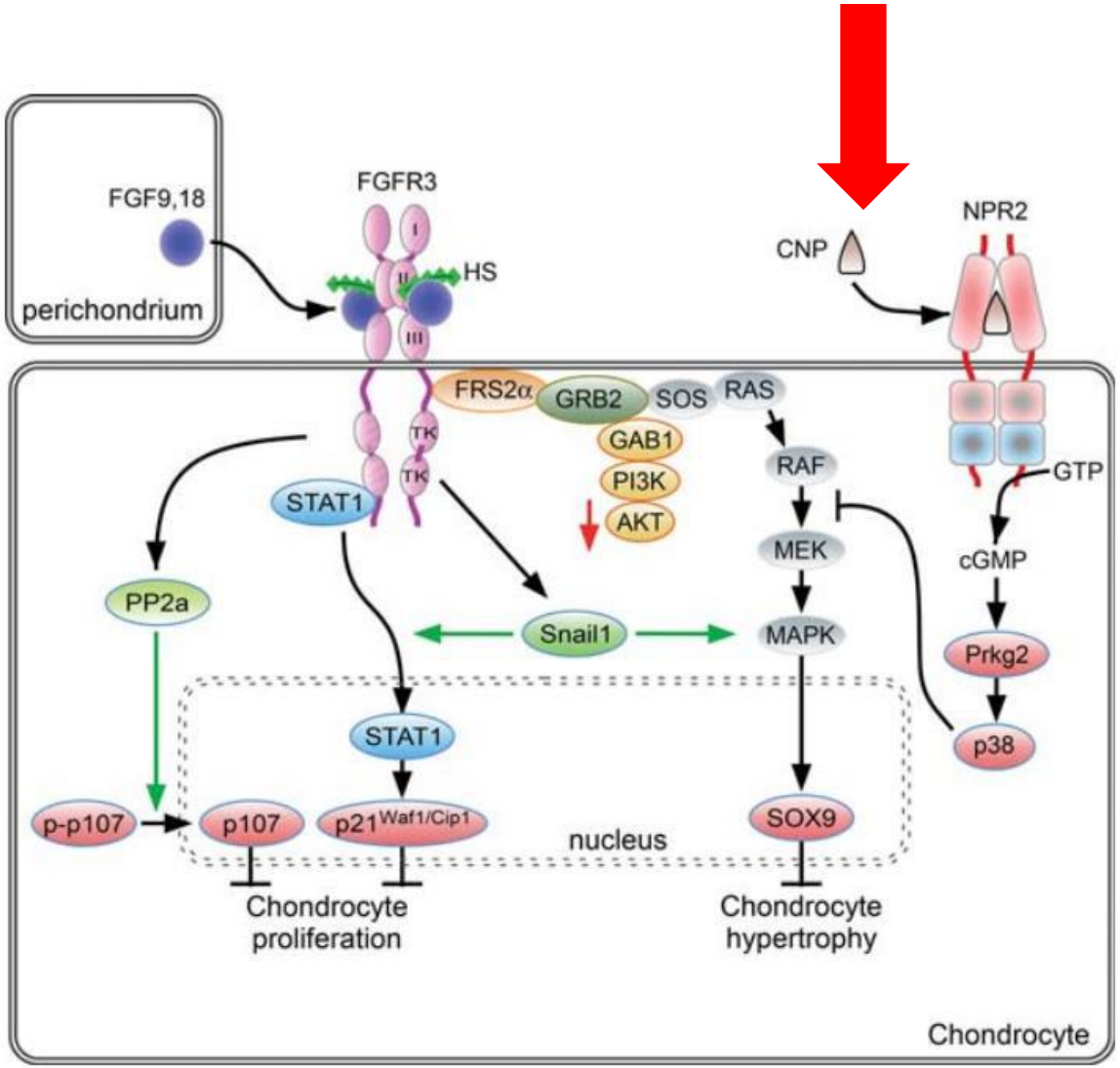
- No other disclosures

What is vosoritide?

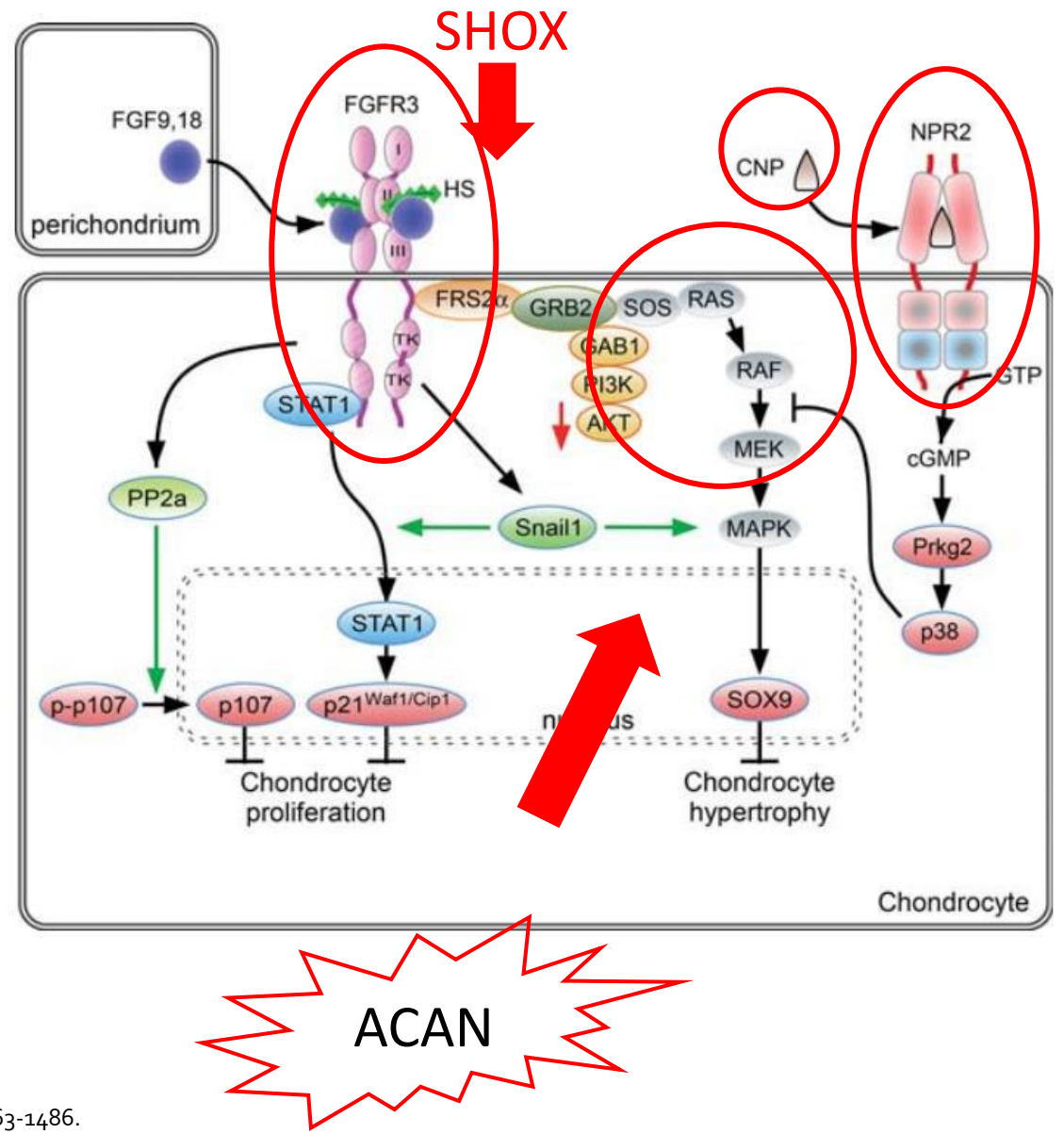




Baron J et al. Short and tall stature: a new paradigm emerges. Nature Reviews Endocrinology 2015;11(12)735-46.
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

Vosoritide for Selected Genetic Causes of Short Stature

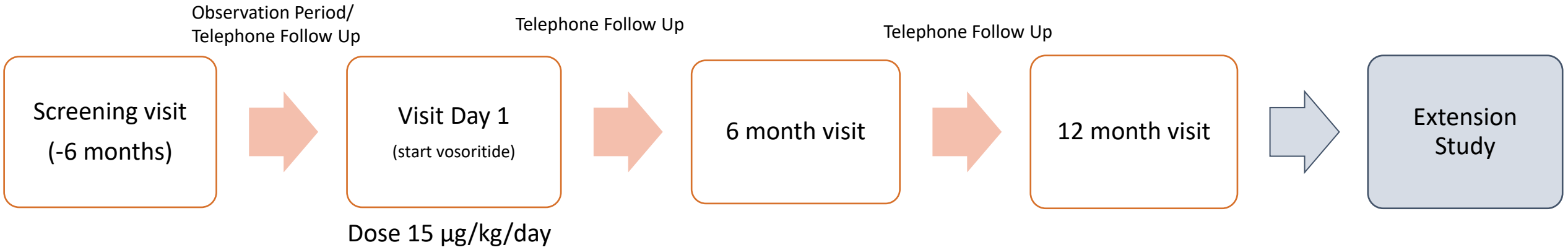
- Hypochondroplasia
- CNP Deficiency
- Heterozygous NPR2 mutation
- RASopathy (Noonan Syndrome)
- SHOX
- Aggrecan Deficiency



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
- Variants in one of the 6 categories
- Absence of growth hormone deficiency
- No concurrent treatment with GH (prior treatment is OK).
- No other significant medical history
- No hypertrophic cardiomyopathy



Study Outcomes

Primary study endpoints:

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

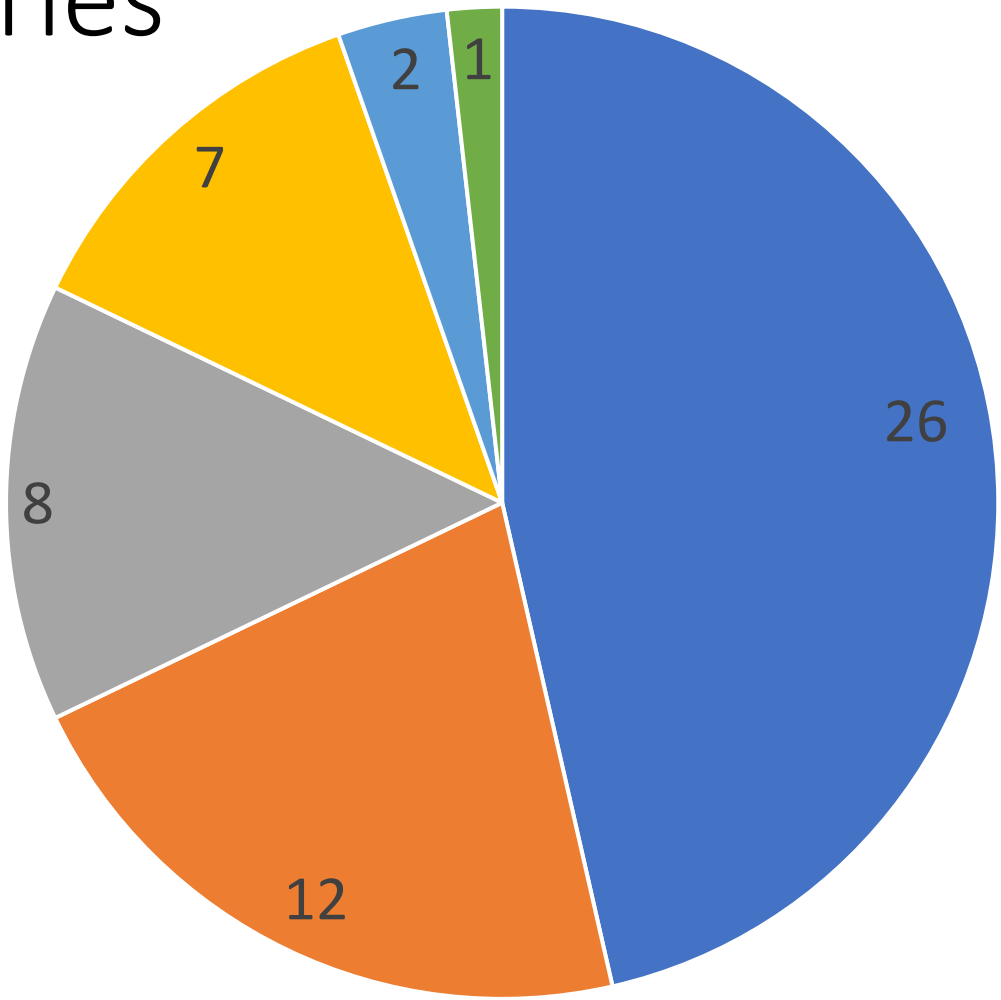
Secondary study endpoints:

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

The exploratory study endpoints include:

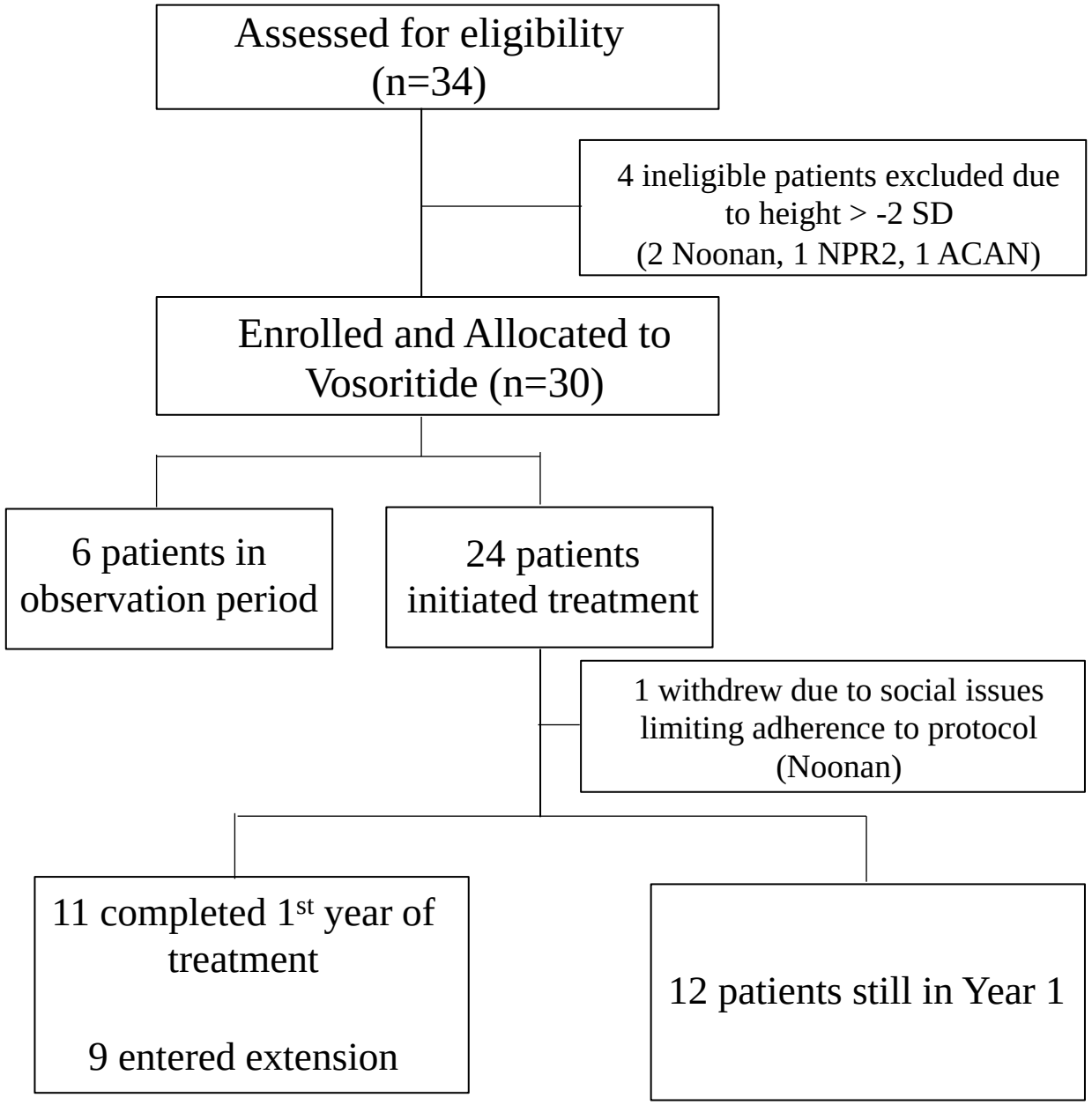
- Pharmacokinetic studies
- Pharmacodynamic markers
- Bone mineral density
- Effect on quality of life

Genetic Categories



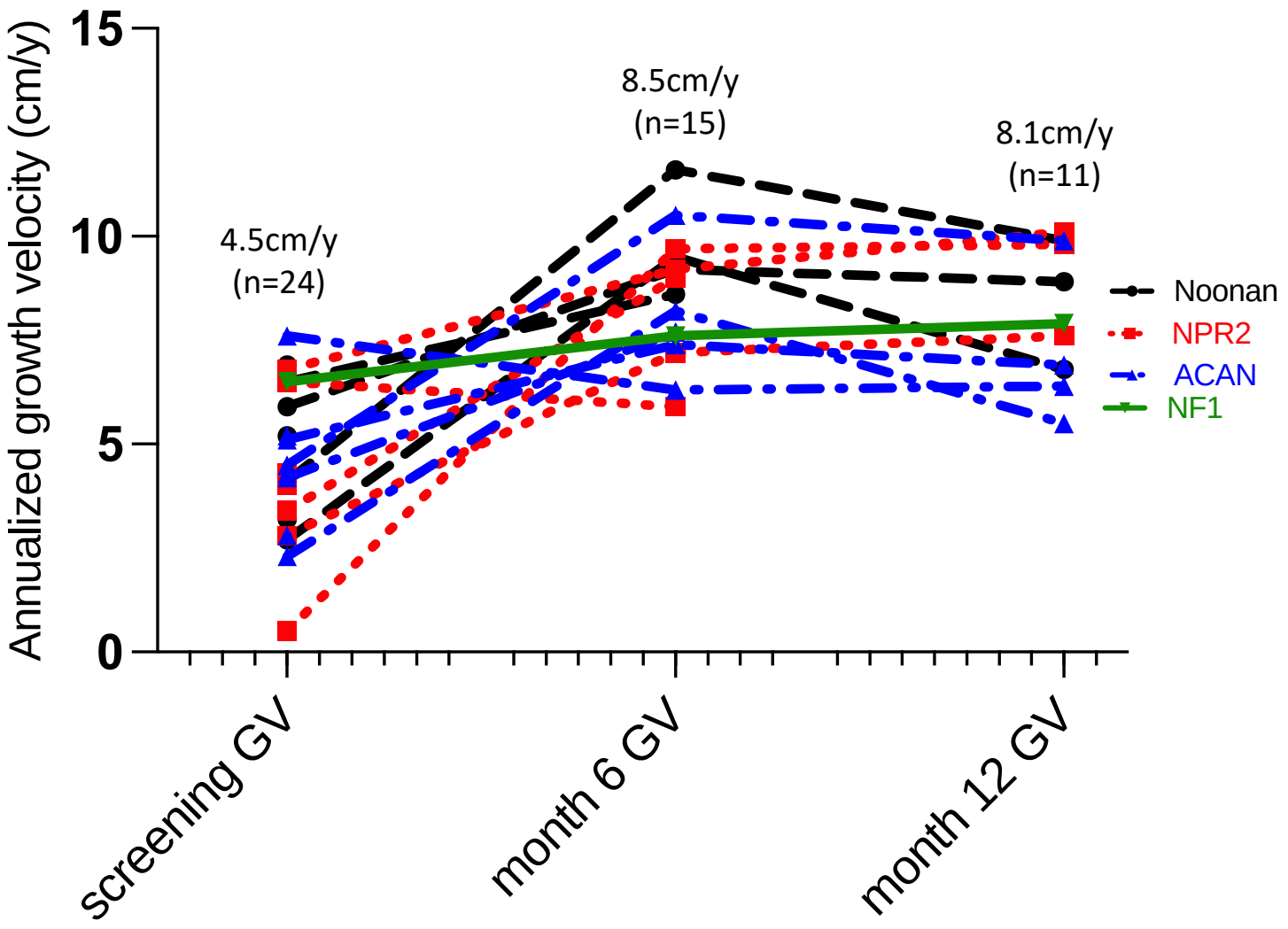
Hypochondroplasia ACAN Noonan NPR2 NF1 Costello

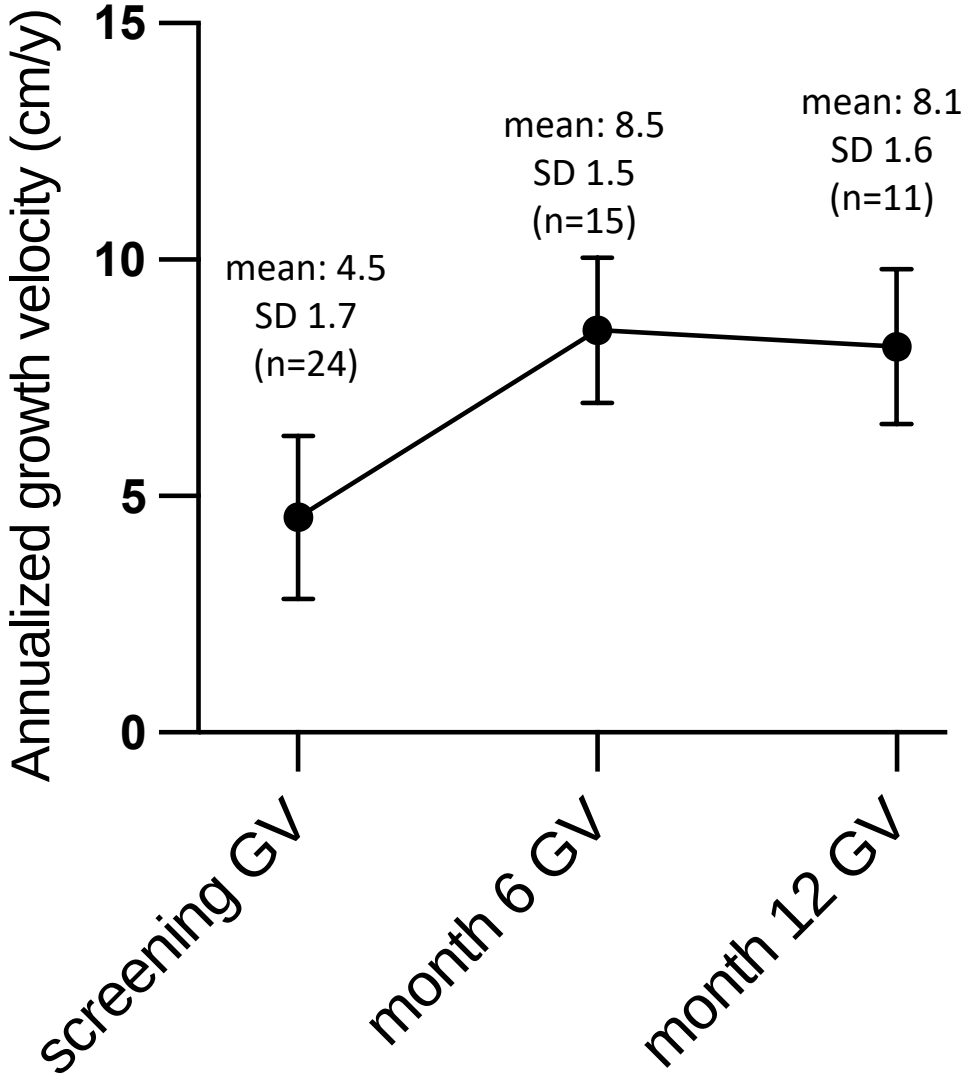
Non-hypochondroplasia patients:



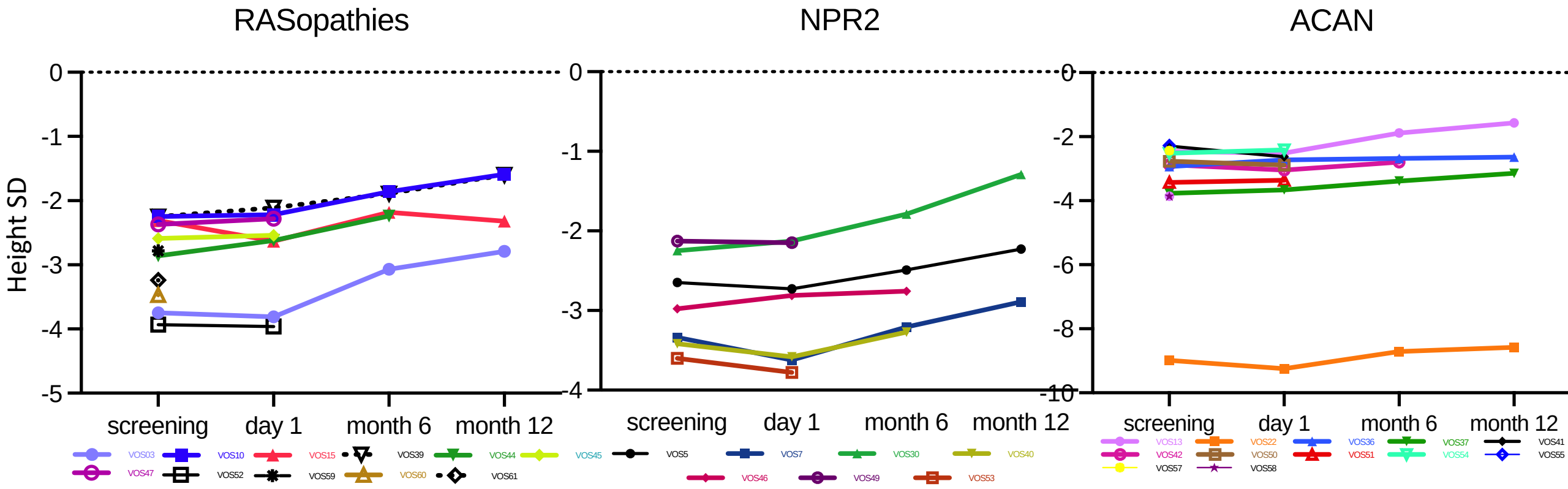
Total enrolled subjects	N=30
Age at enrollment in years, mean (range)	7.1 (3-11)
Age groups # (%)	
3 to <5 y	6 (20%)
5 to <9y	18 (60%)
9 to <11y	6 (20%)
Sex # (%)	
Females	8 (27%)
Males	22 (73%)
Race # (%)	
Caucasian	19 (63%)
Asian	4 (14%)
Other	7 (23%)
Ethnicity # (%)	
Non-Hispanic	24 (80%)
Hispanic	6 (20%)
Baseline height SD, mean (range)	-3.09 (-8.99, -2.16)
Baseline height SD groups # (%)	
< -4 SD	1 (3%)
-4 to <-3 SD	10 (33%)
-3 to -2.16 SD	19 (64%)

Growth Velocity Outcomes:





Outcomes per condition:



Mean Δ Height SD
Observation to D1: -0.03
D1 to month 6: 0.37
D1 to month 12: 0.61

Mean Δ Height SD
Observation to D1: -0.03
D1 to month 6: 0.32
D1 to month 12 : 0.66

Mean Δ Height SD
Observation to D1 : -0.01
D1 to month 6: 0.34
D1 to month 12 : 0.56

Safety Outcomes:

- Overall, well tolerated, no discontinuation due to AEs.
- Injection site reactions are common (33% of patients, all self-resolved, grades 1 or 2)
- No Grade 4 or 5 AE
- 7 Grade 3 AE:

  5 not related to treatment:
  - 1 T&A during observation period
  - 1 hospitalization for asthma attack
  - 1 traumatic nasal fracture during observation period
  - 1 traumatic elbow fracture during treatment period
  - 1 spinal fusion for scoliosis that was planned to occur prior to initiation of treatment

  2 potentially related to treatment:
  - 2 genu valgum (1 Noonan, 1 ACAN): both recovered well s/p surgical correction, ongoing treatment
- 1 additional subject with ACAN noted to have grade 1 genu valgum during the observation period

AEs of special interest:

- No episodes of symptomatic hypotension

  Transient dizziness post injection reported in one subject, self-resolved without intervention
- Echocardiograms were stable with no clinical concerns
- Scoliosis reported in 7 patients:
  - 4 patients present prior to treatment (ACAN x 3, NPR2 x 1)
    - 1 worsened during year 1, but then improved without orthopedic intervention after pause in treatment for 6 months, vosoritide restarted with no further worsening
    - 1 severe preexisting scoliosis underwent planned surgical repair
  - 3 patients (1 NPR2, 1 ACAN, 1 Noonan) developed grade 1 scoliosis during Year 1 of treatment – all less than 20 degrees. No intervention warranted.

Conclusions

- Preliminary results suggest a positive response (>3 cm/year increase) in all subgroups with interindividual variability
- Well-tolerated with similar safety profile to previous reports in patients with achondroplasia
- Unclear if genu valgum and scoliosis are related to the underlying growth disorder, the generalized increase in growth velocity, or specifically due to vosoritide treatment.
- Identifying the molecular etiology for short stature via genetic testing leads to the potential for targeted, precision medicine approaches

QUESTIONS?

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