# Criteria for defining inadequate response to growth hormone in Noonan syndrome, Turner syndrome, and SHOX deficiency

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### Background

### Inadequate growth and human growth hormone therapy

- Human growth hormone (hGH) therapy is standard in many countries for short stature conditions, including Noonan syndrome, Turner syndrome, and short stature homeobox-containing gene deficiency disorders (SHOX-Ds)<sup>1</sup>
- Unfortunately, many children eventually become nonresponsive to hGH therapy<sup>2,3</sup>
- Despite its importance, the criteria for inadequate growth on or after hGH use are poorly defined, and the lack of a definition impacts decisions to initiate and, more importantly, continue treatment

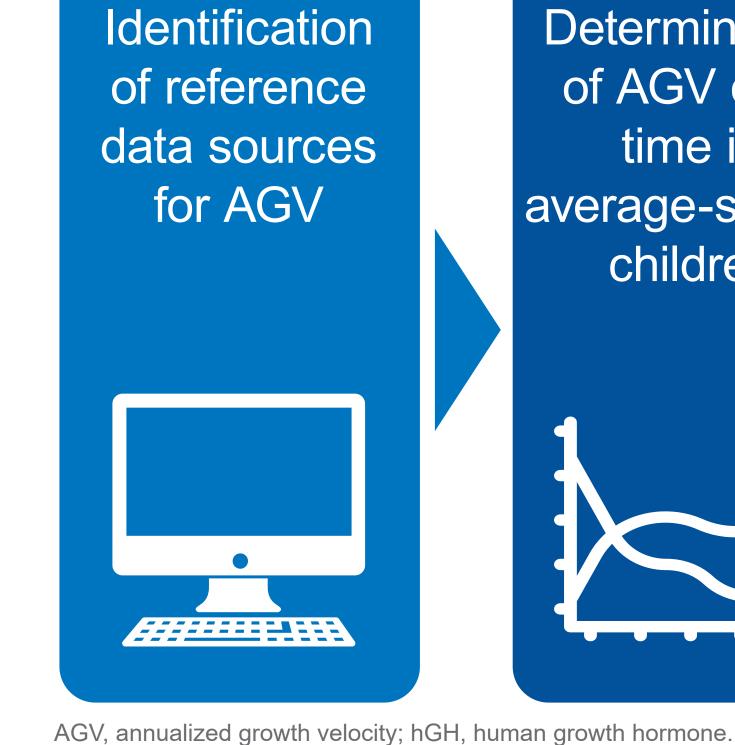
### Introduction to CANOPY NS, TS, SHOX-D-2 study

- Turner syndrome, Noonan syndrome, and SHOX-Ds are associated with excess extracellular signal-regulated kinase (ERK) signaling and characterized by
- Vosoritide, an analogue of the master growth regulator C-type natriuretic peptide, is an approved targeted therapy for achondroplasia that stimulates endochondral bone growth by reducing ERK activity
- CANOPY NS, TS, SHOX-D-2 (111-211; NCT06668805) is a phase 2 randomized, multicenter basket study designed to determine the therapeutic dose of vosoritide in children with genetically confirmed Noonan syndrome, Turner syndrome, or SHOX-D with inadequate growth on or after hGH use for a phase 3 confirmatory study, CANOPY NS, TS, SHOX-D-3 (111-306)
- CANOPY NS, TS, SHOX-D-2 represents the first use case of our established definition of inadequate growth on or after hGH use

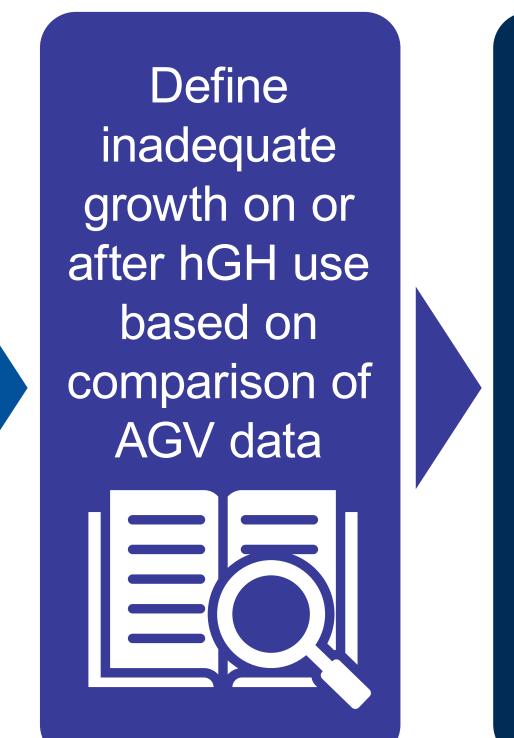
# Objective

 To establish a standard definition for inadequate growth on or after hGH use and to demonstrate its use in a planned study

# Methods







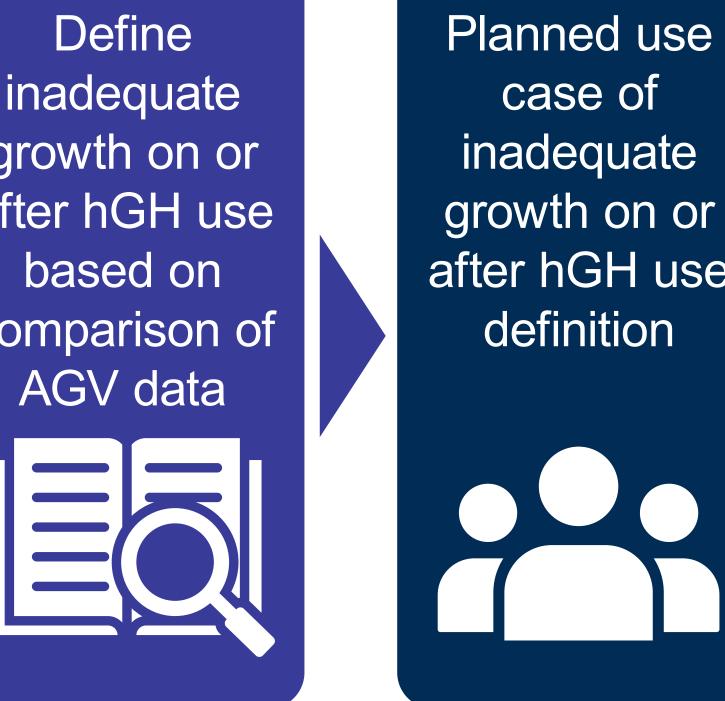


Figure 1. ERK1/2 in normal

differentiation

**NPR-B** activation

Chondrocyte

excess ERK signaling

Turner syndrome, Noonan syndrome,

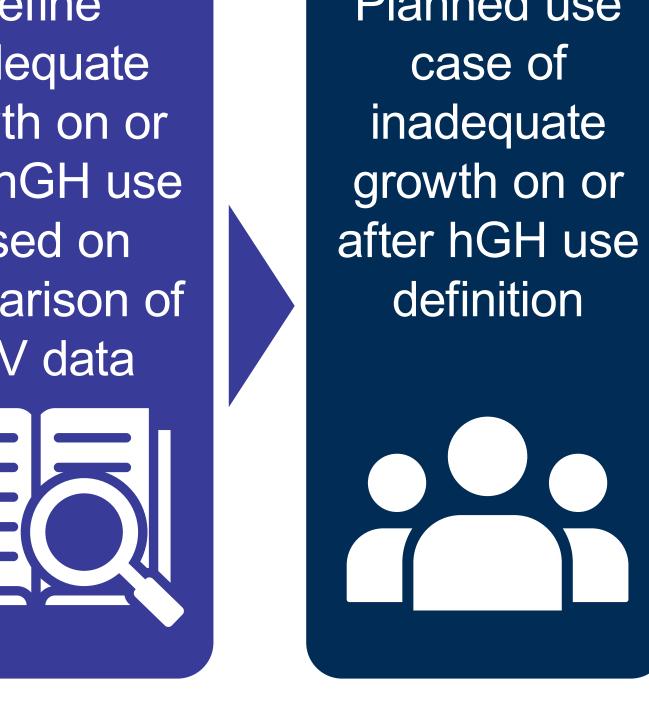
cGMP, cyclic guanosine monophosphate; ERK, extracellular signal-

regulated kinase; NPR-B, atrial natriuretic factor receptor B; PKGII, type II

and SHOX-Ds are associated with

chondrocyte proliferation and

Vosoritide reduces ERK activity via

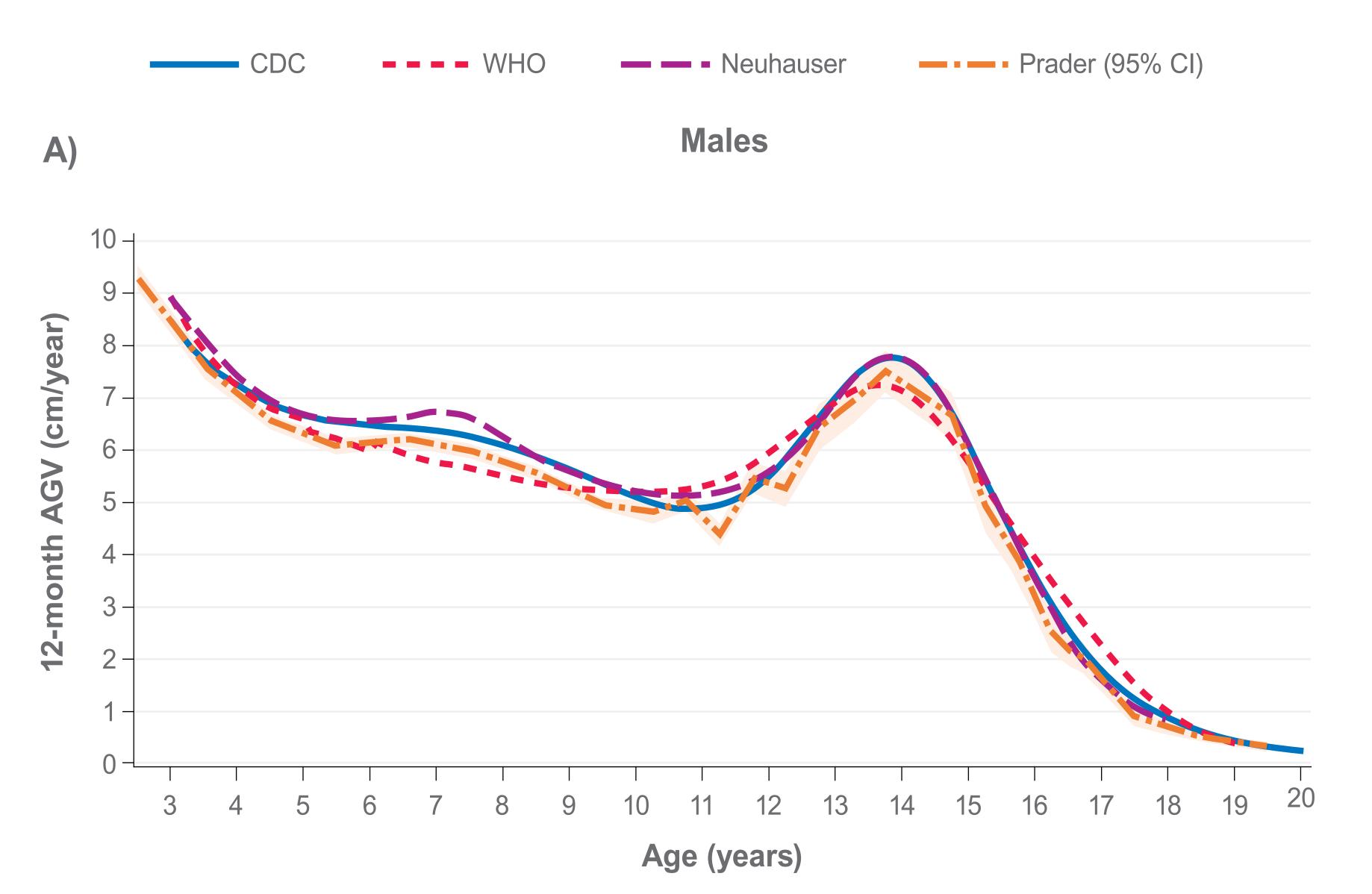


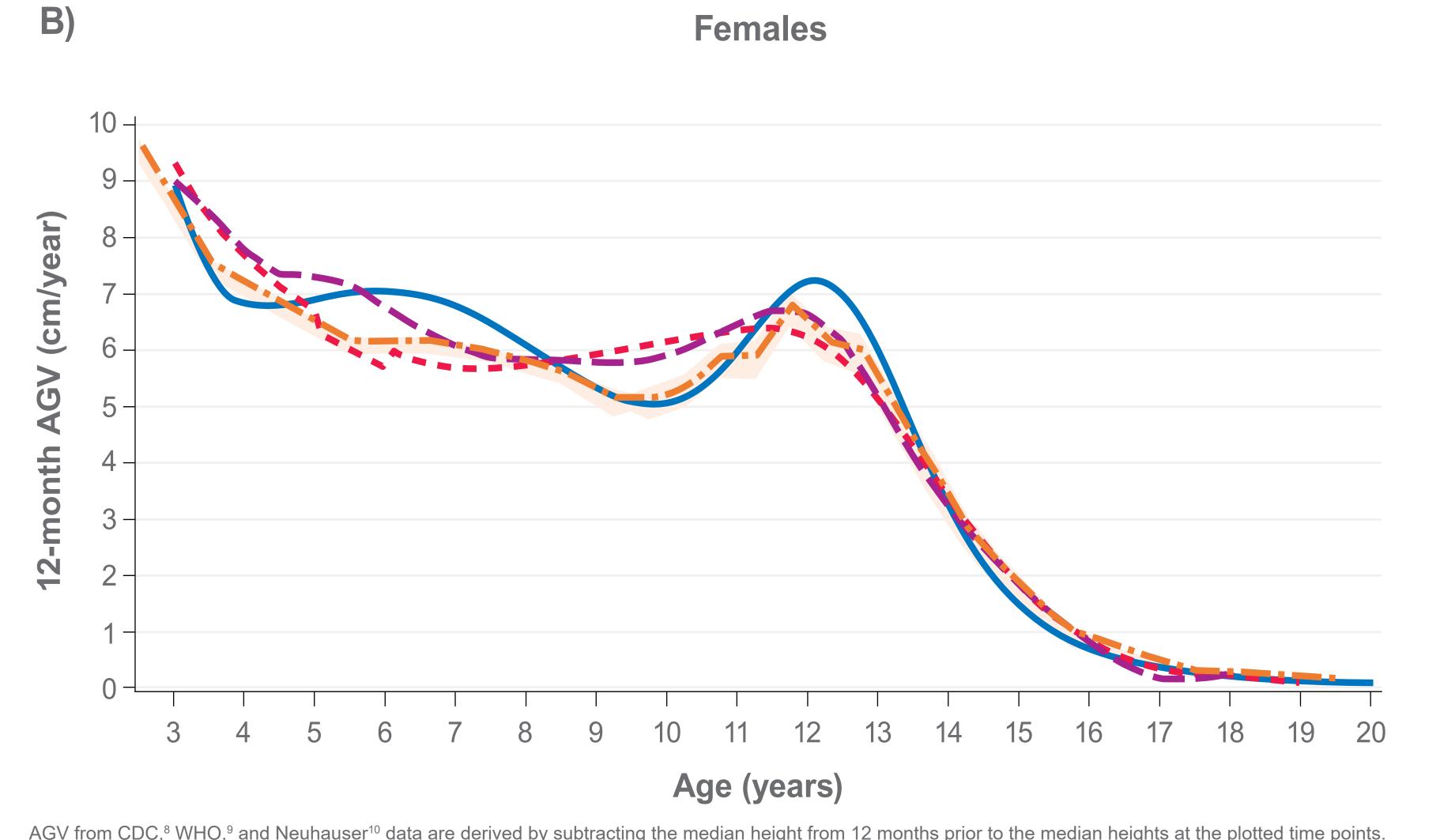
### Results

### Determination of inadequate growth on or after hGH use

- US Centers for Disease Control and Prevention (CDC),8 World Health Organization (WHO),9 and German height chart data (Neuhauser)<sup>10</sup> were used to determine annualized growth velocity (AGV) by deriving the difference in median height assessments among children 12 months apart in age. Pre-derived mean (standard deviation [SD]) for AGV by age and sex (with 95% confidence intervals [CIs]) was available from a Swiss reference (Prader et al)11
- To assess the robustness of the approach, we charted the AGV in average-stature male (Figure 2A) and female (Figure 2B) children aged 3 to 20 years using all 4 data sources
- In general, AGV followed a similar trend in all 4 data sources and was especially consistent

### Figure 2. AGV in average-stature children





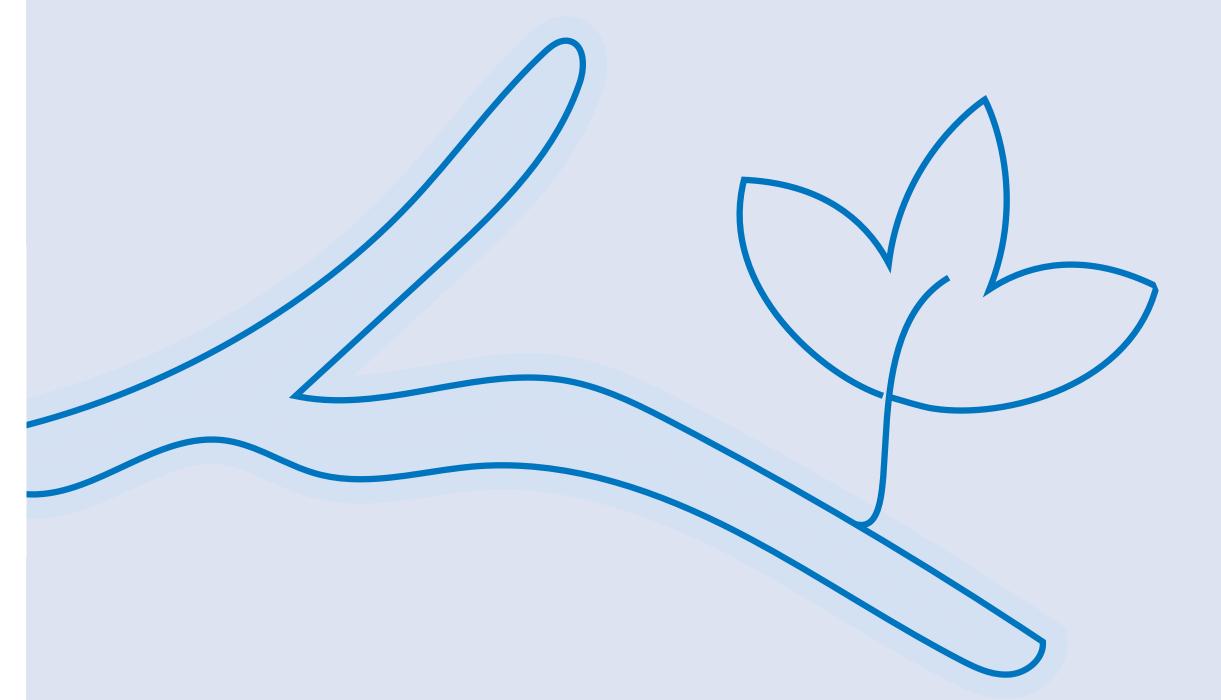
AGV from Prader et al<sup>11</sup> are reported directly from the data; 95% CIs are derived using the t-distribution. AGV, annualized growth velocity; CDC, US Centers for Disease Control and Prevention; CI, confidence interval; WHO, World Health Organization.

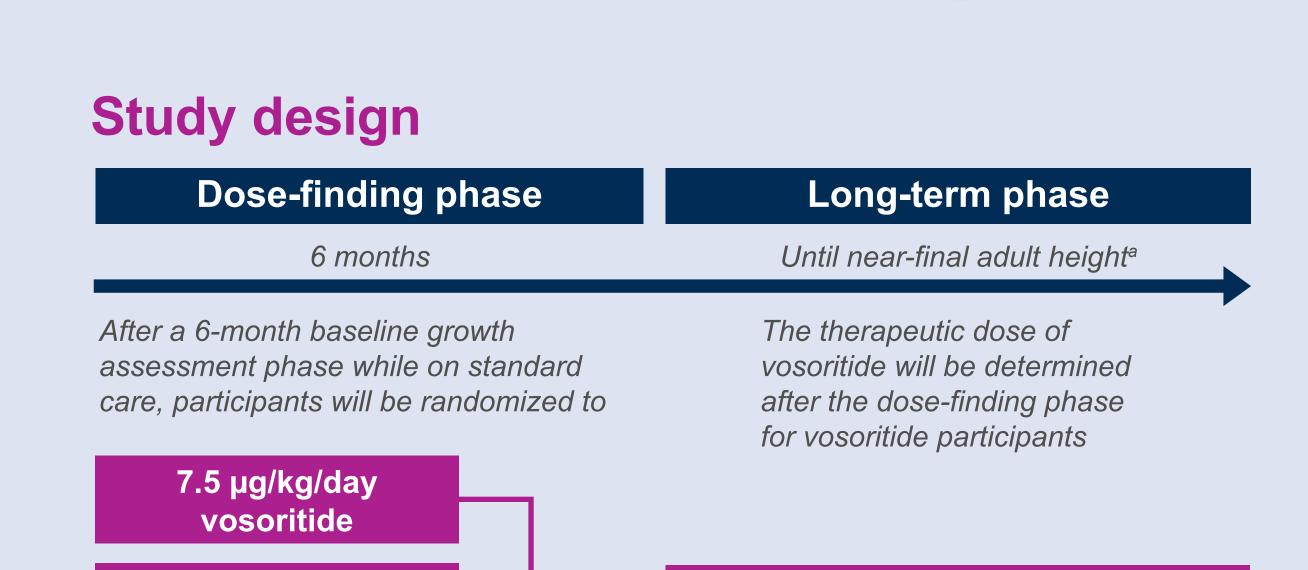
 Using this data, we established a standard definition of inadequate growth on or after hGH use. The definition ensures that children with inadequate growth are no longer displaying catch-up growth to their average-stature peers

# INADEQUATE GROWTH ON OR AFTER hGH USE: An AGV below that of the age- and sex-matched average-stature AGV determined from the CDC growth charts

# Application in CANOPY NS, TS, SHOX-D-2 study (111-211; NCT06668805)\*

#### The newly established definition was used for the first time in the ongoing phase 2 CANOPY NS, TS, SHOX-D-2 study, designed to determine the therapeutic dose of vosoritide in children with Noonan syndrome, Turner syndrome, or SHOX-D with a history of hGH use or current use

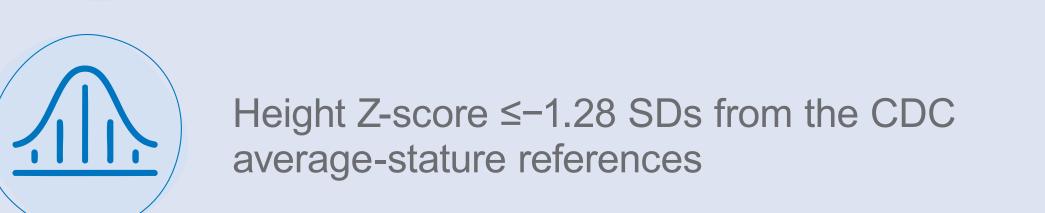




22.5 μg/kg/day <sup>a</sup>Near-final adult height is defined as decreased growth velocity (AGV <1.5 cm/year) assessed over a period of at least 6 months and growth plate fusion. AGV, annualized growth velocity; hGH, human growth hormone; SHOX-D, short stature homeobox-containing gene deficiency disorder.

\*Protocol amendments ongoing.

# **Participants** 54 children with genetically confirmed Turner syndrome, Noonan syndrome, or SHOX-D with a history of hGH use or current use Aged ≥3 to <11 years (females) or <12 years (males)

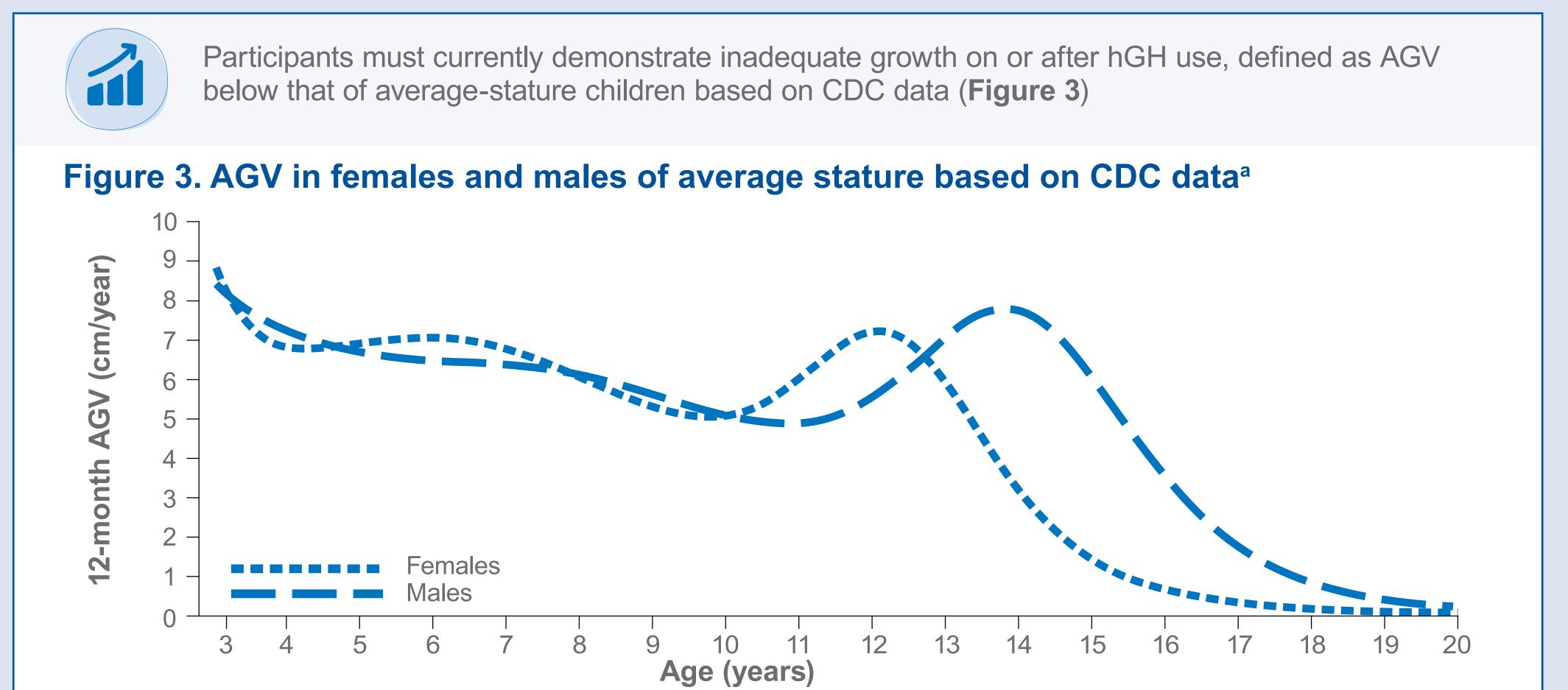


Previously or currently receiving treatment with hGH

### Study sites

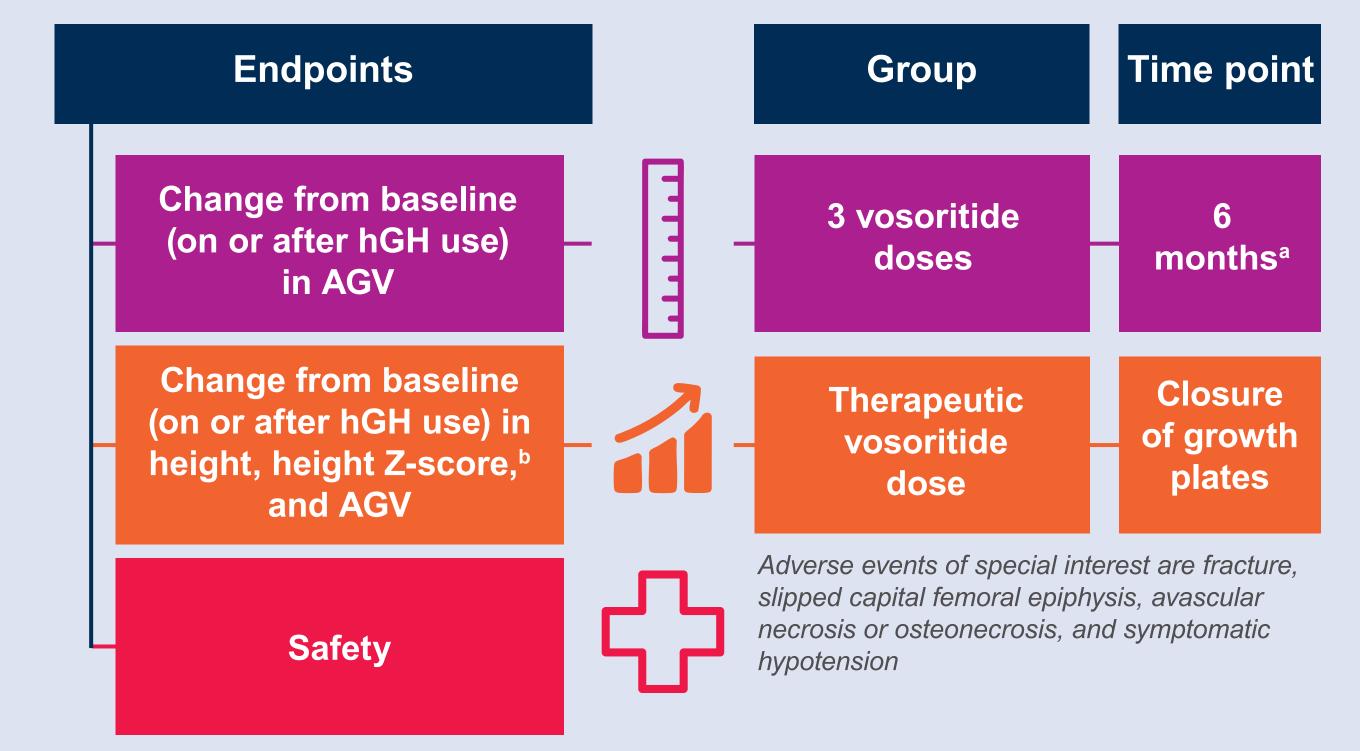
 CANOPY NS, TS, SHOX-D-2 is recruiting at sites in the US, Canada, Turkey, Italy, Germany, Spain, France, and Australia





<sup>a</sup>CDC height chart data were used to determine AGV by deriving the difference in median height assessments 12 months apart in age. AGV, annualized growth velocity; CDC, US Centers for Disease Control and Prevention

### **Endpoints**



<sup>a</sup>An interim analysis will occur when ≥50% of participants in each group have 6 months of follow-up. <sup>b</sup>Based on CDC AGV, annualized growth velocity; CDC, US Centers for Disease Control and Prevention; hGH, human growth hormone.



# Conclusions

 Inadequate growth while on or after hGH therapy, irrespective of timing, can be defined in terms of expected growth in age- and sex-matched reference populations

Therapeutic dose of vosoritide

- These criteria will enable optimized treatment decisions and clinical trial design for children with short stature receiving hGH therapy
- Here we also present the study design of the phase 2 study CANOPY NS, TS, SHOX-D-2 (111-211), a use-case example of the newly established definition of inadequate growth on or after hGH use

### References

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### **Disclosures**

RR and AD are consultants for BioMarin Pharmaceutical Inc. AD has received grant funding from BioMarin Pharmaceutical Inc. and is currently a primary investigator for a trial of vosoritide in children with genetic causes of short stature (NCT04219007). **KM** has received consulting payments from BioMarin Pharmaceutical Inc., Novo Nordisk, and QED Therapeutics; has participated as an investigator for BioMarin Pharmaceutical Inc.; and has received speaker fees and travel support from BioMarin Pharmaceutical Inc. and Novo Nordisk. **LS** is a consultant for BioMarin Pharmaceutical Inc., OPKO Health, and Pfizer and an investigator for BioMarin Pharmaceutical Inc. and Novo Nordisk. AL, MS, IS, NL, and AHL are employees and shareholders of BioMarin (UK) Ltd.

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