Design of a phase 2, randomized, controlled, multicentre study of vosoritide treatment in children with idiopathic short stature

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Introduction

- Idiopathic short stature (ISS) is diagnosed in individuals with height 2.25 standard deviations (SDs) below age- and sex-matched populations with no other defined aetiology[1]
- Human growth hormone (hGH) is approved for ISS in the US, but it is not a targeted therapy and response is often inadequate
- Vosoritide, an analogue of the master growth regulator C-type natriuretic peptide, is an approved targeted therapy for achondroplasia, a condition in which fibroblast growth factor receptor 3 (FGFR3) overactivity causes impaired endochondral ossification and growth[2,3]
- Preliminary experience from an ongoing phase 1/2 study (NCT04219007) supports that vosoritide may offer benefits in a broad spectrum of short-stature conditions beyond achondroplasia
- Here, we present the design of CANOPY ISS-2 (study 111-210; NCT06382155) that will investigate the efficacy and safety of vosoritide in children with ISS

Objective

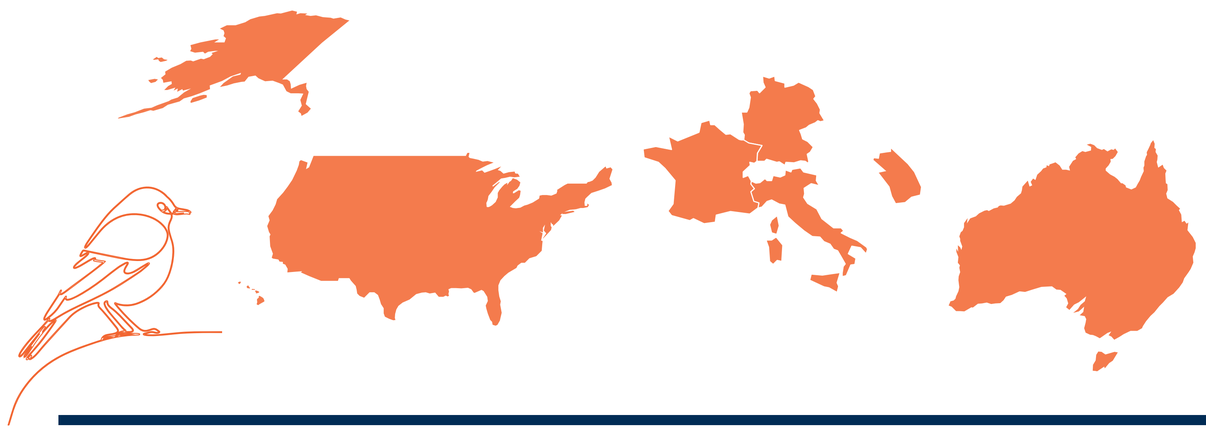
- CANOPY ISS-2 (NCT06382155) is a phase 2, randomized, controlled, multicentre study designed to compare efficacy and safety over a range of vosoritide doses versus placebo (short-term) and human growth hormone (long-term) in children with ISS

Participants

- Approximately 100 children with ISS will be recruited
- Age ≥3 to <10 years (females) or <11 years (males) and prepubertal
- Height Z-score less than or equal to −2.25 SDs from US Centers for Disease Control and Prevention average-stature references
- Naïve to growth-promoting agents, including hGH

Study sites

- CANOPY ISS-2 study will be conducted in the US, Germany, Italy, France, South Korea, and Australia



Key dates

- First site activated: 21 October 2024
- First patient in: 4 February 2025
- First patient randomized: March 2025

Study design

Dose-finding phase[a] (6 months) → **Long-term phase** (Until near-final adult height[b])

After a 6-month baseline growth assessment phase, participants will be randomized 1:1:1:1:1[c] to:

- 7.5 µg/kg/day vosoritide
- 15.0 µg/kg/day vosoritide
- 22.5 µg/kg/day vosoritide
- Placebo (6 months only)

→ **Therapeutic dose of vosoritide**

The therapeutic dose of vosoritide will be determined after all participants have completed at least 6 months of treatment in the dose-finding phase

If a non-US participant is randomized to hGH, the participant will be randomized to the next non-hGH group instead and the hGH group allocation will be backfilled by a future US participant. Participants randomized to hGH may transition to open-label vosoritide at the therapeutic dose after at least 4 years

0.30 mg/kg/week hGH (US only)[d]

[a]At least 6 months of pre-treatment standing height assessments must be completed before randomization. [b]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 indicated by left hand antero-posterior X-rays. [c]The planned sample size of 20/group will have 80% power to achieve statistical significance for at least 1 hypothesis tested. [d]In the dose-finding phase, participants, care providers, investigators, and the sponsor will be blinded to the vosoritide and placebo groups; only the sponsor will be blinded to the hGH group.
AGV, annualized growth velocity; hGH, human growth hormone.

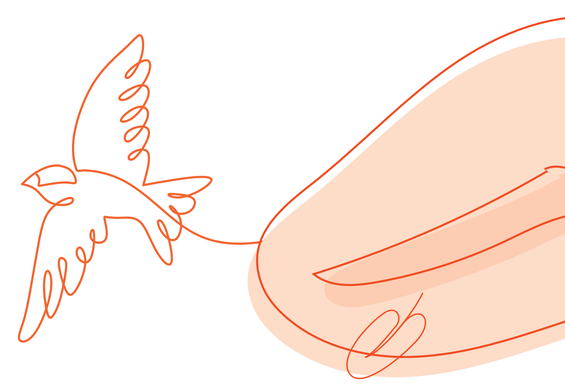
Main endpoints

Endpoints	Comparison	Time point
Change from baseline AGV and height Z-score	Placebo	6 months[a]
Change from baseline height Z-score	hGH	4 years
Safety		
HRQOL (exploratory)		

Based on CDC growth charts

Adverse events of special interest are fracture, slipped capital femoral epiphysis, avascular necrosis or osteonecrosis, and symptomatic hypotension

HRQOL measures include QoLISSY and PedsQL



[a]An interim analysis will occur when ≥50% of participants in each vosoritide and placebo group have 6 months of follow-up.
AGV, annualized growth velocity; CDC, US Centers for Disease Control and Prevention; HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory; QoLISSY, Quality of Life in Short Statured Youth.

References

1. Wit JM, et al. *Growth Horm IGF Res.* 2008;18:89-110. **2.** Pauli RM, et al. *Orphanet J Rare Dis.* 2019;14(1):1. **3.** European Medicines Agency. Voxzogo product information. Accessed February 28, 2025. https://www.ema.europa.eu/en/documents/product-information/voxzogo-epar-product-information_en.pdf.

Acknowledgements

We thank participating sites, staff, and investigators. Medical writing support was provided by Amin Ghane, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

Disclosures

MS, **AHL**, and **IS** are employees and shareholders of BioMarin (UK) Ltd. **RR** is a consultant for BioMarin Pharmaceutical Inc. **BSM** is a consultant for Amgen, Ascendis Pharma, BioMarin Pharmaceutical Inc., Eton Pharmaceuticals, GenSci, Novo Nordisk, Pfizer, Soleno, and Tolmar and has received research support from AbbVie, Aeterna Zentaris, Alexion, Foresee, Lumos Pharma, Novo Nordisk, OPKO Health, Pfizer, and Sangamo. LS is a consultant for BioMarin Pharmaceutical Inc., OPKO Health, and Pfizer and an investigator for Novo Nordisk and BioMarin Pharmaceutical Inc. AD has received grant funding from BioMarin Pharmaceutical Inc., is a consultant for BioMarin Pharmaceutical Inc., and is currently a primary investigator for a trial of vosoritide in children with genetic causes of short stature (NCT04219007).

For more information on CANOPY ISS-2, scan this QR code.

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CANOPY ISS-2 PHASE 2 STUDY

Presented at the Joint Congress of ESPE and ESE 2025: 10–13 May 2025; Copenhagen, Denmark