Once-Weekly Lonapegsomatropin (TransCon hGH) Added to Once-Weekly Navepegritide (TransCon CNP) in Children with Achondroplasia: 26-Week Results from the Phase 2 COACH Trial

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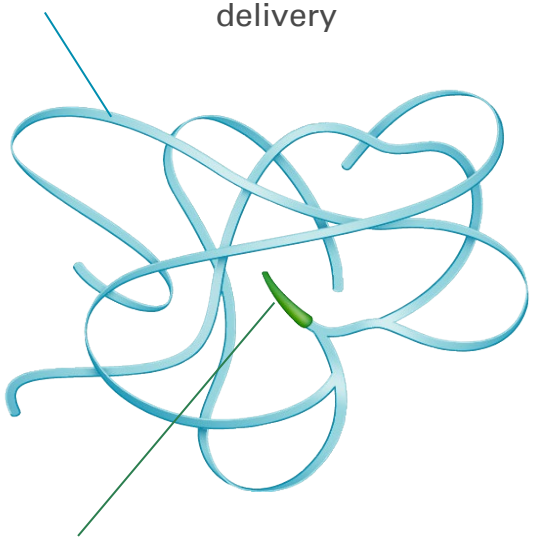
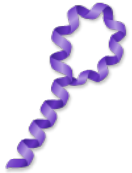
TransCon® technology

TransCon Carrier + Linker + **Parent Drug** = **TransCon Prodrug**

TransCon Carrier : Soluble; allows for systemic delivery



TransCon Linker : Specific for different parent drugs and release profiles (cleavage is dependent upon pH and temperature)



C-type natriuretic peptide (CNP)
Amino acid sequence identical to endogenous CNP (89-126)

Somatropin
human growth hormone (hGH)
Identical 191 amino acid sequence and size (22 kDa) as endogenous hGH

Navepegritide (TransCon CNP)

- Designed to provide continuous exposure to active CNP with once-weekly administration[1]
- Under investinvestigation for the treatment of achondroplasia

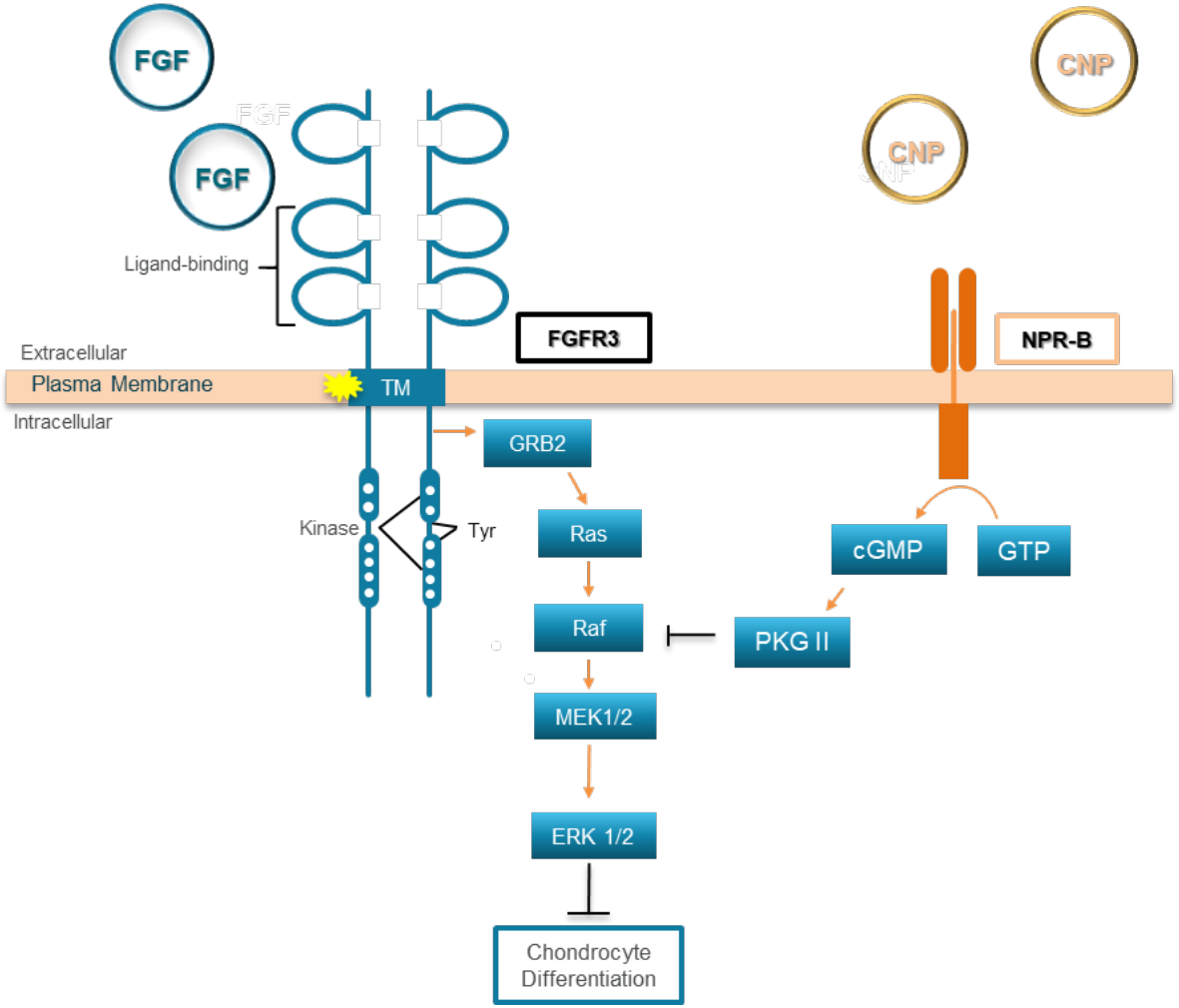
Lonapegsomatropin (TransCon hGH)

- Designed to provide sustained release of active, unmodified somatropin with once-weekly administration[2,3]
- Approved for treatment of GH deficiency in children and adults[4,5]

CNP, C-type natriuretic peptide; hGH, human growth hormone

[1]Breinholt VM, et al. *J Pharmacol Exp Ther* 2019. [2]Sprogøe K, et al. *Endocr Connect* 2017. [3]Thornton PS, et al. *J Clin Endocrinol Metab* 2021. [4]SKYTROFA™ (lonapegsomatropin-tcgd). Ascendis Pharma; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761177lbl.pdf; Accessed: 29Aug2025. [5]Ascendis Pharma (2022) SKYTROFA (previously lonapegsomatropin Ascendis Pharma) SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/skytrofa; Accessed: 29Aug2025.

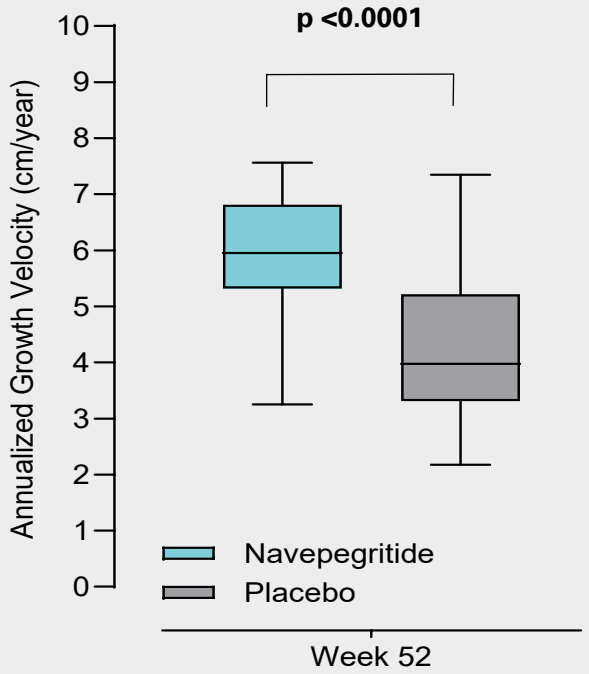
CNP counteracts pathologic FGFR3 signaling in achondroplasia



CNP, C-type natriuretic peptide; FGF, fibroblast growth factor; FGFR3, fibroblast growth factor receptor 3; NPR-B, natriuretic peptide receptor B.
Adapted from Laederich MB & Horton WA. *Current Opin Pediatrics* 2010;22:516-523

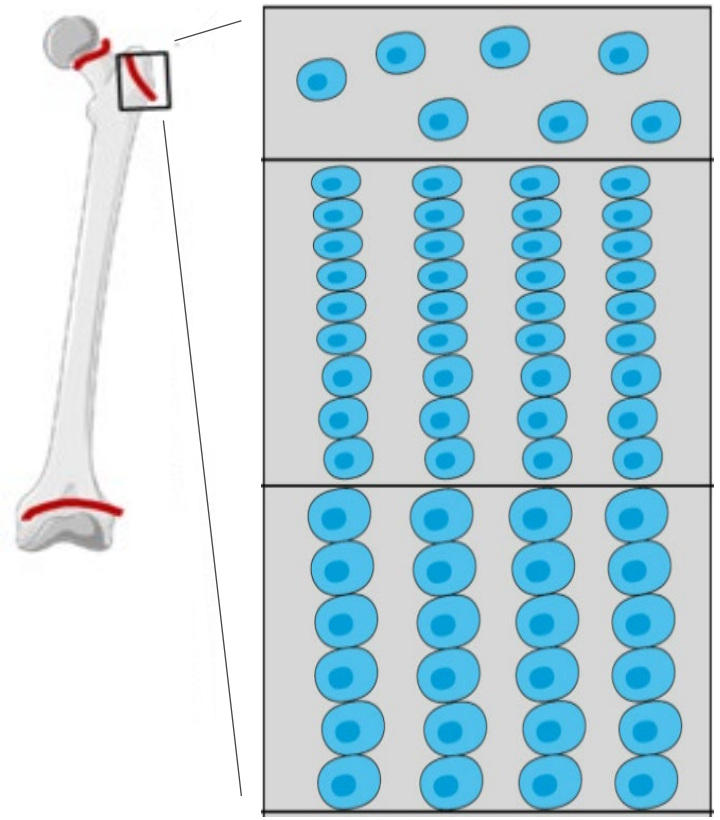
Background: Navepegritide demonstrated superiority in AGV at Week 52 vs. placebo in the pivotal trial

Annualized Growth Velocity at Week 52 by Treatment Arm



The ANCOVA included treatment, stratification factor, baseline age, and baseline ACH-specific height Z-score as covariates
Box and whisker plot derived using observed data at Week 52. Each plot displays the 75th and 25th percentile (box edges), interquartile range (IQR; colored area), median (midline), and minimum and maximum observed values (whiskers) for each treatment arm.

GH and CNP have complementary actions at the growth plate, unlocking the potential for augmented growth in achondroplasia



Effects on growth plate[1-7]

Resting zone	**GH** recruits stem cells to form chondrocytes
Proliferative zone	**GH** and **IGF-1** promote increase in number of chondrocytes
Pre-hypertrophic zone	**CNP** releases the FGFR3-induced transitional block in achondroplasia
Hypertrophic zone	**IGF-1** promotes chondrocyte growth and differentiation

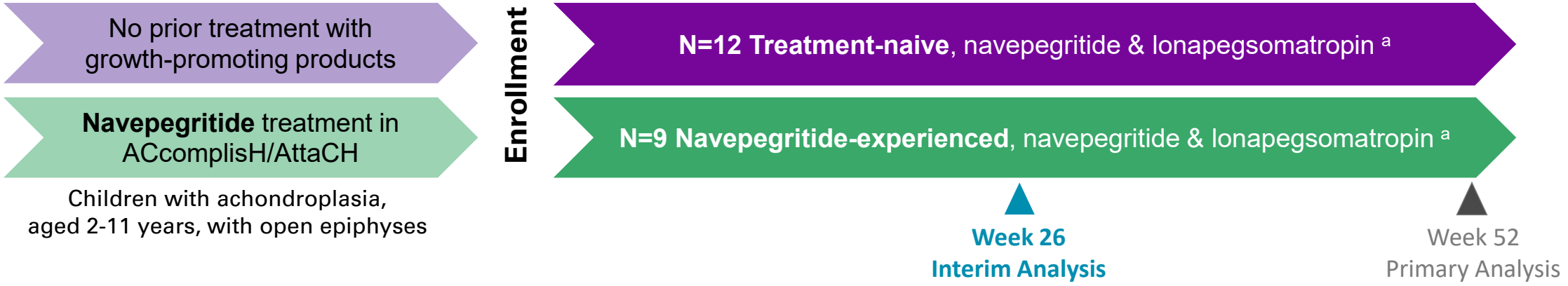
Treatment with **CNP** relieves the pre-hypertrophic block, allowing **GH** to stimulate growth

CNP, C-type natriuretic peptide; FGFR3, fibroblast growth factor receptor 3; GH, growth hormone; IGF-1, insulin-like growth factor-1

[1]Blum WF, et al. *Endocr Connect.* 2018. [2]Devesa J, et al. *Clin Med Insights Endocrinol Diabetes* 2016. [3]Rintz E, et al. *Int J Mol Sci* 2022. [4]Krejci P, et al. *PLoS One* 2008. [5]Horton WA, et al. *Lancet.* 2007. [6]Miyazawa T, et al. *Endocrinology* 2002. [7]Yasoda A, et al. *Nature Medicine* 2004. Figure adapted from Šromová, V, et al. *Cells* 2023.

Phase 2 COACH trial

Lonapegsomatropin added to navepegritide treatment in children with achondroplasia



Primary Efficacy Endpoint: Annualized growth velocity (AGV) at Week 52

Secondary Endpoints include: Change from baseline in height Z-score
Upper-to-lower body segment ratio (body proportionality)

Safety Endpoint: Treatment-emergent AEs, including injection site reactions (ISRs)

Biomarker Endpoint: IGF-1 SDS

AE, adverse event; IGF-1, insulin-like growth factor-1; SDS, standard deviation score
[a] navepegritide (100 µg CNP/kg/week) and lonapegsomatropin (starting dose of 0.30 mg hGH/kg/week) administered as separate once-weekly subcutaneous injections

Demographics and baseline characteristics

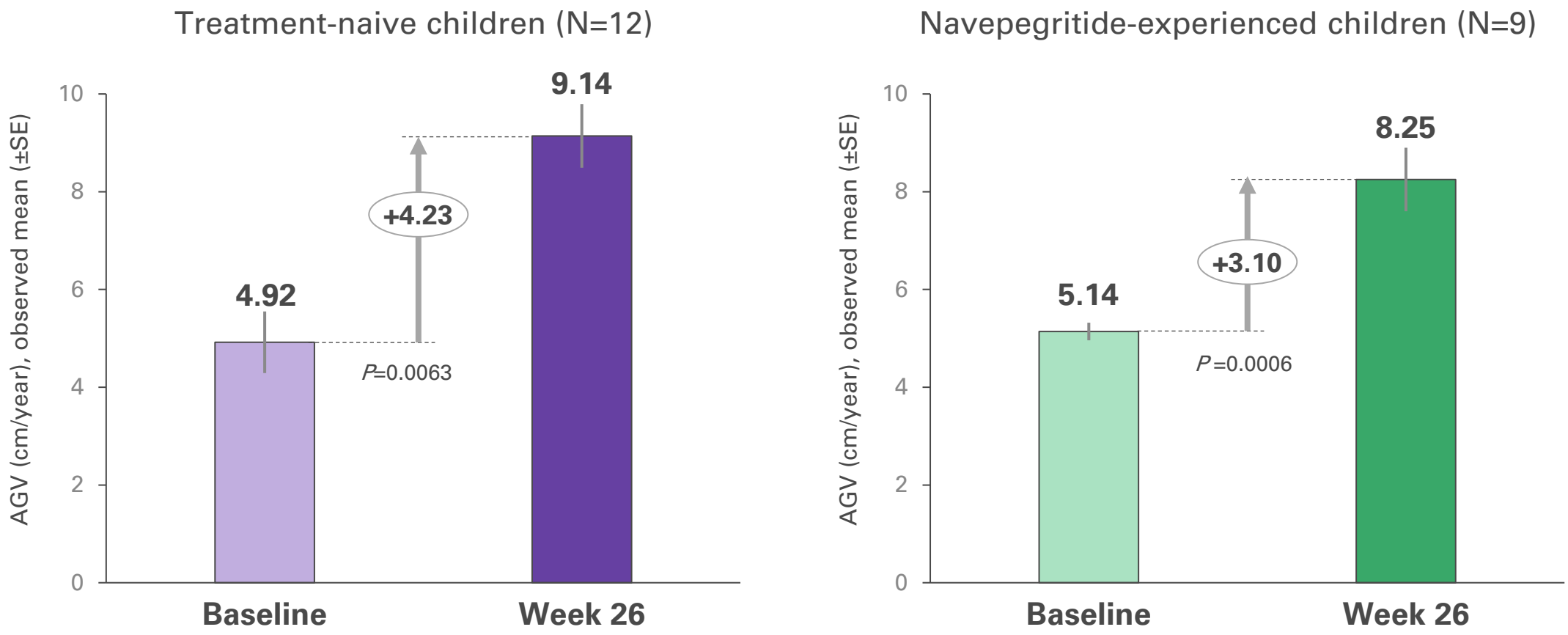
- Mean baseline ACH-specific height Z-score in navepegritide-experienced group reflects prior navepegritide-driven growth

	navepegritide & lonapegsomatropin	
Full Analysis Set	**Treatment-naive (N=12)**	**Navepegritide-experienced (N=9)**
Age, years; mean (SD)	4.7 (2.4)	7.9 (1.8)
Sex, male; n (%)	8 (66.7)	6 (66.7)
Prior exposure to navepegritide 100 µg CNP/kg/wk, years; mean (range)	Not Applicable	2.6 (2.3, 2.9)
AGV (cm/year); mean (SD)	4.92 (2.18)	5.14 (0.53)
ACH-specific height Z-score; mean (SD)[a]	0.46 (0.70)	1.28 (0.81)
CDC-based height Z-score; mean (SD)[b]	-4.46 (0.77)	-4.04 (0.66)
IGF-1 SDS; mean (SD)	-0.63 (1.32)	-0.70 (0.48)

n = number of participants with observation
ACH, achondroplasia; AGV, annualized growth velocity; CDC, Centers for Disease Control and Prevention; IGF-1, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score
[a]Hoover-Fong JE, et al. US. *Orphanet J Rare Dis*. 2021.
[b]CDC growth charts by age and sex available at: https://www.cdc.gov/growthcharts/who-growth-charts.htm

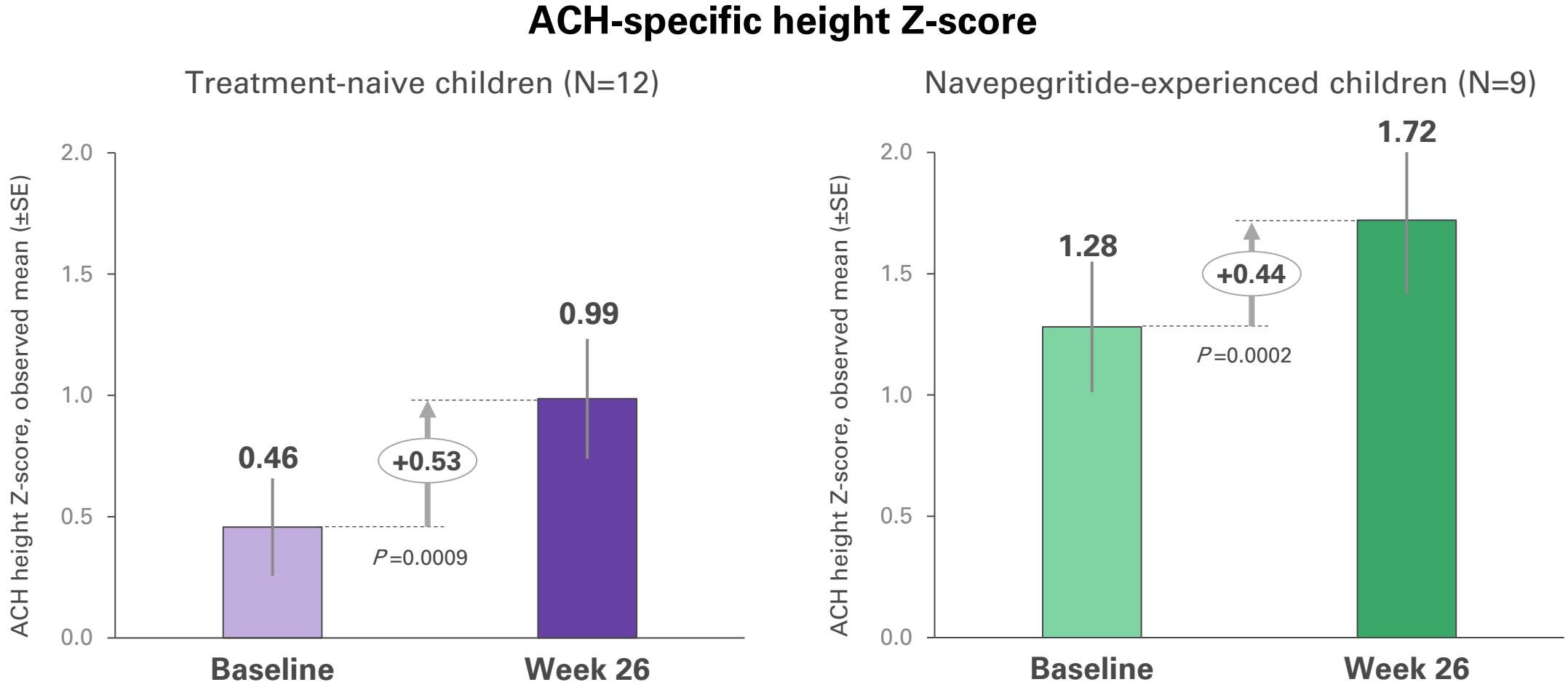
Navepegritide & lonapegsomatropin resulted in significant improvement from baseline in AGV at Week 26

Annualized growth velocity (AGV)



Note: Gray arrow indicates change from baseline. Baseline AGV calculation is based on 6 months and 12 months preceding the COACH trial for treatment-naive children and navepegritide-experienced children, respectively.

Navepegritide & lonapegsomatropin resulted in significant improvement in ACH-specific height Z-score at Week 26



ACH, achondroplasia
Note: Gray arrow indicates change from baseline

AGV with navepegritide & lonapegsomatropin exceeded the 97th percentile for children of average stature

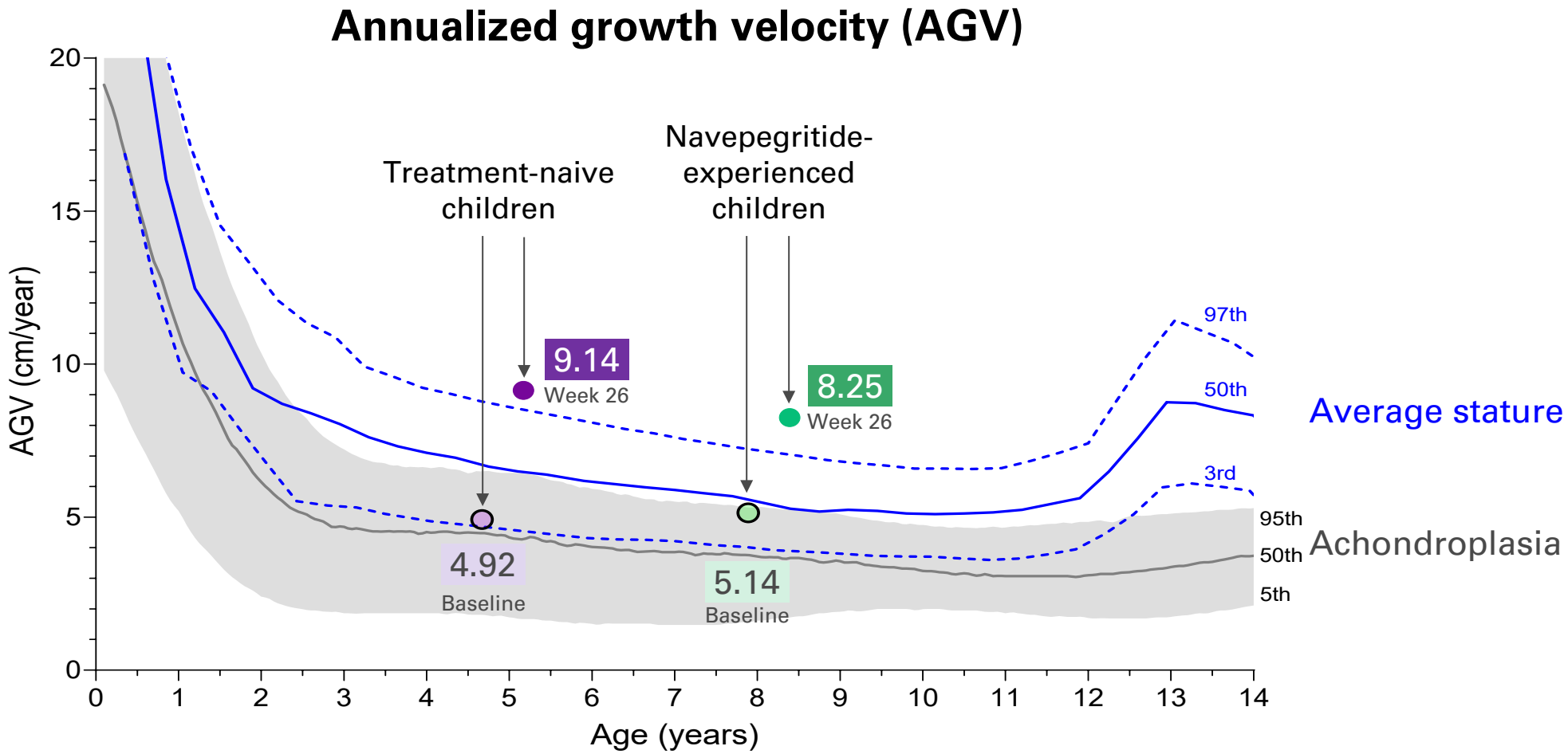
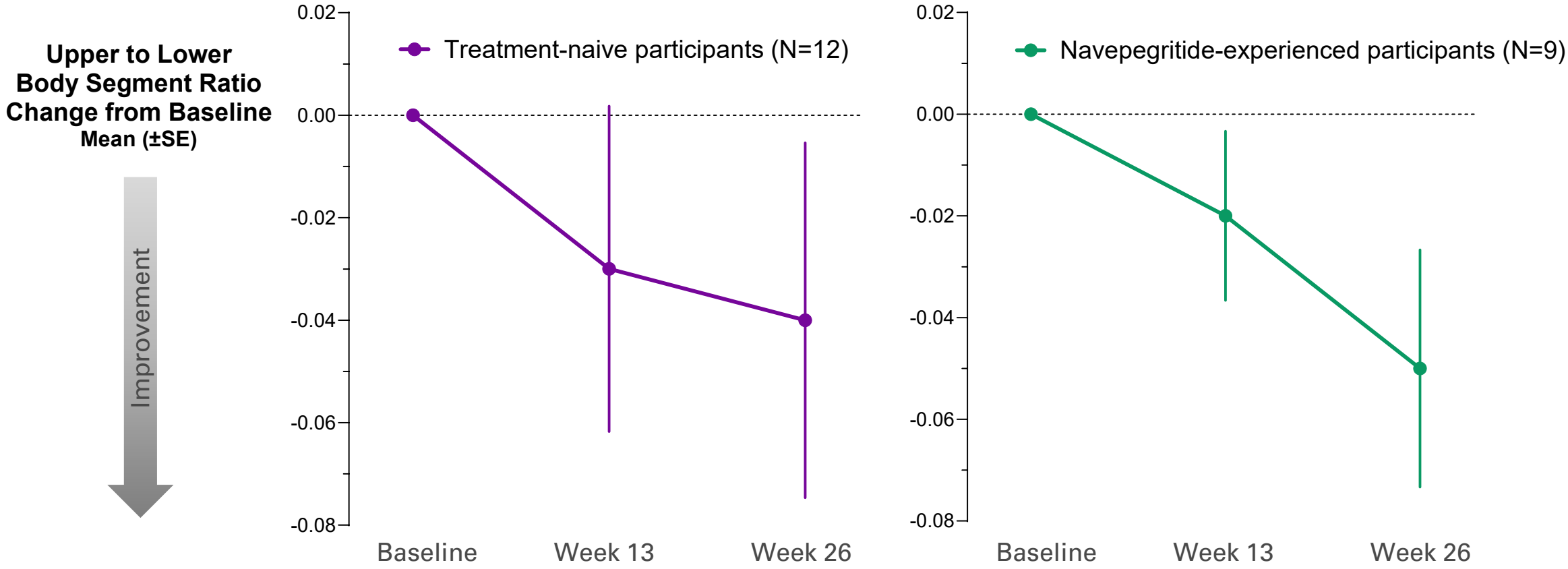
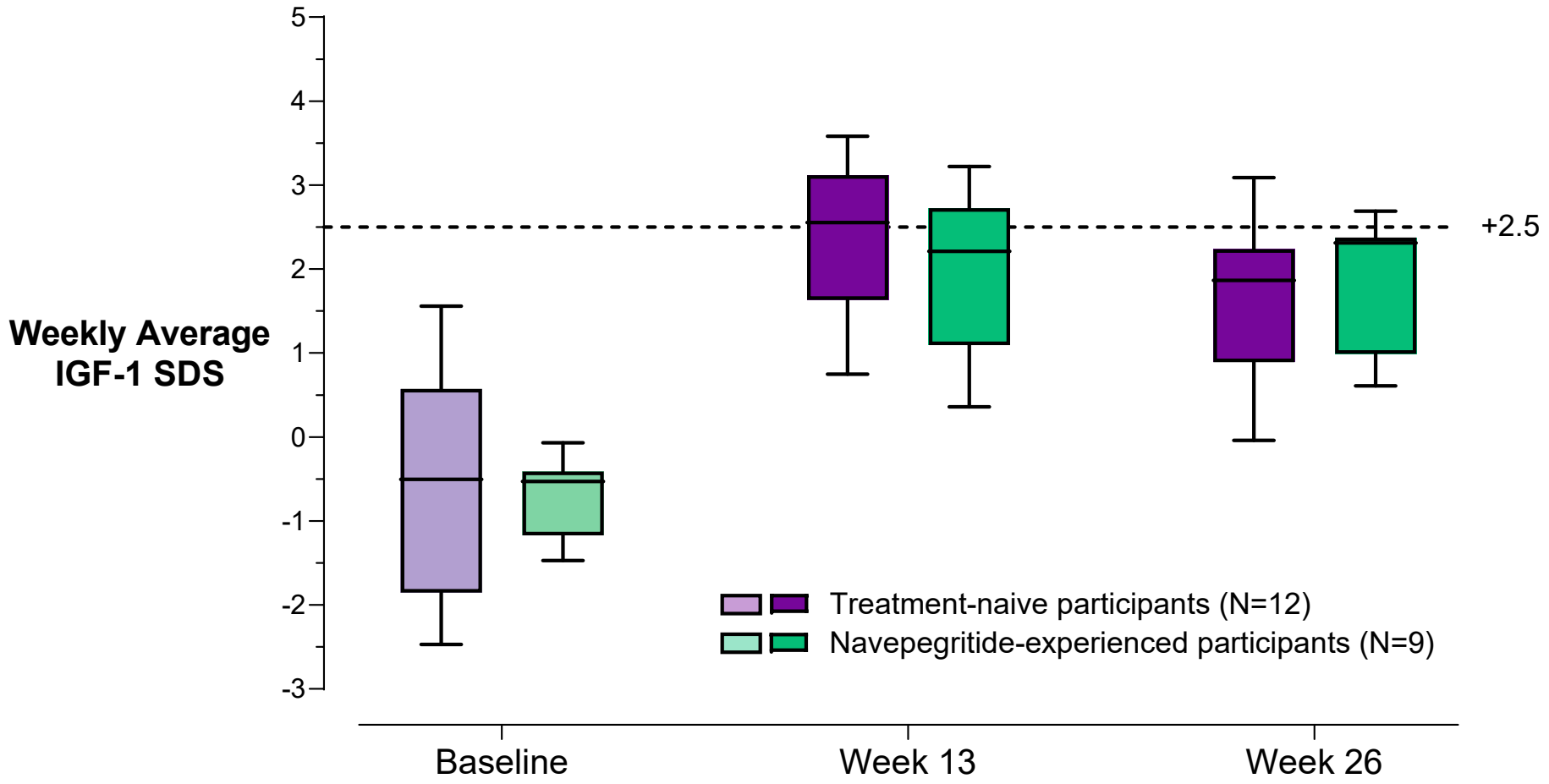


Figure adapted from Hoover-Fong JE, et al. *Am J Clin Nutr* 2008. Natural history AGV curves presented for male children; curves for average stature children from 0-3y reflect 10th, 50th, and 90th percentile; curves for average stature children >3y reflect percentiles as labeled.

Children treated with navepegritide & lonapegsomatropin demonstrated improvement in body proportionality



Average IGF-1 SDS was maintained near protocol-specified threshold of +2.5



IGF-1, insulin-like growth factor-1; SDS, standard deviation score
Weekly average IGF-1 SDS was estimated using Lin et al, *J Endocr Soc* 2021. Plot represents median/IQR/range.

Safety profile of navepegritide & lonapegsomatropin was consistent with safety profile of each monotherapy

Safety Analysis Set	COACH Overall (N=21) n (%)
Treatment-emergent AEs	15 (71.4)
AEs affecting ≥5% of children	
Injection site erythema	5 (23.8)
Nasopharyngitis	5 (23.8)
Viral gastroenteritis	2 (9.5)
Gastroenteritis	2 (9.5)
Lower respiratory tract infection	2 (9.5)
Hand-foot-and-mouth disease	2 (9.5)
Injection site bruising	2 (9.5)
Pyrexia	2 (9.5)
Arthralgia	2 (9.5)
Treatment-related AEs	7 (33.3)
Lonapegsomatropin-related AE	6 (28.6) [a]
Navepegritide-related AE	4 (19.0) [b]
AEs of special interest (for navepegritide) [c]	
Injection site reactions	3 (14.3)
Symptomatic hypotension	0
Fractures	0
Serious AEs	1 (4.8) [d]
Change in bone age, mean (SE)	0.41 (0.11)

No AEs led to discontinuation of either study drug, withdrawal from trial, or death

AE, adverse event; N, number of children enrolled; n, number of children with observation; SE, standard error

[a] AE related to lonapegsomatropin: injection site erythema (n=2); injection site discoloration (n= 1); injection site pain (n= 1); injection site swelling (n= 1); head circumference abnormal (n= 1); lipoatrophy (n= 1)

[b] AE related to navepegritide: injection site erythema (3); injection site bruising (n= 1); hypertrichosis (n= 1)

[c] Defined for navepegritide per FDA; no AEs of special interest have been defined for lonapegsomatropin.

[d] Viral respiratory tract infection, assessed as moderate and not related to either study drug by the investigator.

Summary

- COACH is the first clinical trial to evaluate combination treatment with once-weekly navepegritide and once-weekly lonapegsomatropin in children with achondroplasia
- At Week 26, children receiving navepegritide and lonapegsomatropin demonstrated notable improvements in growth and body proportionality compared with baseline
- Combination treatment with navepegritide and lonapegsomatropin was well tolerated, with generally mild treatment-emergent adverse events

These results suggest co-administration of lonapegsomatropin with navepegritide results in augmented growth, with a safety profile consistent with the monotherapies

52-week results from the COACH trial are expected in early 2026

The authors and Ascendis Pharma thank
the children, caregivers, study sites, and investigators
who participated in this clinical trial.