Navepegritide Combined with Lonapegsomatropin for the Treatment of Children with Achondroplasia: 52-Week Results from the Phase 2 COACH Trial

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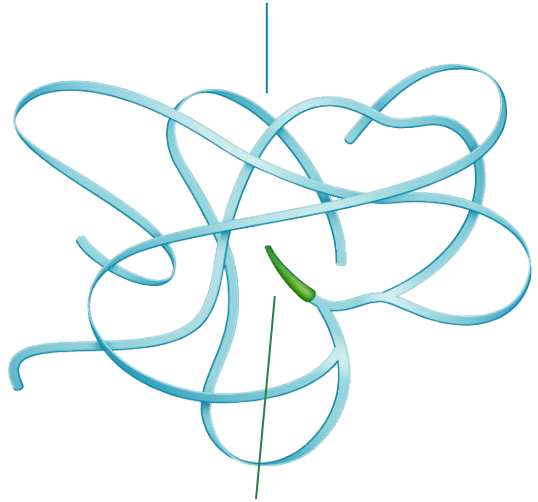
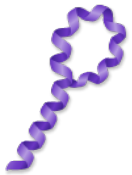
TransCon® technology

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

TransCon Carrier
Soluble; allows for systemic delivery



TransCon Linker
Specific for different parent drugs and release profiles



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

Somatropin
human growth hormone (hGH)
Amino acid sequence and size are identical to endogenous hGH

Navepegritide (TransCon CNP)

- Provides continuous exposure to active CNP with once-weekly administration[1]
- Approved to increase linear growth in children with achondroplasia[2]

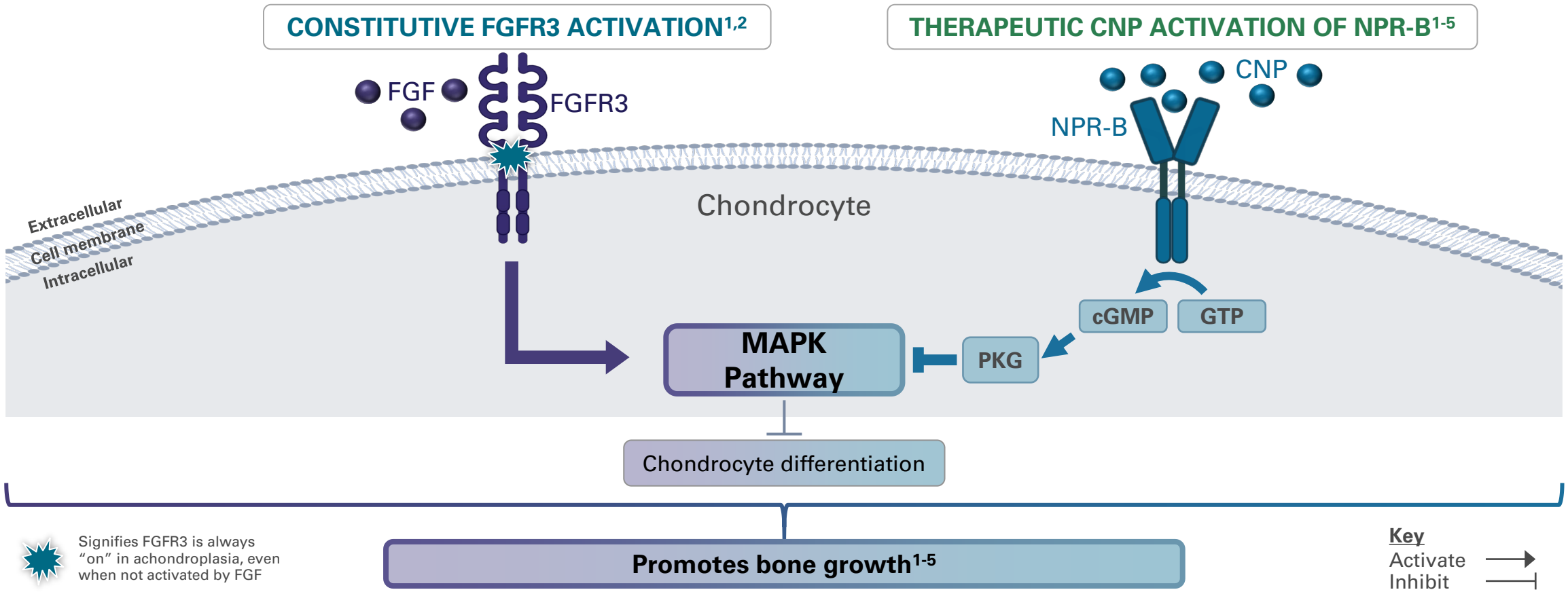
Lonapegsomatropin (TransCon hGH)

- Provides sustained release of unmodified somatropin with once-weekly administration[3,4]
- Approved for treatment of GH deficiency in children and adults[5,6]

[1]Breinholt VM, et al. *J Pharmacol Exp Ther.* 2019. [2]YUVIWEL (navepegritide) prescribing information. [3]Sprogøe K, et al. *Endocr Connect.* 2017.
[4]Thornton PS, et al. *J Clin Endocrinol Metab.* 2021. [5]SKYTROFA (lonapegsomatropin-tcgd) prescribing information. [6]SKYTROFA (lonapegsomatropin) SmPC.

CNP counteracts overactive FGFR3 signaling in achondroplasia

Therapeutic CNP promotes chondrocyte differentiation and bone growth through activation of NPR-B, countering hyperactive MAPK signaling[1-5]

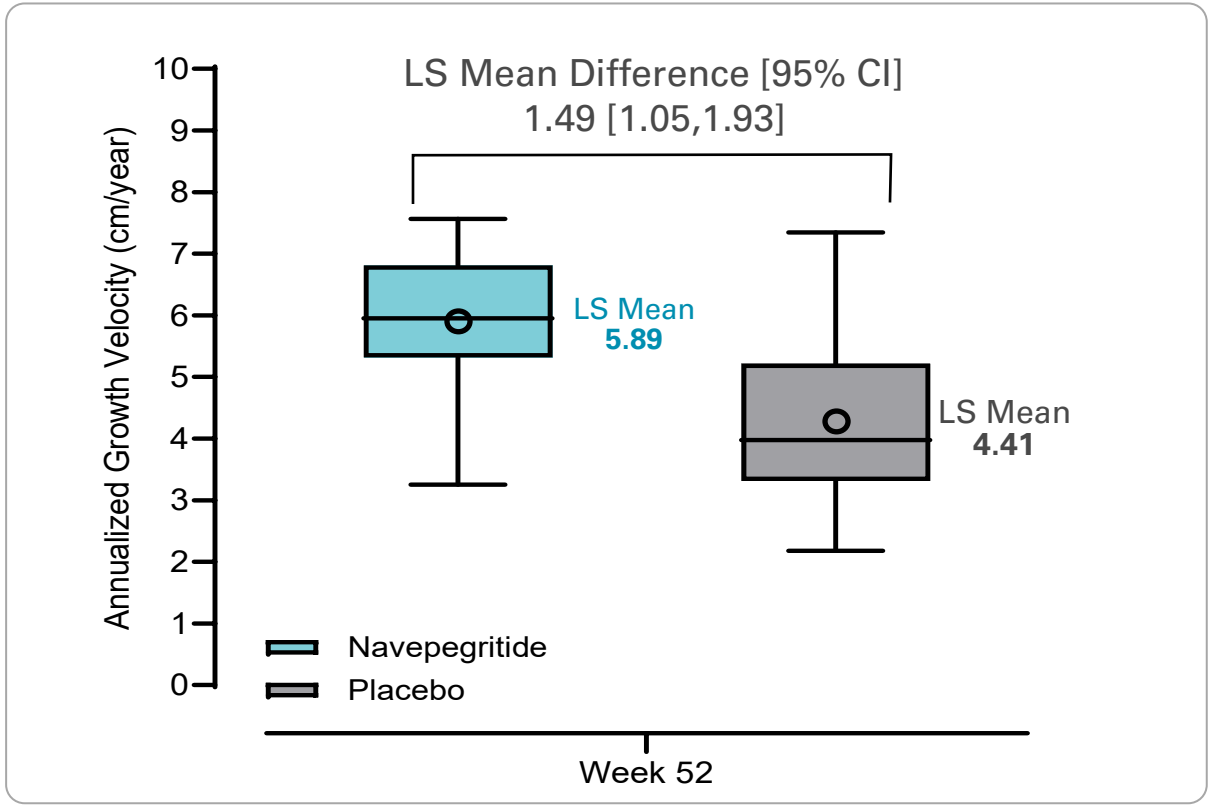


cGMP, 3′–5′ cyclic guanosine monophosphate; CNP, c-type natriuretic peptide; FGF, fibroblast growth factor; FGFR3, fibroblast growth factor receptor 3; GTP, guanosine triphosphate; MAPK, mitogen-activated protein kinase; NPR-B, natriuretic peptide receptor B; PKG, protein kinase G; STAT1, signal transducer and activator of transcription.

1. Horton WA, et al. *Lancet.* 2007;370:162-72. 2. Rintz E, et al. *Int J Mol Sci.* 2022;23. 3. Krejci P, et al. *PLoS One.* 2008;3:e3961. 4. Yasoda A, et al. *Nat Med.* 2004;10:80-6.
5. Miyazawa T, et al. *Endocrinology.* 2002;143: 3604-10.

Navepegritide demonstrated superiority in annualized growth velocity (AGV) at Week 52 vs placebo in the pivotal ApproaCH trial

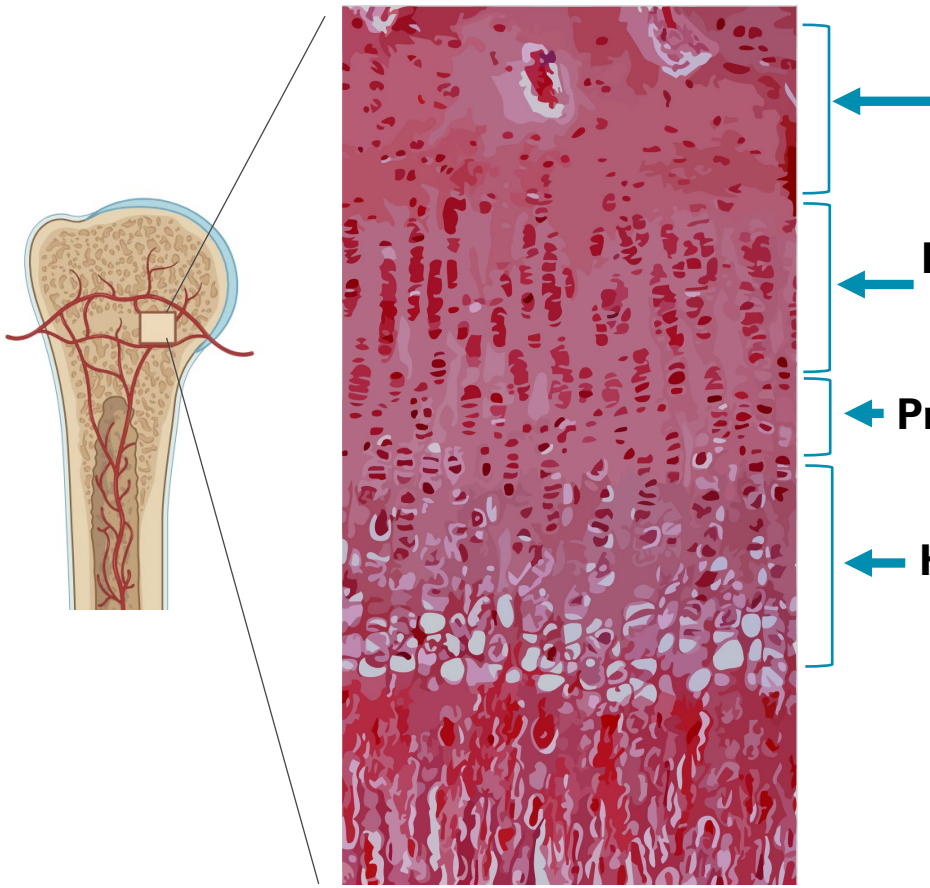
AGV at Week 52[1]



The ANCOVA model included treatment, stratification factor, baseline age, and baseline ACH-specific height Z-score as covariates.
Box and whisker plot was 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; labeled circles represent least squares mean values.

[1]Savarirayan R, et al. *JAMA Pediatr*. 2026;180:18-25.

In children with achondroplasia, navepegritide may enhance the receptivity of the growth plate to lonapegsomatropin



Resting zone

Proliferative zone

Prehypertrophic zone

Hypertrophic zone

Effects on growth plate[1-7]

GH recruits stem cells to form chondrocytes

GH and **IGF-1** promote increase in number of chondrocytes

CNP releases the FGFR3-induced transitional block in achondroplasia

IGF-1 promotes chondrocyte growth and differentiation

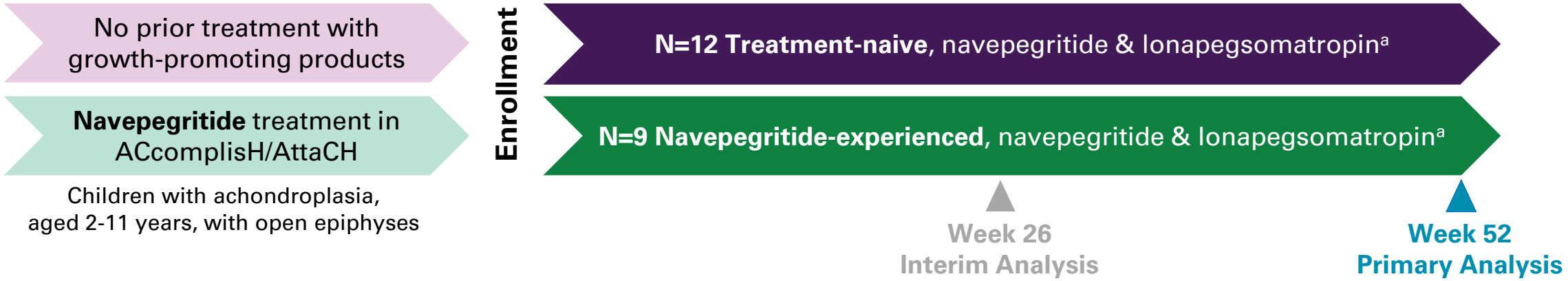
Treatment with **CNP** relieves the pre-hypertrophic block, optimizing the ability of **GH** to stimulate growth

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. Image adapted from: ID 93293021 ©Jlcalvo | Dreamstime.com.

Phase 2 COACH trial

Navepegritide combined with lonapegsomatropin in children with achondroplasia



Primary efficacy endpoint: Annualized growth velocity at Week 52

Selected secondary endpoints include: Change from baseline in height Z-score
Upper-to-lower body segment ratio (body proportionality)
Arm span

Safety endpoint: Treatment-emergent AEs, including injection site reactions

Biomarker endpoint: IGF-1 SDS

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

The concomitant use of navepegritide and lonapegsomatropin is investigational and has not been approved by the U.S. Food and Drug Administration (FDA). The safety and efficacy of this combination therapy have not been established. Content is intended for educational and scientific exchange only. Not for use in promotion or product commercialization.

Demographics and baseline characteristics

Full Analysis Set	Treatment-naive (N=12)	Navepegritide-experienced (N=9)
Mean age, years (SD)	5.3 (2.2)	8.3 (1.9)
Sex, male; n (%)	8 (66.7)	6 (66.7)
Prior exposure to navepegritide 100 µg/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)

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

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. *Orphanet J Rare Dis*. 2021.
[b]CDC growth charts by age and sex available at: https://www.cdc.gov/growthcharts/who-growth-charts.htm.

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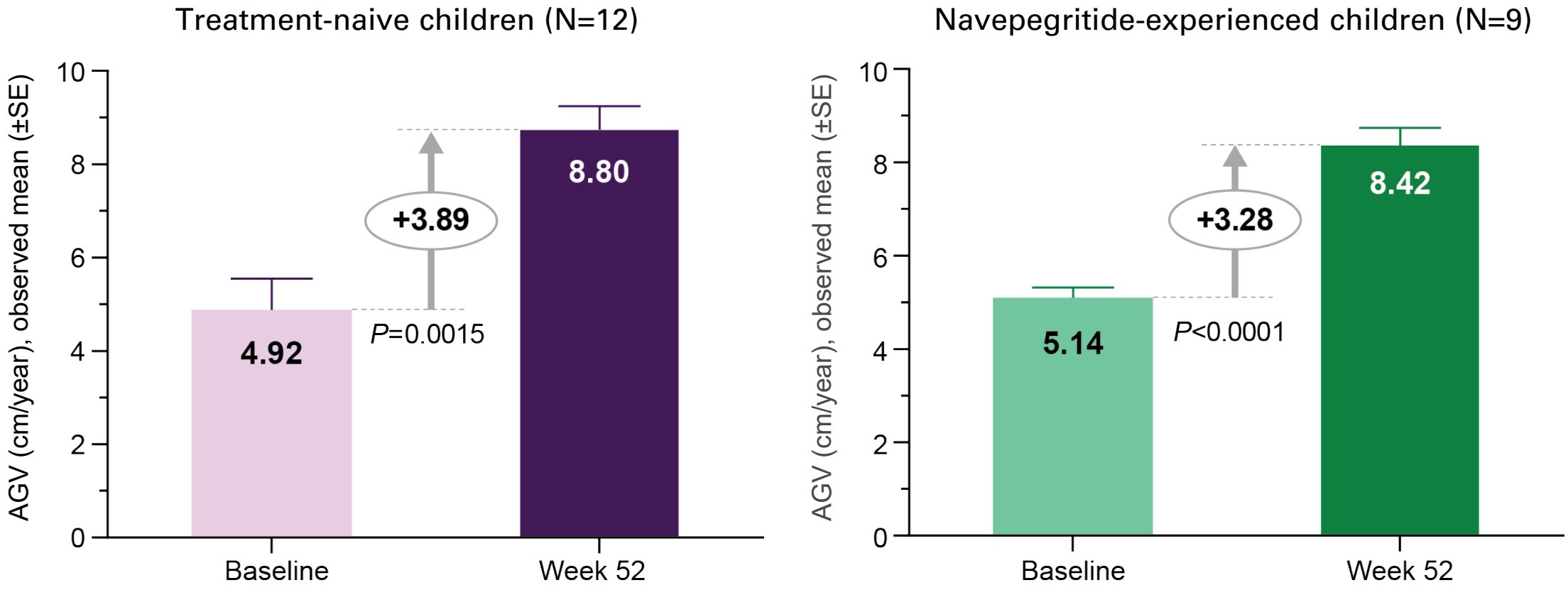
Navepegritide & lonapegsomatropin resulted in significant improvement in AGV at Week 52

Annualized growth velocity (AGV)



SE, standard error
Note: Baseline AGV calculation is based on 6 months and 12 months preceding the COACH trial for treatment-naive children and navepegritide-experienced children, respectively.

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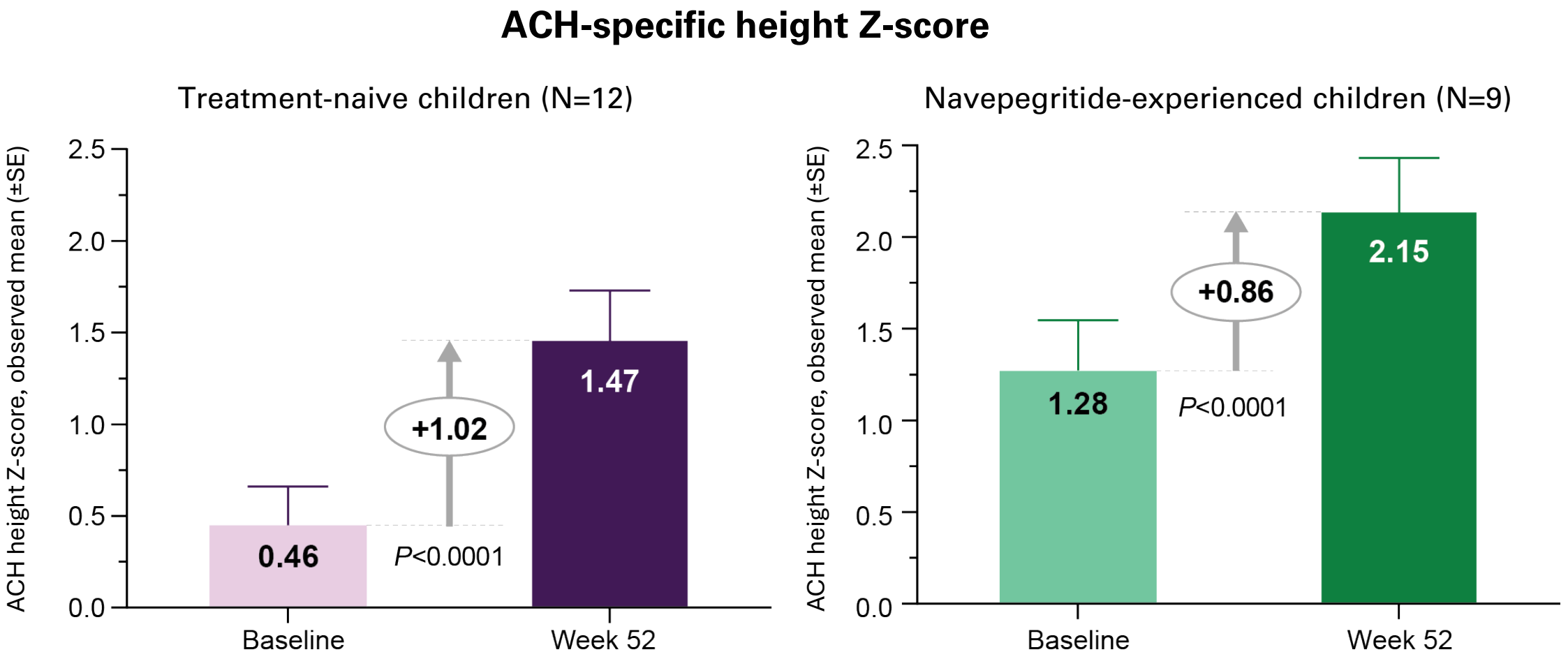
Navepegritide & lonapegsomatropin significantly improved ACH-specific height Z-score at Week 52



Achondroplasia-specific height Z-scores were derived from reference data on children with achondroplasia from Hoover-Fong JE, et al. US. *Orphanet J Rare Dis*. 2021.
ACH, achondroplasia; SE, standard error

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

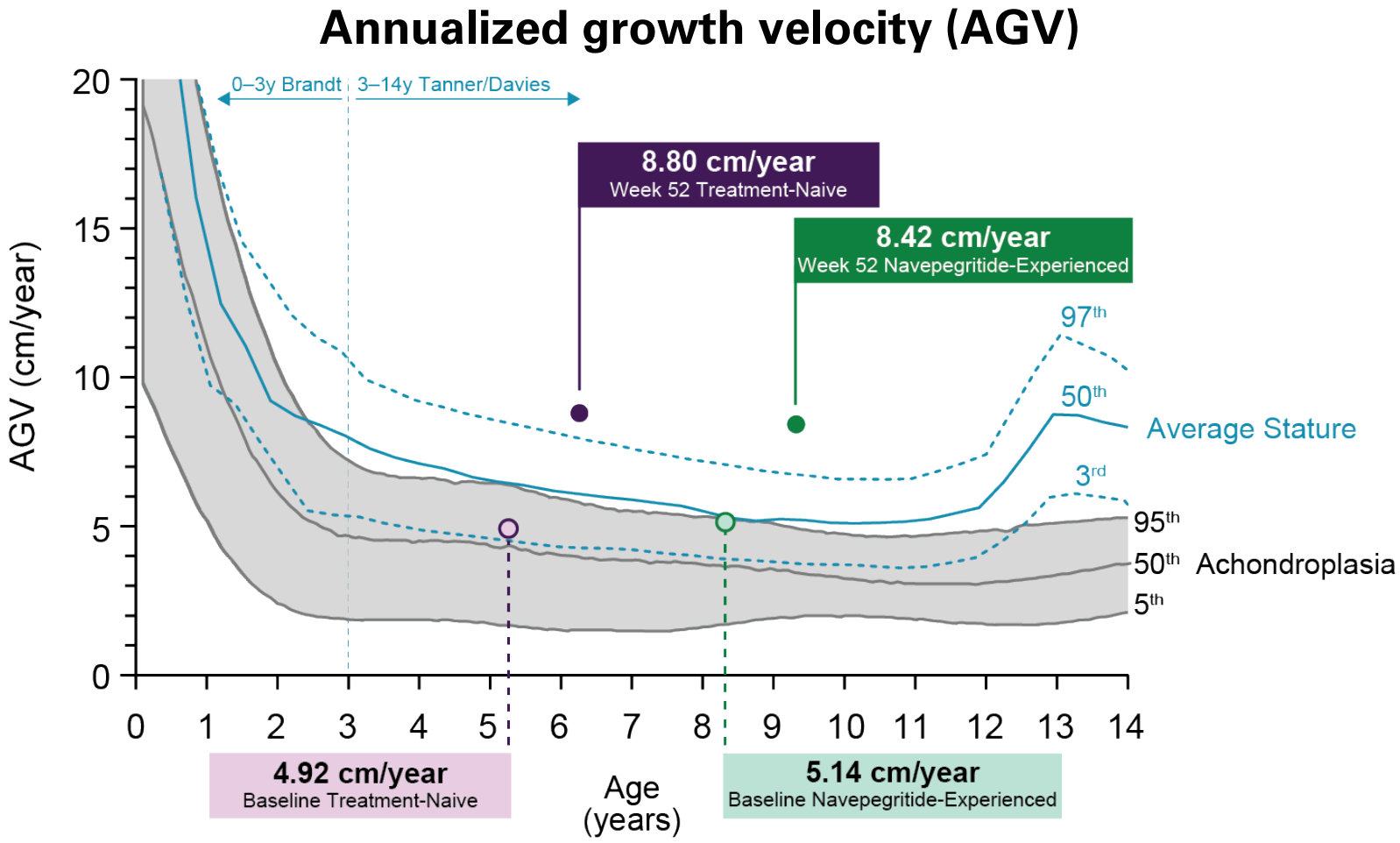

Figure adapted from Hoover-Fong JE, et al. *Am J Clin Nutr.* 2008. Natural history AGV curves presented for male children; curves for average stature children from 0-3y reflect 10th, 50th, and 90th percentile; curves for average stature children >3y reflect percentiles as labeled.

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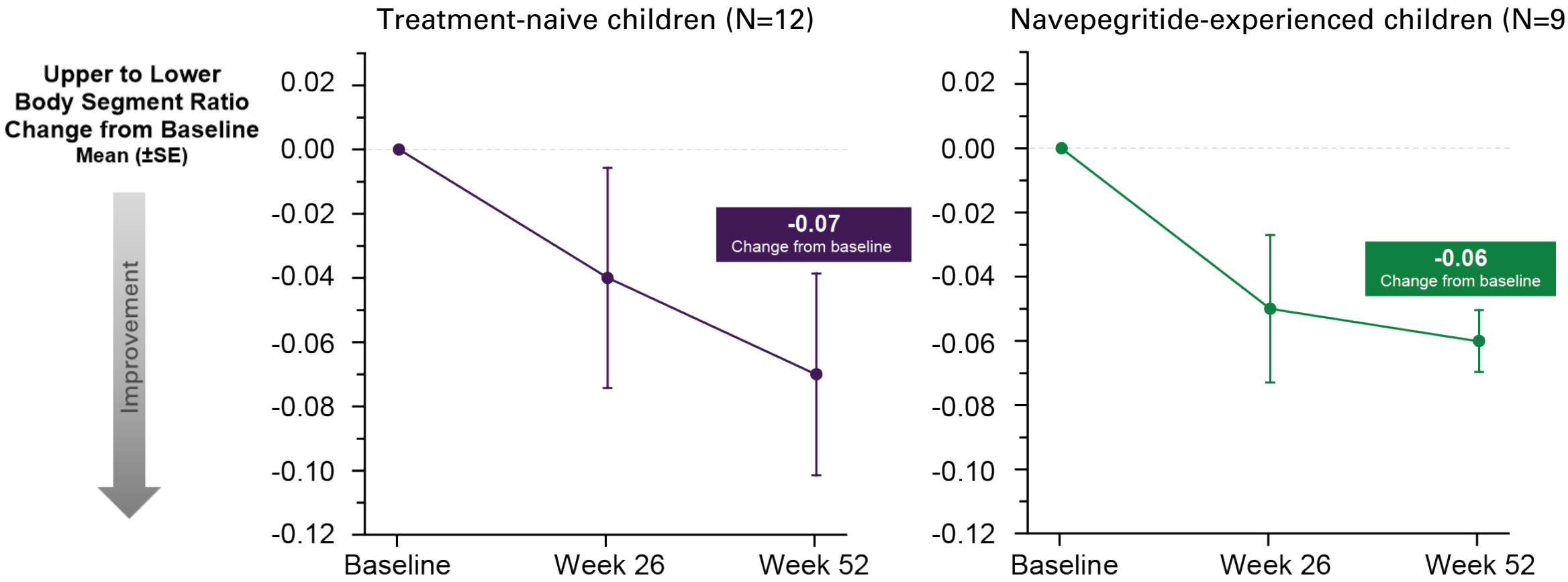
Children treated with navepegritide & lonapegsomatropin demonstrated improvement in body proportionality



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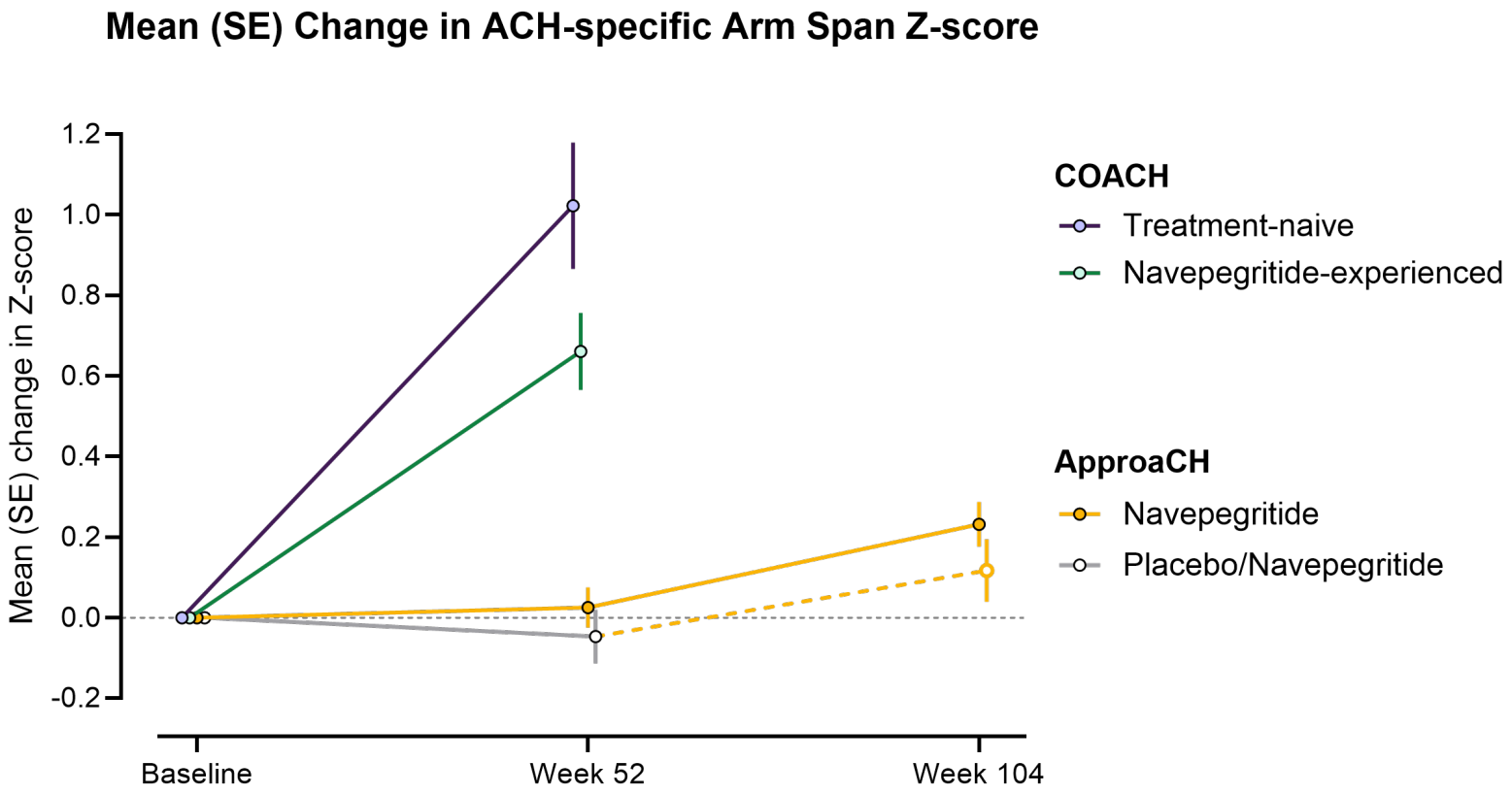
Children treated with navepegritide & lonapegsomatropin showed gain in arm span Z-score of up to +1.0 at Week 52



Arm span increased by +9.4 cm in the treatment-naive group and by +7.9 cm in the navepegritide-experienced group, consistent with gains in height

Z-scores were calculated using natural history of arm span in age/sex matched persons with ACH as reported from Merker A, et al. *Am J Med Genet A.* 2018;176:1819-29.
Values are presented as observed means (SE).

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

Safety Analysis Set	COACH Overall (N=21)
Participants experiencing treatment-emergent AEs, n (%)	18 (85.7)
AEs affecting ≥10% of children	
Respiratory tract infection	8 (38.1)
Injection site reaction	7 (33.3)
Gastroenteritis	7 (33.3)
Nasopharyngitis	5 (23.8)
Ear infection	3 (14.3)
Hand-foot-and-mouth disease	3 (14.3)
Treatment-related AEs	
Lonapegsomatropin-related AE[a]	7 (33.3)
Navepegritide-related AE[b]	4 (19.0)
AEs of special interest (for navepegritide)[c]	
Injection site reactions	3 (14.3)
Symptomatic hypotension	0
Fractures (including slipped capital femoral epiphysis)	0
Serious AEs[d]	1 (4.8)

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

Mean bone age to chronological age ratio remained <1

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

[a] AEs related to lonapegsomatropin were injection site reactions and one case of abnormal head circumference in a child with a history of achondroplasia-related macrocephaly.

[b] AEs related to navepegritide were injection site reactions and one case of hypertrichosis.

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

[d] The SAEs (viral respiratory tract infection and acquired hydrocele) were in the same participant; both were unrelated to treatment.

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Conclusions

- COACH is the first clinical trial to evaluate dual therapy with once-weekly navepegritide and once-weekly lonapegsomatropin in children with achondroplasia
- At Week 52, children receiving dual therapy:
  - achieved significant increases in AGV and height Z-scores
  - showed improvements in body proportionality, including substantial increases in arm span consistent with height gains
- Dual therapy was well tolerated, with generally mild adverse events and no treatment discontinuations

These results suggest co-administration of lonapegsomatropin with navepegritide provides augmented growth, with a safety profile consistent with each as monotherapy

A manuscript on these findings was just published in the *European Journal of Endocrinology*[1]

[1]McDonnell CM, et al. *Eur J Endocrinol.* 2026;194:745-755.

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We would like to thank the children, caregivers, nurses, and site personnel without whose help this clinical trial would not have been possible.

Disclosures

- Ciara M McDonnell: Research support/clinical trial investigator and consultant for Ascendis Pharma; consultant for BioMarin.

- Ascendis Pharma, LLC, funded this trial.

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