Effects of Navepegritide and Lonapegsomatropin on Manifestations of Skeletal Dysplasia in Children With Achondroplasia: 52-Week Results From the Phase 2 COACH Trial

COACH TRIAL

Poster Board Number: LB39

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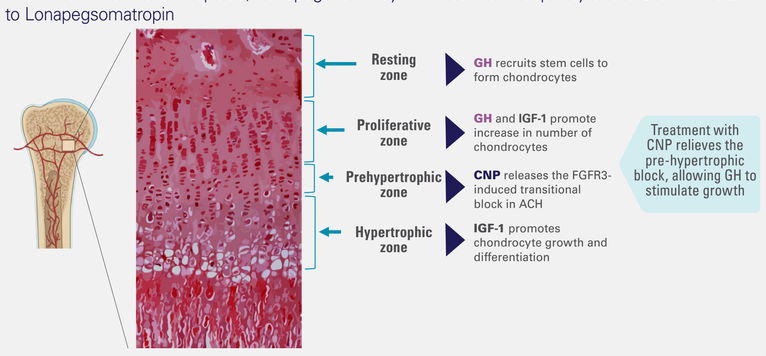
Background

- Children with ACH experience manifestations of skeletal dysplasia beyond short stature, including reduced arm span, narrowed spinal canal dimensions, and lower extremity malalignment, which may contribute to pain, functional impairment, reduced mobility, and increased surgical burden[1]
- Navepegritide is a prodrug of CNP, administered subcutaneously once weekly and designed to provide continuous exposure to active CNP to counteract the constitutively active FGFR3 in ACH[2,3]
  - Navepegritide demonstrated superiority in AGV at Week 52 vs placebo in the pivotal ApproaCH Trial (NCT05598320)[4]
- Lonapegsomatropin is a prodrug of somatropin administered once weekly, designed to provide sustained release of active, unmodified somatropin[5-7]
- Adding lonapegsomatropin to navepegritide is hypothesized to augment the effects observed with navepegritide monotherapy on endochondral bone formation[8,9]
- COACH (NCT06433557) is an ongoing, phase 2, open-label, proof-of-concept trial designed to investigate the efficacy and safety of dual therapy with once-weekly navepegritide and lonapegsomatropin in children with ACH aged 2 to 11 years
  - Dual therapy resulted in significant improvement in AGV at Week 52[10]

Objective

To determine the effect of dual therapy with navepegritide and lonapegsomatropin on skeletal parameters in the COACH trial

In Children With Achondroplasia, Navepegritide May Enhance the Receptivity of the Growth Plate to Lonapegsomatropin



Dual Therapy With Navepegritide and Lonapegsomatropin Resulted in Average Growth Velocity Above the 97th Percentile for Children of Average Stature[10]

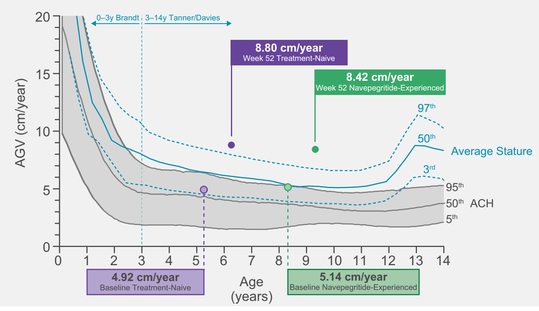


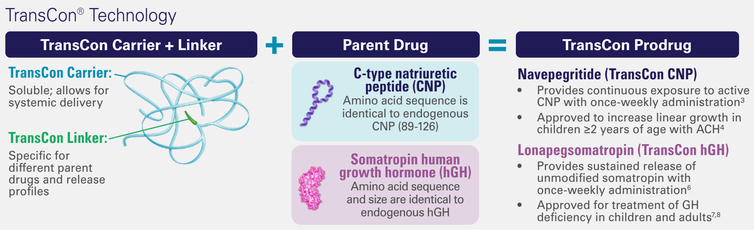
Figure adapted from Hoover-Fong et al.[11] Natural history AGV curves presented for male children; curves for average stature children from 0-3y reflect 10th, 50th, and 90th percentile; curves for average stature children >3y reflect percentiles as labeled. The data have been plotted on the growth curves for male children as the majority of children enrolled in the COACH Trial were male, and the growth curves for female children and male children are similar for the age range enrolled.

Conclusions

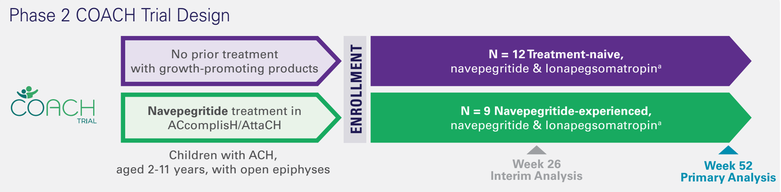
- In the COACH Trial, following 52 weeks of dual therapy with navepegritide and lonapegsomatropin, AGV exceeded the 97th percentile for children of average stature
- At Week 52, children receiving dual therapy achieved substantial increases in arm span that exceeded those observed in untreated children with ACH and were consistent with gains in standing height
- Notable improvements in spinal canal dimensions (IPD) and lower limb alignment (TFA) were also observed
- Dual therapy was generally well tolerated, with predominantly mild AEs reported, no permanent treatment discontinuations, and no observed bone safety events
  - The safety profile of navepegritide and lonapegsomatropin was similar to that observed with either drug as monotherapy in other pediatric trials
- These results provide proof of concept that dual therapy may confer benefits beyond linear growth compared with monotherapy, addressing structural and functional aspects of skeletal dysplasia in ACH
- Navepegritide may enable a complementary effect of lonapegsomatropin in children with ACH

Methods

TransCon® Technology



Phase 2 COACH Trial Design



[a]Navepegritide (100 µg/kg/week) and lonapegsomatropin (starting dose of 0.30 mg hGH/kg/week) administered as separate once-weekly subcutaneous injections

COACH Trial Endpoints

Primary efficacy endpoint	• AGV at Week 52	
Selected secondary efficacy endpoints	• Arm span • Arm span Z-score • IPD (L1-L5)	• IPD (L1-L5) Z-score • TFA • TFA Z-score
Safety endpoints	• Treatment-emergent AEs, including ISRs • Bone age	

Results

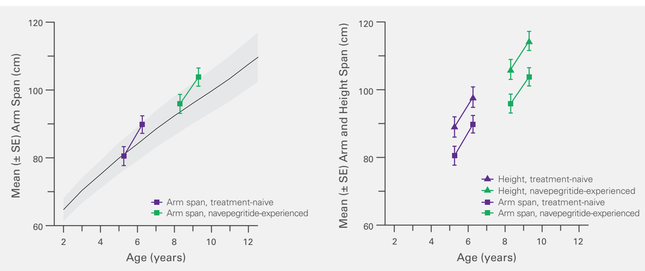
Table 1. **Demographics and Baseline Characteristics**

	navepegritide & lonapegsomatropin	
Full Analysis Set	Treatment-naive (N = 12)	Navepegritide-experienced (N = 9)
Age, years; mean (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)[12]	0.46 (0.70)	1.28 (0.81)
CDC-based height Z-score; mean (SD)[a]	-4.46 (0.77)	-4.04 (0.66)
IGF-1 SDS; mean (SD)	-0.63 (1.32)	-0.70 (0.48)

[a]CDC growth charts by age and sex available at: https://www.cdc.gov/growthcharts/who-growth-charts.htm

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

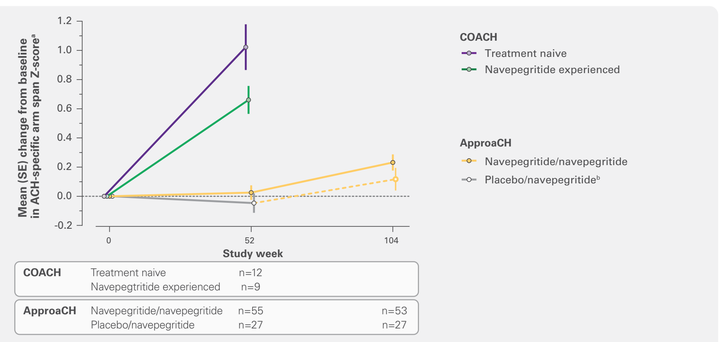
Figure 1. **Arm Span and Height at Baseline and Week 52**



Mean (solid line) and ±1 SD (shaded gray area) represent natural history of arm span in male children with ACH as reported by Merker et al.[13]

- Arm span increased from baseline to Week 52 by +9.4 cm in treatment-naive children and by +7.9 cm in navepegritide-experienced children with navepegritide and lonapegsomatropin treatment
  - Baseline arm spans are representative of treatment-naive children or reflect the impact of prior treatment with navepegritide monotherapy
- Increases in arm span exceeded those observed in untreated children with ACH[13] and were consistent with gains in standing height

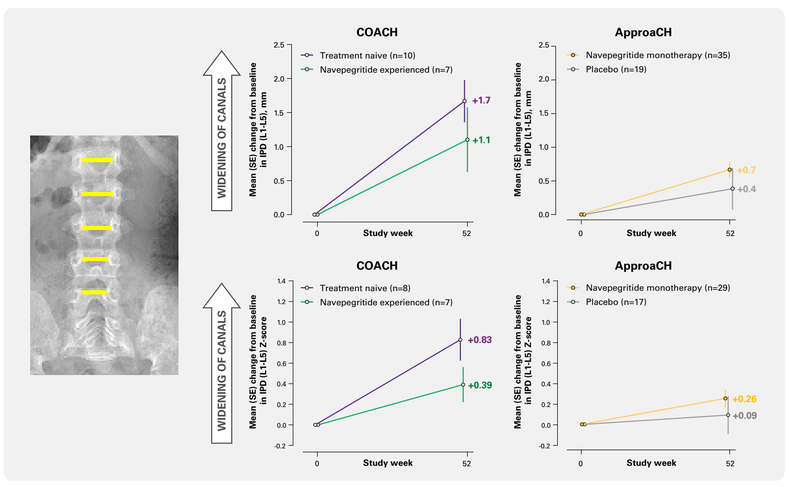
Figure 2. **Arm Span Z-score**



[a]Z-scores were calculated using natural history of arm span in age/sex matched persons with ACH as reported by Merker et al.[13]
[b]Children in the placebo/navepegritide group transitioned from placebo to navepegritide 100 µg/kg/week at Week 52.

- Children treated with navepegritide and lonapegsomatropin showed gain in arm span Z-score of up to +1.0 from baseline to Week 52
- In the pivotal ApproaCH Trial of navepegritide monotherapy, there was a numeric benefit with navepegritide compared with placebo at Week 52 and gain in arm span Z-score at Week 104

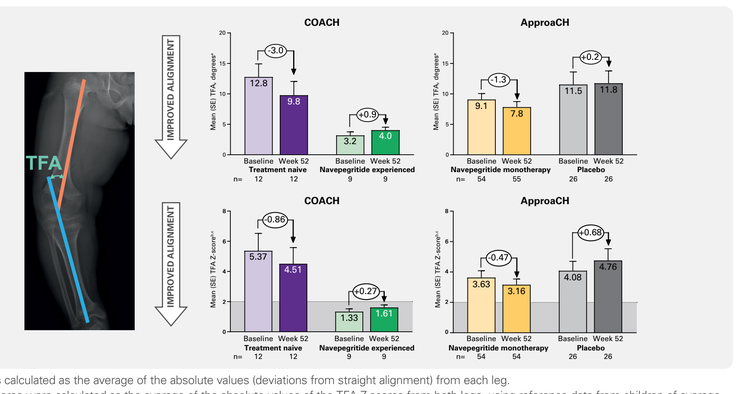
Figure 3. **Interpedicular Distance (Top) and Interpedicular Distance Z-scores (Bottom)**



[a]Z-scores were calculated using reference data from children of average stature as reported by Hinck, Clark, and Hopkins.[14]

- Widening of the canals of the lumbar spine (L1-L5) was observed following 52 weeks of dual therapy in both treatment-naive and navepegritide-experienced children
  - In ApproaCH, the mean change in calibrated IPD (L1-L5) at Week 52 was +0.7 mm in children treated with navepegritide and +0.4 mm in children receiving placebo
- The mean gain in IPD Z-score from baseline to Week 52 with dual therapy was +0.83 in treatment-naive children
  - In ApproaCH, the mean gain in IPD Z-score was +0.26 in children treated with navepegritide and +0.09 in children receiving placebo

Figure 4. **Tibial-Femoral Angle** (top) **and Tibial-Femoral Angle Z-score** (bottom)



[a]TFA was calculated as the average of the absolute values (deviations from straight alignment) from each leg.
[b]TFA Z-scores were calculated as the average of the absolute values of the TFA Z-scores from both legs, using reference data from children of average stature as reported by Sabharwal and Zhao.[15]
[c]Values within gray shaded area are within the range for children of average stature.

- Improvement in lower limb alignment from baseline to Week 52 was observed with dual therapy in the treatment-naive group
  - In ApproaCH, the mean change in TFA was -1.3 degrees in children treated with navepegritide and +0.2 degrees in children receiving placebo
- TFA Z-scores improved with dual therapy in treatment-naive children and remained within the range for children of average stature[15] in navepegritide-experienced children
  - In ApproaCH, the mean change in TFA Z-score was -0.47 in children treated with navepegritide and +0.68 in children receiving placebo

Table 2. **Safety Profile of Navepegritide and Lonapegsomatropin over 52 Weeks of Treatment**

Safety Analysis Set	COACH Overall (N=21)
Participants experiencing any 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)

- In a majority of participants,AEs were mild (85.7%) or moderate (38.1%)
- Treatment-related AEs occurred in 38.1% of participants, most commonly ISRs
  - All ISRs were transient and mild, and none led to changes in treatment or required intervention
- Two SAEs (unrelated to study drugs) were reported by one participant
- Bone age to chronological age ratio (mean [SE]) was 0.92 (0.04) at Week 52 versus 0.83 (0.04) at baseline
- No bone safety events such as fractures, slipped capital femoral epiphysis, or osteonecrosis were reported
- No AEs led to discontinuation of either study drug or withdrawal from the trial

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Abbreviations

ACH = achondroplasia; **AE** = adverse event; **AGV** = annualized growth velocity; **CDC** = Centers for Disease Control and Prevention; **CNP** = C-type natriuretic peptide; **FGFR3** = fibroblast growth factor receptor 3; **GH** = growth hormone; **IGF-1** = insulin-like growth factor-1; **IPD** = interpedicular distance; **ISR** = injection site reaction; **SAE** = serious adverse event; **SD** = standard deviation; **SE** = standard error; **TransCon** = transient conjugation

References:

1. Savarirayan R, Ireland P, Irving M, et al. *Nat Rev Endocrinol*. 2022;18(3):173-89. **2**. Breinholt VM, Rasmussen CE, Mygind PH, et al. *J Pharmacol Exp Ther*. 2019;370(3):459-71. **3**. YUVIWEL® (navepegritide). Prescribing information. Ascendis Pharma. Accessed May 22, 2026. **4**. Savarirayan R, et al. *JAMA Pediatrics*. 2026;180(1):18-25. **5**. Sprogøe K, et al. *Endocr Connect*. 2017;6:R171-R181. **6**. SKYTROFA® (lonapegsomatropin-tcgd). Prescribing information. Ascendis Pharma. Accessed May 22, 2026. **7**. SKYTROFA (lonapegsomatropin) [package insert]. Hellerup, Denmark. Ascendis Pharma Endocrinology Division A/S; 2021. **8**. Yasoda A, et al. *Endocrinology*. 2009;150(7):3138-44. **9**. Blum WF, et al. *Endocr Connect*. 2018;7:R212-R222. **10**. McDonnell CM, et al. *Eur J Endocrinol*. 2026;, lvag082, https://doi.org/10.1093/ejendo/lvag082. **11**. Hoover-Fong JE, et al. *Am J Clin Nutr*. 2008;88:364-71. **12**. Hoover-Fong JE, et al. *Orphanet J Rare Dis*. 2021;16:522. **13**. Merker A, et al. *Am J Med Genet A*. 2018;176:1819-29. **14**. Hinck VC, Clark WM Jr, and Hopkins CE. *Am J Roentgenol Radium Ther Nucl Med*. 1966;97(1):141-53. **15**. Sabharwal S, Zhao C. *J Bone Joint Surg Am*. 2009;91(10):2461-8.

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