ApproaCH Trial Open Label Extension: Week 104 Results in Children With Achondroplasia Aged 5 Years or Older Treated With Navepegritide

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PES 2026 ANNUAL MEETING

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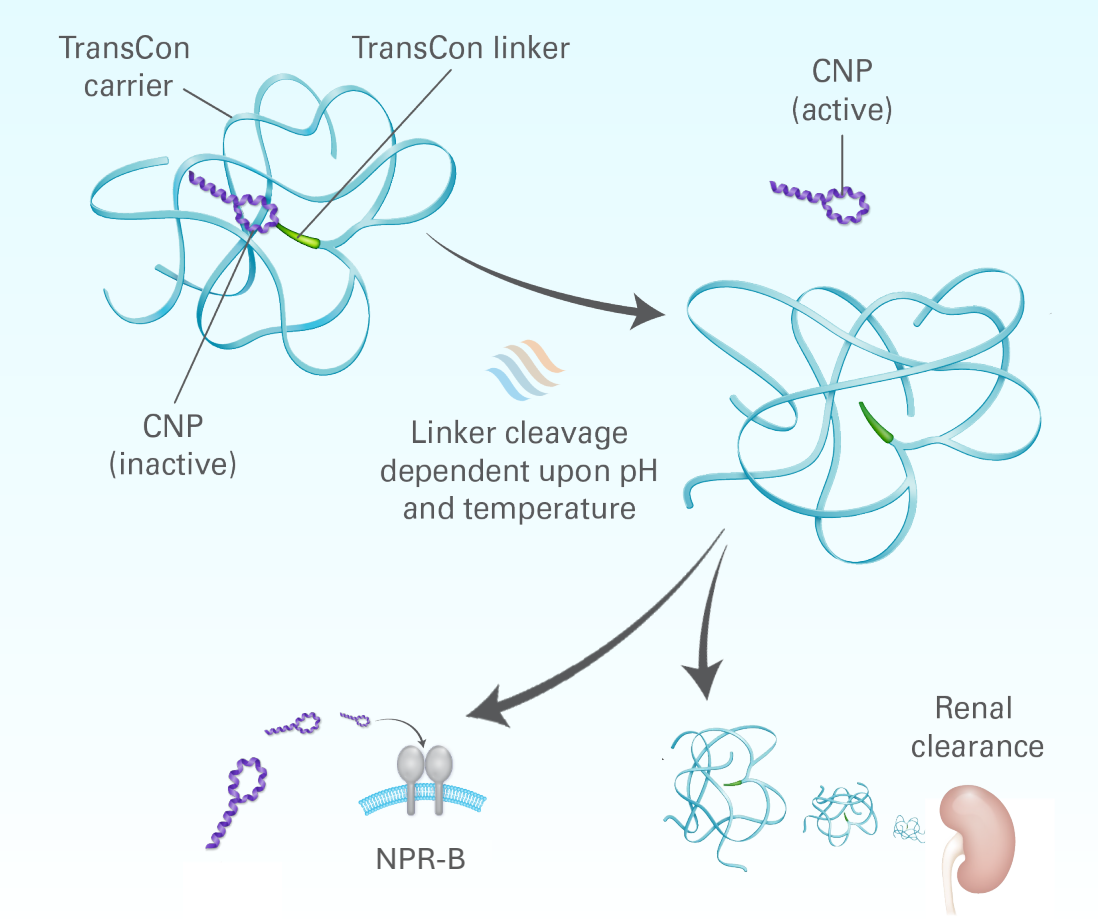
Navepegritide (TransCon® CNP)

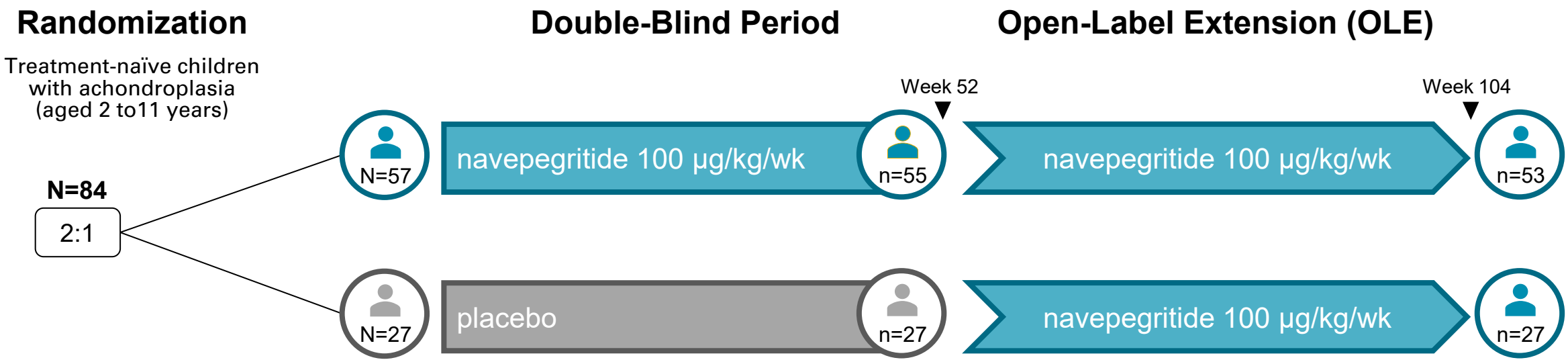


- Navepegritide is a prodrug of C-type natriuretic peptide (CNP) administered once weekly and designed to provide continuous exposure to active CNP
- Active CNP released from navepegritide has an amino acid sequence identical to endogenous CNP [89-126] and binds to NPR-B throughout the body to counteract the constitutively active FGFR3 signaling in achondroplasia[1]
- Navepegritide is approved by the US FDA to increase linear growth in children 2 years and older with achondroplasia with open epiphyses[2]

CNP, C-type natriuretic peptide; FGFR3, fibroblast growth factor receptor 3; NPR-B; natriuretic peptide receptor B; US FDA, United States Food and Drug Administration

[1]Breinholt VM, et al. *J Pharmacol Exp Ther* 2019;370(3):459-471. [2]Yuviwel (navepegritide). Package Insert. Ascendis Pharma 2026.

Trial Design and Disposition



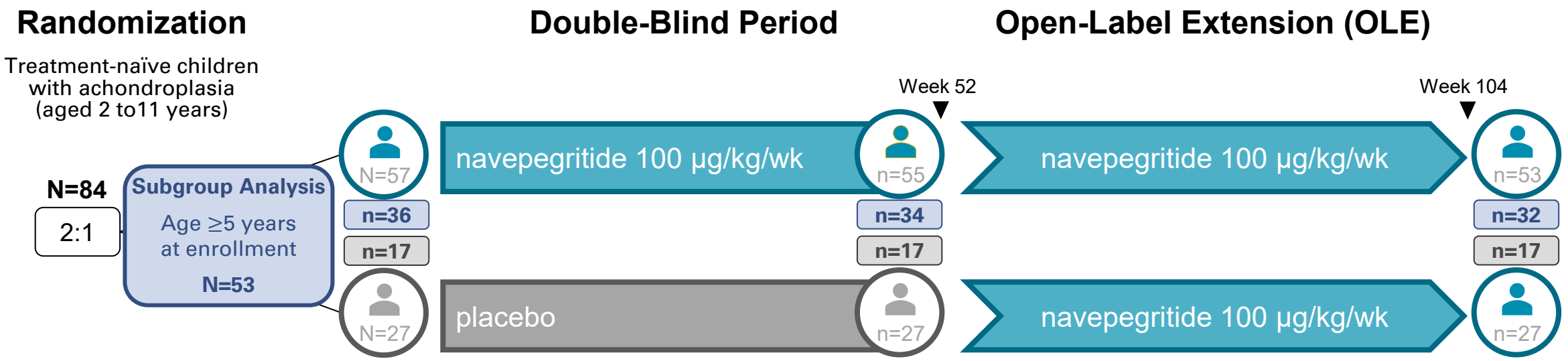
Primary Endpoint: Annualized growth velocity (**AGV**) at Week 52

Additional Efficacy Assessments: Change from baseline in **height Z-scores**
AGV at Week 104

Safety and Tolerability Assessments: Treatment-emergent adverse events (AEs)
Bone age

N = number of participants that received at least one dose of investigational medicinal product.

Subgroup Analysis: Children Aged ≥5 Years



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Additional Efficacy Assessments: Change from baseline in **height Z-scores**
AGV at Week 104

Safety and Tolerability Assessments: Treatment-emergent adverse events (AEs)
Bone age

N = number of participants that received at least one dose of investigational medicinal product.

Demographics: Children Aged ≥5 Years

	At Week 0 (Baseline)	
Treatment in Double-Blind Period:	**navepegritide**	**placebo**
Treatment in Open-Label Extension:	**n/a**	**n/a**
	n=36	n=17
Age (years), mean (SD) [min, max]	7.0 (2.1) [5.0, 11.9]	7.6 (1.9) [5.0, 12.0]
Sex, Male, n (%)	19 (52.8)	9 (52.9)
Height (cm), mean (SD)	96.2 (9.3)	96.5 (6.7)
Achondroplasia-specific height Z-score, mean (SD)	0.27 (0.90)	-0.10 (0.72)
CDC-based height Z-score, mean (SD)	-4.96 (0.99)	-5.40 (0.93)
AGV (cm/year), observed mean (SD)	3.45 (1.67)	3.65 (1.28)

AGV, annualized growth velocity; CDC, Centers for Disease Control and Prevention

Demographics: Children Aged ≥5 Years

	At Week 0 (Baseline)		At Week 52 (start of OLE)	
Treatment in Double-Blind Period:	**navepegritide**	**placebo**	**navepegritide**	**placebo**
Treatment in Open-Label Extension:	**n/a**	**n/a**	**navepegritide**	**navepegritide**
	n=36	n=17	n=34	n=17
Age (years), mean (SD) [min, max]	7.0 (2.1) [5.0, 11.9]	7.6 (1.9) [5.0, 12.0]	8.2 (2.1) [6.0, 13.0]	8.7 (1.9) [6.1, 13.0]
Sex, Male, n (%)	19 (52.8)	9 (52.9)	17 (50.0)	9 (52.9)
Height (cm), mean (SD)	96.2 (9.3)	96.5 (6.7)	102.3 (9.4)	100.4 (6.1)
Achondroplasia-specific height Z-score, mean (SD)	0.27 (0.90)	-0.10 (0.72)	0.61 (0.89)	-0.03 (0.66)
CDC-based height Z-score, mean (SD)	-4.96 (0.99)	-5.40 (0.93)	-4.76 (0.95)	-5.44 (0.78)
AGV (cm/year), observed mean (SD)	3.45 (1.67)	3.65 (1.28)	5.84 (0.95)	3.88 (1.1)

At the start of the OLE, AGV and height Z-scores reflected the positive effect of navepegritide on growth outcomes in the double-blind period

AGV, annualized growth velocity; CDC, Centers for Disease Control and Prevention; OLE, Open-Label Extension

Annualized Growth Velocity (AGV) at Week 52

Savarirayan R, et al. Once-Weekly Navepegritide In Children With Achondroplasia: The APPROACH Randomized Trial. *JAMA Pediatrics* 2026;180;(1):18-25.

Primary Endpoint analysis
All children

AGV at Week 52, cm/year	**navepegritide n=57**	**placebo n=27**
LS Mean [95% CI]	**5.89** [5.66, 6.13]	**4.41** [4.04, 4.77]
LS Mean Difference [95% CI] Navepegritide vs. Placebo	**+1.49** [1.05, 1.93] p <0.0001	

Navepegritide was superior to placebo for the primary endpoint of AGV at Week 52

Note: ANCOVA model includes treatment, stratification factor, baseline age and baseline achondroplasia-specific height Z-score as covariates. Missing height data at Week 52 for 2 participants in the navepegritide group were imputed using the multiple imputation method.
AGV, annualized growth velocity; CI, confidence interval; LS, least squares

Annualized Growth Velocity (AGV) at Week 52

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	Primary Endpoint analysis **All children**		*Subgroup analysis* **Children aged ≥5 years at enrollment**	
AGV at Week 52, cm/year	**navepegritide n=57**	**placebo n=27**	**navepegritide n=36**	**placebo n=17**
LS Mean [95% CI]	**5.89** [5.66, 6.13]	**4.41** [4.04, 4.77]	**5.79** [5.51, 6.07]	**4.02** [3.54, 4.49]
LS Mean Difference [95% CI] Navepegritide vs. Placebo	**+1.49** [1.05, 1.93] p <0.0001		**+1.78** [1.22, 2.33] p <0.0001	

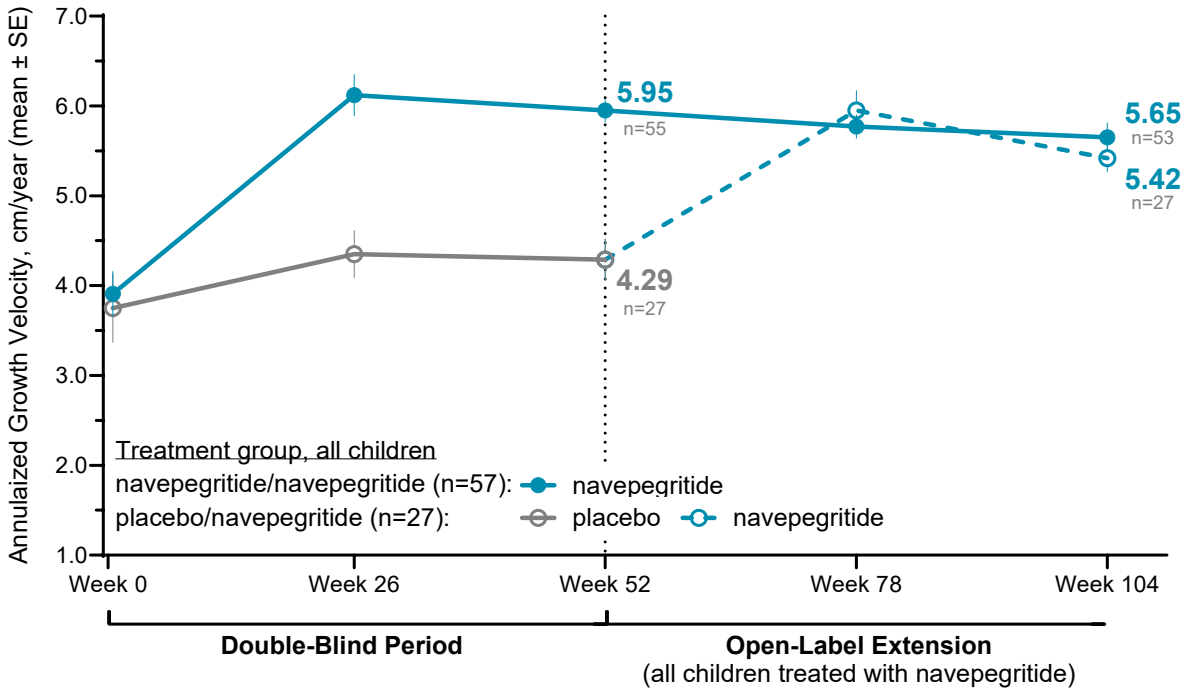
Navepegritide was superior to placebo for the primary endpoint of AGV at Week 52

Navepegritide-treated children aged ≥5 years also had significantly higher AGV at Week 52

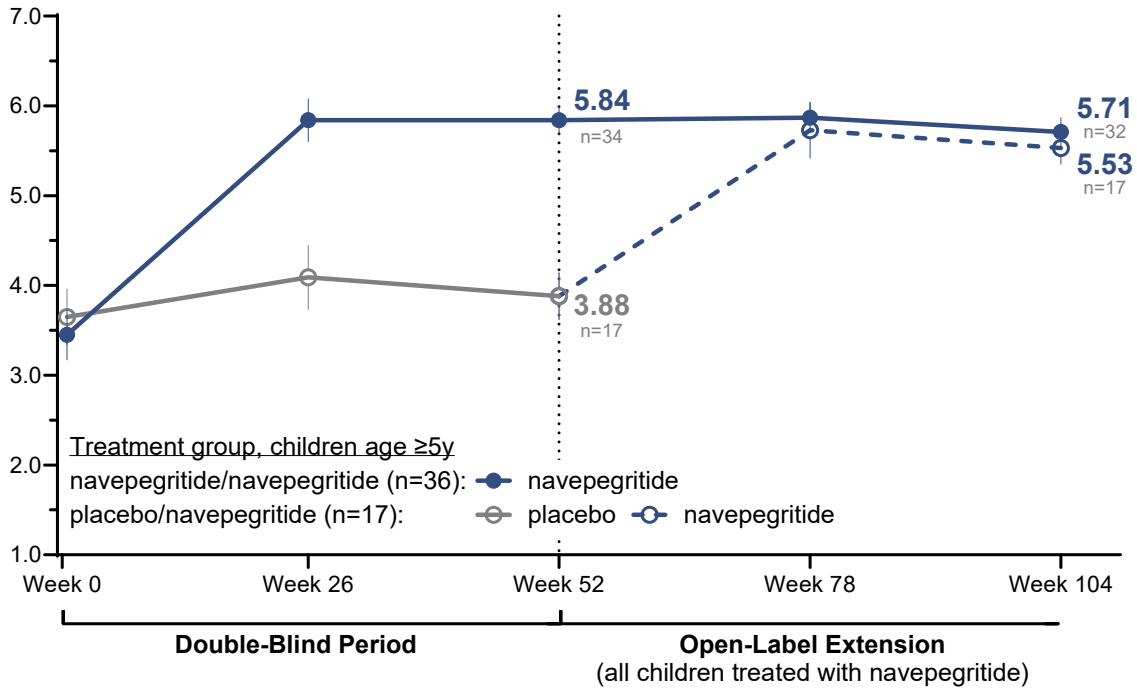
Note: ANCOVA model includes treatment, stratification factor, baseline age and baseline achondroplasia-specific height Z-score as covariates. Missing height data at Week 52 for 2 participants in the navepegritide group were imputed using the multiple imputation method.
AGV, annualized growth velocity; CI, confidence interval; LS, least squares

Observed AGV Through Week 104

All children



Children aged ≥5 years at enrollment

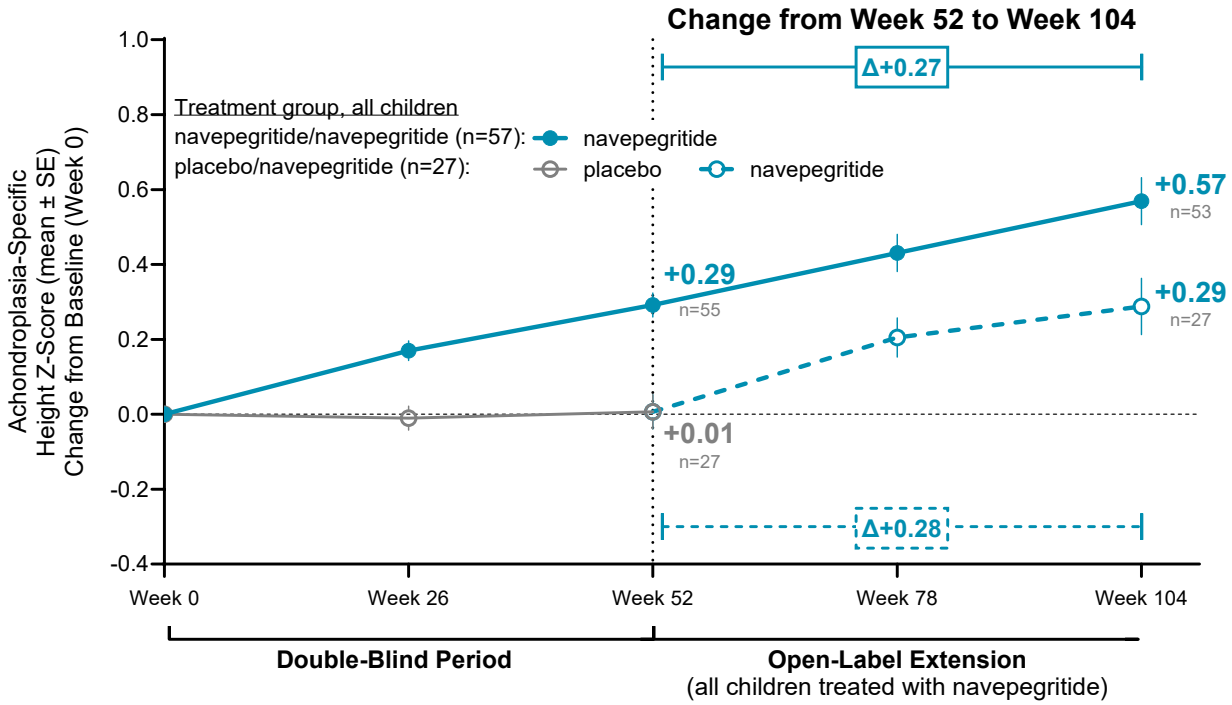


Improvements in AGV with navepegritide treatment were maintained through Week 104 of the OLE

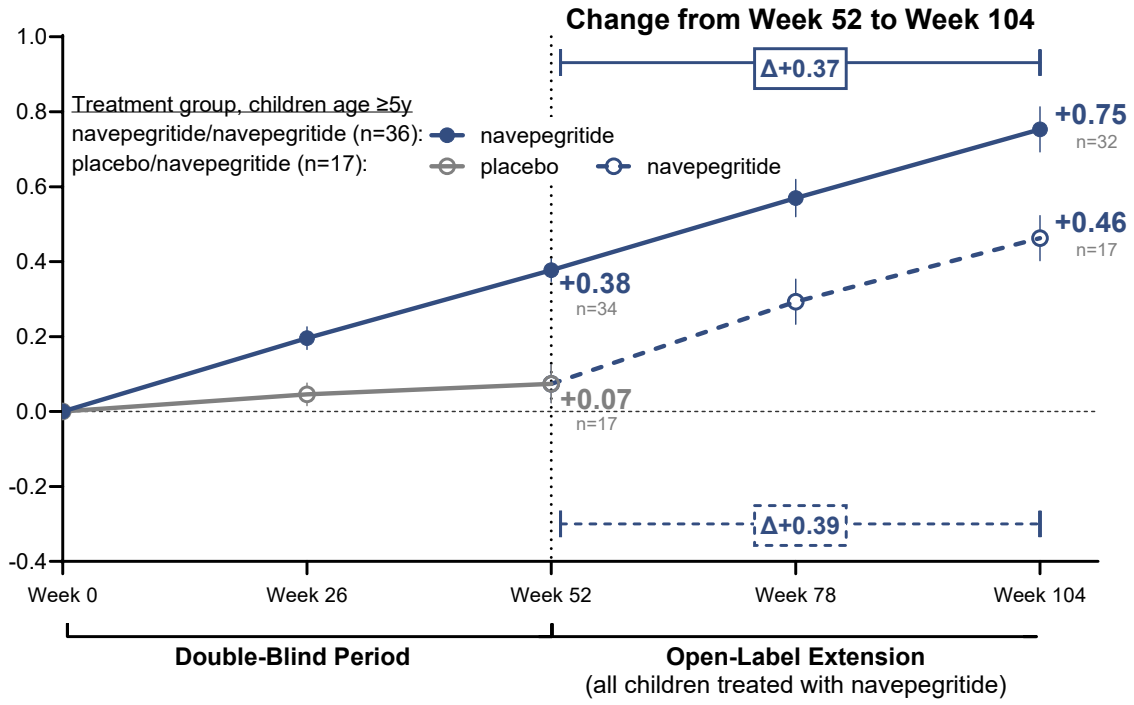
Note: Data shown are observed mean (±SE) AGV.
AGV, Annualized Growth Velocity; OLE, open-label extension

Change in Achondroplasia-Specific Height Z-score

All children



Children aged ≥5 years at enrollment

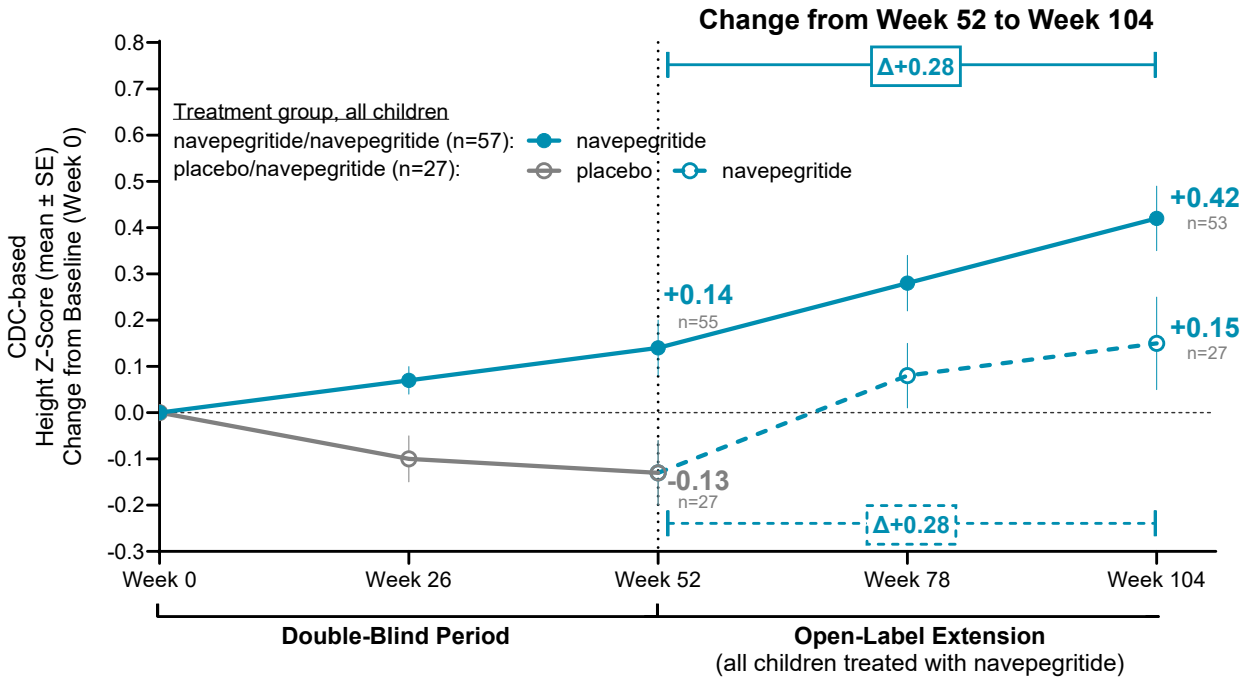


Achondroplasia-specific height Z-scores continued to improve with navepegritide in the OLE, with greater gains observed in children ≥5 years of age relative to the overall population

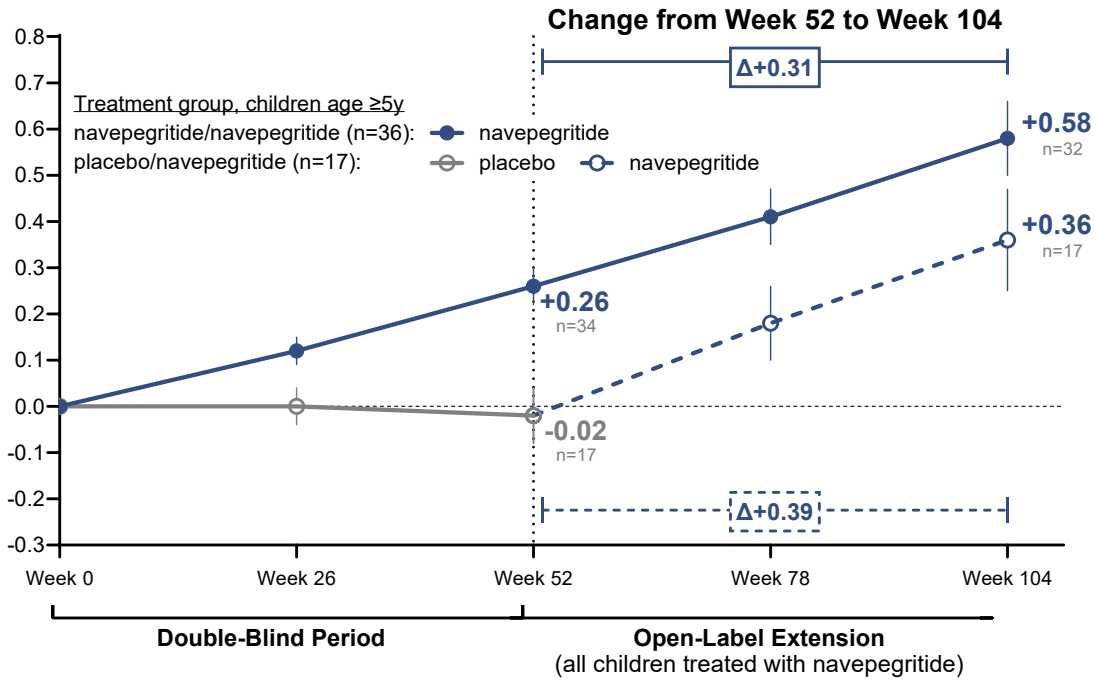
Note: Data shown are observed mean (±SE) change from trial baseline.
OLE, open-label extension

Change in CDC-Based Height Z-score

All children



Children aged ≥5 years at enrollment



Improvements in CDC-based height Z-scores with navepegritide treatment were more pronounced in children ≥5 years of age

Note: Data shown are observed mean (±SE) change from trial baseline.

Safety and Tolerability Through 104 Weeks

	All navepegritide-treated children (N=84)
Treatment exposure	**137.1 person-years**
Adverse events (AE) through Week 104	**n (%)**
Any treatment-emergent AE	76 (90.5)
Treatment-related AEs	19 (22.6)
Injection site reaction (ISR)	17 (20.2)
Serious AEs (SAE)	3 (3.6)
Treatment-related SAEs	0 (0.0)

- Overall rate of ISRs was low, and all ISRs were mild
  - 0.35 ISRs per person-year of exposure (equivalent to approx. 1 ISR for every 3 years of treatment)
- No symptomatic hypotension occurred through 104 weeks
- Bone maturation did not accelerate with navepegritide treatment

Most adverse events in navepegritide-treated children were mild or moderate, with none leading to treatment discontinuation or withdrawal from the trial

n = number of participants with observation

Most Common AEs

	All navepegritide-treated children (N=84)	Navepegritide-treated children aged ≥5 years at enrollment (N=53)
Treatment exposure	**137.1 person-years**	**84.9 person-years**
Adverse events (AEs) through Week 104	**n (%)**	**n (%)**
Any treatment-emergent AE	76 (90.5)	47 (88.7)
Most frequent AEs (≥15% of participants)		
Otitis media	31 (36.9)	18 (34.0)
Nasopharyngitis	29 (34.5)	20 (37.7)
Pyrexia	29 (34.5)	13 (24.5)
Upper respiratory tract infection	19 (22.6)	9 (17.0)
Headache	17 (20.2)	12 (22.6)
Vomiting	16 (19.0)	8 (15.1)
Influenza	13 (15.5)	7 (13.2)
Arthralgia	10 (11.9)	9 (17.0)

The safety profile of navepegritide in children ≥ 5 years of age was similar to that in the full trial population

n = number of participants with observation
AE, adverse event

Conclusions

- Improvements in AGV with navepegritide treatment were sustained through Week 104 of the ApproaCH Trial
- Height Z-scores continued to increase through Week 104 with ongoing navepegritide treatment
- Children aged 5 years or older at the time of enrollment experienced more pronounced gains in growth outcomes relative to the overall population
- The safety and tolerability profile of navepegritide remained consistent with that observed for placebo

Results from the ApproaCH Trial support the efficacy and safety of navepegritide through up to 104 weeks of treatment

AGV, annualized growth velocity

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