Growth Outcomes and Safety of Navepegritide in Children with Achondroplasia: Results of the ApproaCH Trial Open-Label Extension

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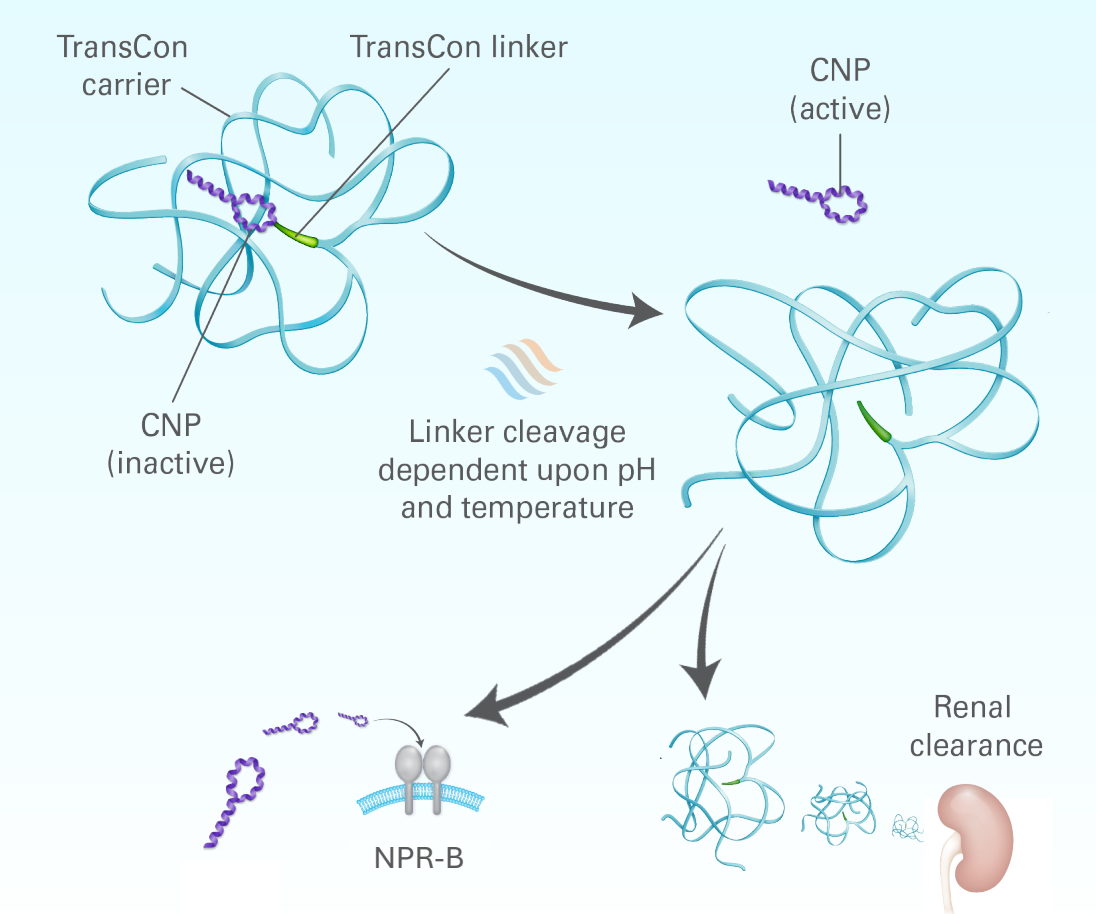
Navepegritide (TransCon® CNP)

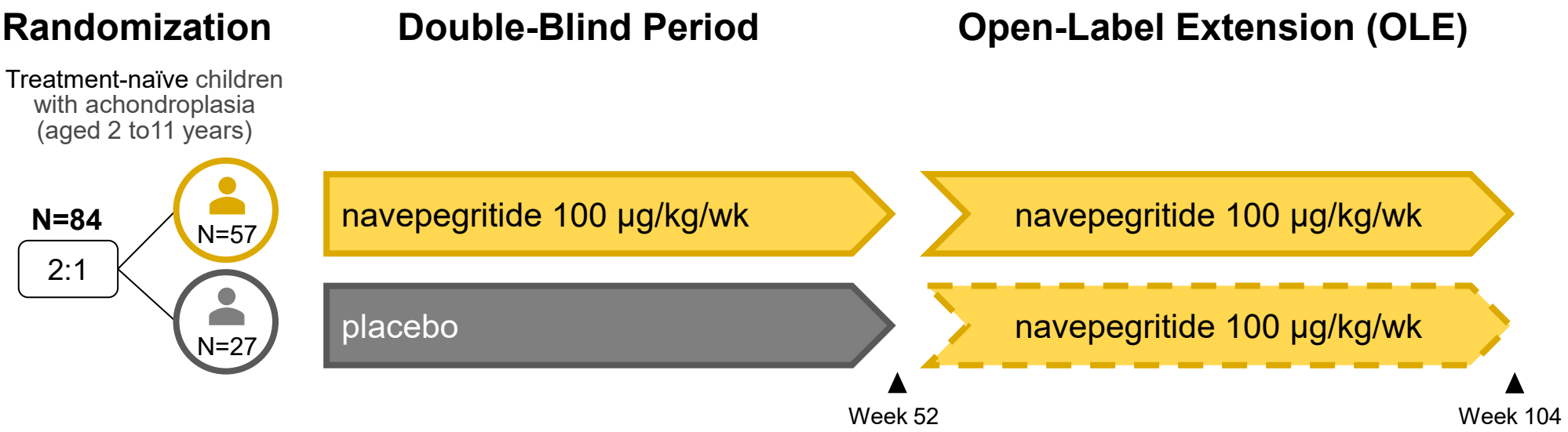


- Navepegritide is prodrug of CNP administered once weekly and designed to provide continuous exposure to active CNP (amino acid sequence identical to endogenous CNP [89-126])
- Active CNP released from navepegritide binds to NPR-B throughout the body to counteract the constitutively active FGFR3 signaling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

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

Breinholt VM, et al. *J Pharmacol Exp Ther* 2019;370(3):459-471.

ApproaCH Trial Design



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

Key Secondary Endpoints: Change from baseline in achondroplasia-specific and CDC-based **height Z-scores**

Safety and Tolerability Assessments: Treatment emergent adverse events (TEAEs) and bone age

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

ApproaCH Primary Endpoint: Annualized Growth Velocity (AGV) at Week 52

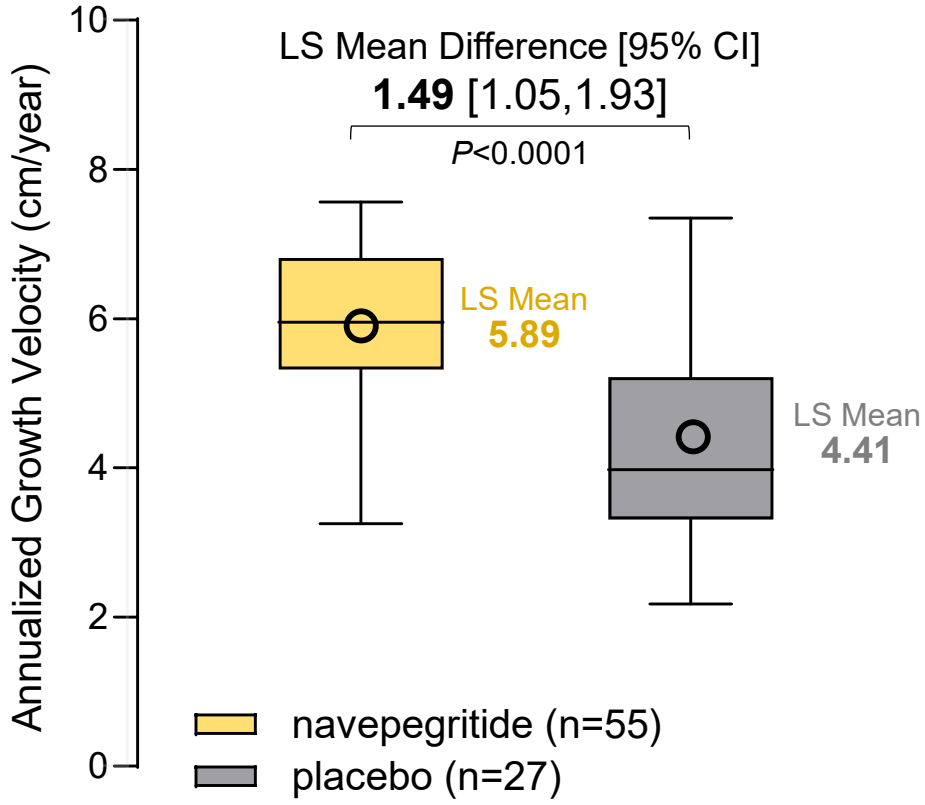
Results from the double-blind period demonstrated superiority of once-weekly navepegritide over placebo for AGV at Week 52

JAMA Pediatrics

Original Investigation

Once-Weekly Navepegritide in Children With Achondroplasia
The APPROACH Randomized Clinical Trial

Savarirayan R, et al. *JAMA Pediatr* 2026;180;(1):18-25.
doi:10.1001/jamapediatrics.2025.4771



Note: Box-and-whisker plots derived using observed data at Week 52 and display the 75th and 25th percentile (box edges), IQR (colored area), median (midline), and minimum and maximum observed values; labeled circles represent least squares mean values. 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; IQR, interquartile range; LS, least squares

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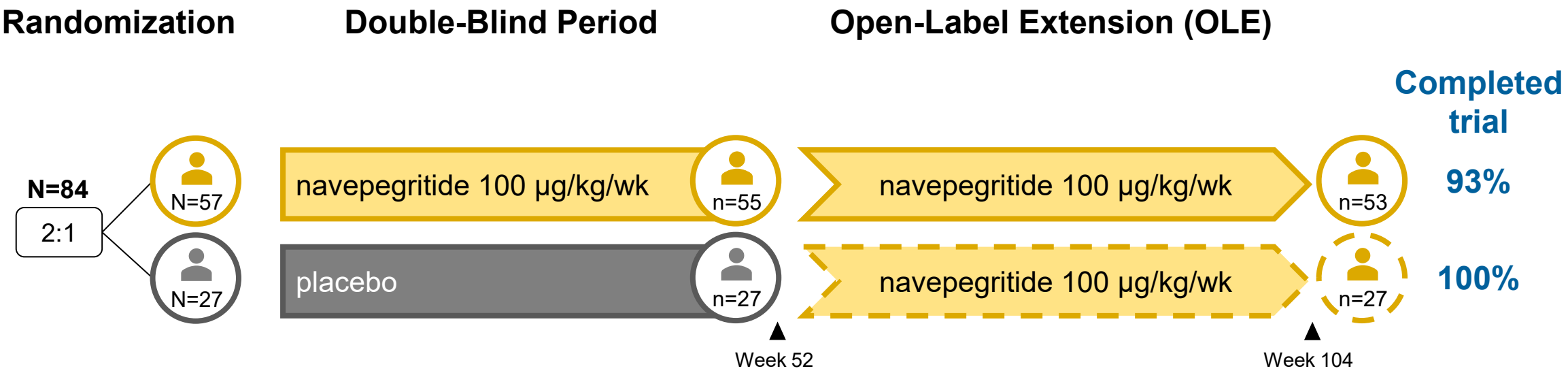
ApproaCH Trial Disposition



N = number of participants that received at least one dose of investigational medicinal product; n=number of participants that received at least one dose and completed the respective trial period. In the navepegritide group, 2 participants withdrew in the double-blind period (both were withdrawn by parent/guardian), and 2 participants discontinued treatment during the OLE (1 was lost to follow-up; 1 was withdrawn by parent/guardian).
OLE, Open-Label Extension

ApproaCH Trial Participant Characteristics

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

Demographics and clinical characteristics at the start of the OLE (Week 52)	navepegritide/navepegritide (N=55)	placebo/navepegritide (N=27)	Total population (N=82)
Age (years), mean (SD) [min, max]	6.6 (2.7) [3.0, 13.0]	7.0 (2.8) [3.1, 13.0]	6.8 (2.7) [3.0, 13.0]
Sex, Male, n (%)	29 (52.7)	14 (51.9)	43 (52.4)
Height (cm), mean (SD)	94.7 (13.0)	93.3 (10.8)	94.3 (12.3)
Achondroplasia-specific height Z-score, mean (SD)	0.44 (0.97)	-0.11 (0.73)	0.26 (0.93)
CDC-based height Z-score, mean (SD)	-4.81 (1.03)	-5.35 (0.87)	-4.99 (1.01)
AGV (cm/year), observed mean (SD)	5.95 (0.99)	4.29 (1.21)	5.40 (1.32)

N = number of participants that received at least one dose of investigational medicinal product
AGV, annualized growth velocity; CDC, Centers for Disease Control and Prevention; OLE, Open-Label Extension

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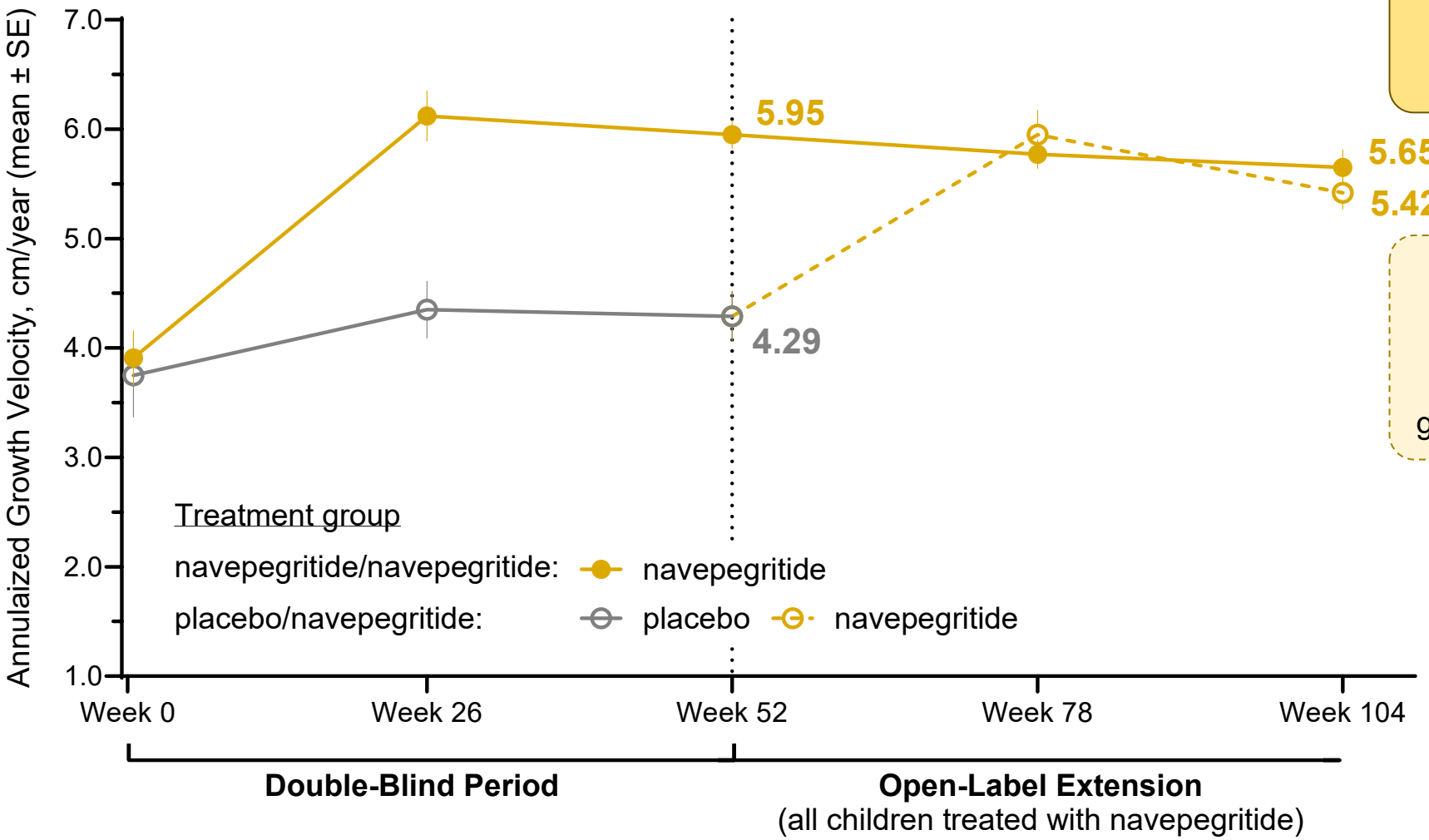
Annualized Growth Velocity (AGV) through Week 104



Children continuing navepegritide in the Open-Label Extension maintained AGV through 104 weeks

Children who switched from placebo to navepegritide at Week 52 had increased AGV at Week 104, comparable to navepegritide-related gains observed in the double-blind period

Note: Data shown are observed mean (±SE) Annualized Growth Velocity (AGV).

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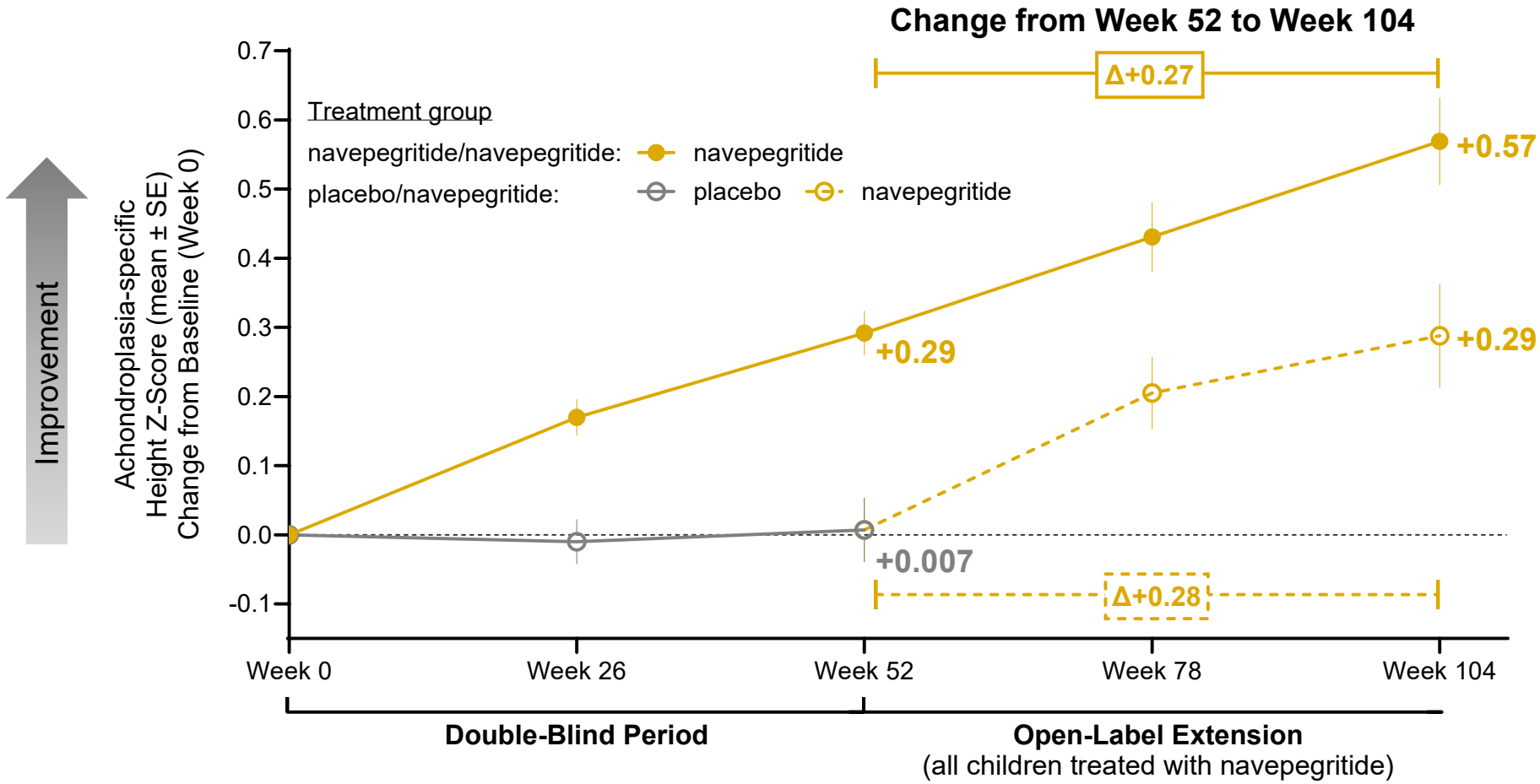
Change in ACH-specific Height Z-score

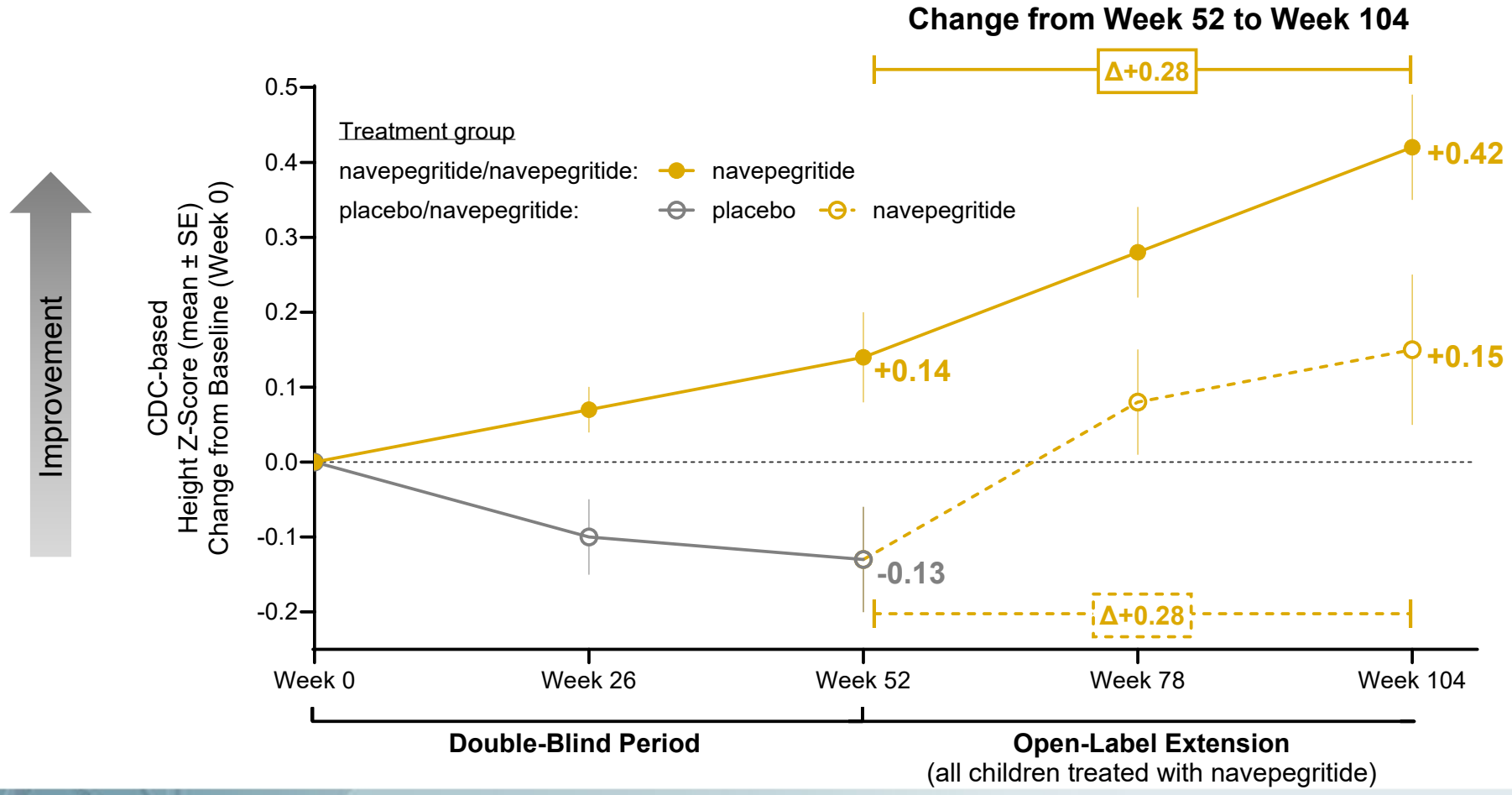
In the Open-Label Extension, ACH-specific height Z-score increased with navepegritide treatment, consistent with navepegritide-related improvements seen in the double-blind period



ACH, achondroplasia

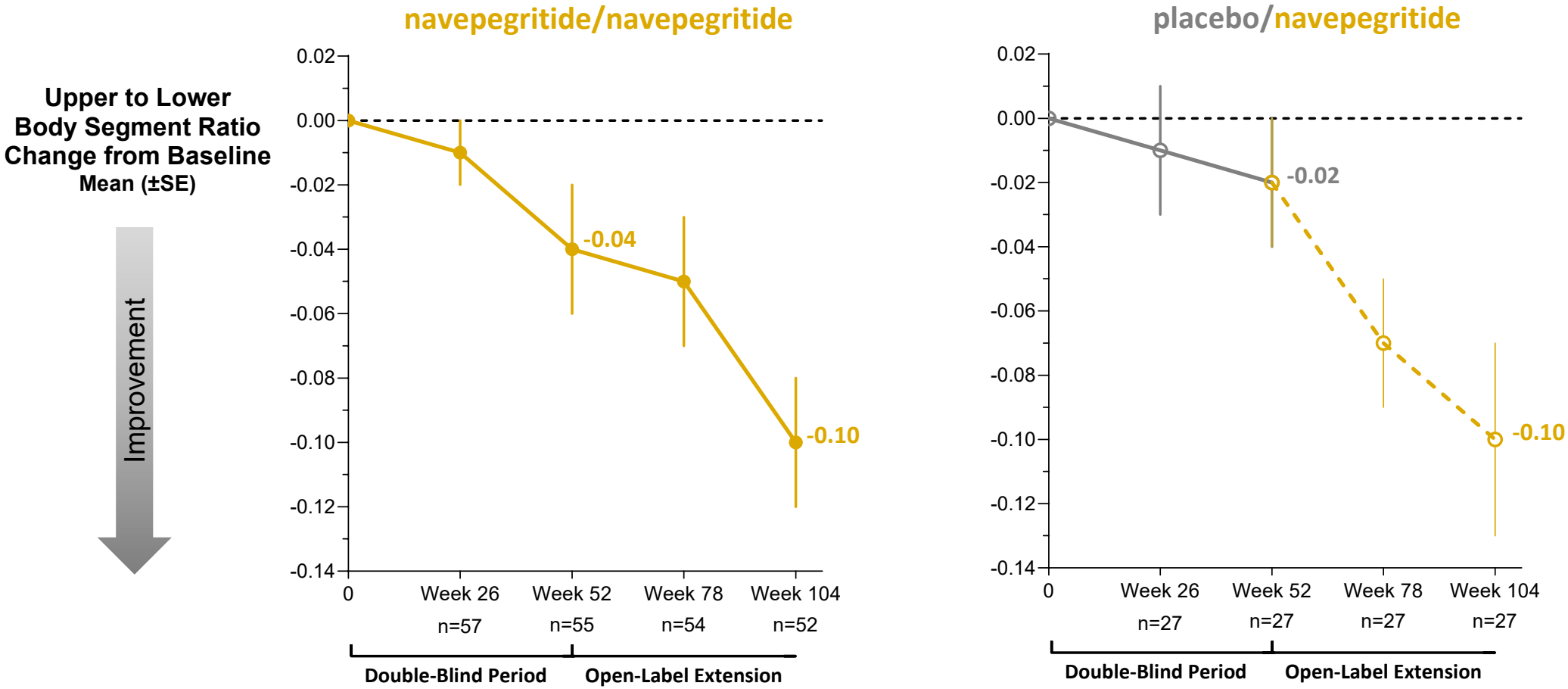
Change in CDC-based Height Z-score

CDC-based height Z-score improved with navepegritide treatment in the double-blind period, and continued to increase with navepegritide treatment in the Open-Label Extension



Change in Upper-to-Lower Body Segment Ratio

In the Open-Label Extension, numeric improvement was observed in both groups, indicating promotion of proportional growth with navepegritide treatment



Safety and Tolerability Through 104 Weeks

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

	Total navepegritide-treated population (N=84)
Treatment exposure	**137.1 person-years**
Events through Week 104	**n (%)**
Any Treatment-Emergent Adverse Event (AE)	76 (90.5)
Grade 1 (Mild)	74 (88.1)
Grade 2 (Moderate)	39 (46.4)
Grade 3 (Severe)	7 (8.3)
Grade 4 (Life-threatening) or 5 (Death)	0 (0.0)
Treatment-related AEs	19 (22.6)
Injection Site Reaction (ISR)	17 (20.2)
Serious Adverse Events (SAE)	3 (3.6)
Treatment-related SAEs	0 (0.0)
Symptomatic hypotension	0 (0.0)

- The overall rate of ISRs was low, and all events were mild
  - 0.35 ISRs per person-year of exposure is equivalent to approx. 1 ISR for every 3 years of treatment
- No symptomatic hypotension occurred through up to 104 weeks of navepegritide treatment

n = number of participants with observation.

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Bone Health During the Open-Label Extension

Bone maturation did not accelerate with navepegritide treatment, and no fractures related to treatment were observed in the Open-Label Extension

	navepegritide/navepegritide (N=55)		placebo/navepegritide (N=27)	
Ratio of Bone Age to Chronological Age	N	Mean (SE)	n	Mean (SE)
Week 52 (start of Open-Label Extension)	55	0.84 (0.02)	27	0.85 (0.03)
Week 104	53	0.91 (0.02)	27	0.92 (0.02)
Change from Week 52 to Week 104	53	0.07 (0.02)	27	0.07 (0.02)

- There were 2 fractures reported in the Open-Label Extension
  - Both fractures were associated with trauma, and neither was considered by the investigator to be related to study treatment

Note: Reported fractures were a clavicle fracture in a 2.1-year-old male participant, and a radius fracture in a 5.7-year-old female participant.

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Key Take-Aways

During the Open-Label Extension phase of the ApproaCH Trial

- Children continuing treatment with navepegritide maintained the elevated AGV observed during the double-blind period through Week 104
- Children who switched from placebo to navepegritide at Week 52 exhibited increased AGV at Week 104, comparable to the navepegritide-related improvements seen in the double-blind period
- In both groups, achondroplasia-specific and CDC-based height Z-scores improved with navepegritide treatment; gains were consistent with those observed with navepegritide in the double-blind period
- Improvement in upper-to-lower body segment ratio with navepegritide treatment indicates promotion of proportional growth during the Open-Label Extension

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

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

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

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