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

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MED-US-CNP-2600030
April 2026

Presented at the 2026 Annual Meeting of the American College of Medical Genetics and Genomics, Baltimore, MD, USA, March 10-14, 2026.

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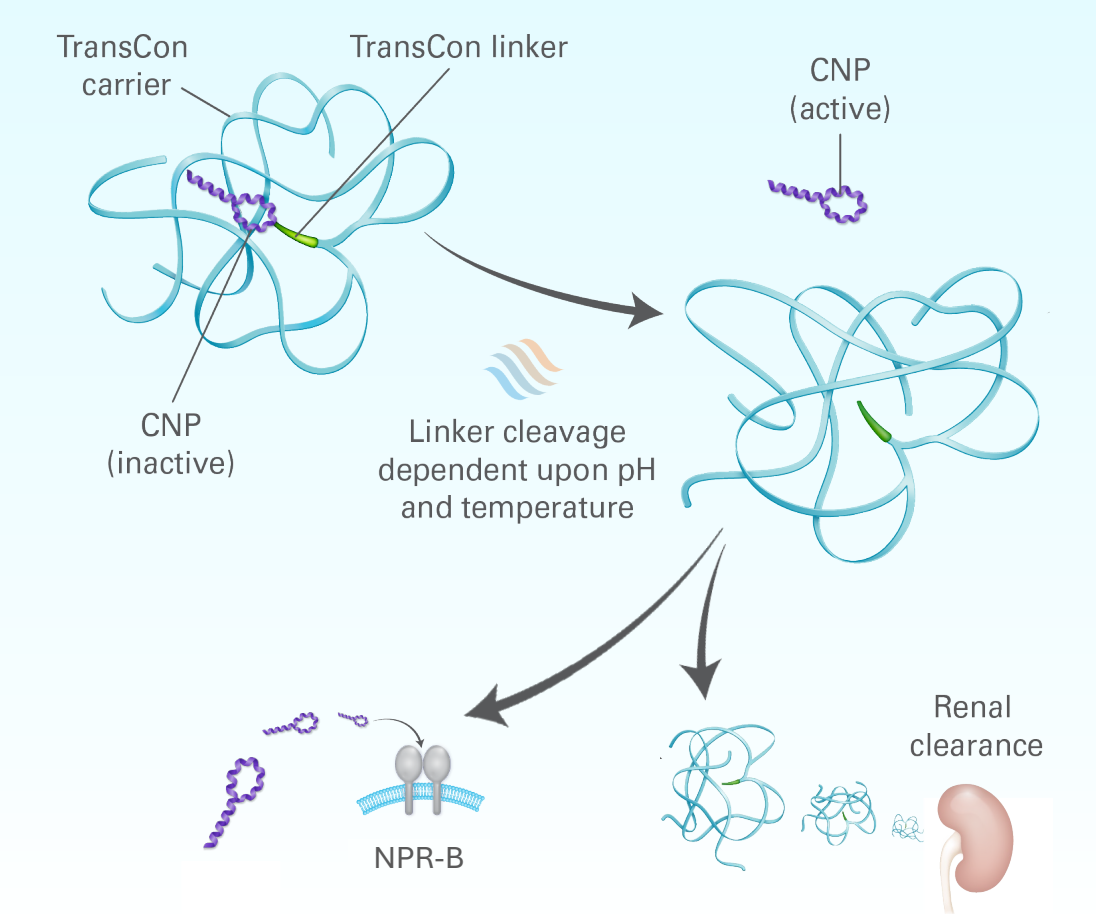
Navepegritide (TransCon® CNP)



- 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.

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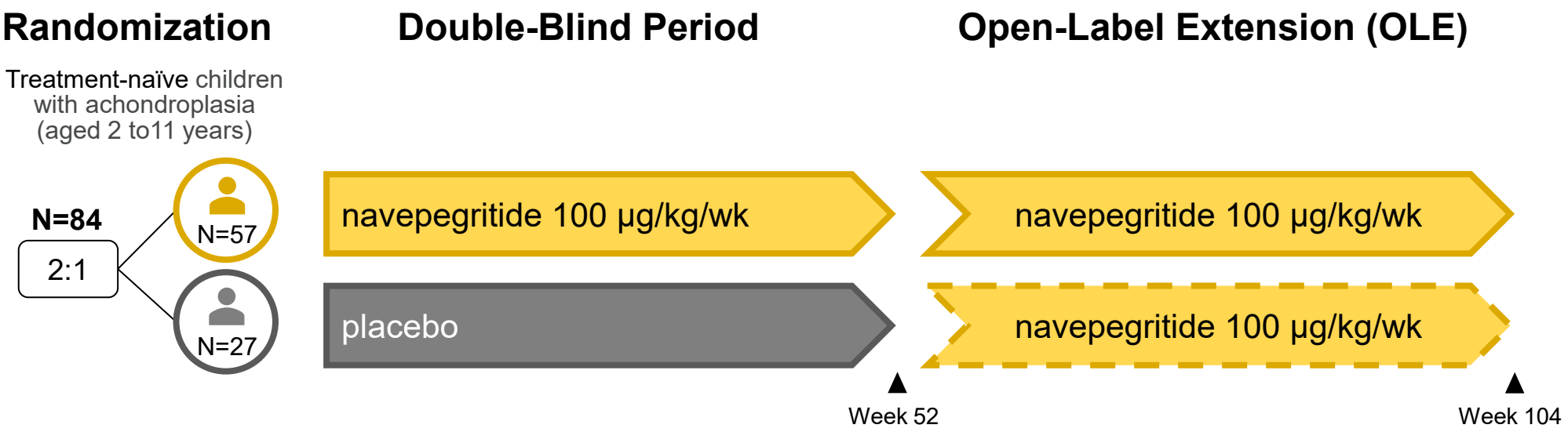
ApproaCH Trial Design



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

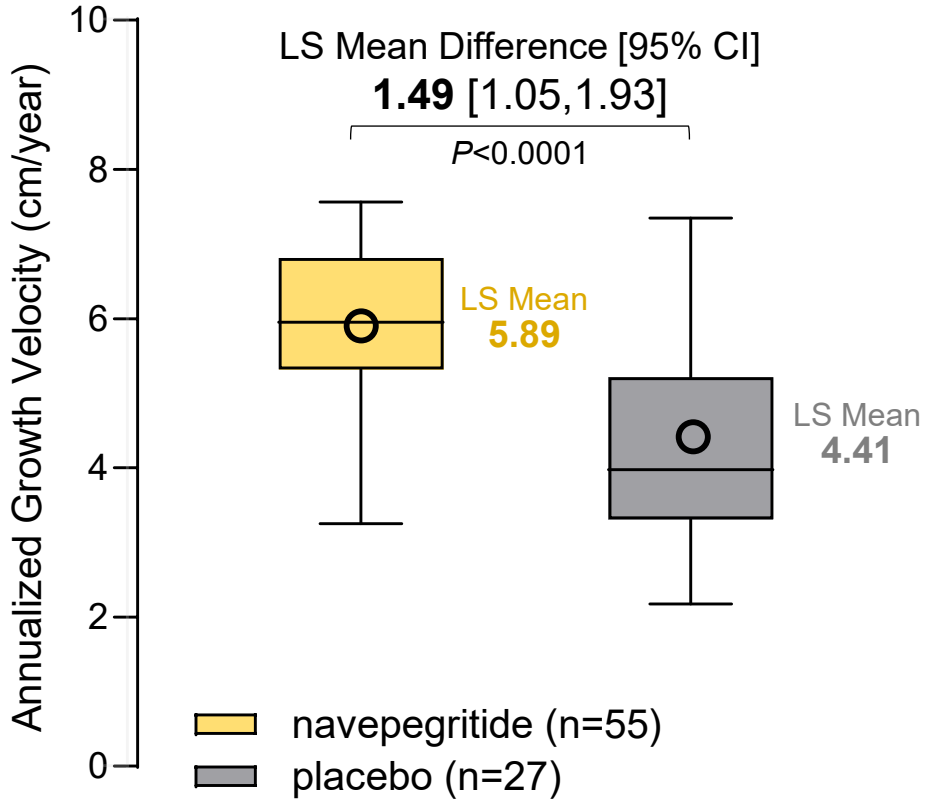
Results from the double-blind period demonstrated superiority of once-weekly navepegritide over placebo for AGV at Week 52

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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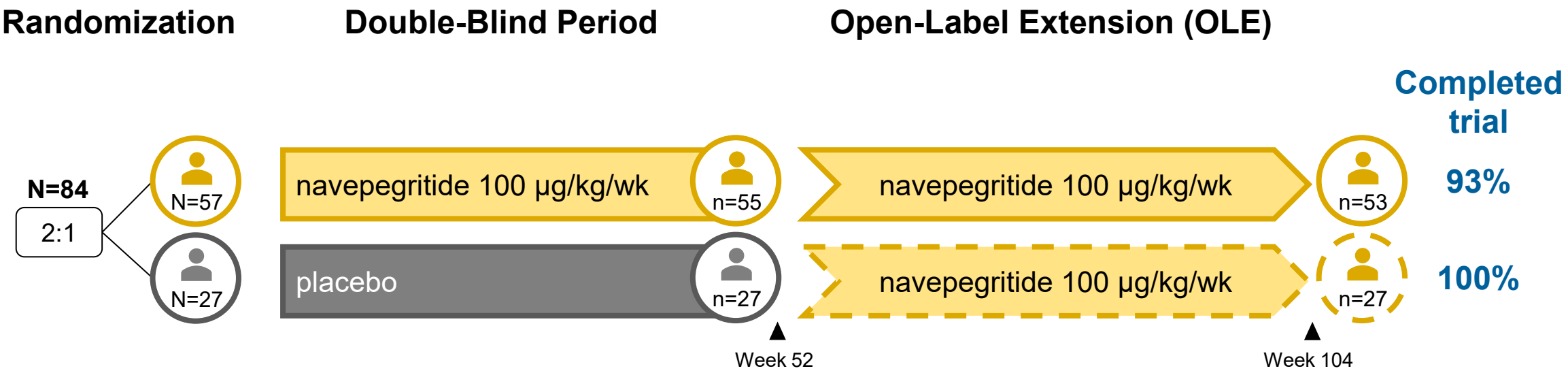
ApproaCH Trial Disposition



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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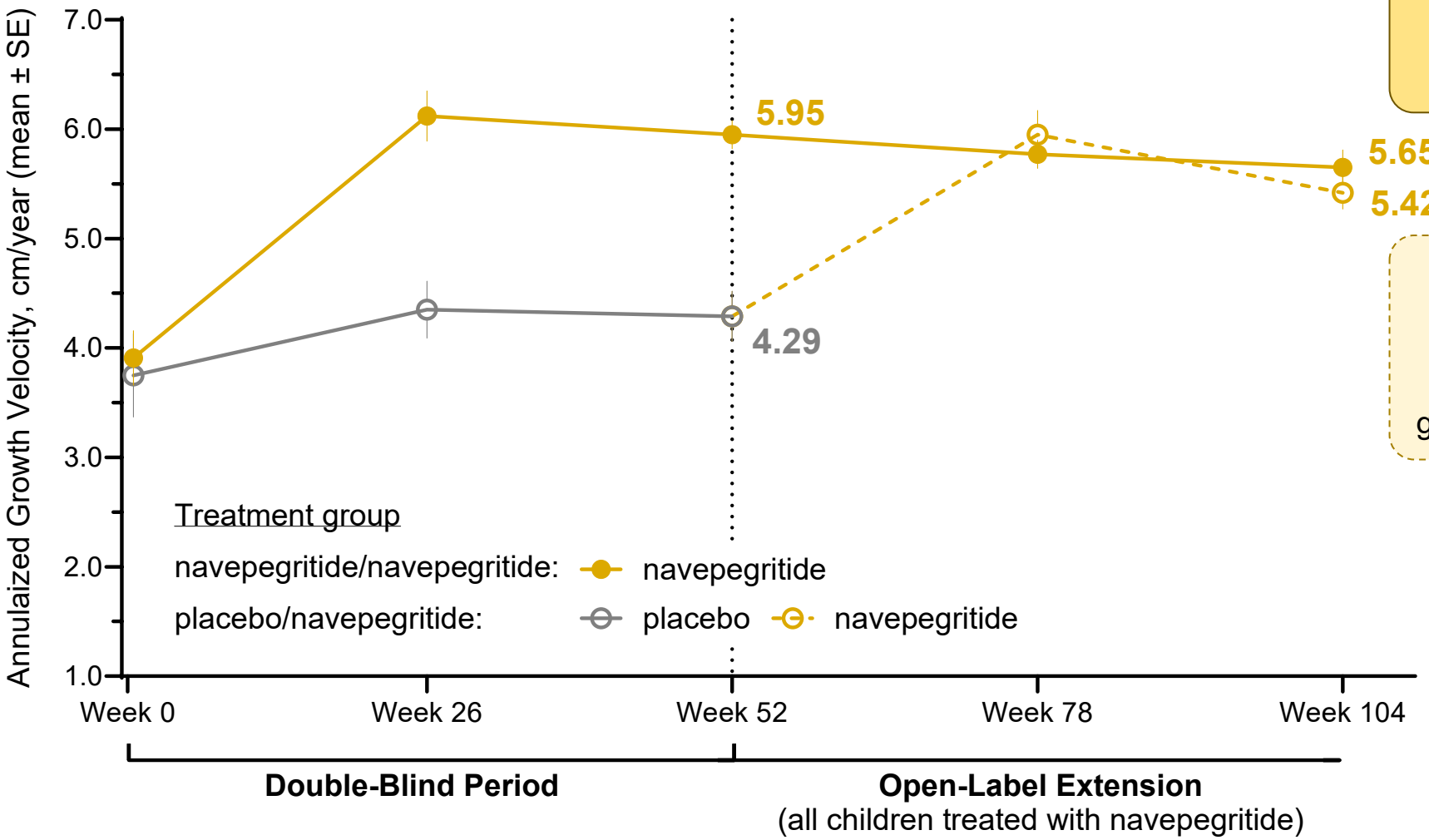
Annualized Growth Velocity (AGV) through Week 104



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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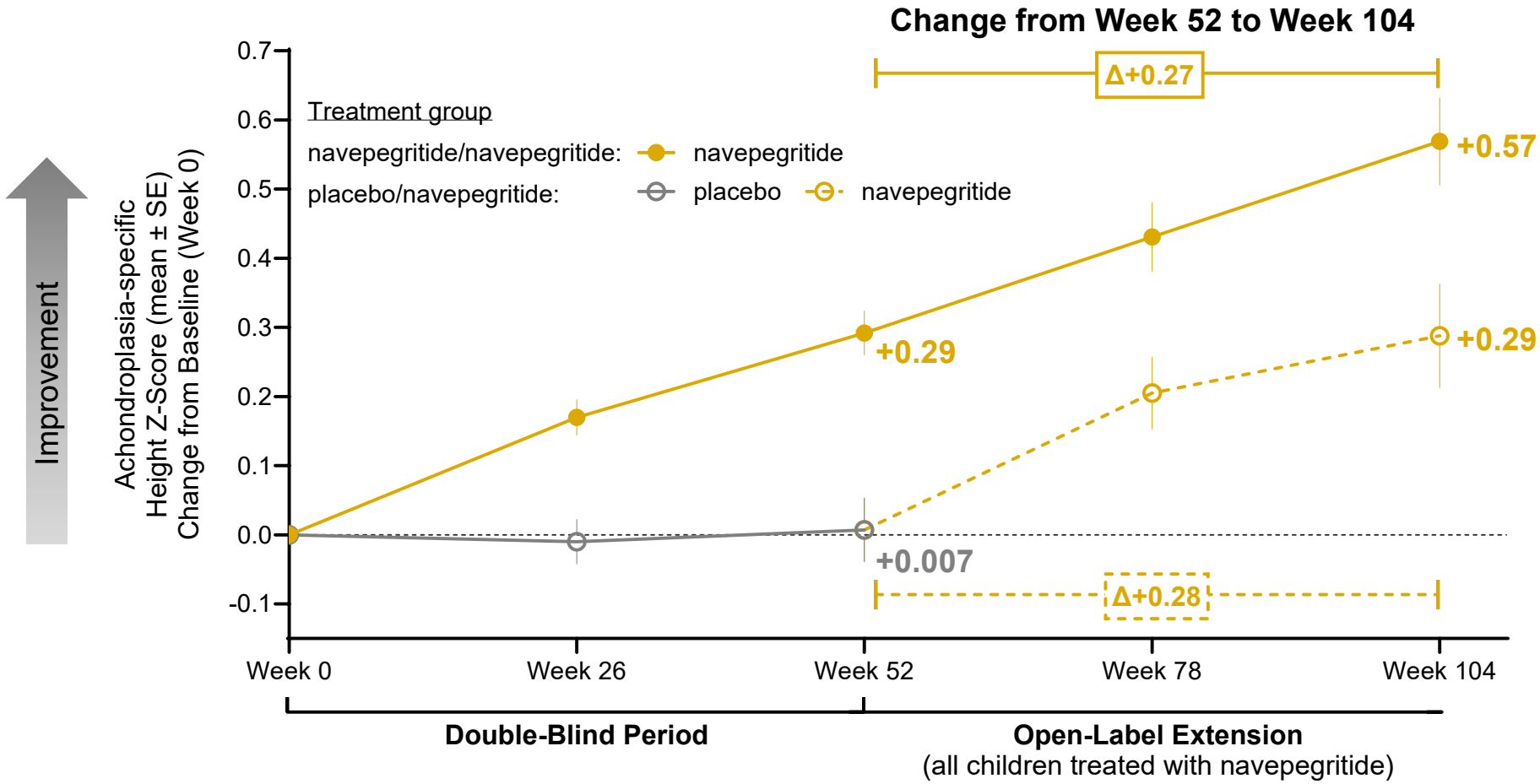
Change in ACH-specific Height Z-score

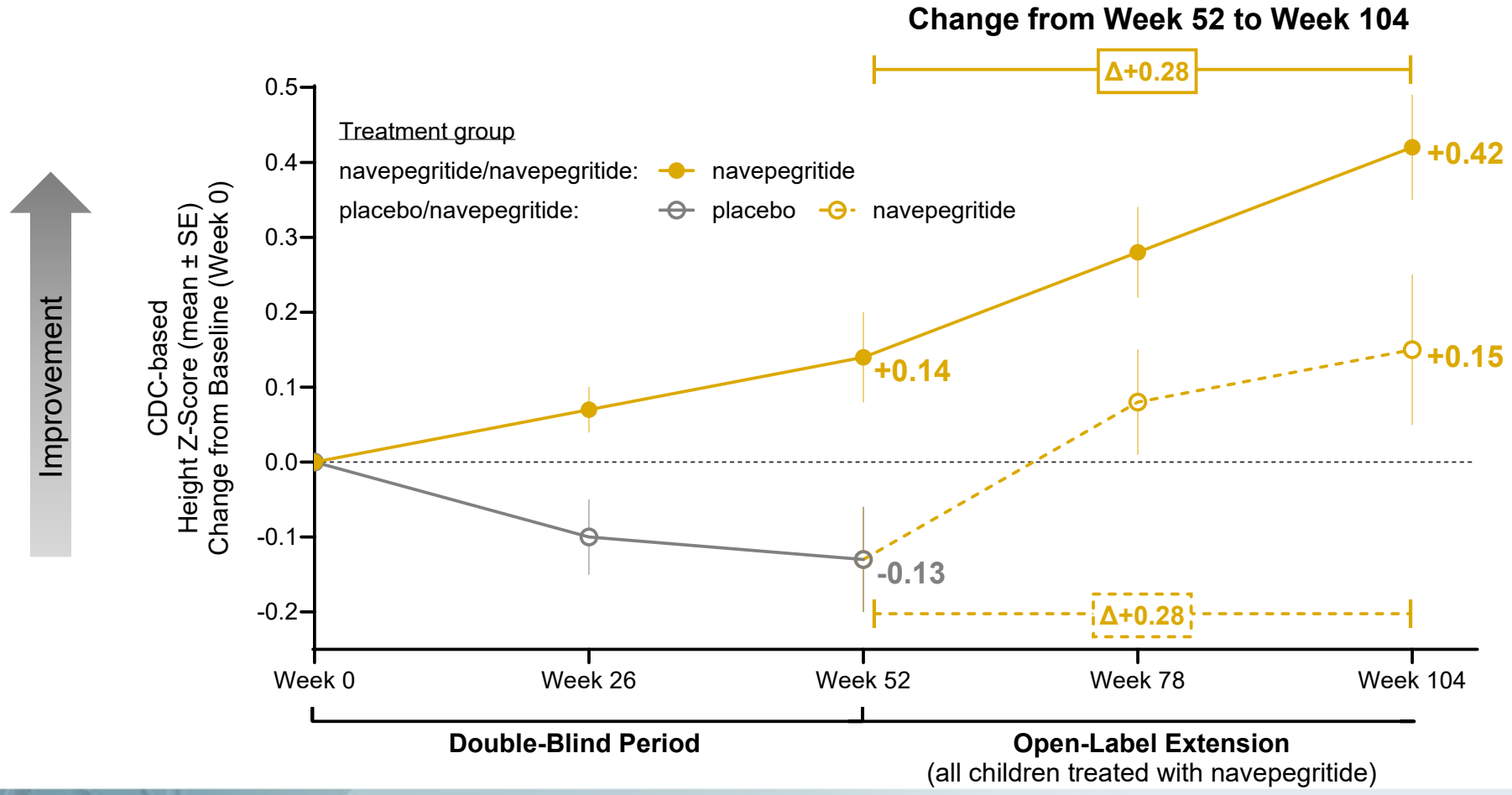
In the Open-Label Extension, ACH-specific height Z-score increased with navepegritide treatment, consistent with navepegritide-related improvements seen in the double-blind period



ACH, achondroplasia

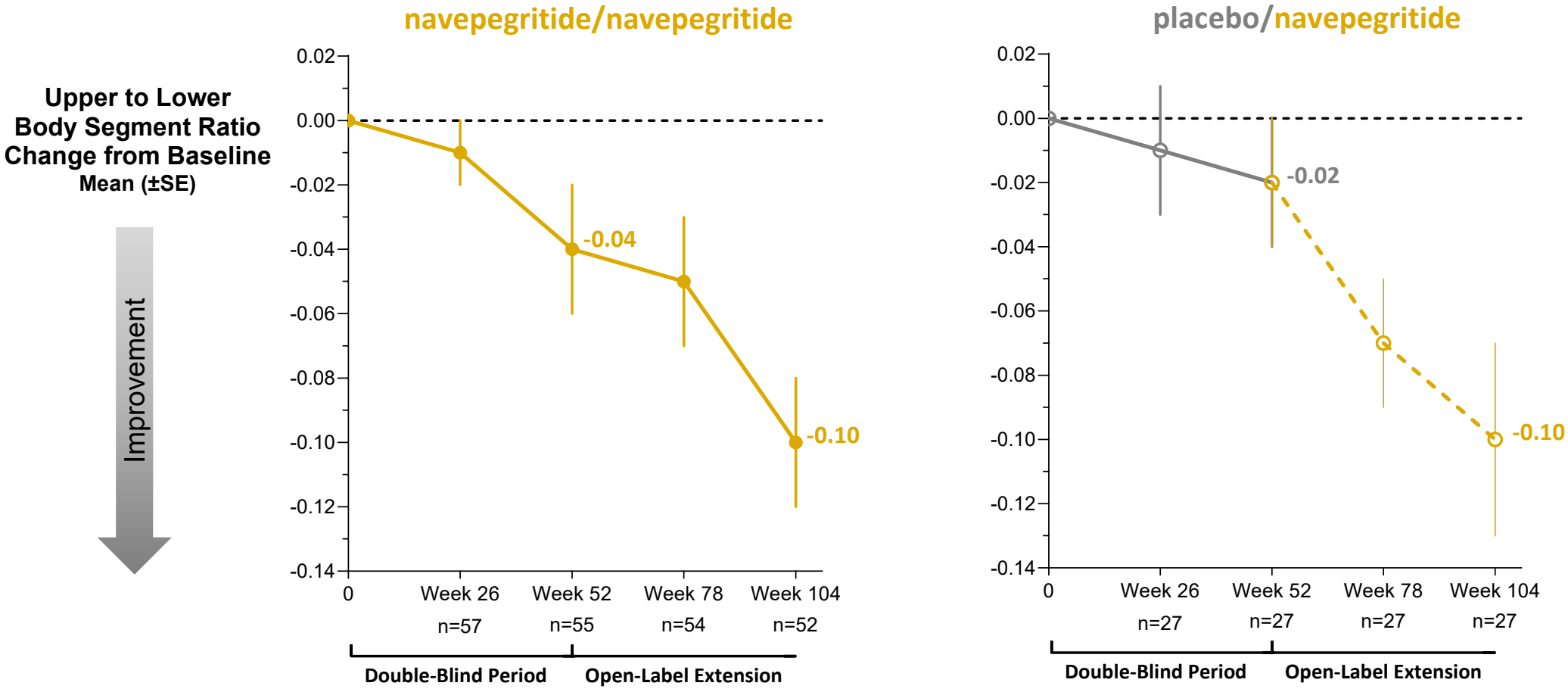
Change in CDC-based Height Z-score

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

Financial Disclosure

Ravi Savarirayan, MBBS, MD
Discloses the following relevant relationships with ineligible companies. Any potential interests have been mitigated.

- Consultant: Ascendis Pharma, BridgeBio Pharma, BioMarin Pharmaceuticals, Inc.
- Grant/Research Support: BioMarin Pharmaceuticals, Inc.

The ApproaCH Trial was funded by Ascendis Pharma A/S