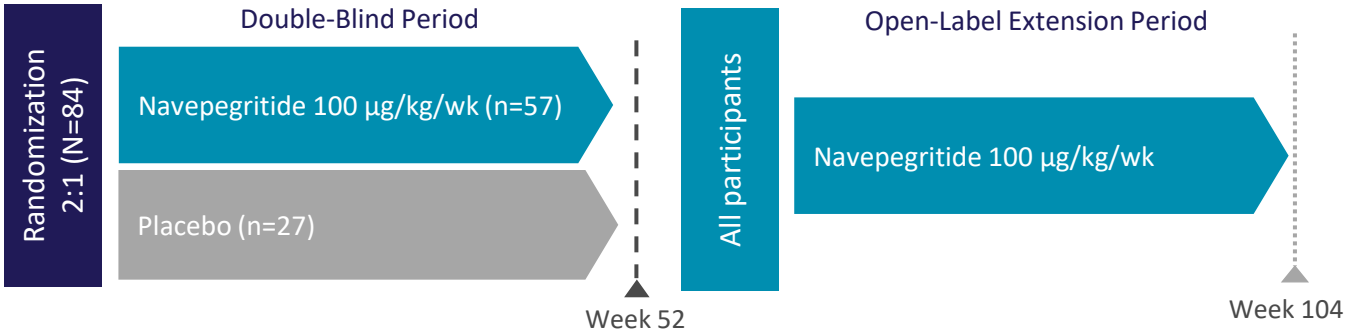
ApproaCH Trial

A pivotal randomized, double-blind, placebo-controlled, multicenter trial that evaluated the safety and efficacy of once-weekly navepegritide in children with achondroplasia aged 2 to 11 years



Primary & Select Secondary Endpoints

- AGV at Week 52
- Change from baseline in height Z-score at Week 52
- Change from baseline in HRQoL at Week 52 (ACEM-PF, ACEM-DF, ACEM-OSM scores)

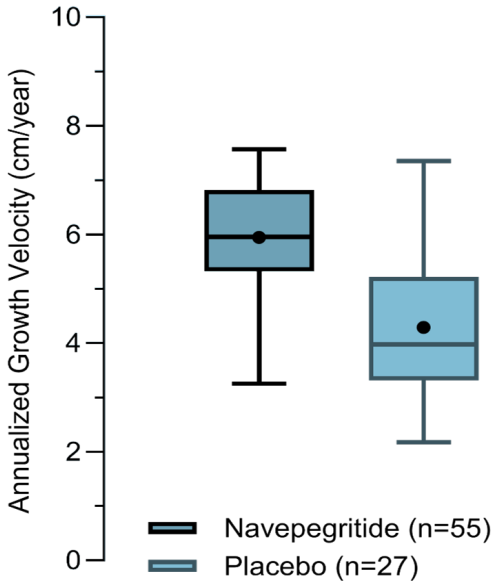
Exploratory Endpoints

- Measures of skeletal proportionality: upper-to-lower body segment ratio and fibula-to-tibia length ratio
- Degree of lower limb malalignment: TFA and MAD

Safety Endpoints

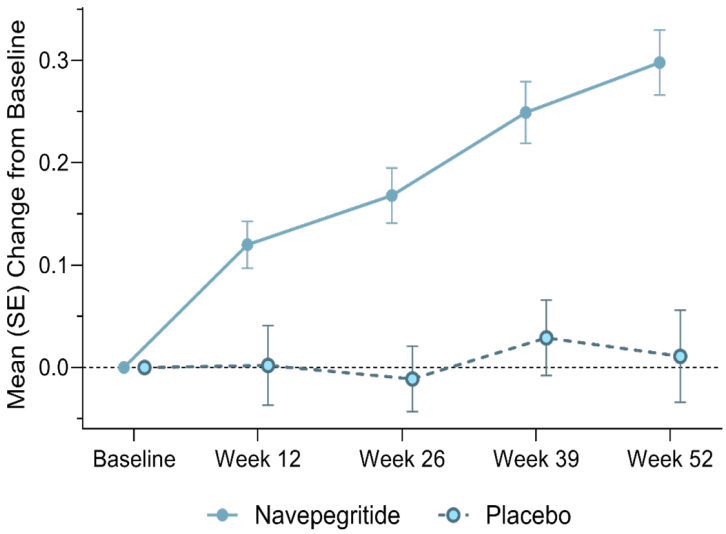
- TEAEs
- AESI: ISRs, symptomatic hypotension, and fractures
- Bone age
- Immunogenicity

AGV at Week 52



Treatment with navepegritide demonstrated superiority in AGV at Week 52 vs placebo (LS mean difference 1.49 cm/year; 95% CI 1.05 to 1.93; p<0.0001)

ACH-specific height Z-score



The LS mean difference between navepegritide and placebo in change from baseline at Week 52 was 0.28 for the ACH-specific height Z-score and 0.30 for the CDC-based height Z-score

AGV at Week 52 figure: Each plot displays the 75th and 25th percentile (box edges), IQR (colored area), median (midline), mean (black circles), and minimum and maximum observed values (whiskers) for each treatment arm

Abbreviations: ACEM, Achondroplasia Child Experience Measures; ACEM-DF, ACEM-Daily Living Functioning; ACEM-OSM, ACEM-Observable Signs Measure; ACEM-PF, ACEM-Physical Functioning; ACH, achondroplasia; AESI, adverse event of special interest; AGV, annualized growth velocity; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HRQoL, Health-related quality of life; ISRs, injection site reactions; LS, least squares; MAD, mechanical axis deviation; SE, standard error; TEAEs, treatment-emergent adverse events; TFA, tibial-femoral angle

Reference: Savarirayan R, et al. *JAMA Pediatr.* 2026;180(1):18–25.

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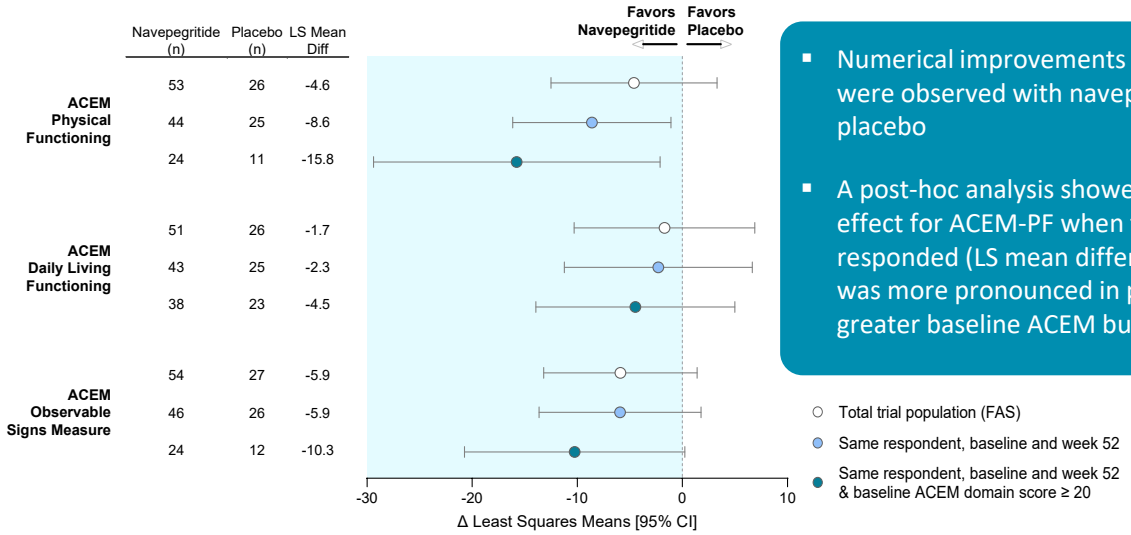
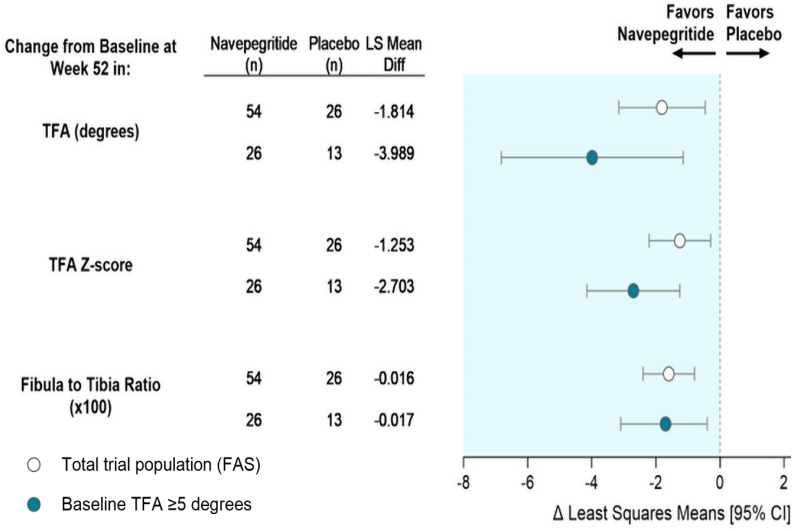
Change from baseline in HRQoL at Week 52



- Numerical improvements in key ACEM domains were observed with navepegritide compared with placebo
- A post-hoc analysis showed notable treatment effect for ACEM-PF when the same caregiver responded (LS mean difference of -8.61), which was more pronounced in participants with greater baseline ACEM burden (score ≥20)

Improvement in Proportional Growth and Lower Limb Alignment at Week 52

- Improvements in lower limb alignment demonstrated by a reduction in TFA (LS mean difference of -1.81°) and MAD (LS mean difference of -2.78 mm) compared with placebo
- The effect of navepegritide on TFA reduction at Week 52 was more pronounced in participants with greater baseline leg bowing (TFA ≥ 5°), showing a treatment difference of −3.99°
- After 52 weeks, the fibula-to-tibia length ratio was stable in the navepegritide group with a mean change from baseline of 0.001 in the navepegritide group, compared with 0.017 in the placebo group



Navepegritide showed a safety and tolerability profile comparable to placebo

No. %

Parameter	Navepegritide (n=57)	Placebo (n=27)
TEAE	52 (91.2)	26 (96.3)
Grade 1	52 (91.2)	25 (92.6)
Grade 2	16 (28.1)	11 (40.7)
Grade 3	4 (7.0)	1 (3.7)
Grade 4 or 5	0	0
SAE	3 (5.3)	3 (11.1)
Treatment-Related AEs, n (%)	12 (21.1)	7 (25.9)
Treatment-Related SAEs	0	0
AESI, n (%)		
ISR	11 (19.3)	4 (14·8)
ISR events per PYE	0.41	0.15
Symptomatic Hypotension	0	0
Fracture	0	0

- No AEs led to discontinuation of treatment or withdrawal from the trial
- All ISRs were transient and mild, and none led to changes in treatment or required medical intervention
- At Week 52, the mean bone age to chronological age ratio remained unchanged from baseline
- Anti-CNP (89-126) antibodies were transiently detected at a low level in 4 of 54 (7.4%) participants in the navepegritide group and did not influence pharmacokinetics, efficacy, or safety

Abbreviations: ACEM, Achondroplasia Child Experience Measure; ACEM-PF, ACEM-Physical Functioning; AEs, adverse events; AESI, adverse event of special interest; CI, confidence interval; Diff, difference; FAS, full analysis set; HRQoL, Health-related quality of life; ISRs, injection site reactions; LS, least squares; MAD, mechanical axis deviation; PYE, patient-year of exposure; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TFA, tibial-femoral angle

Reference: Savarirayan R, et al. *JAMA Pediatr.* 2026;180(1):18–25.