Continued Improvements in Lower Extremity Alignment in Navepegritide-Treated Children With Achondroplasia: Week 104 Results From the ApproaCH Trial

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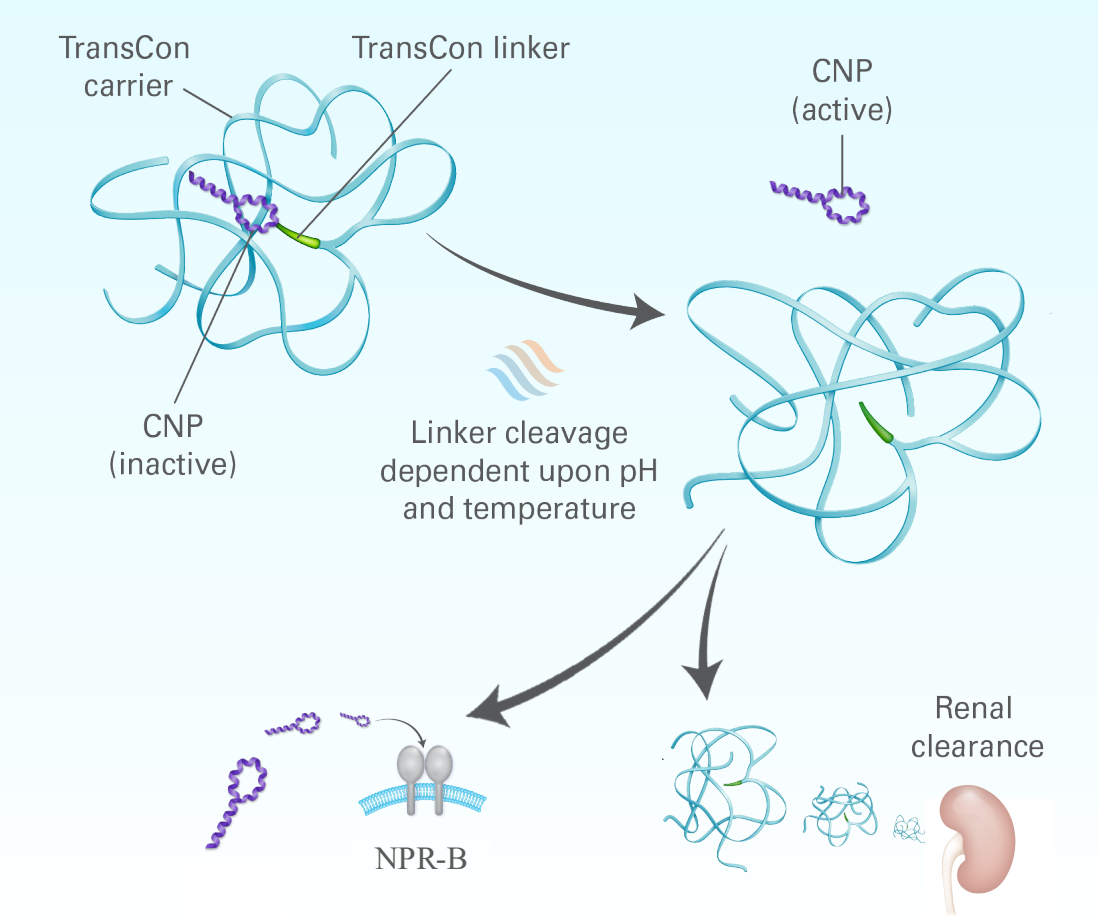
Navepegritide (TransCon® CNP)

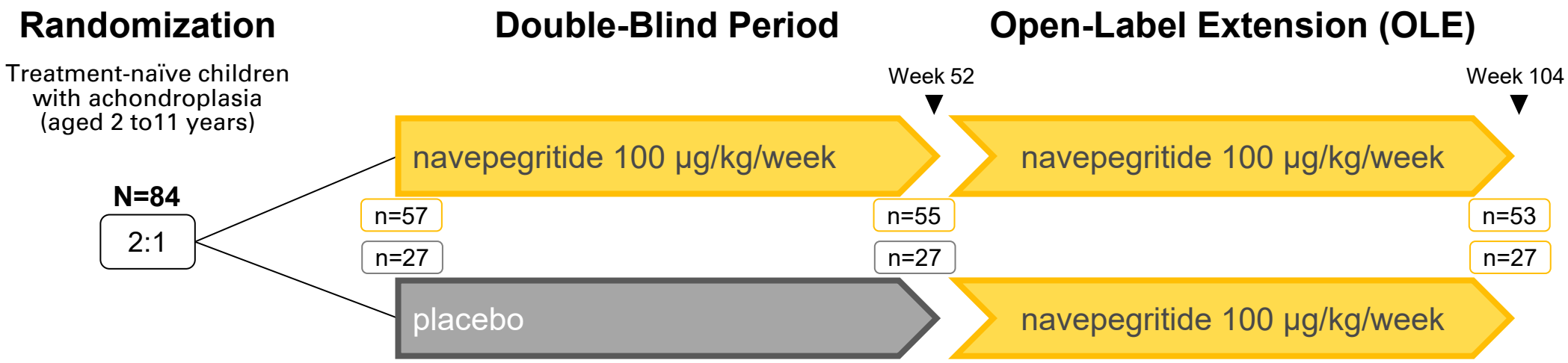


- Navepegritide is a prodrug of C-type natriuretic peptide (CNP) administered once weekly and designed to provide continuous exposure to active CNP
- Active CNP released from navepegritide has an amino acid sequence identical to endogenous CNP [89-126] and binds to NPR-B throughout the body to counteract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

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

[1]Breinholt VM, et al. *J Pharmacol Exp Ther* 2019. [2]Yuviwel (navepegritide). Prescribing information. 2026. Accessed 10 March 2026. https://www.accessdata.fda.gov

ApproaCH Trial Design, Disposition, and Demographics



Key Assessments

Growth

- AGV through Week 104
- Change from baseline in ACH-specific height Z-score

Safety

- Treatment emergent adverse events (AEs)
- Tolerability

Exploratory

- Change from baseline in key orthopedic features of skeletal dysplasia
  - Radiographs collected at baseline, Week 52, and Week 104 were assessed by blinded, expert central readers

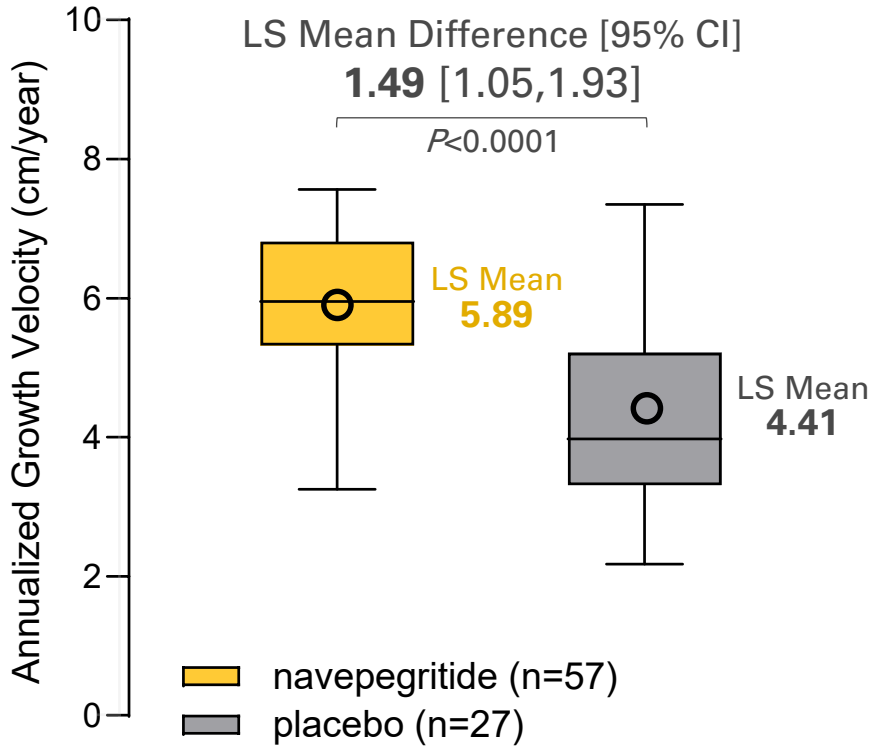
Baseline Characteristics

	navepegritide N=57	placebo N=27
Age, years; mean (SD) [min, max]	5.6 (2.6) [2.0, 11.9]	6.0 (2.7) [2.1, 12.0]
Sex, male; n (%)	31 (54.4)	14 (51.9)
ACH-specific height Z-score; mean (SD)	0.18 (0.92)	-0.11 (0.73)

N = number of children that received at least one dose of investigational medicinal product.
ACH, achondroplasia; AGV, annualized growth velocity

ApproaCH Primary Endpoint: 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.

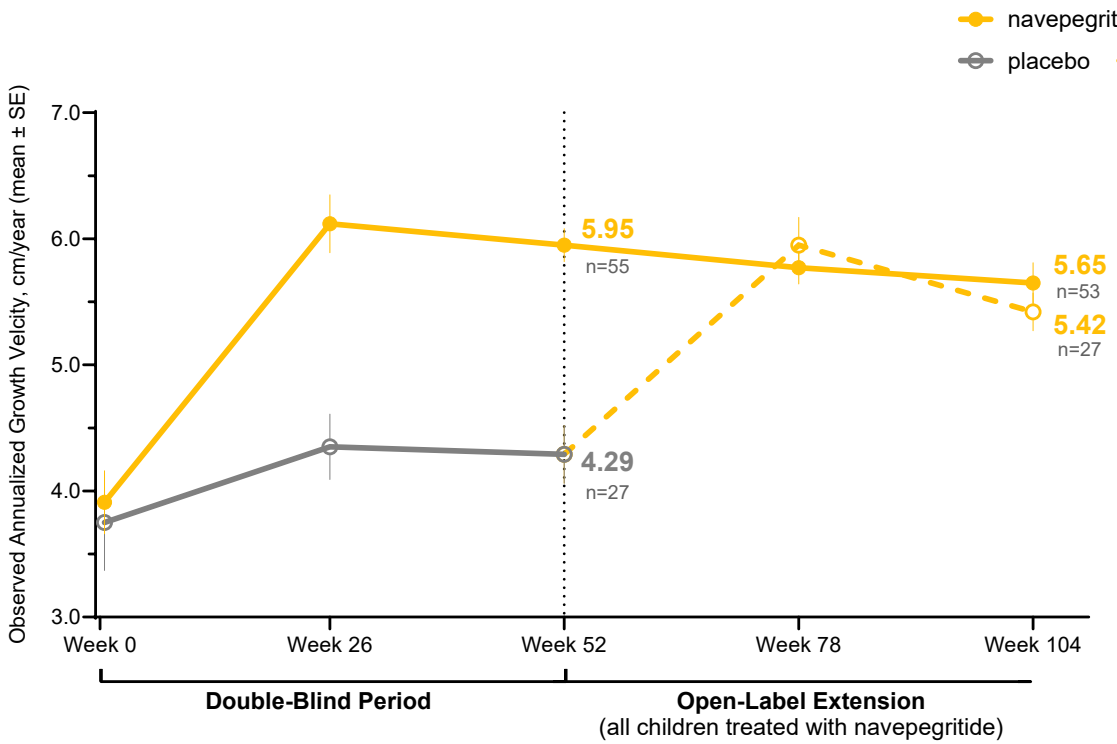


Results from the double-blind period demonstrated superiority of once-weekly navepegritide over placebo for AGV at Week 52

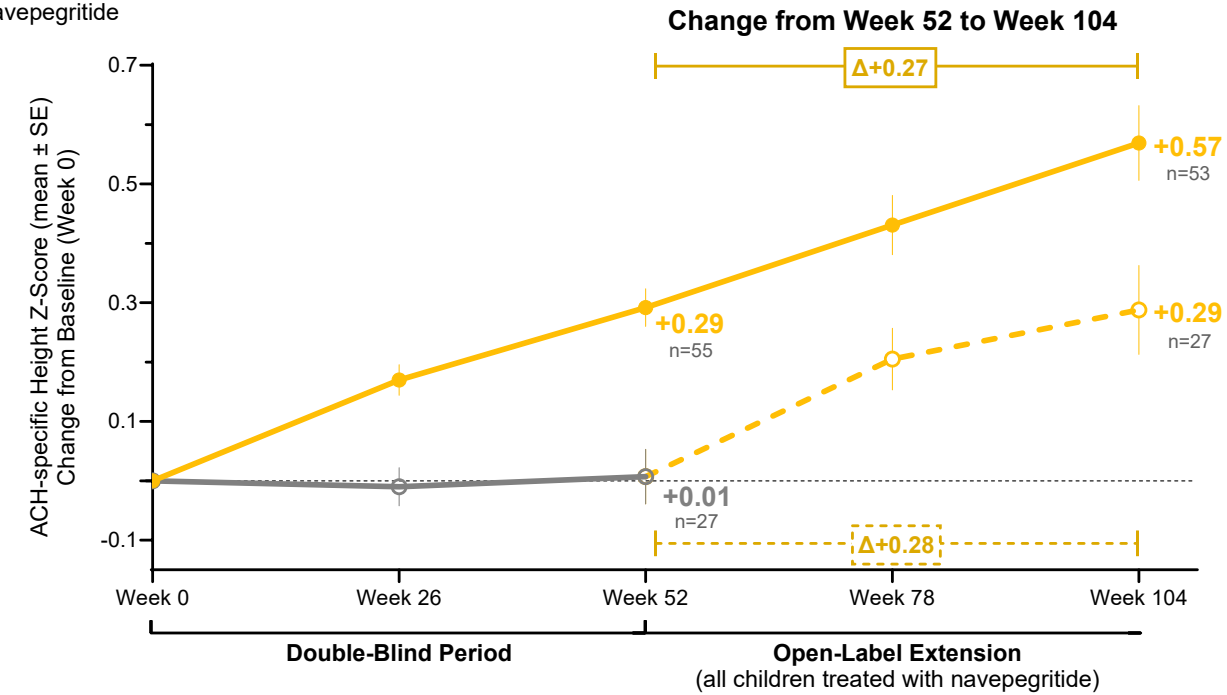
Note: Box-and-whisker plots derived using observed data at Week 52 and display the 75th and 25th percentile (box edges), IQR (colored area), median (midline), and minimum and maximum observed values; labeled circles represent least squares mean values. Missing height data at Week 52 for 2 participants in the navepegritide group were imputed using the multiple imputation method. AGV, annualized growth velocity; CI, confidence interval; IQR, interquartile range; LS, least squares

Improvements in AGV were maintained and ACH-specific height Z-score increased with navepegritide through Week 104

Annualized Growth Velocity (AGV)



Change in ACH-specific Height Z-score

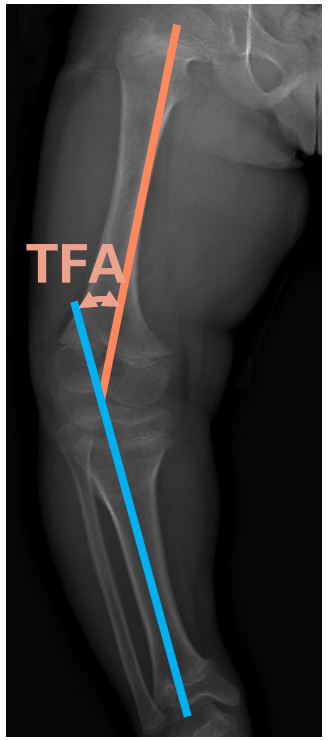


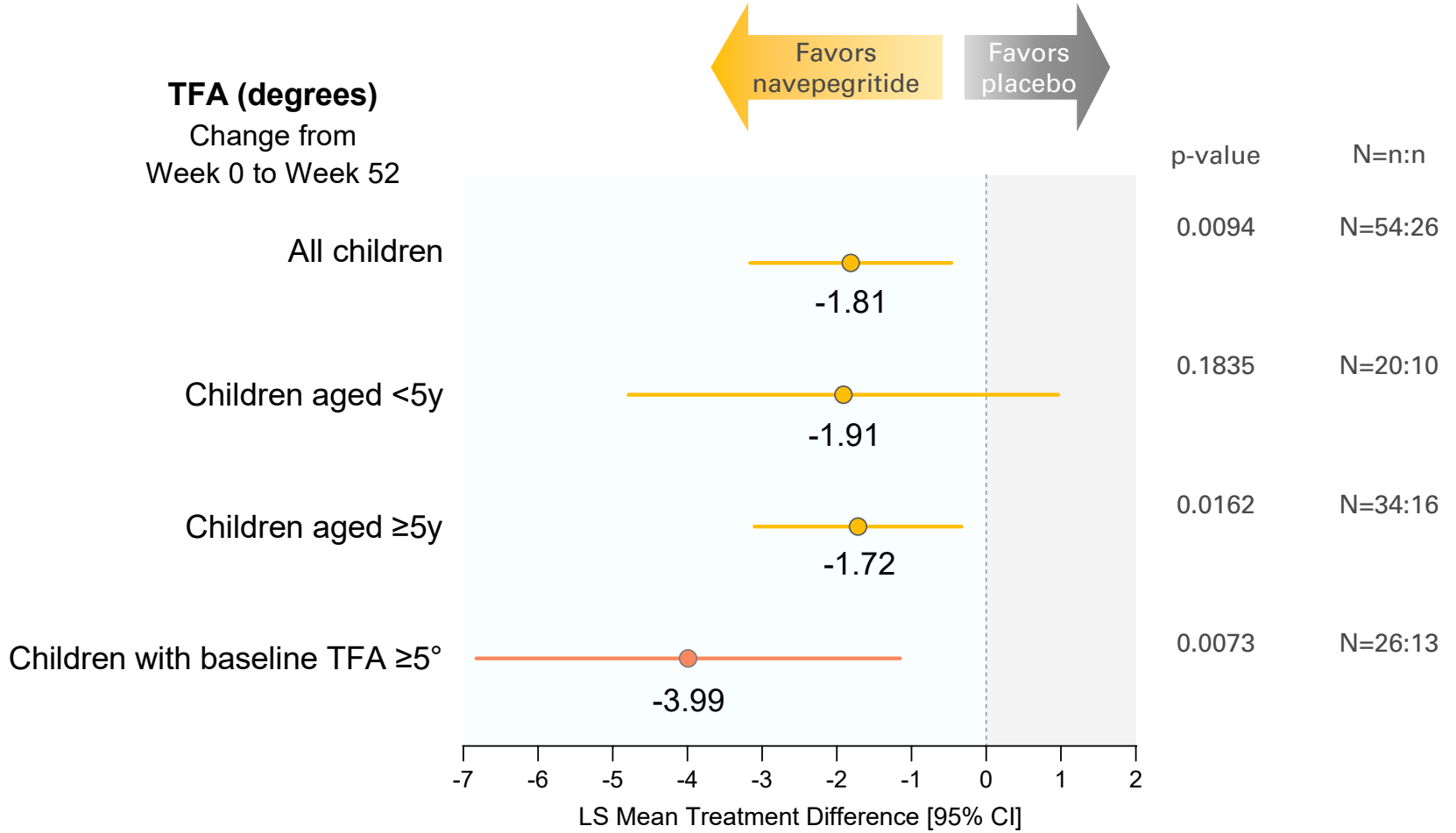
ACH, achondroplasia; AGV, annualized growth velocity; OLE, open-label extension

Navepegritide improved lower extremity alignment compared with placebo at Week 52

TFA: Tibial-Femoral Angle

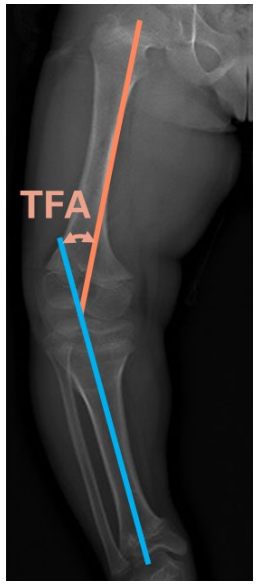
Angle between the mechanical axes of the femur and the tibia





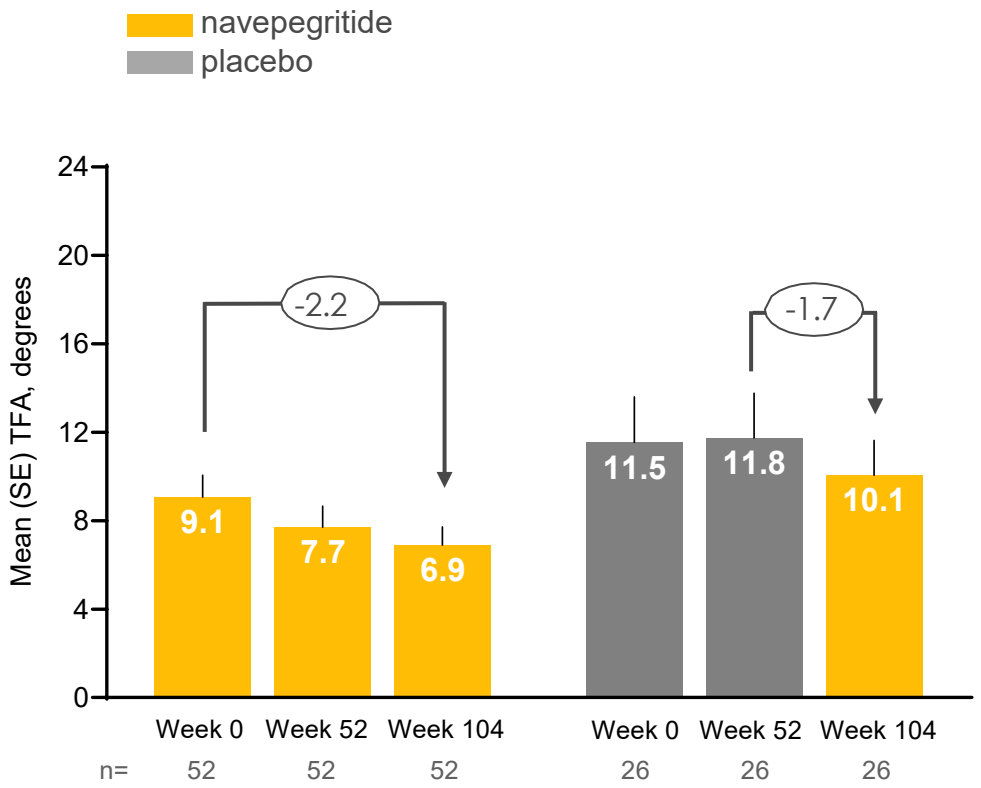
N=n:n refers to number of children for navepegritide:placebo; age subgroups determined by age at time of enrollment. Figure shows TFA with dot indicating LS mean difference between navepegritide and placebo; error bar indicates 95% CI. ANCOVA model included treatment, stratification factor, baseline age and baseline value as covariates. With the exception of the subgroup of children with baseline TFA ≥5°, change from baseline represents absolute change from Week 0.
ANCOVA, Analysis of covariance; CI, confidence interval; LS, least squares; TFA, Tibial-femoral angle

TFA decreased with navepegritide treatment through Week 104



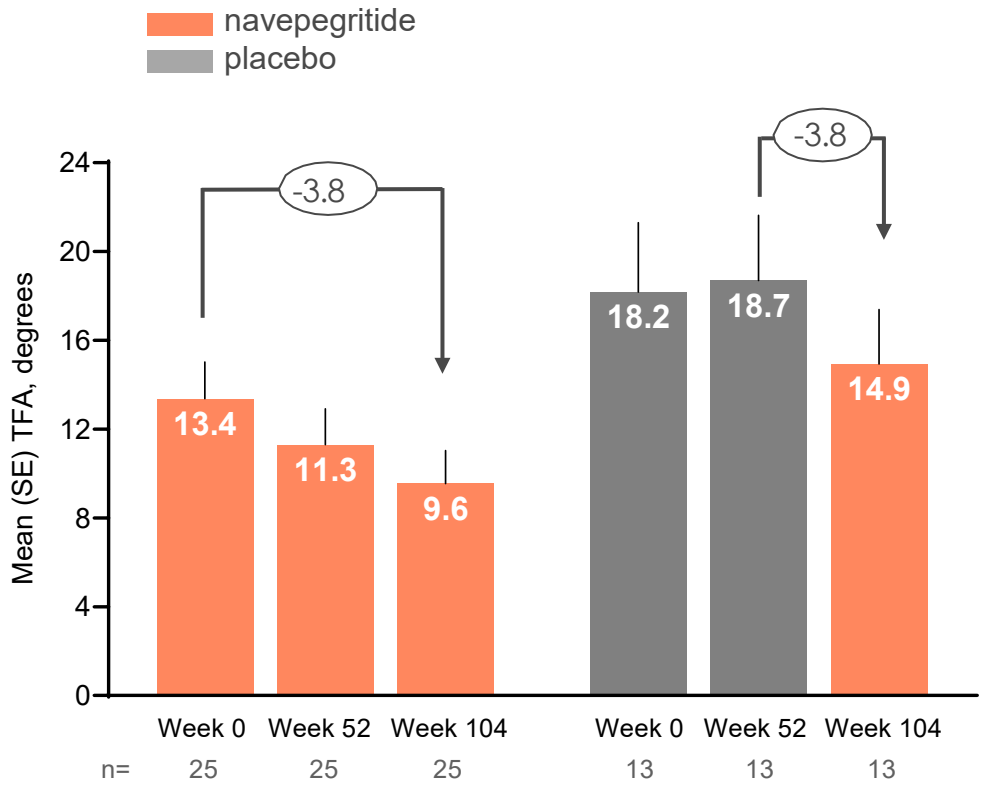
Improved alignment

All children



Fibula-to-tibia length ratio remained stable, reflecting proportional growth of the lower leg

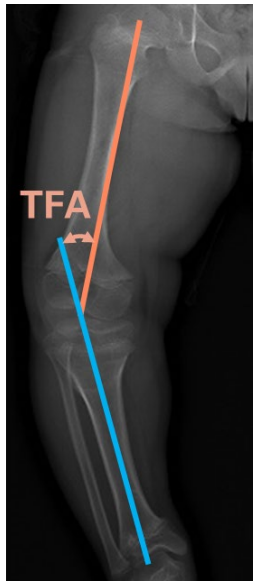
Children with baseline TFA ≥5°



Greater effects observed in children with preexisting genu varum

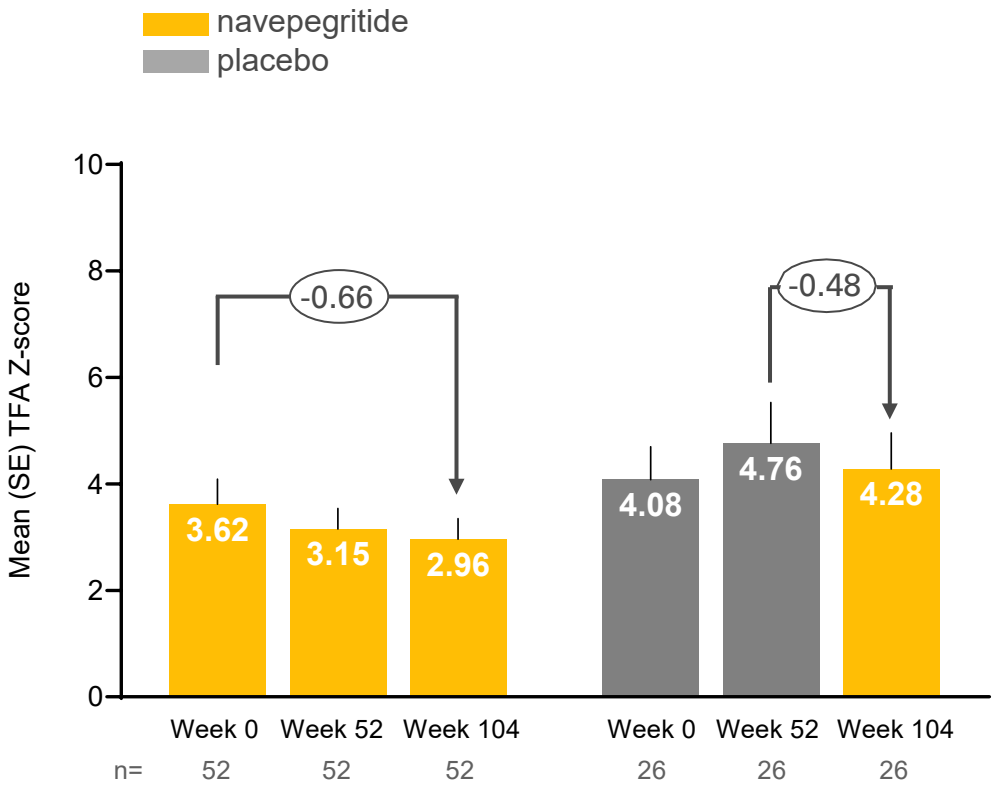
Data reported are paired analyses for children with data available at all timepoints; error bars indicate standard error. TFA is reported as the average of the absolute values (deviations from straight alignment) from each leg; change from baseline represents absolute change from Week 0.
TFA, tibial-femoral angle

TFA Z-scores continued to decrease through Week 104 with navepegritide treatment

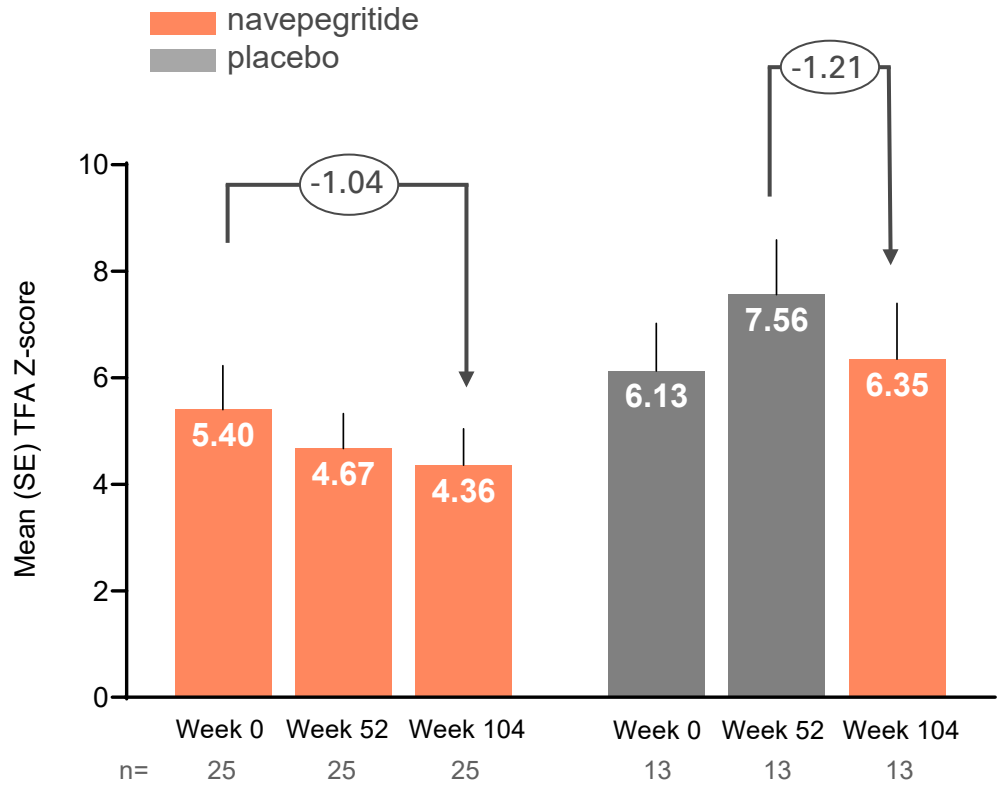


Improved alignment

All children



Children with baseline TFA ≥5°



Data reported are paired analyses for children with data available at all timepoints; error bars indicate standard error. 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 (Sabharwal S and Zhao C, *J Bone Joint Surg Am* 2009); change from baseline represents absolute change from Week 0.
TFA, tibial-femoral angle

Most AEs with navepegritide treatment were mild or moderate, with none leading to treatment discontinuation or trial withdrawal through Week 104

	Navepegritide-treated children N=84
Treatment exposure	**137.1 person-years**
Any treatment-emergent AE, n (%)	76 (90.5)
Most frequent AEs (≥15% of children)	
Otitis media	31 (36.9)
Nasopharyngitis	29 (34.5)
Pyrexia	29 (34.5)
Upper respiratory tract infection	19 (22.6)
Headache	17 (20.2)
Vomiting	16 (19.0)
Influenza	13 (15.5)
Injection site reaction (ISR), n (%)	17 (20.2)
ISRs per person-year of exposure	0.35†
Symptomatic hypotension, n (%)	0 (0.0)

- Bone age advanced consistently with chronological age
  - Mean bone age to chronological age ratio remained below 1 at Week 104
- In the OLE, two children experienced fractures associated with trauma
  - Neither fracture (1 clavicle, 1 forearm) included the growth plate
- No osteonecrosis or slipped capital femoral epiphysis (SCFE)

n = number of children with observation.
†Equivalent to approximately 1 ISR for every 3 years of treatment
AE, adverse event; ISR, injection site reaction; OLE, open-label extension

Conclusions

In the ApproaCH Trial

- Treatment with once-weekly navepegritide in children with achondroplasia was generally well tolerated and resulted in gains in AGV that were maintained through 104 weeks
- Once-weekly navepegritide continued to improve lower limb alignment in children with achondroplasia through Week 104
- Greater improvement in lower limb alignment was evident in children with preexisting genu varum (baseline tibial-femoral angle ≥5°) compared to the overall study population

Navepegritide may address features of skeletal dysplasia that contribute to major health-related complications associated with achondroplasia

CONFLICT OF INTEREST DISCLOSURE

Leanne M. Ward

I have a relationship with for-profit/not-for-profit organisations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organisation(s)	Description of relationship
Any direct financial payments including receipt of honoraria	BioMarin	Consultancy, with funds to institution
Membership on advisory boards or speaker's bureaus		
Funded grants or clinical trials	Ascendis Pharma, BridgeBio, BioMarin	Research support/clinical trial investigator
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

The ApproaCH Trial was funded by Ascendis Pharma Growth Disorders A/S