Improvements in Lower Extremity Alignment are Associated with Physical Functioning in Children With Achondroplasia Treated With Navepegritide: 52-Week Results From the ApproaCH Trial

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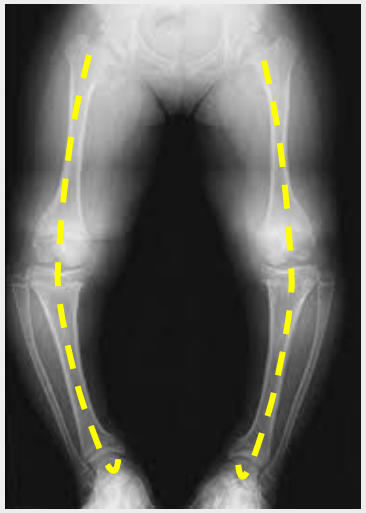
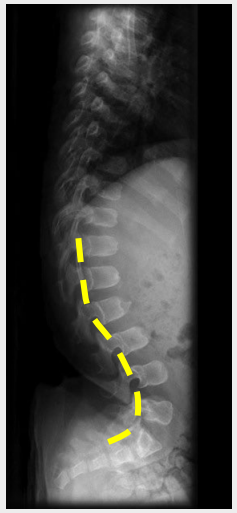
Achondroplasia: a skeletal dysplasia with orthopedic complications

The pathogenic *FGFR3* variants of achondroplasia result in skeletal abnormalities beyond short stature, which are associated with pain, impaired physical functioning, orthopedic surgeries, and reduced HRQoL[1-5]

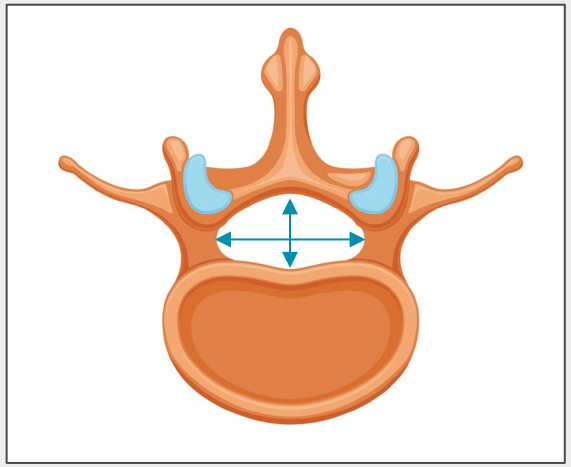
Genu Varum



Kyphosis/Lordosis



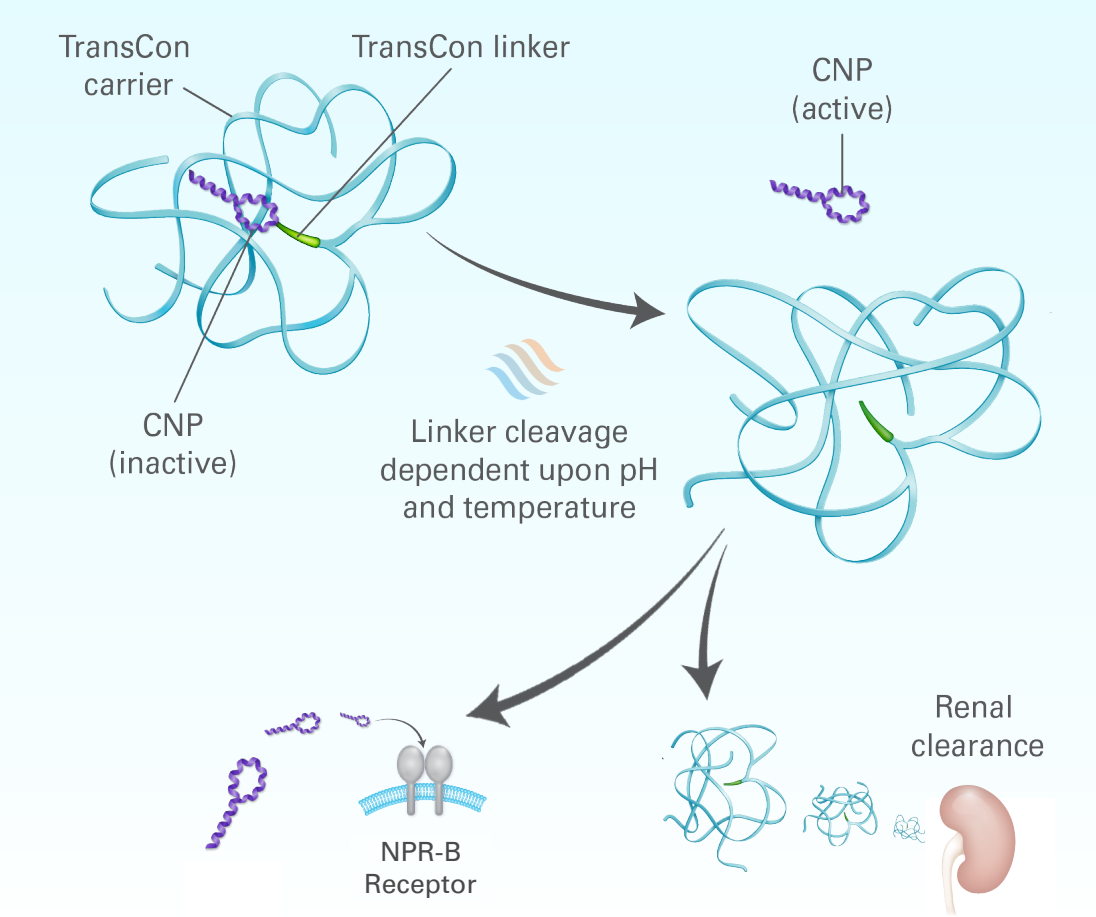
Spinal Stenosis



FGFR3, fibroblast growth factor receptor 3; HRQoL, health-related quality of life

[1]Hunter AG, et al. *J Med Genet* 1998. [2]Matsushita M, et al. *Calcif. Tissue Int* 2019. [3]Savarirayan R, et al. *Nat Rev Endocrinol* 2022. [4]Murton MC, et al. *Adv Ther* 2023. [5]Nahm NJ, et al. *Orphanet J Rare Dis* 2023.

Navepegritide (TransCon® CNP)

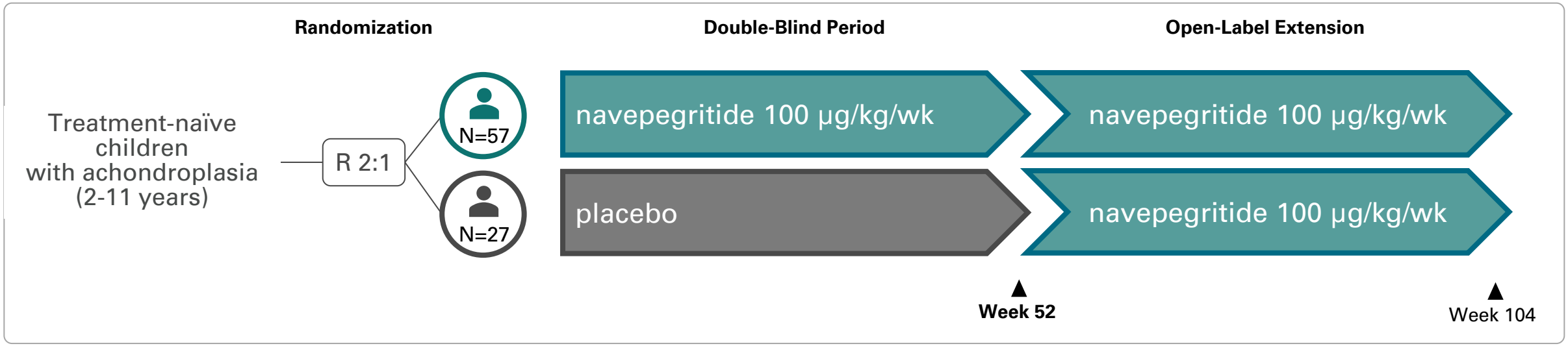


- Navepegritide, an investigational prodrug of C-type natriuretic peptide (CNP), binds to the NPR-B receptor to counteract overactive fibroblast growth factor receptor 3 (FGFR3) signaling in achondroplasia
- Navepegritide is administered once weekly, and is designed to provide continuous exposure of active CNP (amino acid sequence identical to endogenous CNP [89-126])

CNP, C-type natriuretic peptide; FGFR3, fibroblast growth factor receptor 3; NPR-B; natriuretic peptide receptor B

Breinholt VM, et al. *J Pharmacol Exp Ther* 2019.

ApproaCH trial design



Primary Endpoint

- Annualized growth velocity (**AGV**) at Week 52

Key Secondary Endpoints

- Change from baseline in height Z-score at Week 52
- **HRQoL**, including Achondroplasia Child Experience Measure (ACEM)

Safety Endpoints

- Treatment emergent adverse events (TEAEs)
- Tolerability

Exploratory Endpoint

- Change from baseline in key orthopedic features of the skeletal dysplasia (with radiographs were collected at baseline and Week 52 and assessed by blinded, expert central readers)

HRQoL, health-related quality of life
N = number of children that received at least one dose of investigational medicinal product

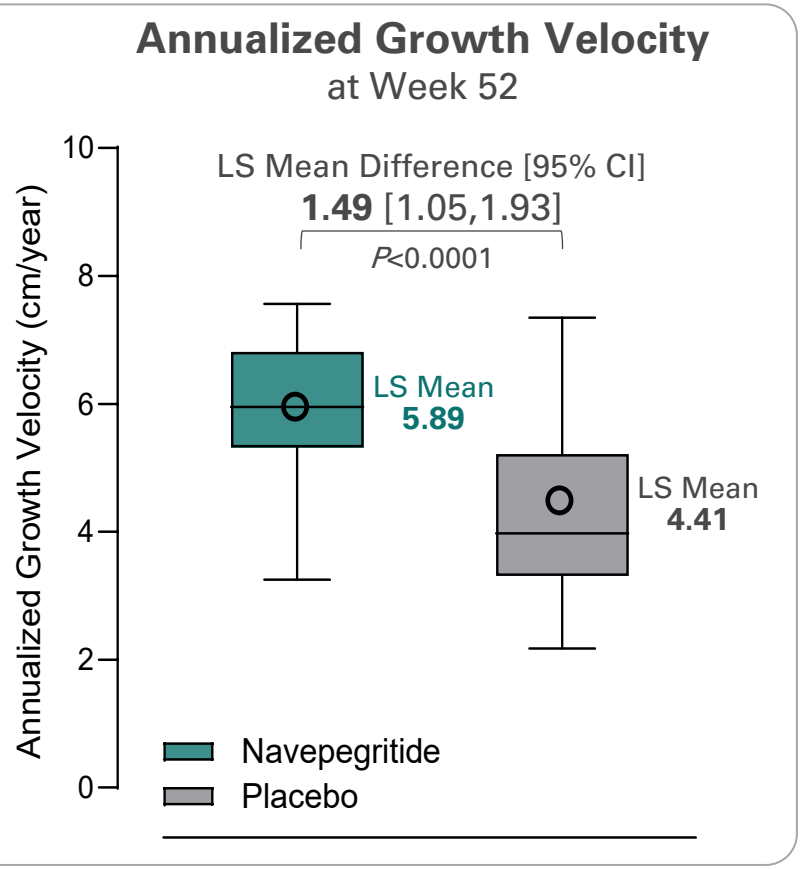
ApproaCH trial population is representative of children with achondroplasia

Full Analysis Set	Navepegritide (N=57)	Placebo (N=27)	Overall (N=84)
Age (years), mean (SD) [min, max]	5.6 (2.6) [2.0, 11.9]	6.0 (2.7) [2.1, 12.0]	5.7 (2.6) [2.0, 12.0]
Age (years) group, n (%)			
<5 years	21 (36.8)	10 (37.0)	31 (36.9)
≥5 years	36 (63.2)	17 (63.0)	53 (63.1)
Sex, n (%)			
Female	26 (45.6)	13 (48.1)	39 (46.4)
Male	31 (54.4)	14 (51.9)	45 (53.6)
Height (cm), mean (SD)	88.9 (12.9)	89.1 (11.5)	89.0 (12.4)
Achondroplasia-specific height Z-score, mean (SD)	0.18 (0.92)	-0.11 (0.73)	0.09 (0.87)
CDC height Z-score, mean (SD)	-4.90 (0.98)	-5.21 (0.93)	-5.00 (0.97)
AGV (cm/year), mean (SD)	4.0 (1.9)	3.8 (2.0)	3.9 (1.9)

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

Once-weekly navepegritide demonstrated superior AGV at Week 52 with a safety and tolerability profile comparable to placebo

ApproaCH Primary Endpoint



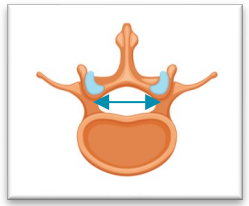
ApproaCH Safety Summary

Event, n (%)	Navepegritide (N=57)	Placebo (N=27)
Any treatment-emergent AE	52 (91.2%)	26 (96.3%)
Mild Moderate Severe Life-threatening or death	52 (91.2%) 16 (28.1%) 4 (7.0%) 0	25 (92.6%) 11 (40.7%) 1 (3.7%) 0
Serious adverse events (SAE)	3 (5.3%)	3 (11.1%)
Treatment-related SAE	0	0
Injection site reaction	11 (19.3%)	4 (14.8%)
Symptomatic hypotension	0	0
Fracture / SCFE / Osteonecrosis	0	0
Mean change (SD) from baseline in ratio of bone age/chronological age	0.000 (0.0887)	-0.013 (0.1137)

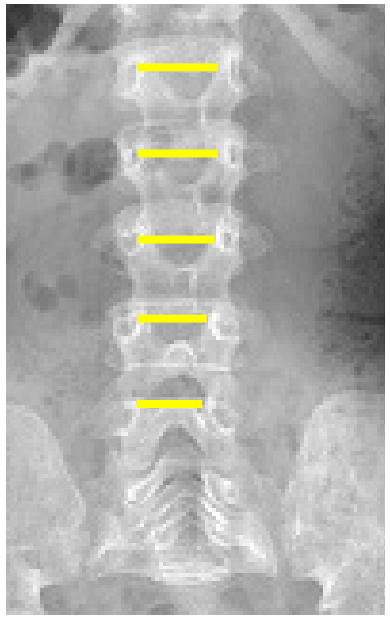
n = number of participants with observation

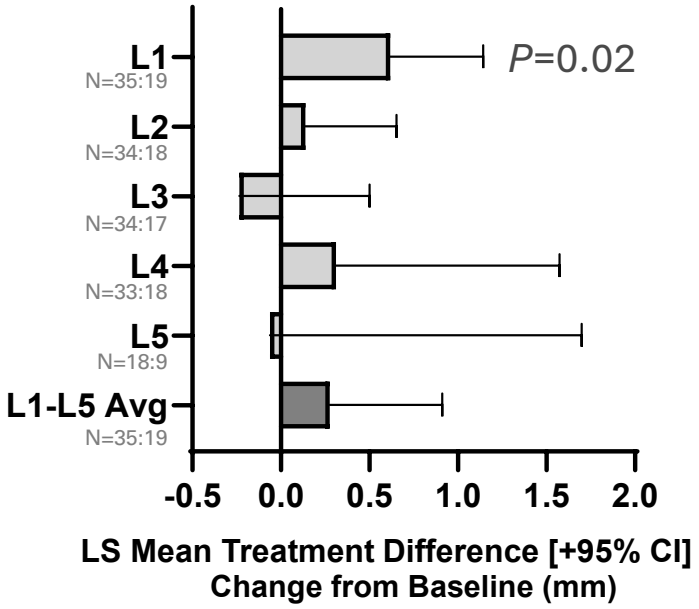
Note: Box plot represents observed data; labeled circles represent least squares mean values
Data originally presented by L. Ward at the Joint Congress of ESPE and ESE 2025, Copenhagen, Denmark, on behalf of the ApproaCH investigators
AE, adverse event; AGV, annualized growth velocity; LS, least squares; SCFE, slipped capital femoral epiphysis; SD, standard deviation

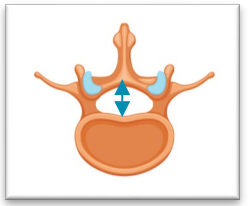
Navepegritide-treated children in the ApproaCH trial had greater expansion of the spinal canal vs placebo at Week 52



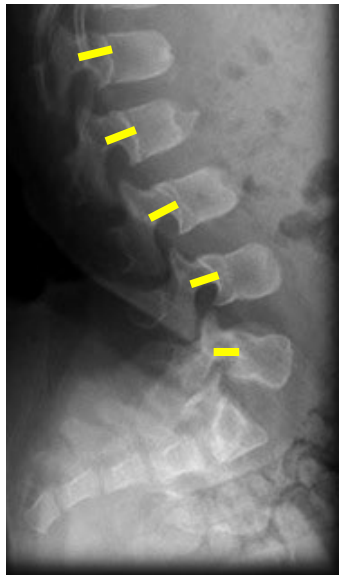
Interpedicular Distance (IPD)

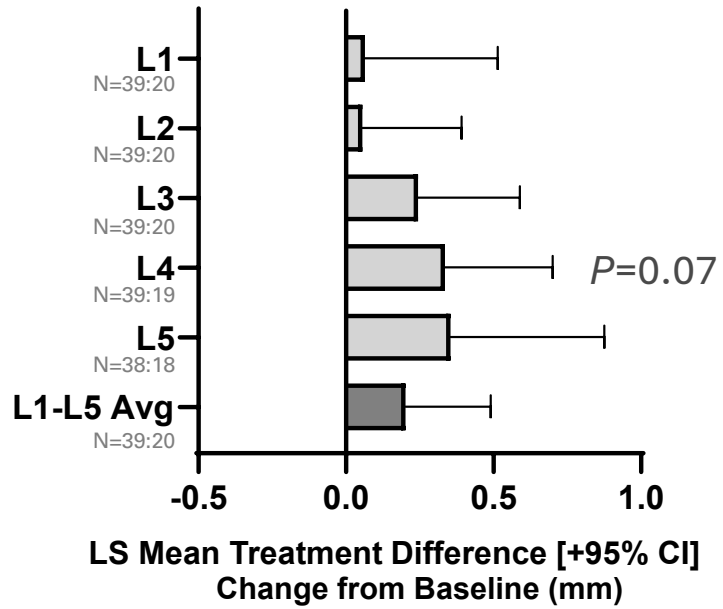






Pedicle Width (PW)





Data originally presented by L. Ward at the Joint Congress of ESPE and ESE 2025, Copenhagen, Denmark, on behalf of the ApproaCH investigators
Note: N=n:n represents number of children treated with navepegritide or placebo, respectively. Error bars indicate 95% CI (upper bound).
CI, confidence interval; LS, Least squares

Orthopedic measurement on standing lower limb X-rays used for evaluation of lower extremity alignment and proportionality

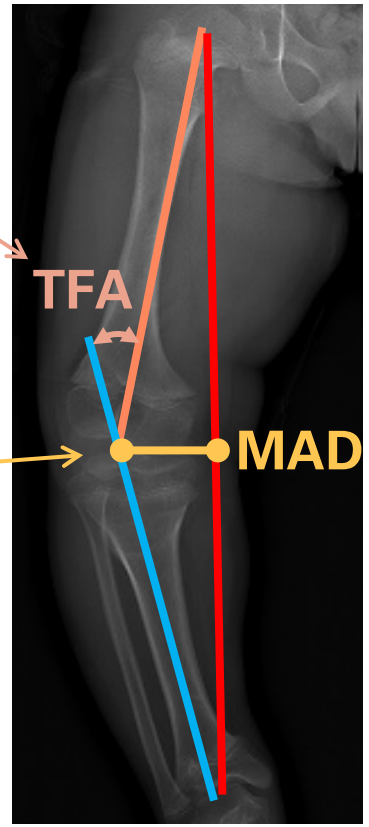
TFA
Tibial-Femoral Angle

Angle between the mechanical axes of the femur and the tibia

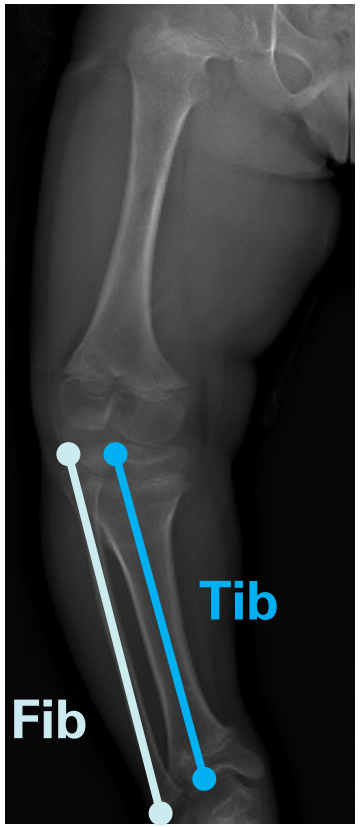
MAD
Mechanical Axis Deviation

Distance from the center of the knee to a line drawn from the center of the femoral head to the ankle *(mechanical axis of the leg)*

Alignment



Proportionality

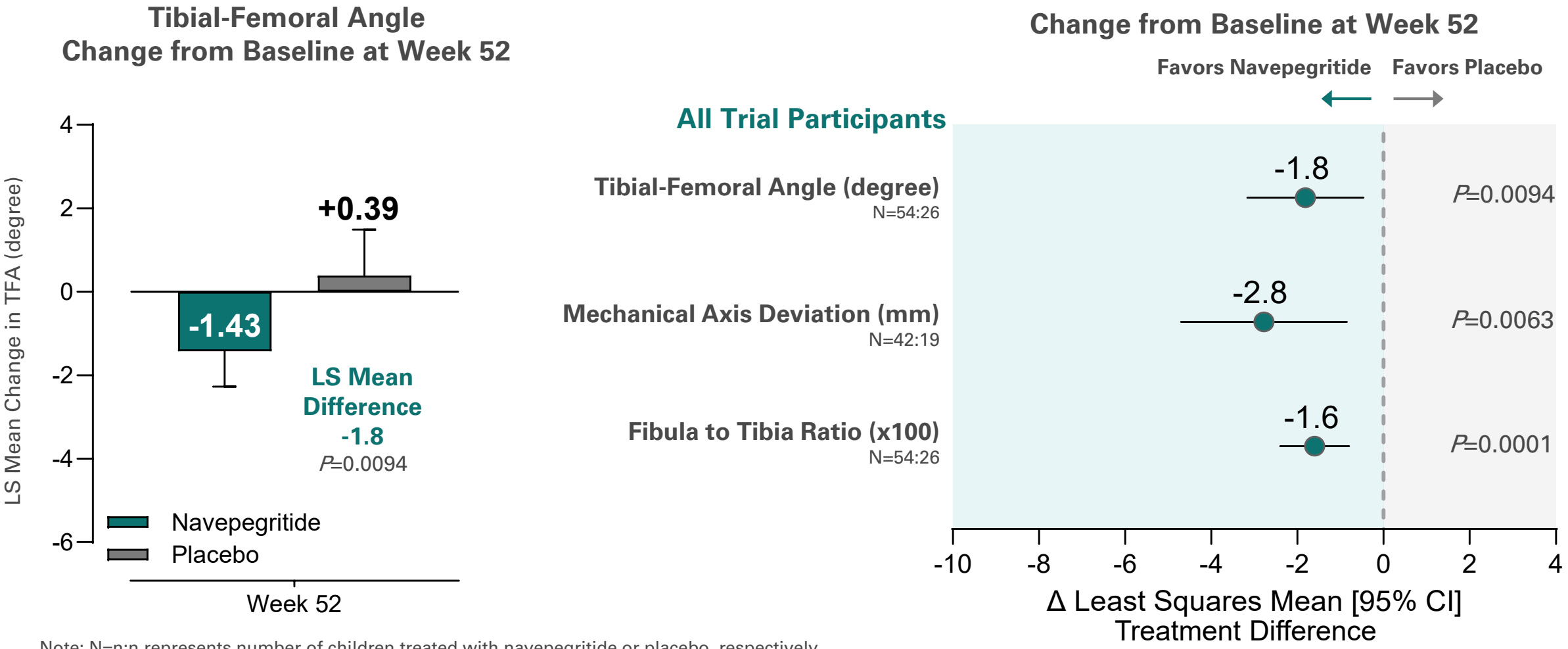


Fibular "overgrowth" is a key contributor to the progression of leg curvature

Fib / Tib
Fibula to Tibia Ratio

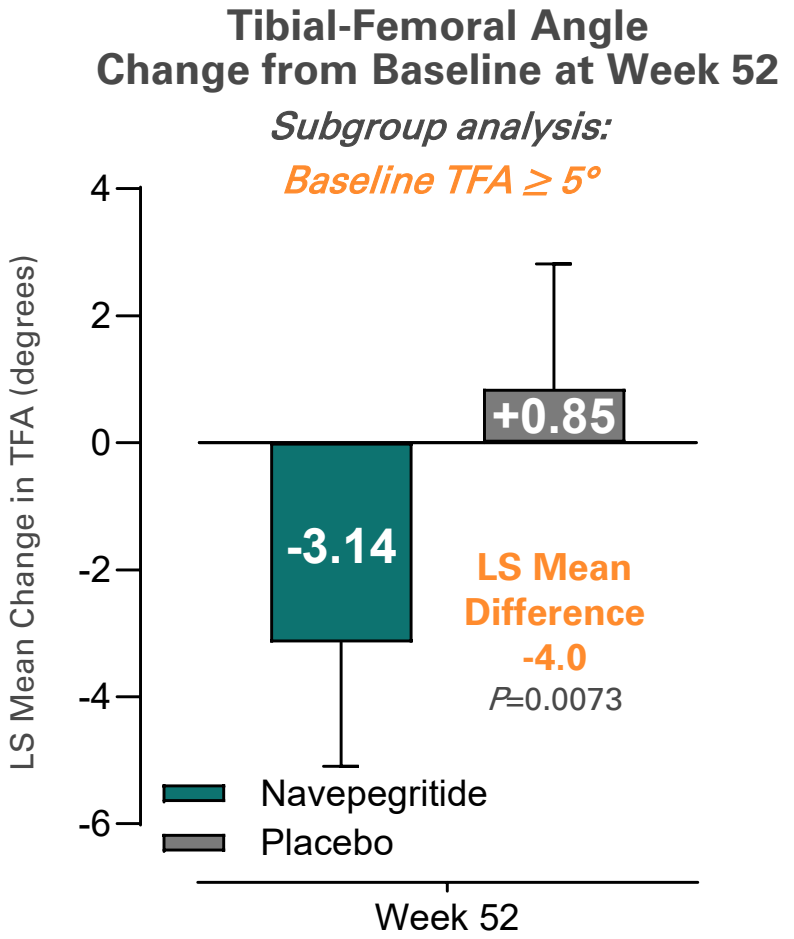
Ratio of fibula length to tibia length

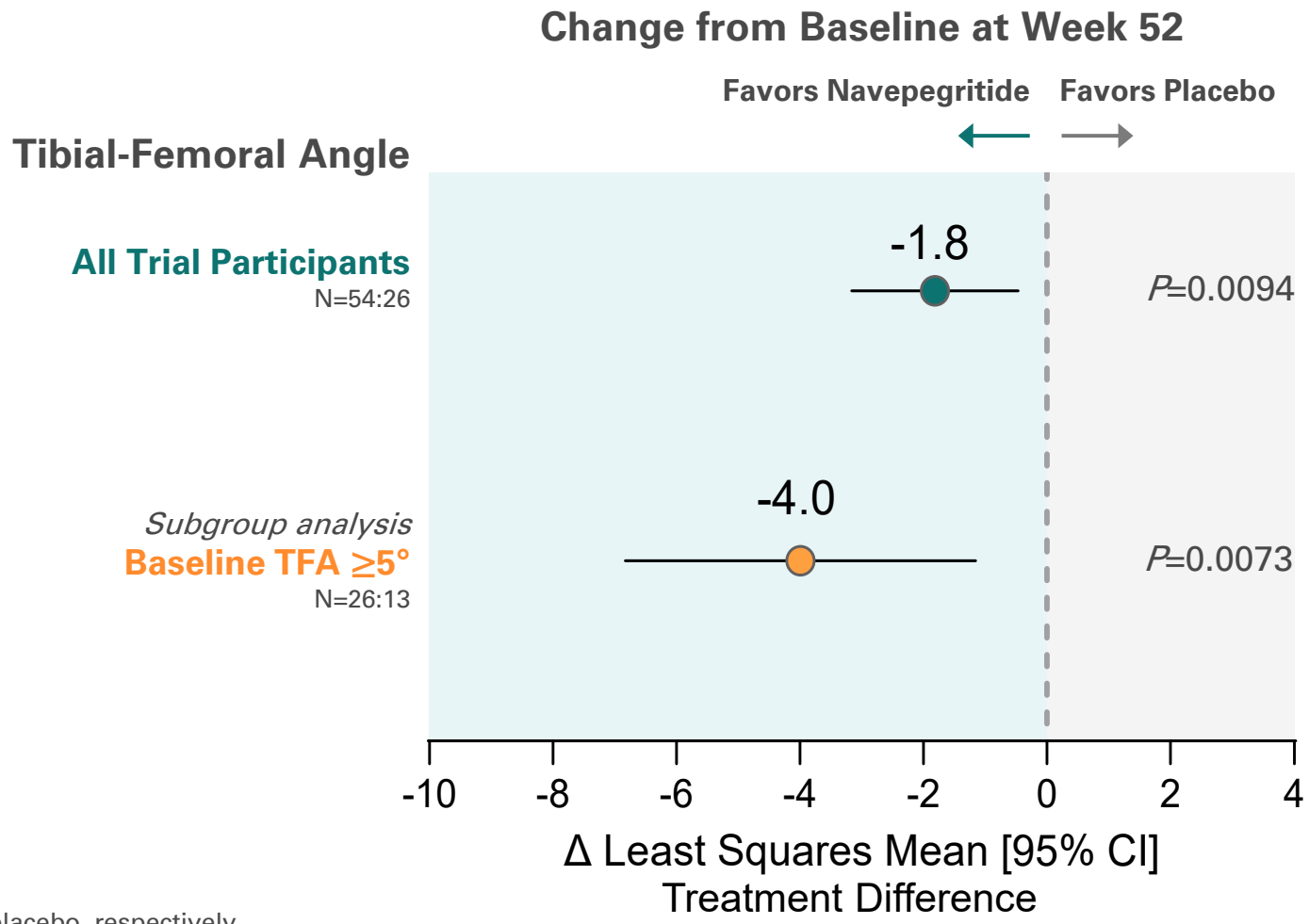
Navepegritide improved lower extremity alignment and fibula:tibia ratio



Note: N=n:n represents number of children treated with navepegritide or placebo, respectively.
LS, least squares; TFA, tibial-femoral angle

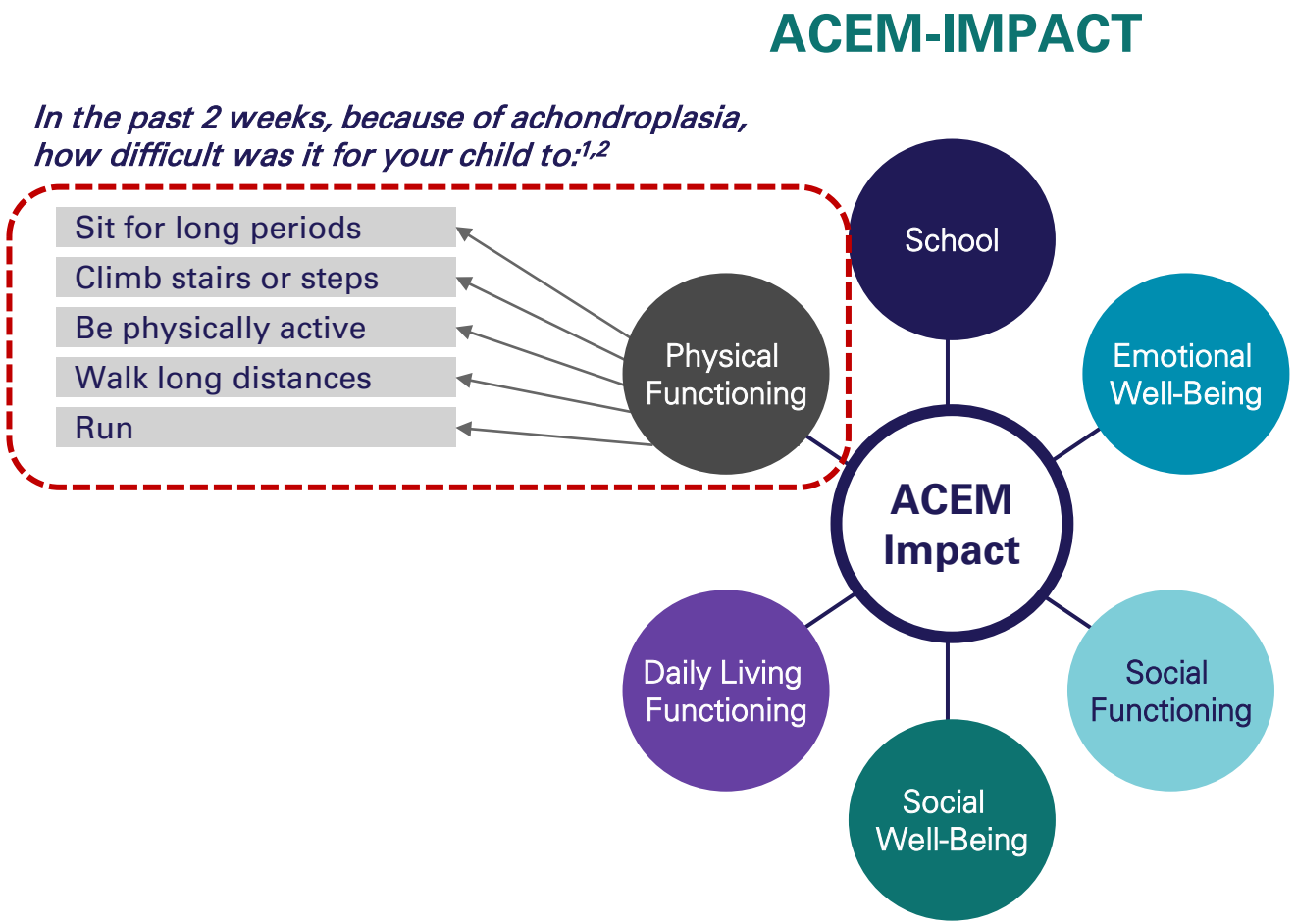
Greater benefits in alignment observed with navepegritide in children with genu varum ≥5° at baseline





Note: N=n:n represents number of children treated with navepegritide or placebo, respectively.
LS, least squares; TFA, tibial-femoral angle

Condition-specific clinical outcome assessments: Achondroplasia Child Experience Measure (ACEM)

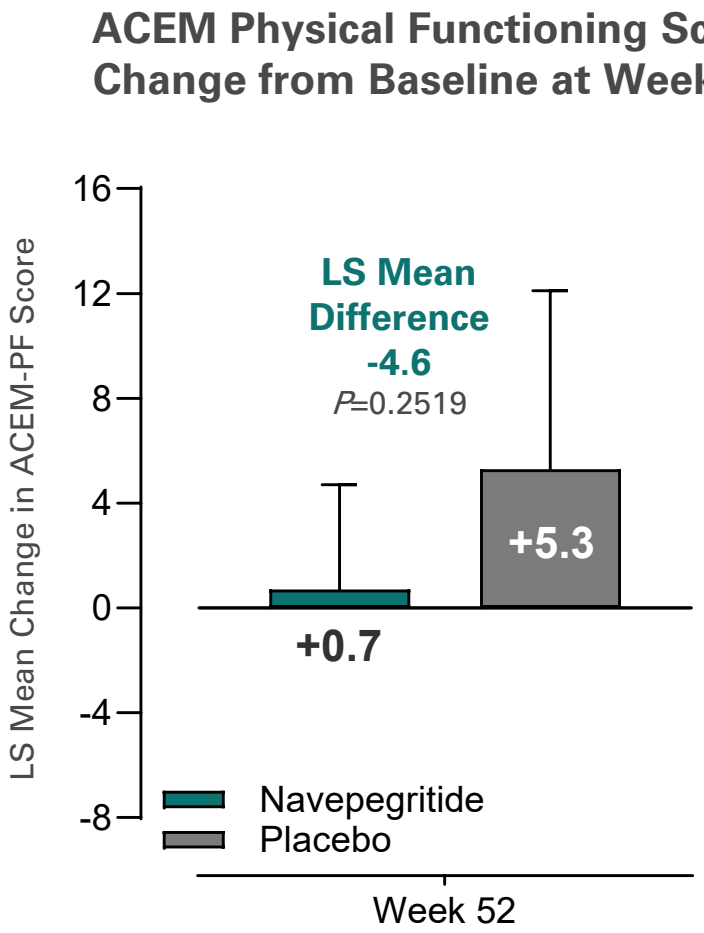


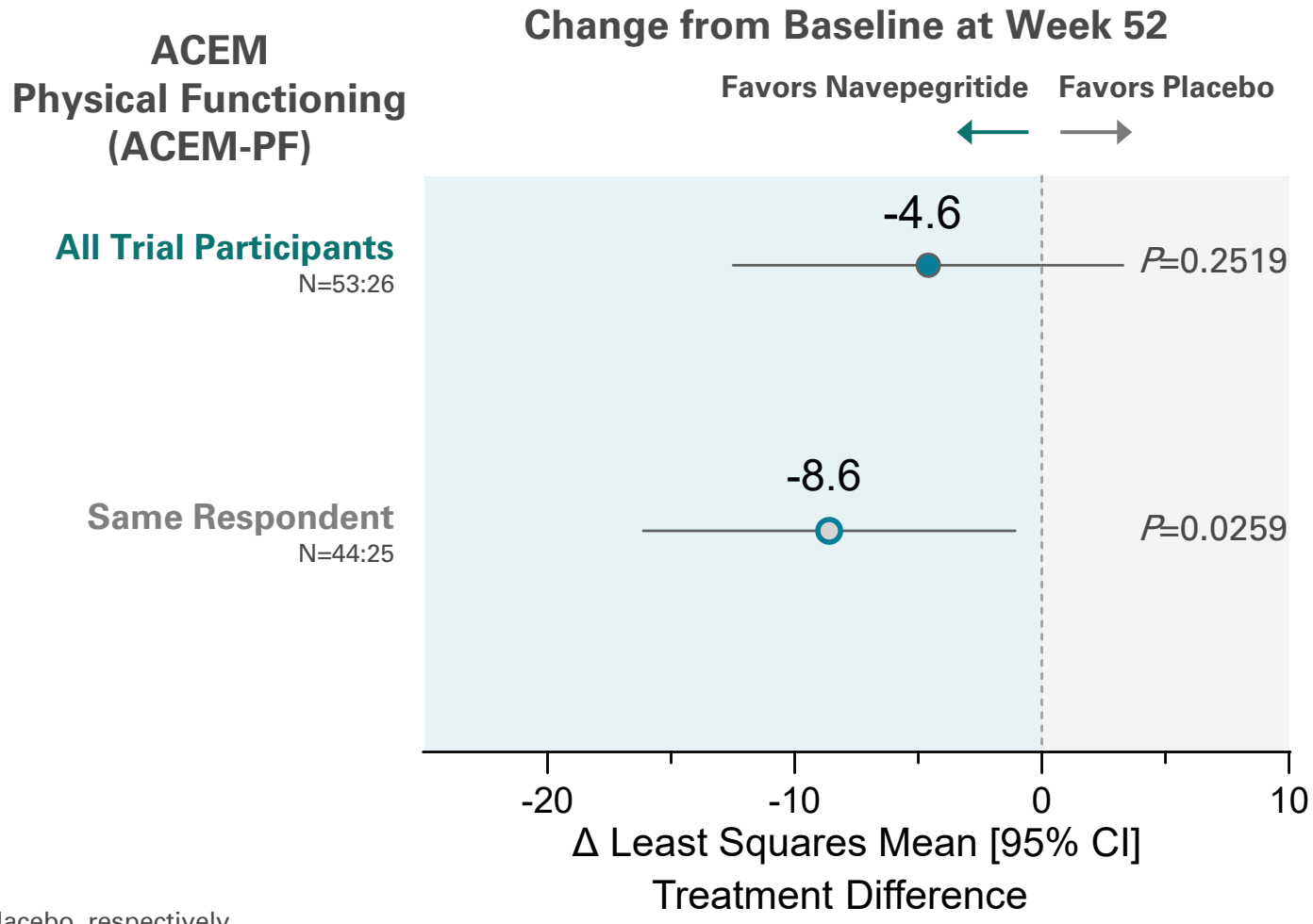
The measure is completed by the caregiver and scored on a 0-100 scale with higher scores indicating greater impairment

ACEM, Achondroplasia Child Experience Measure

[1]Pfeiffer KM, et al. *Am J Med Genet A* 2021. [2]Savariryan R, et al. International Conference on Children's Bone Health (ICCBH) 2024. Oral Presentation

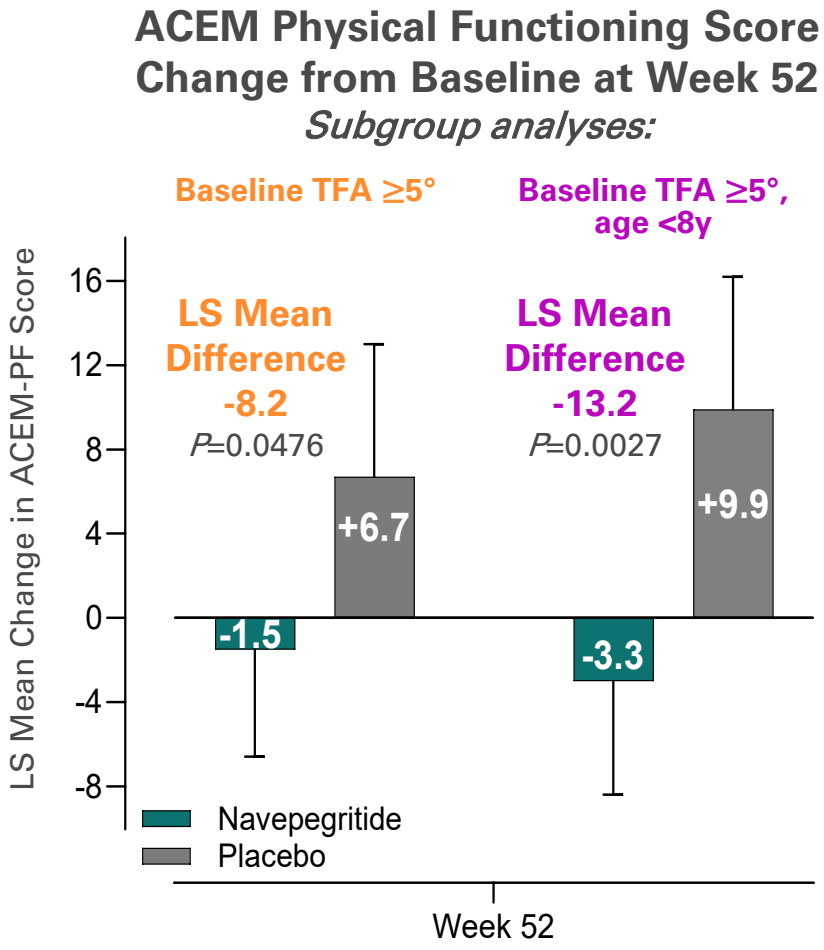
Change from baseline in physical functioning score favors navepegritide treatment vs placebo

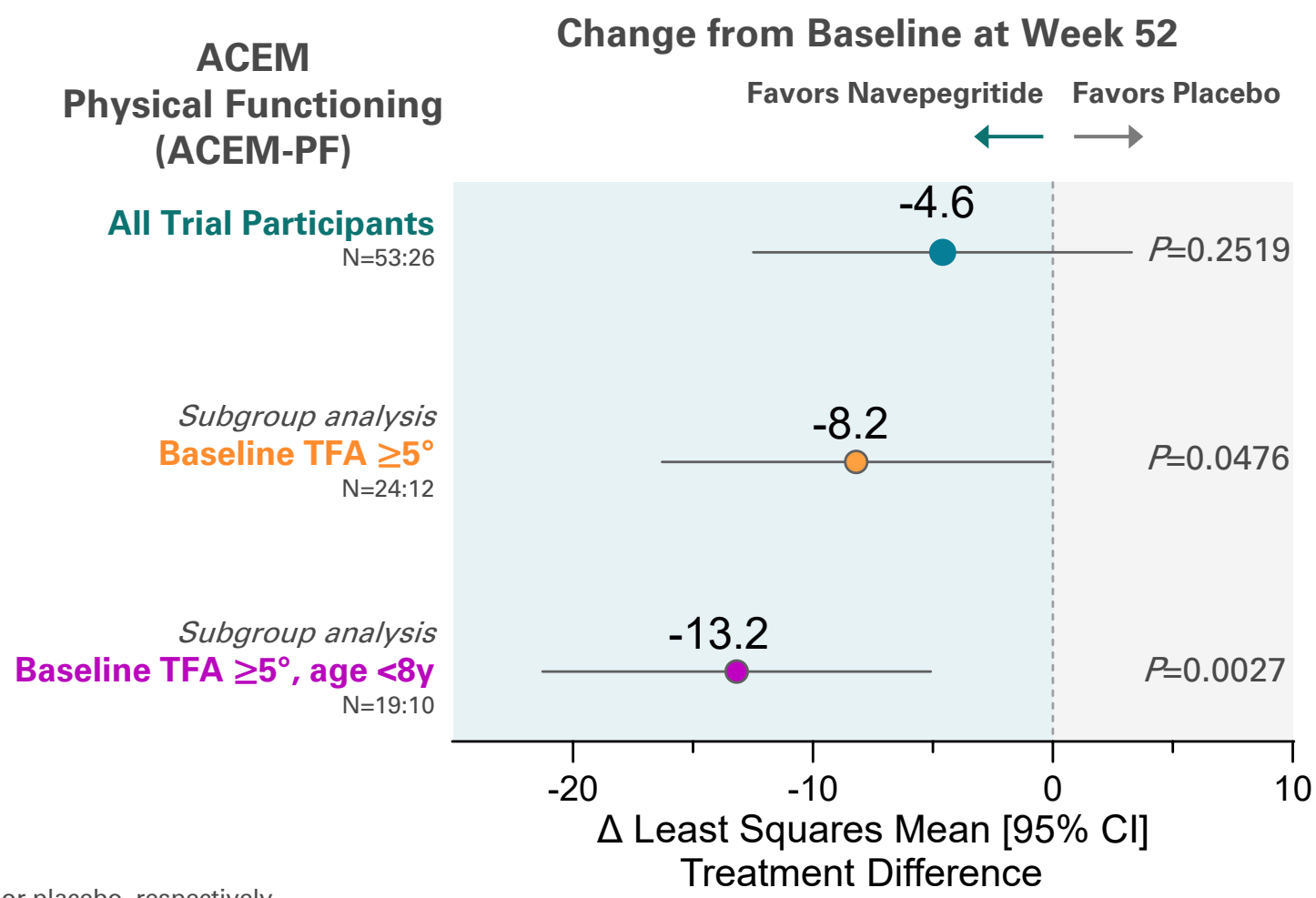




Note: N=n:n represents number of children treated with navepegritide or placebo, respectively.
ACEM, Achondroplasia Child Experience Measure; LS, least squares; PF, physical functioning

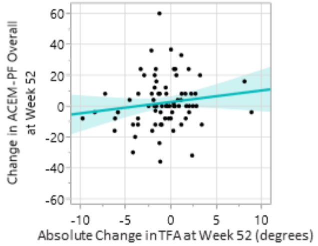
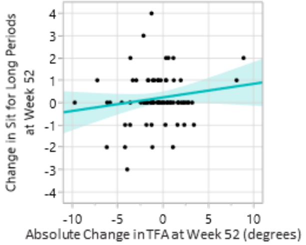
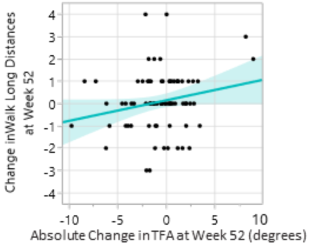
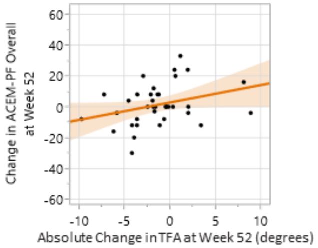
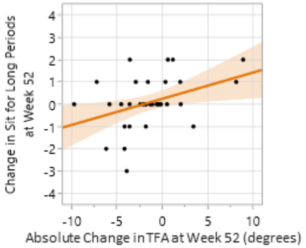
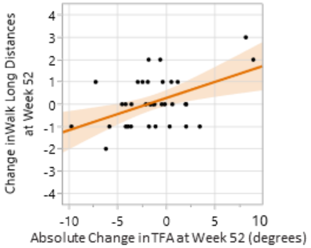
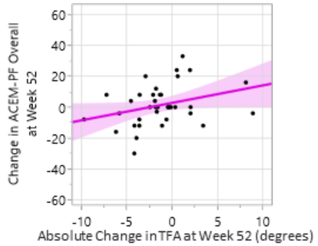
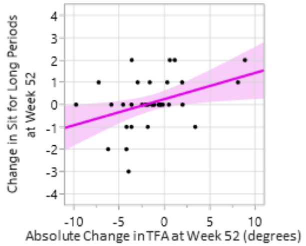
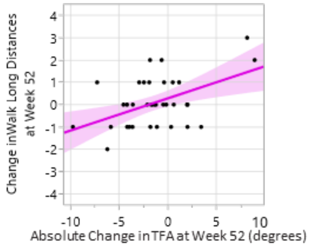
Children with genu varum ≥5° at baseline reported greater improvement in physical functioning with navepegritide





Note: N=n:n represents number of children treated with navepegritide or placebo, respectively.
ACEM, Achondroplasia Child Experience Measure; LS, least squares; PF, physical functioning; TFA, tibial-femoral angle

Changes in physical functioning correlated with improvements in lower limb alignment in children aged <8 years and with genu varum ≥5° at baseline

	Absolute change in TFA (in degrees) vs. change in:					
	ACEM-PF Overall		Sit for Long Periods		Walk Long Distances	
All Trial Participants						
Pearson R	0.14		0.16		0.21	
P-value	0.22		0.17		0.07	
Subgroup analysis **TFA ≥5°**						
Pearson R	0.31		***0.39***		***0.48***	
P-value	0.062		***0.020***		***0.003***	
Subgroup Analysis **TFA ≥5°, age <8y**						
Pearson R	***0.39***		***0.47***		***0.62***	
P-value	***0.035***		***0.013***		***0.0003***	

ACEM, Achondroplasia Child Experience Measure; PF, physical functioning; TFA, tibial-femoral angle

Summary

- Navepegritide demonstrated statistically significant improvements in growth endpoints at Week 52 in the ApproaCH trial
- Navepegritide improved indices of lower limb alignment and proportional growth at Week 52, suggesting the potential to reduce future complications
- Significant improvement was observed with navepegritide in the Physical Functioning domain of the Achondroplasia Child Experience Measure (ACEM-PF), with greater benefits in children with more severe genu varum at baseline, particularly those less than 8 years of age

Once-weekly navepegritide may offer benefits beyond promoting linear growth that translate into meaningful improvements in the lives of children living with achondroplasia

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involved in the central imaging assessments

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