TransCon CNP (Navepegritide) Improved Physical Functioning in Children with Achondroplasia in the ApproaCH Trial

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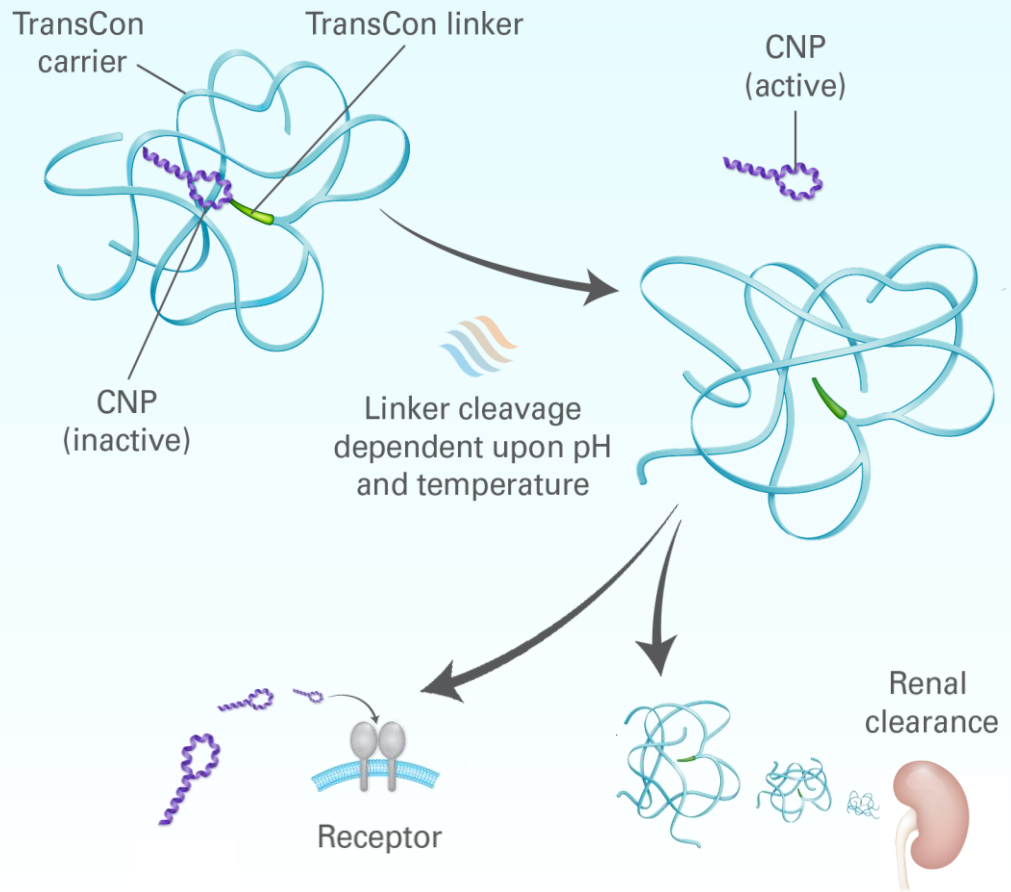
Introduction

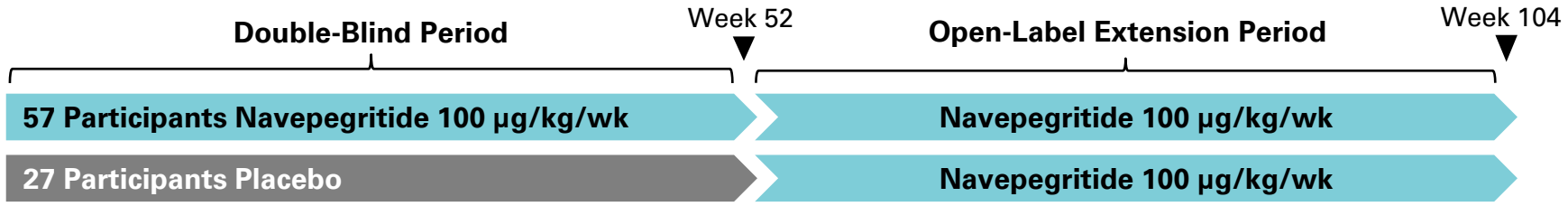
- Clinical manifestations of achondroplasia are associated with limitations in physical functioning and reduced HRQoL[1-3]
- While achondroplasia has historically been considered a growth disorder, manifestations beyond short stature, including reduced muscle strength and stamina, may also be debilitating[4,5]
- Navepegritide is an investigational prodrug of C-type natriuretic peptide (CNP), administered once-weekly and designed to provide continuous exposure to active CNP for the treatment of achondroplasia[6]

Navepegritide (TransCon® CNP) Design



HRQoL; health-related quality of life. 1. Savarirayan R, et al. *Nat Rev Endocrinol.* 2022;18(3):173-89. 2. Murton MC, et al. *Adv Ther.* 2023;40(9):3639-80. 3. Constantinides C, et al. *Disabil Rehabil.* 2022;44(21):6166-6178. 4. Sims DT, et al. *J Appl Physiol.* 2018;124:696-703. 5. Takken T, et al. *J Pediatr.* 2007;150(1):26-30. 6. Breinholt VM, et al. *J Pharmacol Exp Ther*. 2019;370:459-471.

ApproaCH Trial Design



Trial Population

- 84 treatment-naïve participants with achondroplasia (2-11 years), stratified by age and sex
- Randomized 2:1 (navepegritide:placebo)

Countries

- United States, Canada, Denmark, Ireland, Spain, Australia, New Zealand

Primary Endpoint

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

Secondary Endpoints

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

Selected Exploratory Endpoint

- **Physical functioning**, including maximal knee extensor muscle strength

Safety Endpoints

- Incidence of treatment emergent adverse events (**TEAEs**) and safety assessments
- Tolerability

HRQoL, health-related quality of life

Condition-Specific Clinical Outcome Assessments: Achondroplasia Child Experience Measure (ACEM)

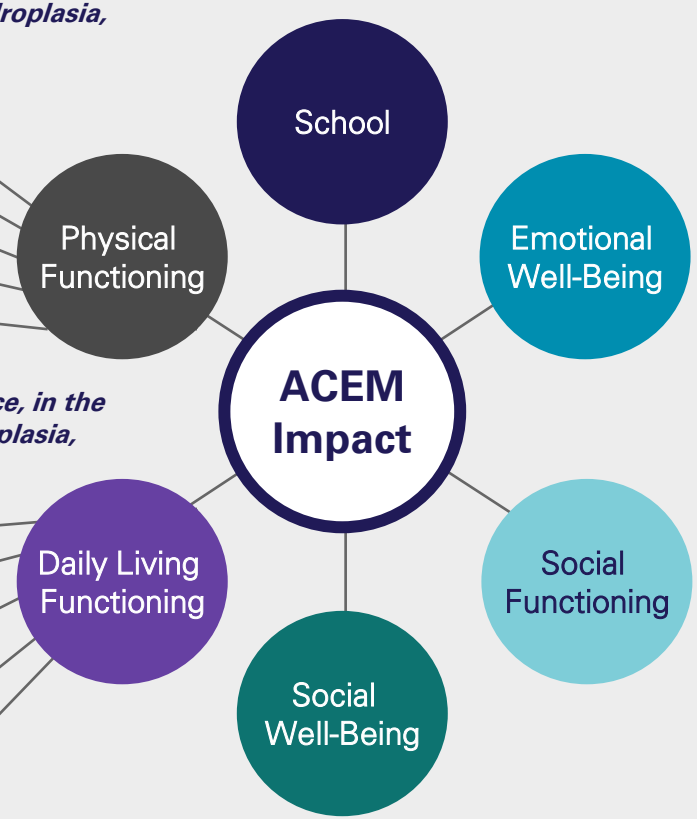
ACEM-IMPACT

In the past 2 weeks, because of achondroplasia, how difficult was it for your child to:

- Sit for long periods
- Climb stairs or steps
- Be physically active
- Walk long distances
- Run

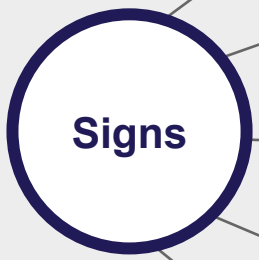
<u>Without</u> assistance or an adaptive device, in the past 2 weeks, and because of achondroplasia, how difficult was it for your child to:

- Reach objects or high places
- Toilet themselves
- Bathe/shower, wash, and/or brush/comb hair
- Perform tasks requiring fine motor skills
- Dress or undress



ACEM-Observable Signs Measure (OSM)

In the past 2 weeks because of achondroplasia, how often did your child experience:



- **Ear problems** (such as ear infections/fluid draining from the ear, child complaining of ear pain, and/or tugging on ear)
- **Pain** (such as in back, legs, joints, which child complains of and/or may interfere with activities)
- **Sleep apnea** (sleep disturbances such as pauses in breathing, loud snoring or breathing, and/or daytime sleepiness)
- **Low stamina** (such as tiring easily and/or decreased physical activity)
- **Balance issues** (such as falls/trips often and/or loses balance easily)

The measures are scored on a 0-100 scale (by the caregiver), with higher scores indicating greater impairment

ACEM, Achondroplasia Child Experience Measure

ApproaCH Trial Baseline Characteristics

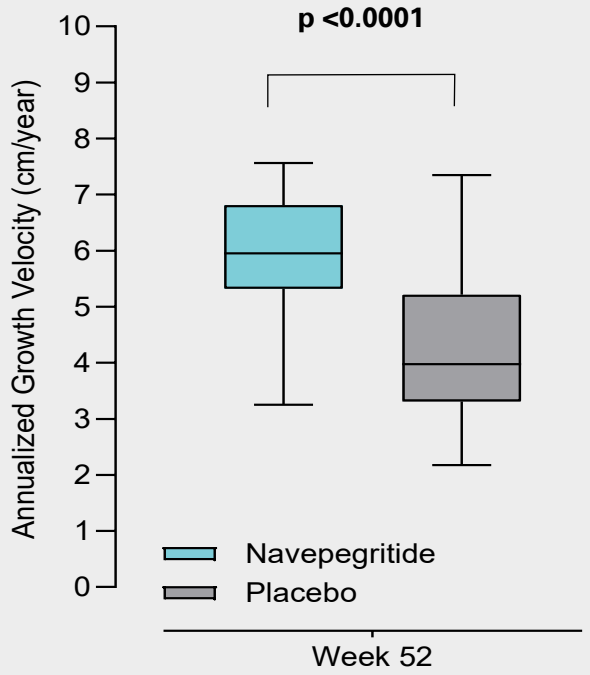
Full Analysis Set	Navepegritide (N=57)	Placebo (N=27)	Overall (N=84)
Age (years), mean (SD)	5.6 (2.6)	6.0 (2.7)	5.7 (2.6)
Sex, n (%) Female Male	 26 (45.6) 31 (54.4)	 13 (48.1) 14 (51.9)	 39 (46.4) 45 (53.6)
Height (cm), mean (SD)	88.9 (12.9)	89.1 (11.5)	89.0 (12.4)
Achondroplasia-specific height Z-score, 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

Navepegritide Demonstrated Superiority in Annualized Growth Velocity at Week 52 vs Placebo

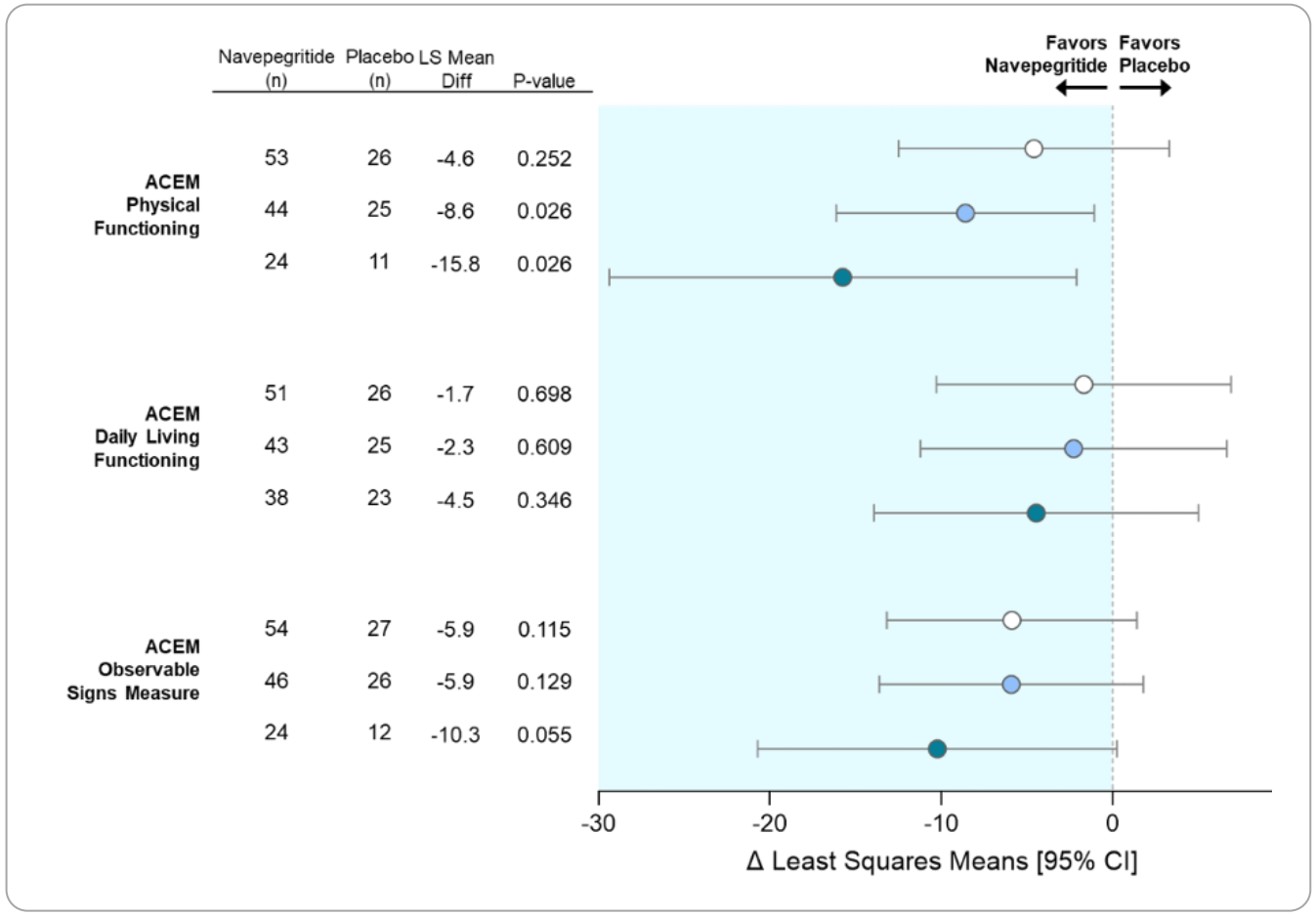
Full Analysis Set	LS Mean [95% CI] AGV at Week 52 (cm/year)	LS Mean Difference [95% CI] Navepegritide *vs.* Placebo (cm/year)
Navepegritide n=57*	**5.89** [5.66, 6.13]	**1.49** [1.05, 1.93] p <0.0001
Placebo n=27	**4.41** [4.04, 4.77]	

Annualized Growth Velocity at Week 52 by Treatment Arm (Full Analysis Set)



* Data for 2 patients were imputed. AGV, annualized growth velocity; CI, confidence interval; LS, least squares

Consistent Improvements With Navepegritide in Key ACEM Domains



- Total trial population (FAS)
- Same respondent
- Same respondent with baseline ACEM domain score ≥ 20

Significant improvement was observed in ACEM-Physical Functioning in 'same respondent' (Baseline & Week 52) analysis, especially in participants with higher baseline burden

ACEM, Achondroplasia Child Experience Measure; Diff, difference; FAS, Full Analysis Set; LS, least squares

Greater Improvements in ACEM-Physical Functioning in Participants <5 years vs total population

	Navepegritide (N=57)		Placebo (N=27)		Treatment Difference	p-value
Population	**n**	**LS Mean [95% CI]**	**n**	**LS Mean [95% CI]**	**LS Mean [95% CI]**	
Overall	53[a,b]	0.7 [-3.2, 4.7]	26[c]	5.3 [-1.5, 12.1]	-4.6 [-12.5, 3.3]	0.2519
<5 years (pre-specified subset)	20[a]	-1.6 [-8.8, 5.7]	10	9.6 [0.9, 18.3]	**-11.1 [-21.5, -0.8]**	**0.0366**

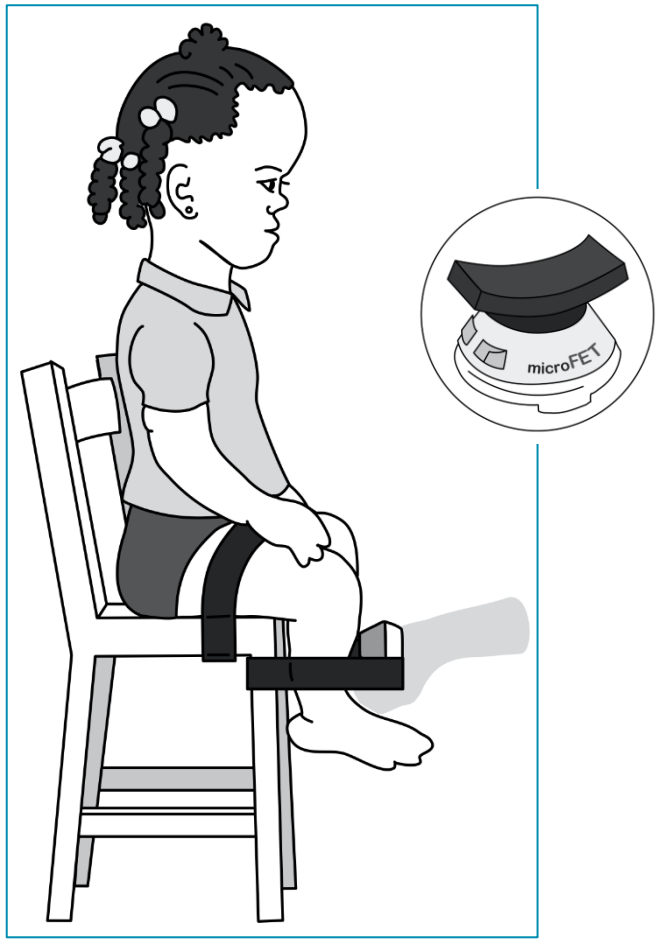
N = number of participants in the analysis set, n = number of subjects with non-missing data.
[a] Baseline value missing for 1 participant.
[b] Data for 3 participants imputed using multiple imputation.
[c] Data for 1 participant imputed using multiple imputation.

ACEM, Achondroplasia Child Experience Measure; CI, confidence interval; LS, least squares

Greater Lower Limb Strength With Navepegritide vs Placebo at Week 52

	Treatment difference navepegritide vs. placebo		
Subjects 5 to <8 years	**LS Mean**	**[95% CI]**	**p-value**
Torque (N-m)	**4.16**	[1.09, 7.24]	p=0.0121
Torque Z-score	**0.43**	[0.06, 0.79]	p=0.0228
Torque relative to BW (N-m/kg)	**0.20**	[0.05, 0.34]	p=0.0117

- Maximal knee extensor torque at Week 52 was an exploratory endpoint assessed in participants ≥5 years of age at time of testing to elucidate any impact of navepegritide on lower limb muscle strength
- A post hoc analysis in subjects 5 to <8 years at time of test* showed significantly greater torque, torque Z-score and torque relative to body weight in the navepegritide vs placebo group at Week 52



*4 to <7 years old at baseline. BW, body weight; CI, confidence interval

Navepegritide Showed a Safety and Tolerability Profile Comparable to Placebo

	Navepegritide (n=57)	Placebo (n=27)
Any Treatment-Emergent Adverse Event, n (%)	52 (91.2)	26 (96.3)
Adverse Events ≥15% in Either Treatment Group, n (%)		
Pyrexia	20 (35.1)	6 (22.2)
Nasopharyngitis	18 (31.6)	10 (37.0)
Otitis media	14 (24.6)	7 (25.9)
Upper respiratory tract infection	11 (19.3)	3 (11.1)
Vomiting	11 (19.3)	3 (11.1)
Headache	10 (17.5)	3 (11.1)
Serious Adverse Events	3 (5.3)	3 (11.1)
Treatment-Related Adverse Events, n (%)	12 (21.1)	7 (25.9)
Treatment-Related Serious Adverse Events	0	0
Injection Site Reaction (ISR), n (%)	11 (19.3)	4 (14.8)
ISR Events Per Patient Year of Exposure	0.41	0.15

Treatment with navepegritide showed:

- no treatment-related SAEs
- few occurrences of ISRs
- no cases of symptomatic hypotension
- no accelerated bone age or fractures

ISR, injection site reaction; SAE, serious adverse event

Conclusions

- Navepegritide demonstrated superior **AGV** compared to placebo at Week 52, with a similar safety and tolerability profile
- **Physical functioning benefits** were most evident in younger children with achondroplasia, including greater improvements in both caregiver-reported outcomes and greater lower limb muscle strength with navepegritide vs placebo at Week 52

Navepegritide, administered once weekly and designed to provide continuous exposure to active CNP, is the first pharmacological treatment in development for achondroplasia to have demonstrated significant benefits extending beyond growth in a placebo-controlled trial

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