

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

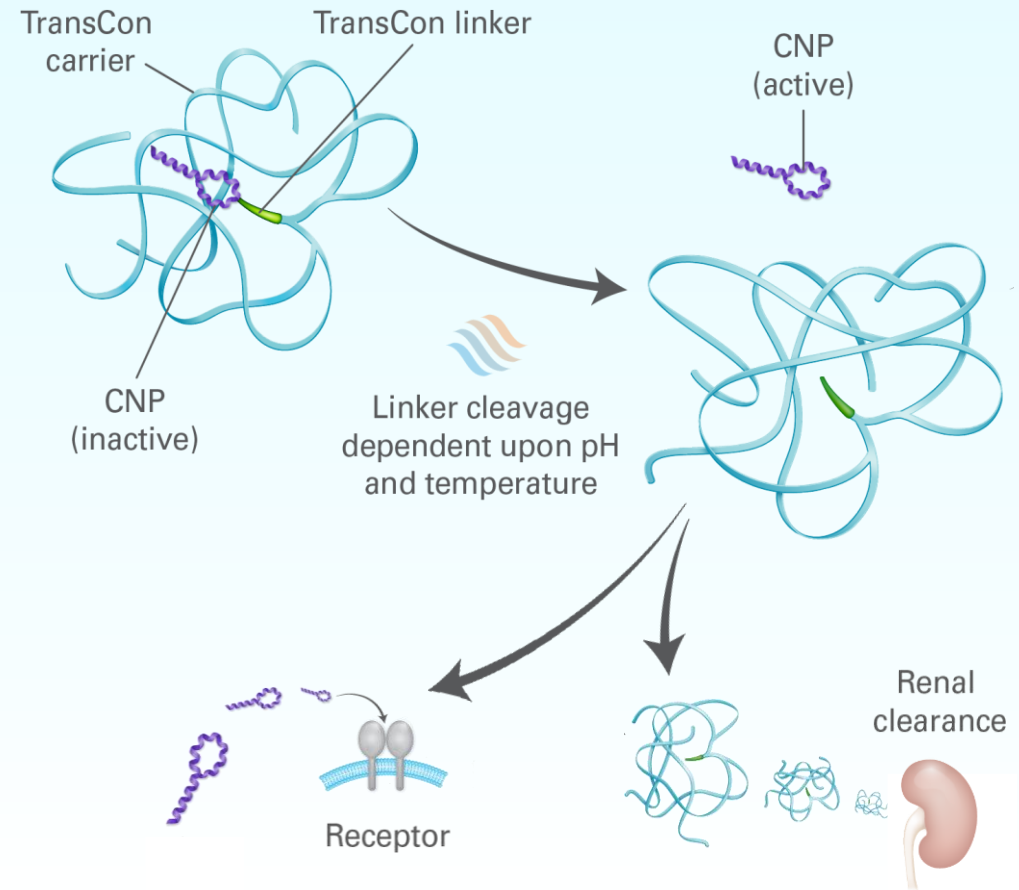
Carlos A. Bacino¹, Ravi Savarirayan²⁻⁴, Hanne B. Hove⁵, Daniel G. Hoernschemeyer⁶, Janet M. Legare⁷, M. Jennifer Abuzzahab⁸, Paul L. Hofman⁹, Philippe M Campeau¹⁰, Josep Maria de Bergua Domingo¹¹, Alden Smith¹², Anders N. Jørgensen¹², Lærke C. Freiberg¹², Michael Ominsky¹², Aimee D. Shu¹², Ciara McDonnell¹³

¹Baylor College of Medicine, Houston, TX, USA; ²Murdoch Children's Research Institute, Parkville, Australia; ³Royal Children's Hospital, Parkville, Australia; ⁴University of Melbourne, Parkville, Australia; ⁵Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; ⁶University of Missouri Children's Hospital, Columbia, MO, USA; ⁷University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ⁸Children's Minnesota, Minneapolis, MN, USA; ⁹The Liggins Institute, University of Auckland, Auckland, New Zealand; ¹⁰CHU Sainte-Justine Research Center, Montreal, Canada; ¹¹Universitat Autònoma de Barcelona, Barcelona, Spain; ¹²Ascendis Pharma Inc., Palo Alto, CA, USA; ¹³Children's Health Ireland at Temple Street, Dublin, Ireland; University of Dublin, Trinity College, Dublin, Ireland

Introduction

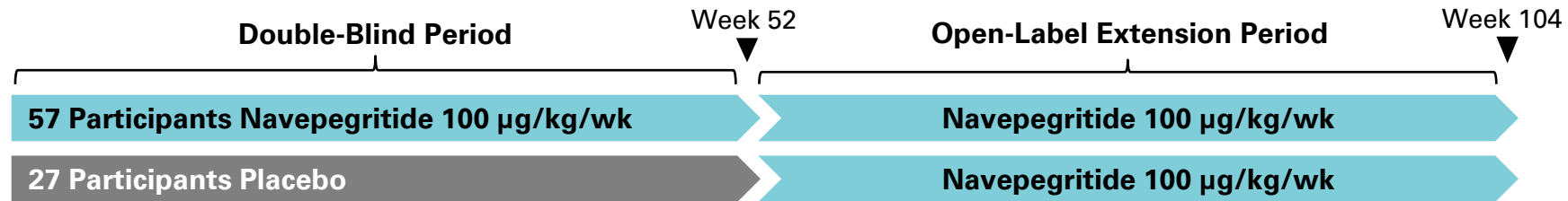
- Clinical manifestations of achondroplasia are associated with limitations in physical functioning and reduced HRQoL¹⁻³
- While achondroplasia has historically been considered a growth disorder, manifestations beyond short stature, including reduced muscle strength and stamina, may also be debilitating^{4,5}
- 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 achondroplasia⁶

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

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

Without 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

Physical
Functioning

School

Emotional
Well-Being

ACEM
Impact

Social
Functioning

Social
Well-Being

Daily Living
Functioning

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)

Signs

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

ApproaCH Trial Baseline Characteristics

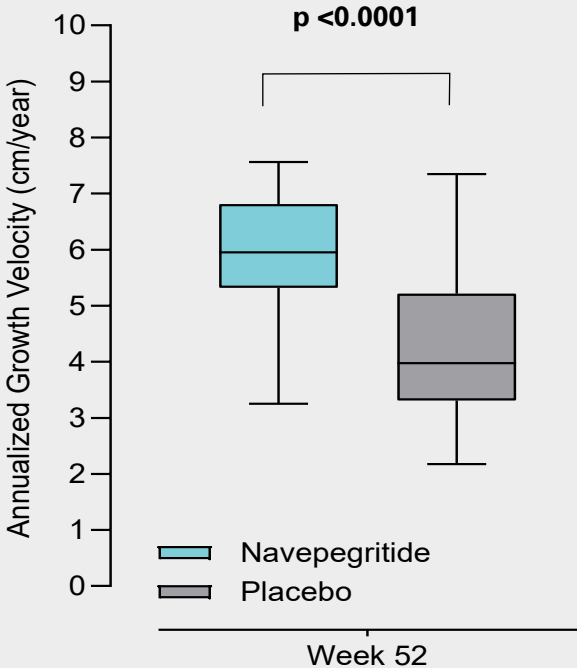
Full Analysis Set	Navepegritide (N=57)	Placebo (N=27)	Overall (N=84)
Age (years), mean (SD)	5.6 (2.6)	6.0 (2.7)	5.7 (2.6)
Sex, n (%)			
Female	26 (45.6)	13 (48.1)	39 (46.4)
Male	31 (54.4)	14 (51.9)	45 (53.6)
Height (cm), mean (SD)	88.9 (12.9)	89.1 (11.5)	89.0 (12.4)
Achondroplasia-specific height Z-score,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

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

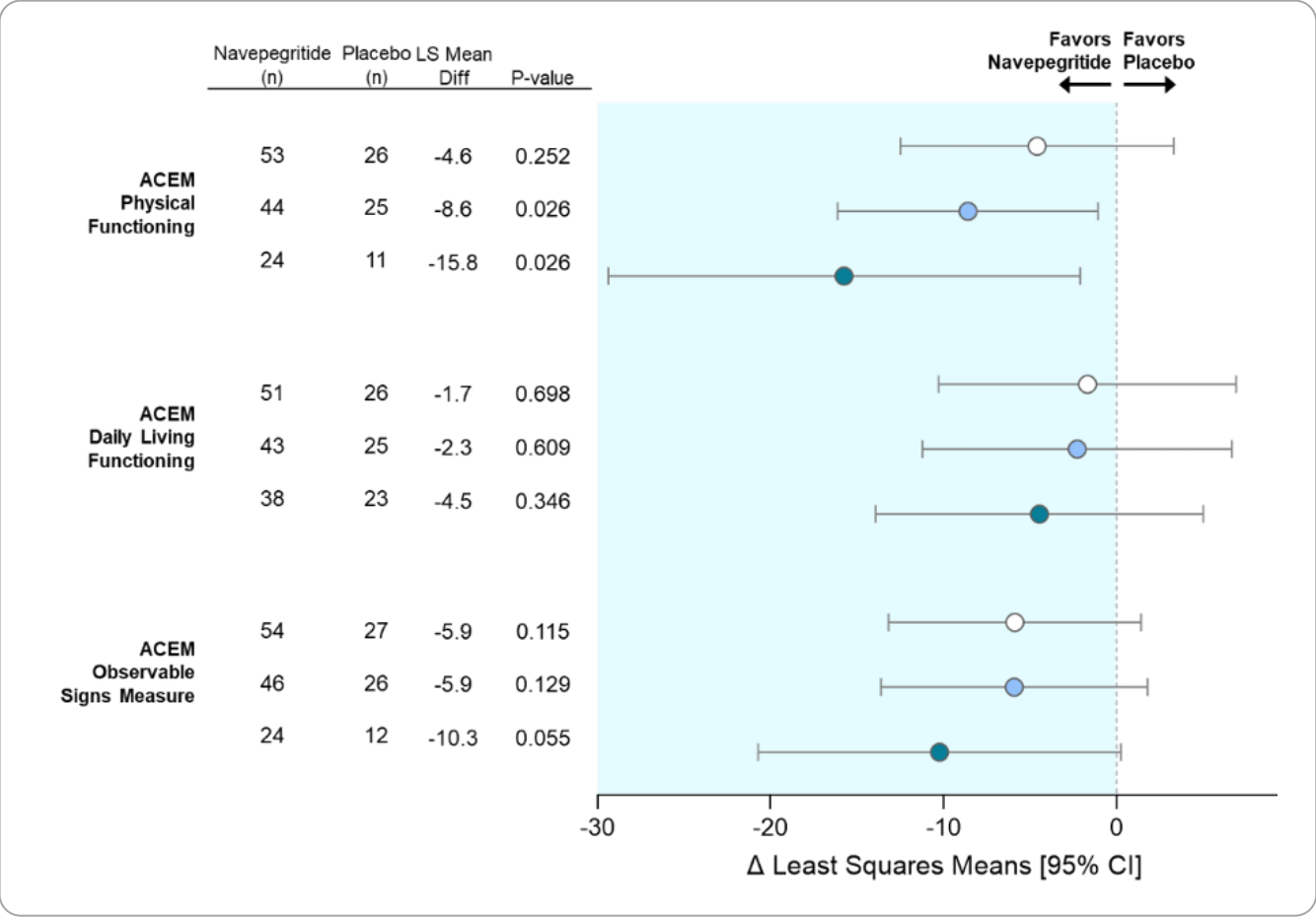
Full Analysis Set	LS Mean [95% CI] AGV at Week 52 (cm/year)	LS Mean Difference [95% CI] Navepegritide vs. Placebo (cm/year)
Navepegritide n=57*	5.89 [5.66, 6.13]	1.49 [1.05, 1.93]
Placebo n=27	4.41 [4.04, 4.77]	p <0.0001

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.

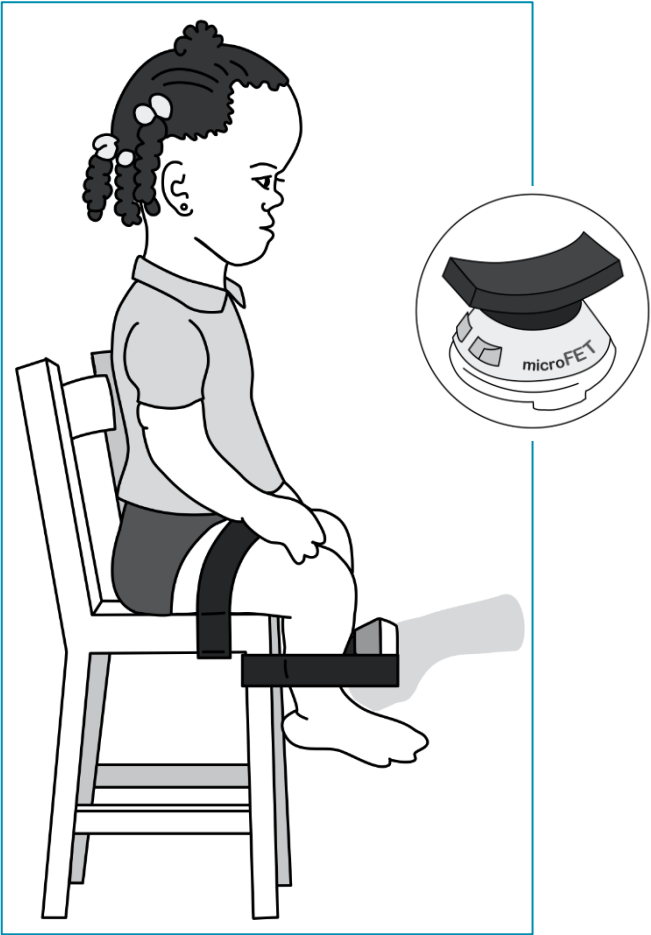
ACEM, Achondroplasia Child Experience Measure; CI, confidence interval; LS, least squares

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

Disclosures, Acknowledgments, and Funding

- Jennifer Abuzzahab: Institutional research support from Ascendis Pharma, Medtronic, Lumos, Soleno, Rhythm, Novo Nordisk; consultant for Ascendis Pharma, Soleno, Rhythm and Pfizer; Speaker for Rhythm and Neurocine
- Ascendis Pharma Growth Disorders A/S funded this trial and participated in the trial design, research, analysis, data collection, interpretation of the data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Bart Degrevè, PhD, MBA.
- Financial arrangements of the authors with companies whose products may be related to this presentation are listed as declared by the authors: **DGH**: Research support/site PI for Ascendis Pharma, BioMarin and BridgeBio/QED, royalty stock holder for OrthoPediatrics, and speaker faculty for Highridge; **JML**: Speaker faculty for BioMarin, site PI for Ascendis Pharma, and BridgeBio/QED; **HBH**: member of the advisory board for Ascendis Pharma and consulting role for Ascendis Pharma; **CAB**: Participated in clinical trials with Ascendis Pharma; **PMC**: Participated in clinical trials with Ascendis Pharma; **JdB**: Participated in clinical trials with Ascendis Pharma, BioMarin and BridgeBio/QED; **MJA**: Institutional research support from Ascendis Pharma, Medtronic, Lumos, Soleno, rhythm, Novo Nordisk; consultant for Ascendis Pharma, Soleno, rhythm and Pfizer; Spear for rhythm and Neurocine; **KS**: Research Support: Medtronics, ZimVie, SpinoModulation, Ascendis Pharma, Ultragenix; **SC**: Research support: Ascendis Pharma; **AT**: Research Support: Ascendis Pharma; **SJ**: Research Support: Ascendis Pharma; **MS**: Research support: Ascendis Pharma; **RS**: Consulting fees and honoraria from BMN, Ascendis Pharma, QED, and tyra; **CM**: Research support grants/advisory boards/presentations from Ascendis Pharma, Abbott, Pfizer, Kyowa Kirin, Ultragenyx, BioMarin, Regeneron and Alexion; **MM**, **LCF**, **MM**, **MO**, and **ADS** are employees of Ascendis Pharma, Inc.