Novel therapeutic options in achondroplasia

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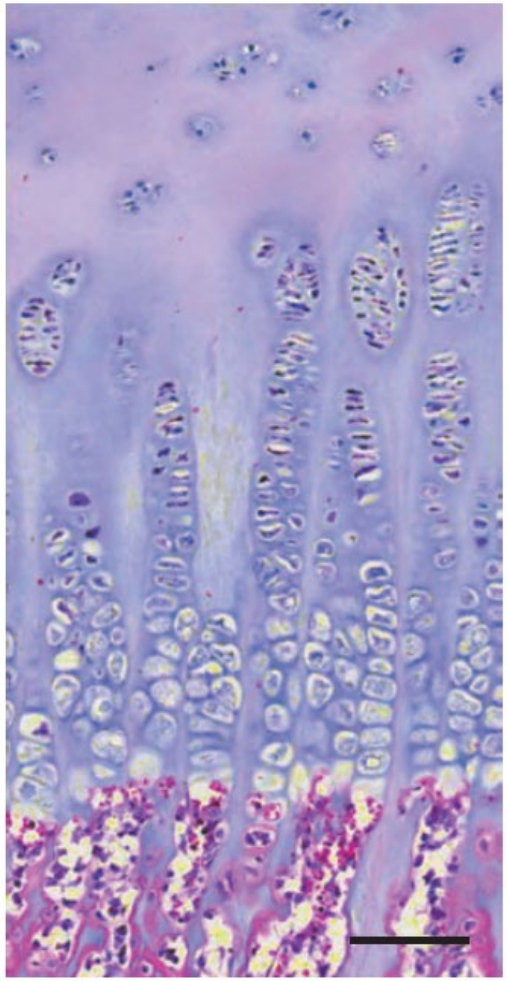
Current treatment of achondroplasia

- Prior to this past year, there were no approved medical treatments for achondroplasia in the US or Europe

- Growth hormone therapy is approved for the treatment of achondroplasia in Japan
  - What is the expected benefit of growth hormone therapy for patients with achondroplasia?

- Limb-lengthening surgery can be used to increase height and improve body proportionality

Precision medicine approaches to the treatment of achondroplasia

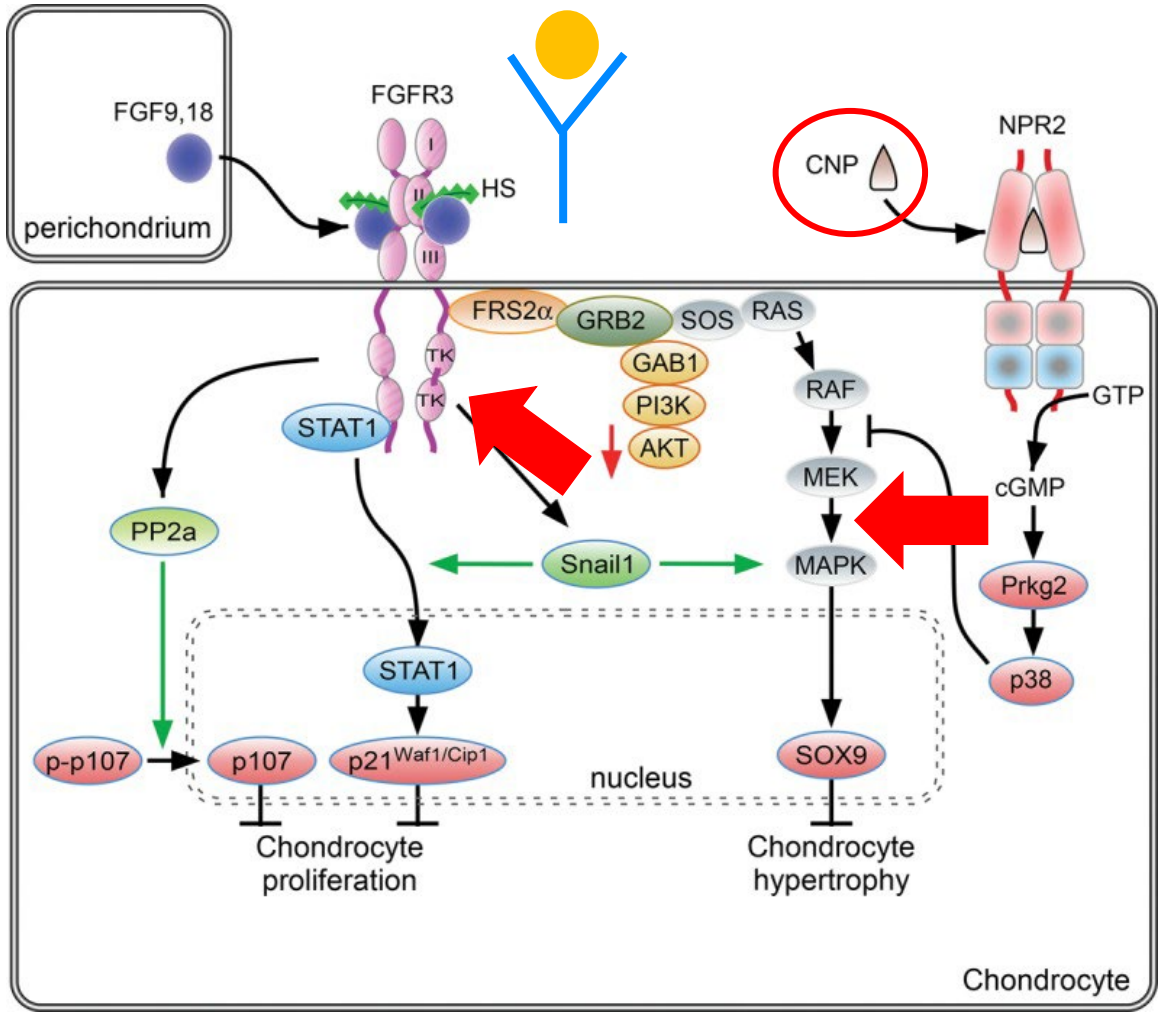


Resting zone

Proliferative zone

Hypertrophic zone

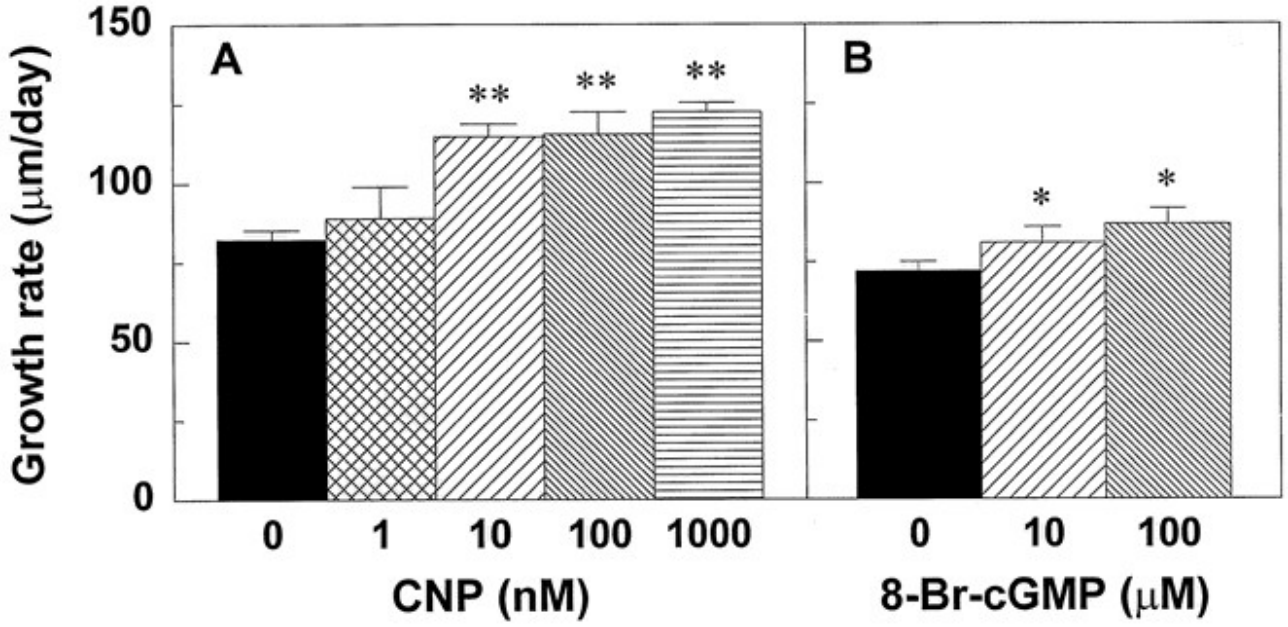
Metaphyseal zone



cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; FGFR3, fibroblast growth factor receptor 3.

Baron J, et al. *Nat Rev Endocrinol* 2015;11735–46; Ornitz DM, et al. *Genes Dev* 2015;29:1463–1486.

CNP increases growth of rat growth plates

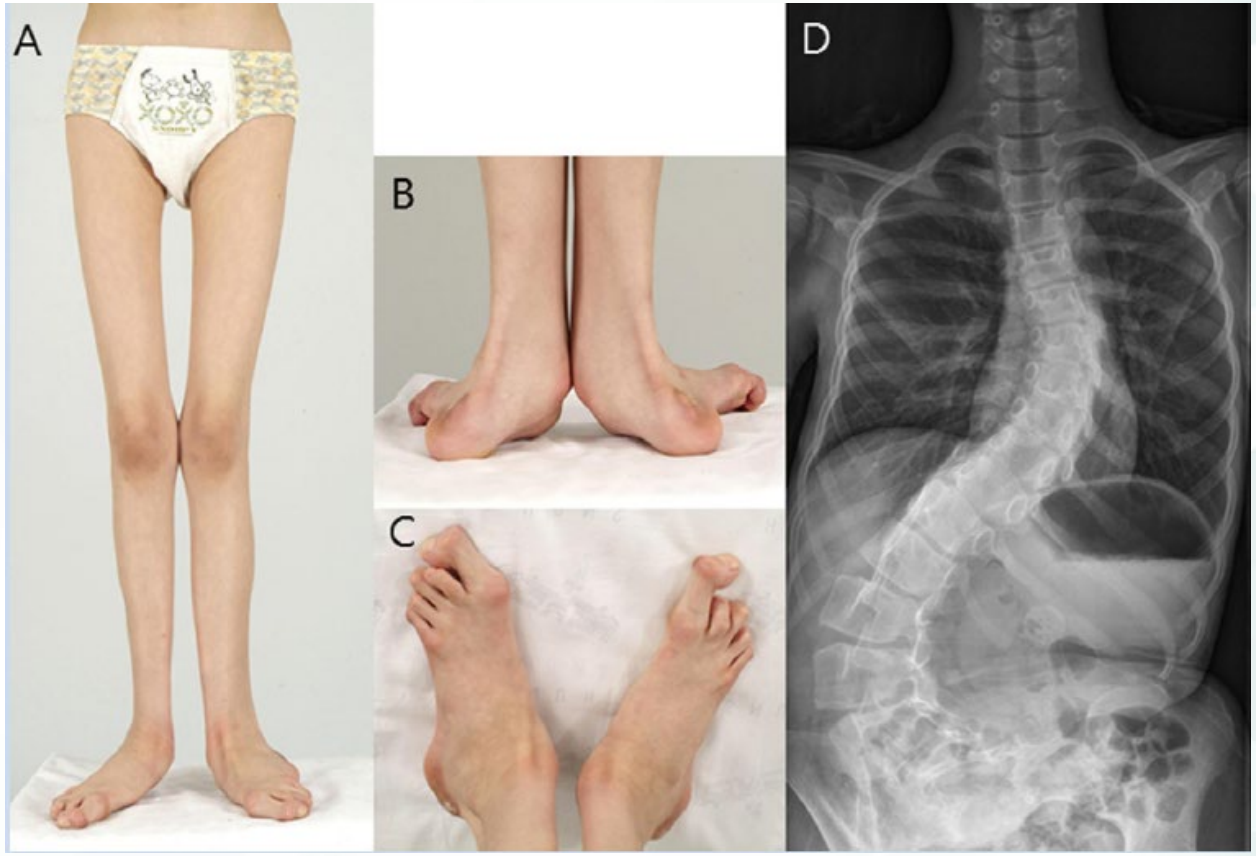


- Increased chondrocyte proliferation in the proliferative zone
- Increased number and size of hypertrophic chondrocytes
- Stimulated cartilage matrix production

cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide.
Mericq V, et al. *Pediatr Res* 2000;47:189–193.

CNP overexpression causes tall stature

- Four patients with translocations leading to increased CNP expression
- Clinical features:
  - Very tall stature
  - Marfanoid habitus
  - Arachnodactyly
  - Very long hallux
  - Scoliosis



CNP, C-type natriuretic peptide.

Bocciardi R, et al. *Hum Mutat* 2007;28:724–731; Moncla A, et al. *Hum Mut* 2007;28:1183–1188; Ko JM, et al. *Am J Med Genet A* 2015;167A:1033–1038.

Increased CNP signaling leads to tall stature in humans!

An Overgrowth Disorder Associated with Excessive Production of cGMP Due to a Gain-of-Function Mutation of the Natriuretic Peptide Receptor 2 Gene

PLoS ONE 7(8): e42180. doi:10.1371/journal.pone.0042180

Overgrowth Syndrome Associated With a Gain-of-Function Mutation of the Natriuretic Peptide Receptor 2 (*NPR2*) Gene

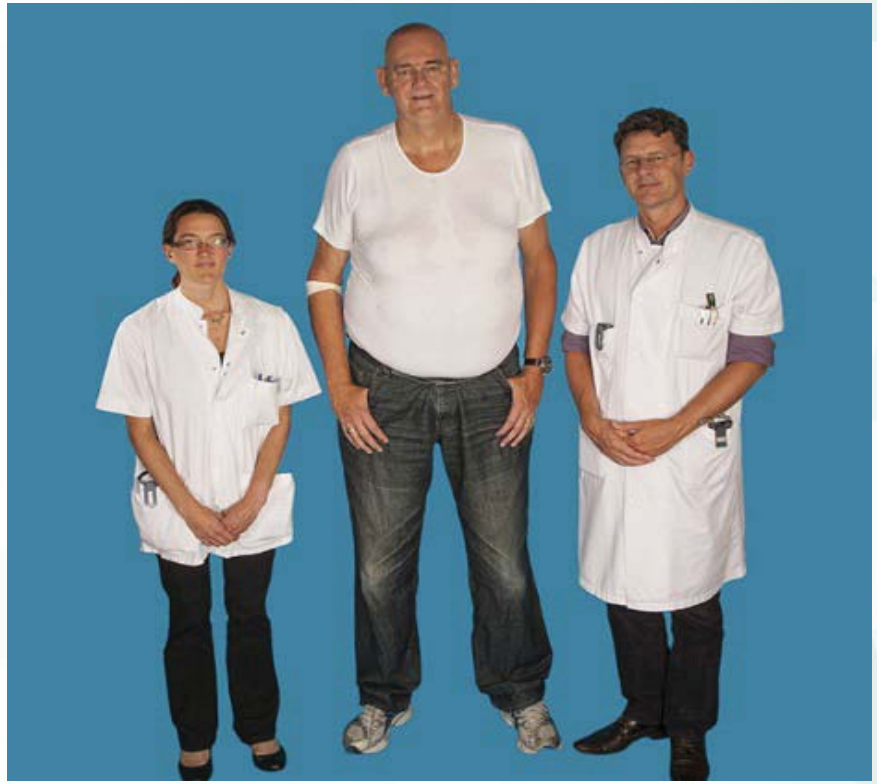
Am J Med Genet Part A 164A:156–163.

An Activating Mutation in the Kinase Homology Domain of the Natriuretic Peptide Receptor-2 Causes Extremely Tall Stature Without Skeletal Deformities

J Clin Endocrinol Metab, December 2013, 98(12):E1988–E1998

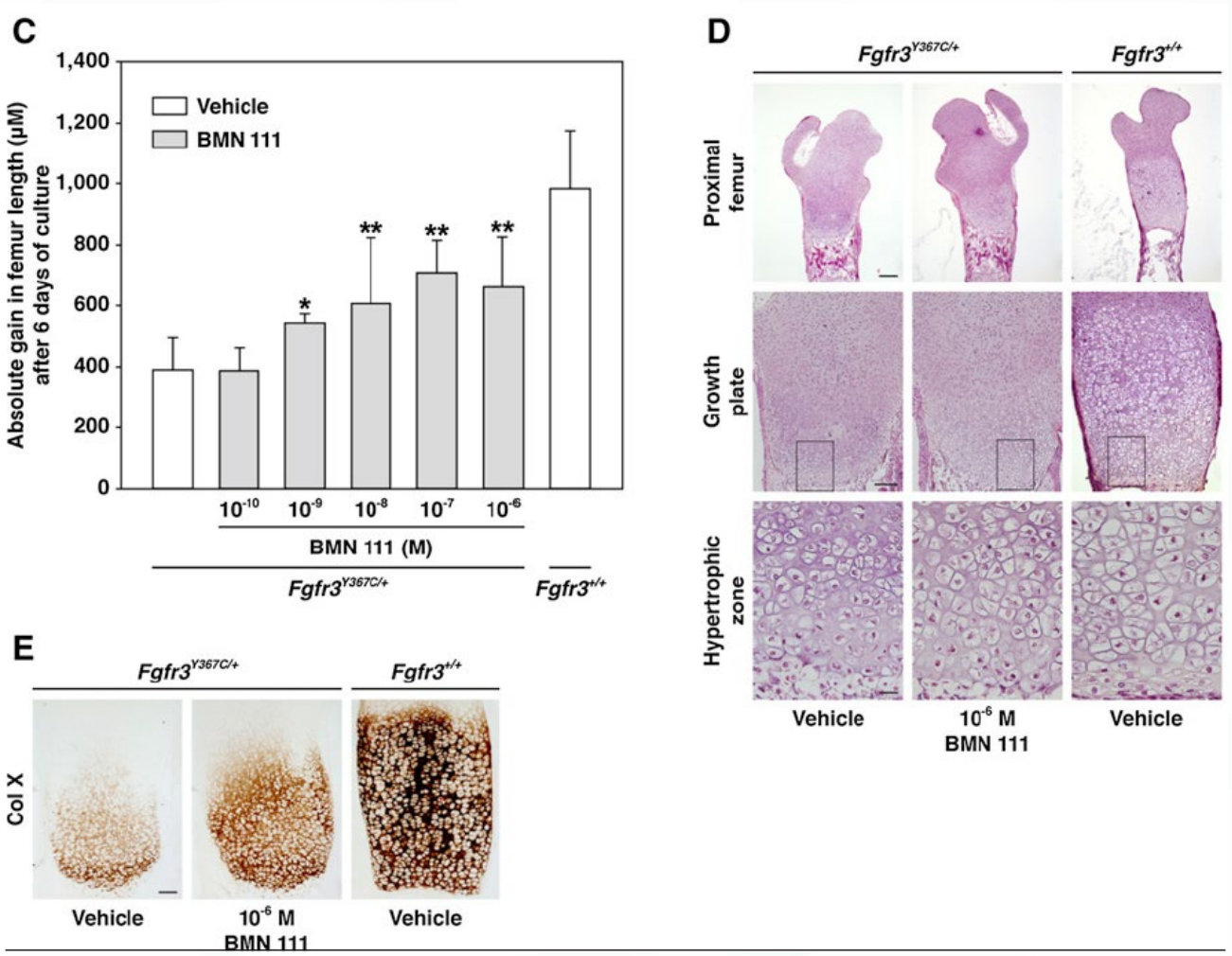
An Activating Deletion Variant in the Submembrane Region of Natriuretic Peptide Receptor-B Causes Tall Stature

J Clin Endocrinol Metab, July 2020, 105(7):2354–2366



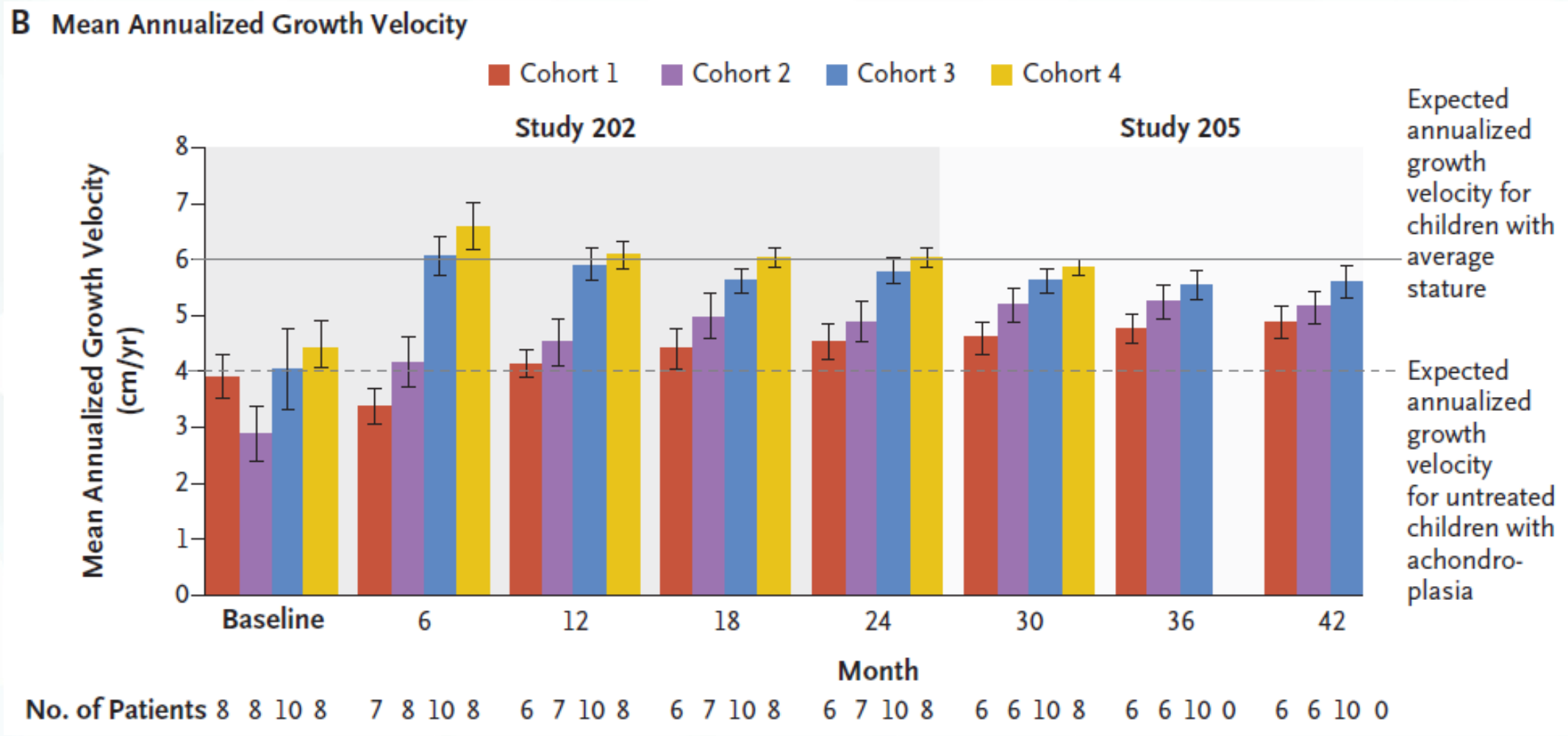
Height 7’3”

CNP analog as therapy for achondroplasia



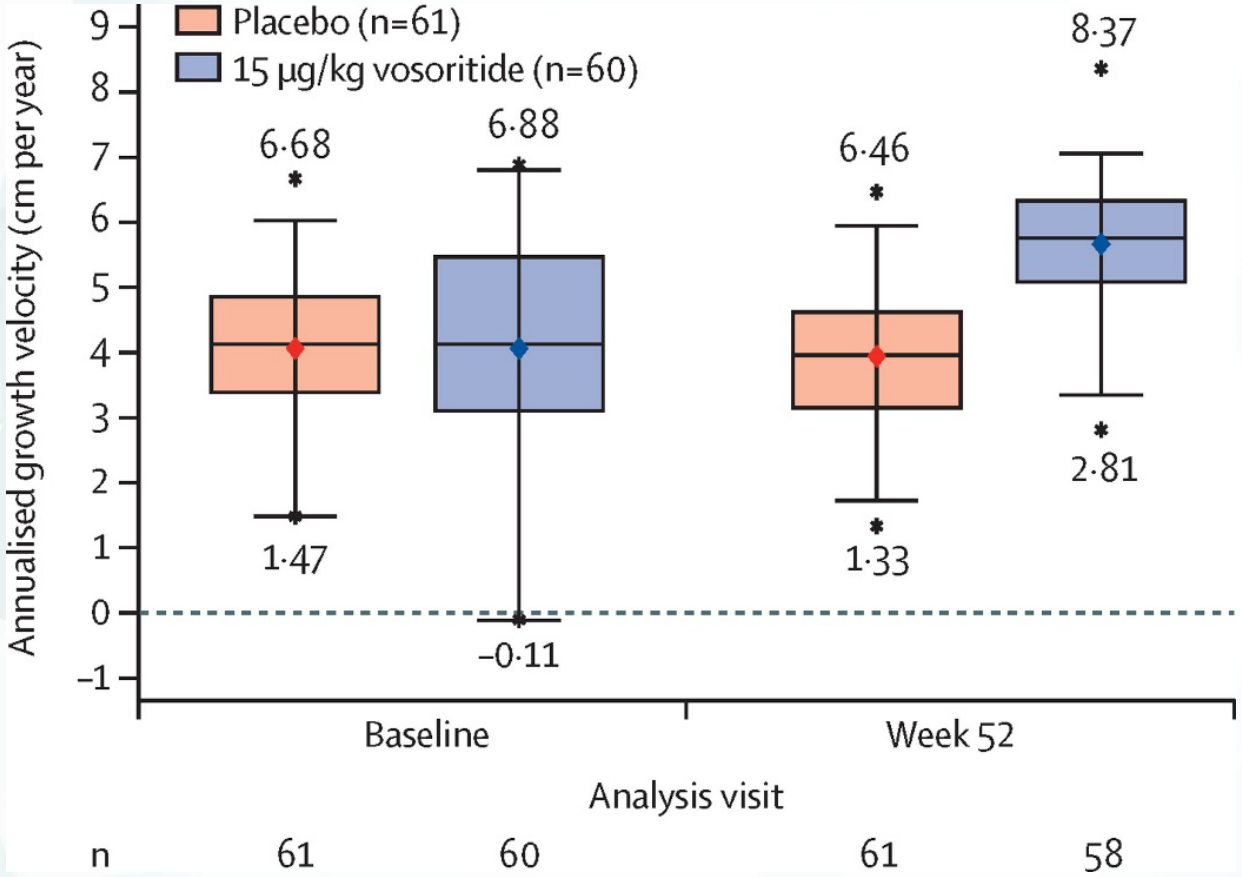
CNP, C-type natriuretic peptide; FGFR3, fibroblast growth factor receptor 3.
Lorget F, et al. *Am J Hum Genet* 2012;91:1108–1114.

C-Type Natriuretic Peptide Analogue therapy in Children with Achondroplasia

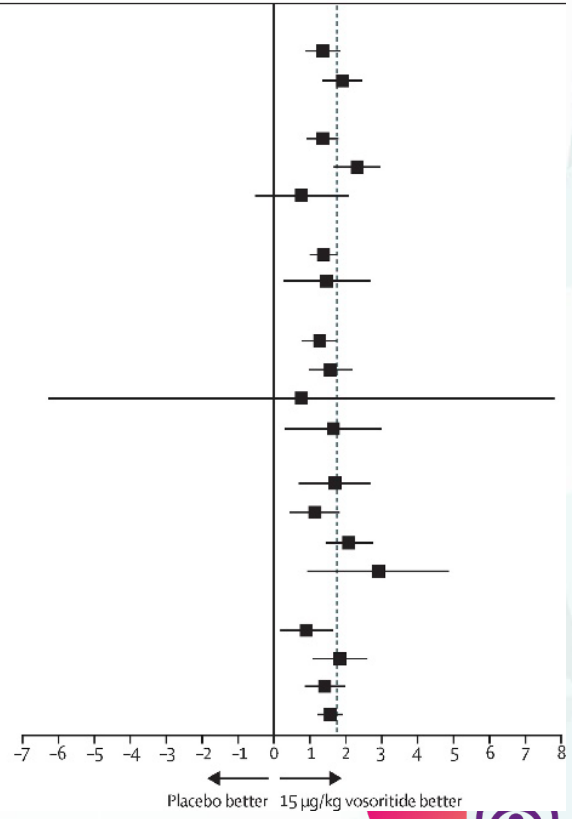


Savarirayan R, et al. *N Engl J Med* 2019;381:25–35.

Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial

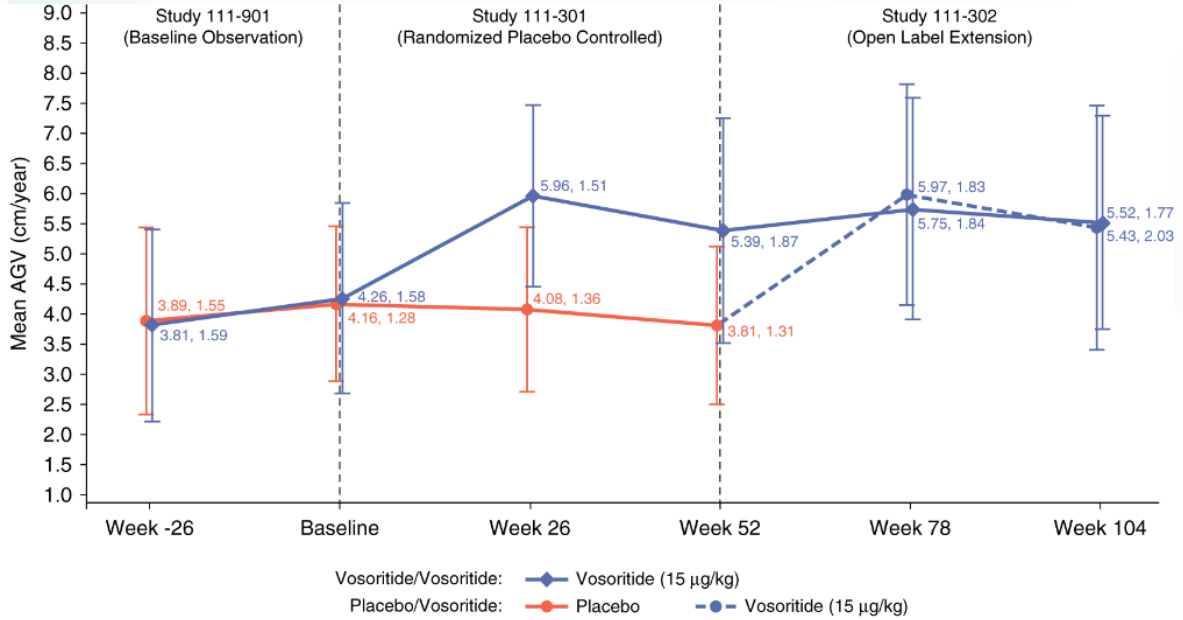


	Number of subjects (%)		LS mean change from baseline	Difference (95% CI) in least-squares mean change from baseline
	15 µg/kg vosoritide	Placebo	Difference (cm)	15 µg/kg vosoritide minus placebo
Sex				
Male	31 (51·7)	33 (54·1)	1·36	
Female	29 (48·3)	28 (45·9)	1·91	
Age group (years)				
≥5 to <8	31 (51·7)	24 (39·3)	1·35	
≥8 to <11	17 (28·3)	24 (39·3)	2·32	
≥11 to <15	12 (20·0)	13 (21·3)	0·77	
Tanner stage				
I	48 (80·0)	48 (78·7)	1·38	
>I	12 (20·0)	13 (21·3)	1·47	
Strata				
Male Tanner Stage I	28 (46·7)	28 (45·9)	1·27	
Female Tanner Stage I	20 (33·3)	20 (32·8)	1·57	
Male Tanner Stage >I	3 (5·0)	5 (8·2)	0·76	
Female Tanner Stage >I	9 (15·0)	8 (13·1)	1·65	
Height Z score category				
≤−6	15 (25·0)	10 (16·4)	1·69	
>−6 to ≤−5	18 (30·0)	24 (39·3)	1·14	
>−5 to ≤−4	22 (36·7)	19 (31·1)	2·09	
>−4	5 (8·3)	8 (13·1)	2·90	
Annualised growth velocity category				
≤3·5 cm/year	19 (31·7)	19 (31·1)	0·90	
>3·5 to ≤4·5 cm/year	14 (23·3)	18 (29·5)	1·84	
≥4·5 cm/year	27 (45·0)	24 (39·3)	1·42	
Overall	**60 (100·0)**	**61 (100·0)**	**1·57**	

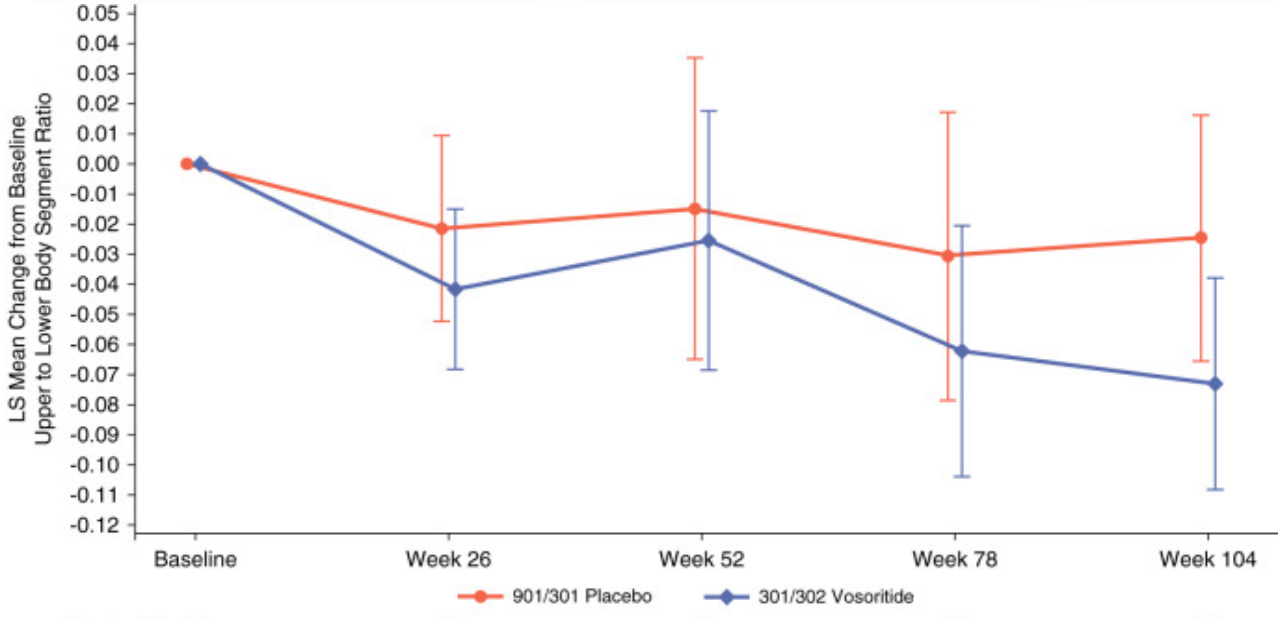


CI, confidence interval; LS, least squares.
Savarirayan R, et al. *Lancet* 2020;396:684–692.

Second-year results: Sustained increased in growth velocity and improvement in body proportions



Vosoritide/Vosoritide (N):	43	60	58	58	49	44
Placebo/Vosoritide (N):	44	61	61	61	54	47



Placebo (N):	38	38	38	38	38
15 µg/kg Vosoritide (N):	45	45	45	37	45

AGV, annualized growth velocity; LS, least squares.

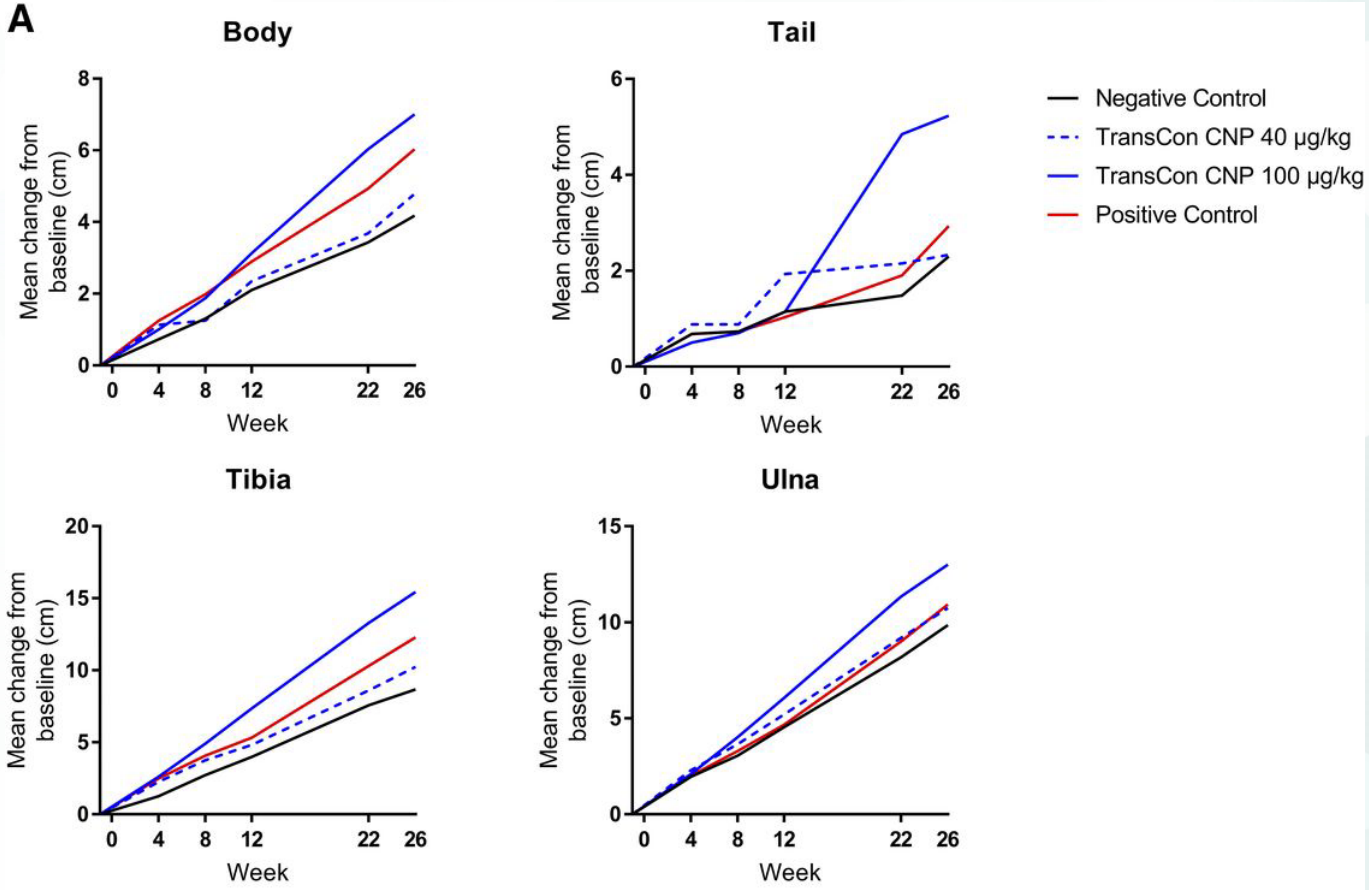
Savarirayan R, et al. *Genet Med* 2021;23:2443–2447.

Impact of therapy on achondroplasia

- Is an increase of ~1.6 cm/year a significant increase in growth velocity?
- Are there any data on whether this intervention affects the rate of medical complications seen in achondroplasia?
- What is the optimal age to start therapy?

Alternative approaches to modulate CNP

- TransCon CNP – sustained release form of CNP (Ascendis)
- Phase 2 study underway for achondroplasia
  - Aged 2–10 years
  - Enrollment completed (N=57)
  - Data expected Q4 2022



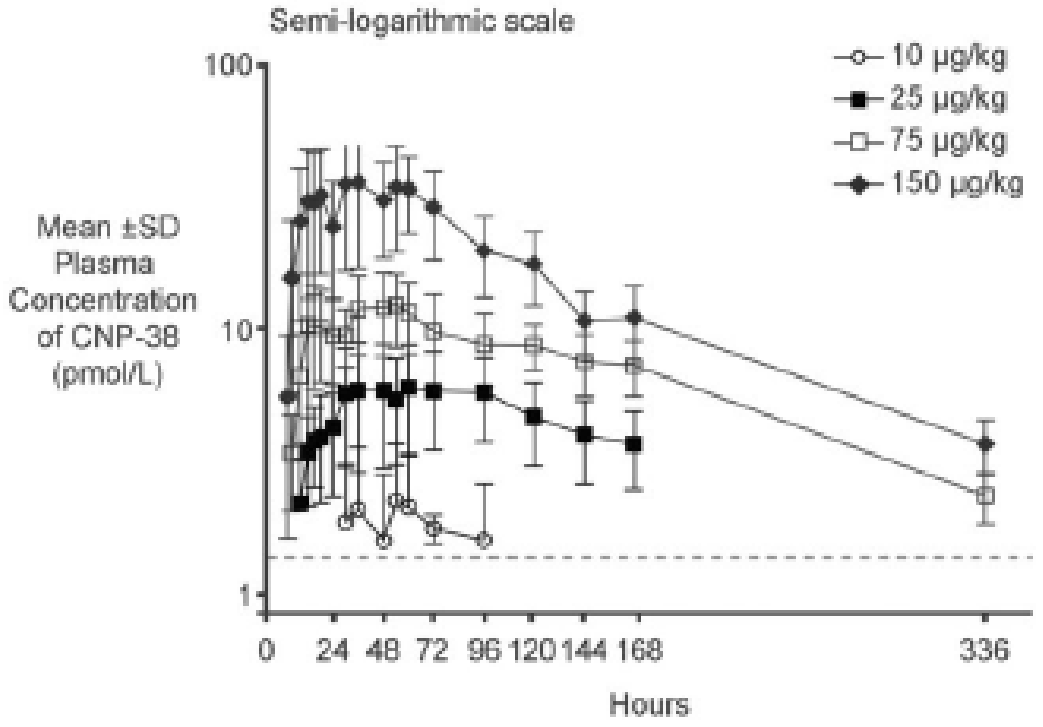
Effect of TransCon CNP in monkeys compared with daily CNP (positive control)

CNP, C-type natriuretic peptide.

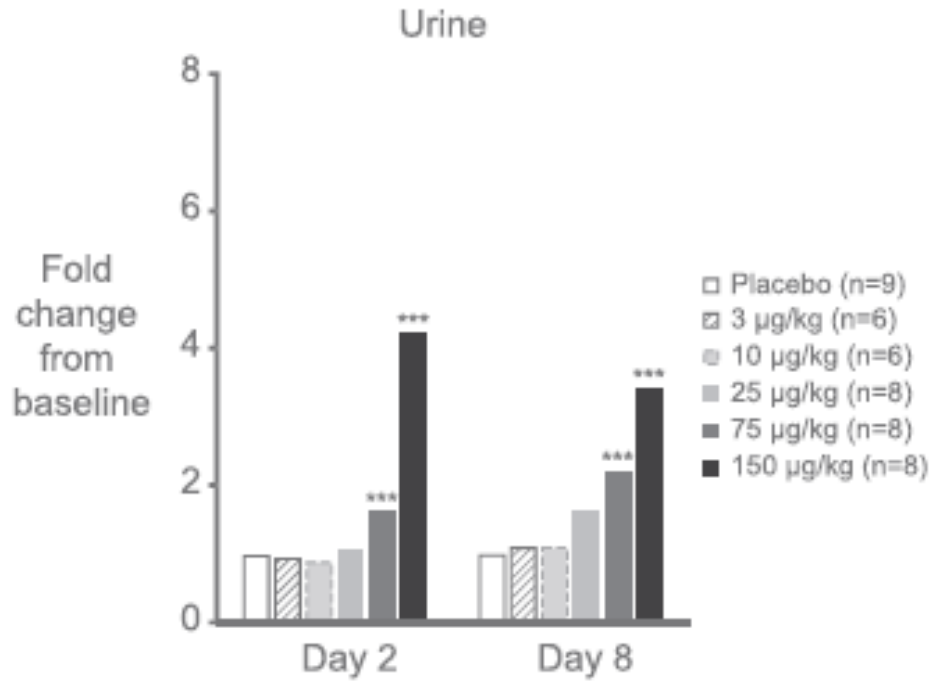
Breinholt VM, et al. *J Pharmacol Exper Ther* 2019;370:459–471; ClinicalTrials.gov NCT04085523. Study update information from Ascendis Website.

TansCon CNP: Pharmacokinetic and pharmacodynamic results

PK results



PD results – urine cGMP



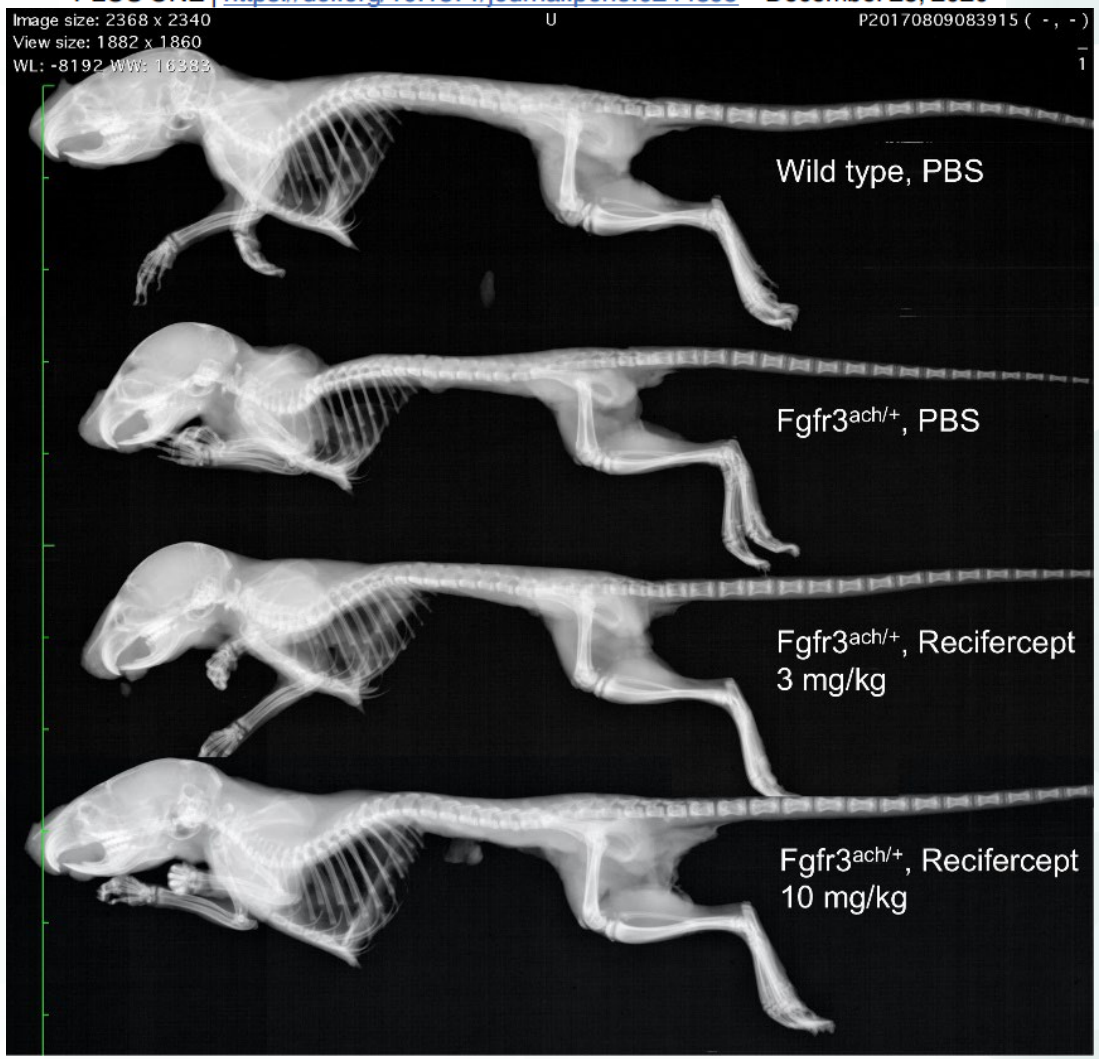
cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation.

Breinholt VM, et al. *Br J Clin Pharmacol* 2022. doi: 10.1111/bcp.15369 [Epub ahead of print].

Recifercept – a FGFR3 decoy receptor

- FGFR3 requires binding by FGFs in order to induce signaling
- Recifercept is a soluble form of the extracellular domain of FGFR3
- Phase 2 trial underway
  - 3 doses, subcutaneous
  - 12-month study

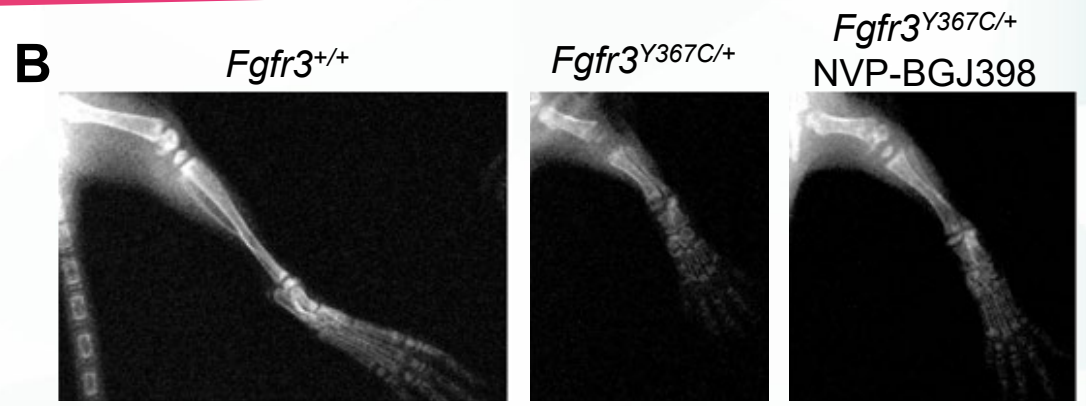
PLOS ONE | https://doi.org/10.1371/journal.pone.0244368 December 28, 2020

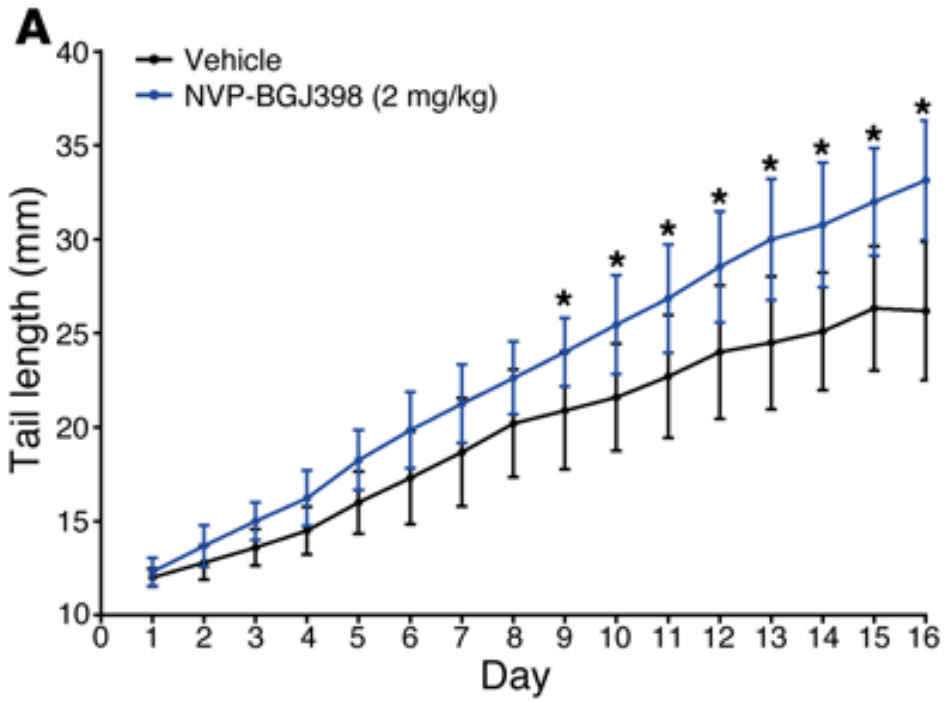


FGF(R3), fibroblast growth factor (receptor 3); PBS, phosphate-buffered saline.
Gonçalves D, et al. *PLoS One* 2020;15:e0244368; ClinicalTrials.gov NCT04638153.

Infigratinib – a tyrosine kinase inhibitor

- FGFR 1–3 tyrosine kinase inhibitor
- Reduces FGFR3 phosphorylation and downstream signaling
- Approved for cholangiocarcinoma
- Larger effect in mouse model than vosoritide
- Oral medication
- Phase 2 study underway
  - 4 doses

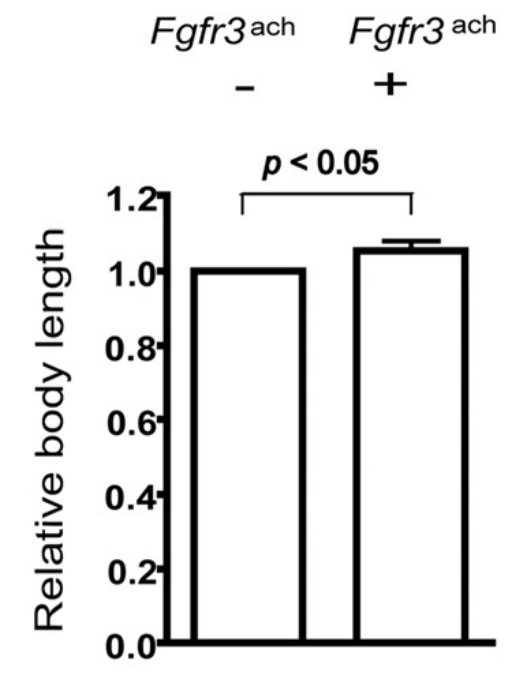


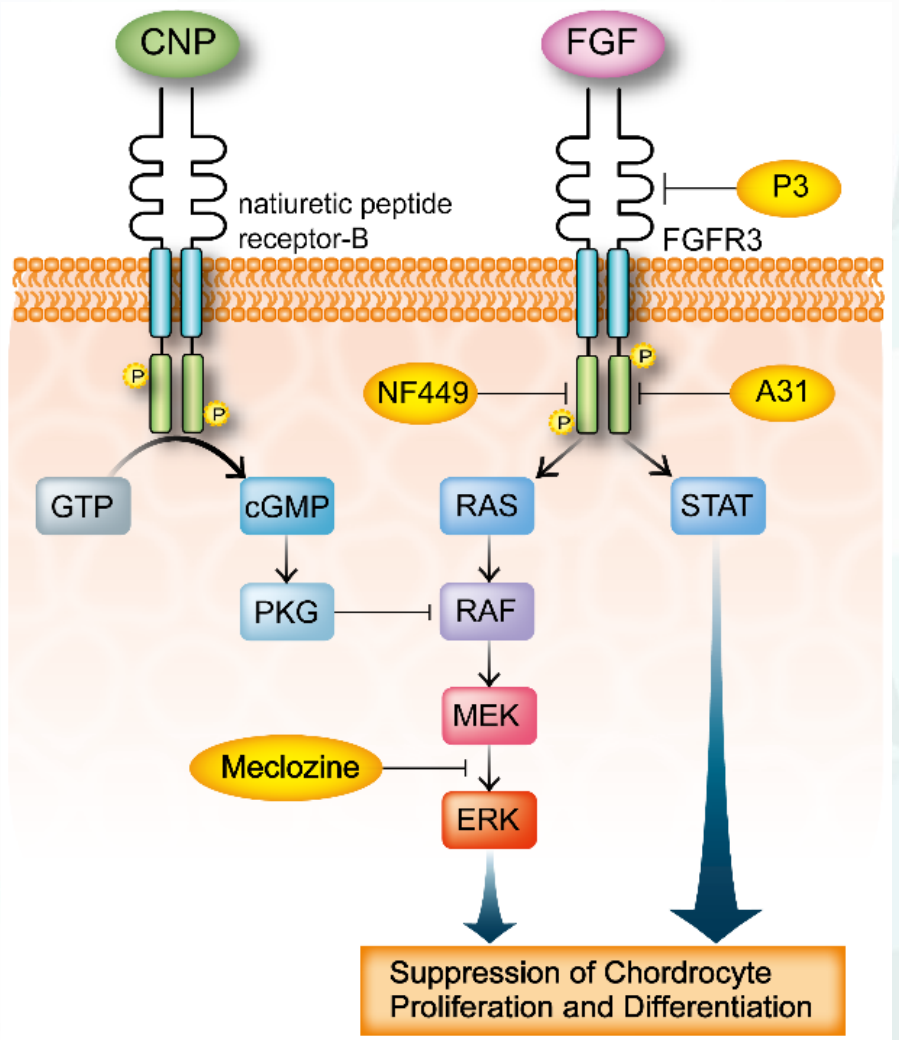


FGFR, fibroblast growth factor receptor.
Komla-Ebri D, et al. *J Clin Invest* 2016;126:1871–1884; ClinicalTrials.gov NCT04265651.

Meclizine – an H1 blocker

- On large unbiased drug screen, found to decrease FGFR3 downstream signaling by blocking ERK phosphorylation
- Improved growth in achondroplasia mouse model
- Completed Phase 1 study in Japan examining PK
- Phase 2 study in Japan
- Oral agent





CNP, C-type natriuretic peptide; ERK, extracellular-signal-regulated kinase; FGFR3, fibroblast growth factor receptor 3; PK, pharmacokinetic.

Matsushita M, et al. *PLoS One* 2013;8:e81569;
Matsushita M, et al. *Endocrinol* 2015;156:548–554.

Conclusions

- There are multiple novel therapeutic approaches for achondroplasia on the horizon
- Vosoritide is currently approved in the US (age >5 years), in Europe, Brazil, and Australia (age >2 years), and in Japan (all ages) for the treatment of achondroplasia in children whose growth plates are not closed
- Long-term data on the effects of these therapies on medical comorbidities are pending