

# Ascendis Pharma A/S

June 2020

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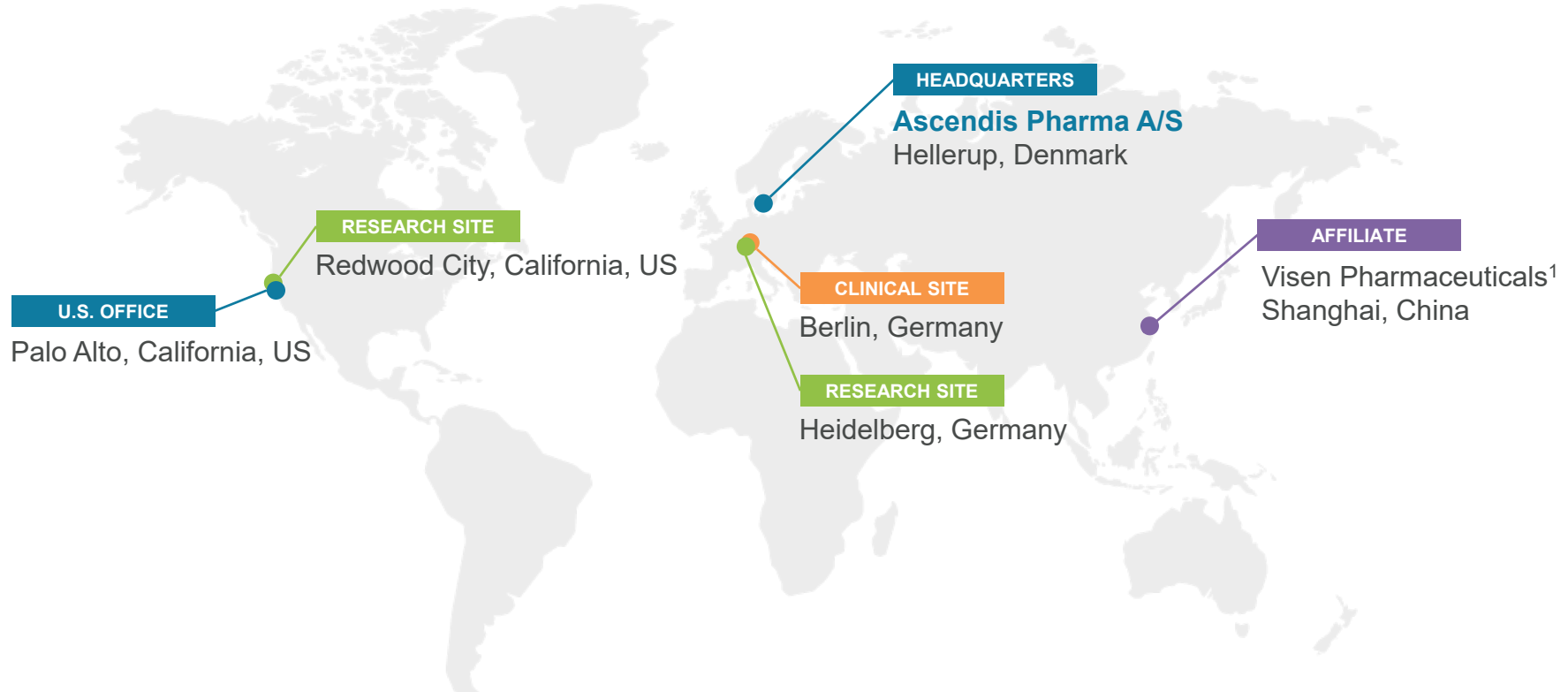
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This presentation concerns product candidates that are or have been under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration, European Medicines Agency or other foreign regulatory authorities. These product candidates are currently limited by U.S. Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

# Company Overview

- Create best-in-class products addressing unmet medical needs by applying TransCon™ technologies to parent drugs with clinical proof-of-concept
- Endocrinology rare disease
  - TransCon hGH for pediatric GH deficiency: BLA submitted June 25, 2020 and MAA planned in Q3
  - TransCon PTH for hypoparathyroidism: Long-term data from open-label extension portion of PaTH Forward Q3
  - TransCon CNP for achondroplasia: Phase 2 ACcomplish dose escalation and initiate second trial in China<sup>1</sup> Q4
  - Build leading market positions for each product with commercial focus on maximizing global reach
  - Partnership with VISEN Pharmaceuticals for endocrinology rare disease products in China
- Oncology
  - First IND filing or similar expected for TransCon TLR7/8 Agonist in Q4
  - TransCon IL-2  $\beta/\gamma$  IND filing or similar expected in 2021
- As of March 31, 2020, cash and cash equivalents of ~€534 million

# Ascendis Pharma Global Presence



<sup>1</sup>Visen Pharmaceuticals (known as Visen) was established in 2018 to develop and commercialize endocrinology rare disease therapies in Greater China. Ascendis Pharma has 50% ownership in the outstanding shares of Visen.

All product candidates are investigational. For investor communication only. Not for use in promotion or product commercialisation.










# Vision 3x3: Building a Leading BioPharma Company

## Our Goal is to Achieve Sustainable Growth through Multiple Approaches

- Obtain regulatory approval for three independent Endocrinology Rare Disease products
  - TransCon Growth Hormone for pediatric growth hormone deficiency
  - TransCon PTH for adult hypoparathyroidism
  - TransCon CNP for achondroplasia
- Grow Endocrinology Rare Disease pipeline through
  - Global clinical reach
  - Pursuing 9 total indications, label optimization, and life cycle management
  - New endocrinology products
- Establish global commercial presence for our Endocrinology Rare Disease area
  - Build integrated commercial organization in North America and select European countries
  - Establish global commercial presence through partners with local expertise and infrastructure
- Advance a high value oncology pipeline with one IND or similar filing each year
- Create a third independent therapeutic area with a diversified pipeline

# Diverse Pipeline of Independent Product Candidates

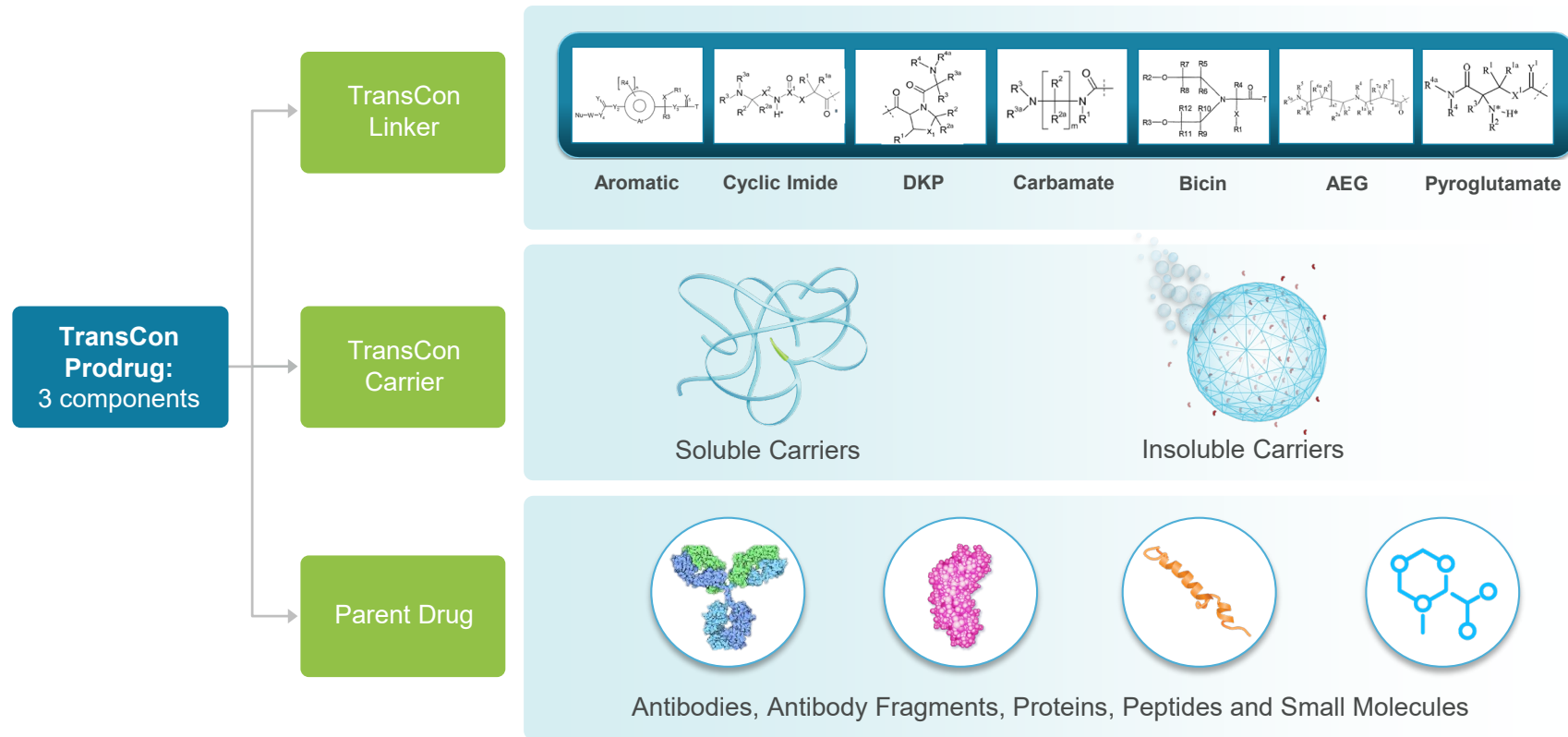
PRODUCT CANDIDATE	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	REGULATORY FILING	COMMERCIAL RIGHTS
Endocrinology rare diseases <sup>1</sup>						
TransCon hGH	Pediatric growth hormone deficiency <sup>2</sup>			U.S. BLA SUBMITTED JUNE 2020		
	Adult growth hormone deficiency					
TransCon PTH	Hypoparathyroidism					
TransCon CNP	Achondroplasia					
Oncology						
TransCon TLR7/8 Agonist						
TransCon IL-2 β/γ						
TransCon VEGF-TKI						

<sup>1</sup> Excludes rights granted to VISEN Pharmaceuticals in Greater China

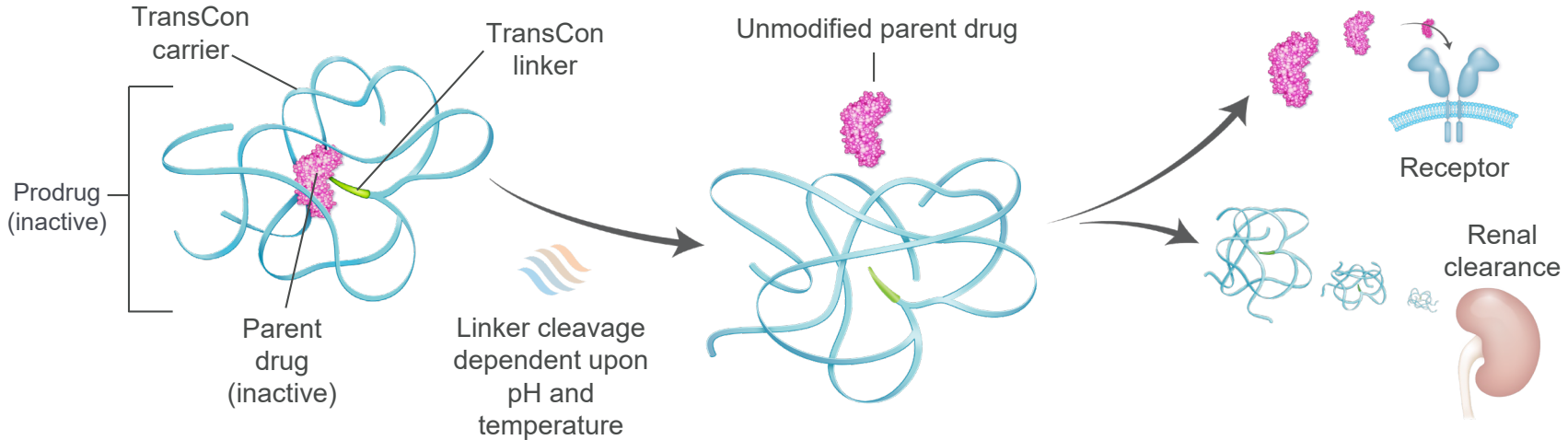
<sup>2</sup> In phase 3 development for pediatric growth hormone deficiency in Greater China through strategic investment in VISEN Pharmaceuticals

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# Transient Conjugation: A Powerful, Flexible Platform



# TransCon Technology: Sustained Systemic Release

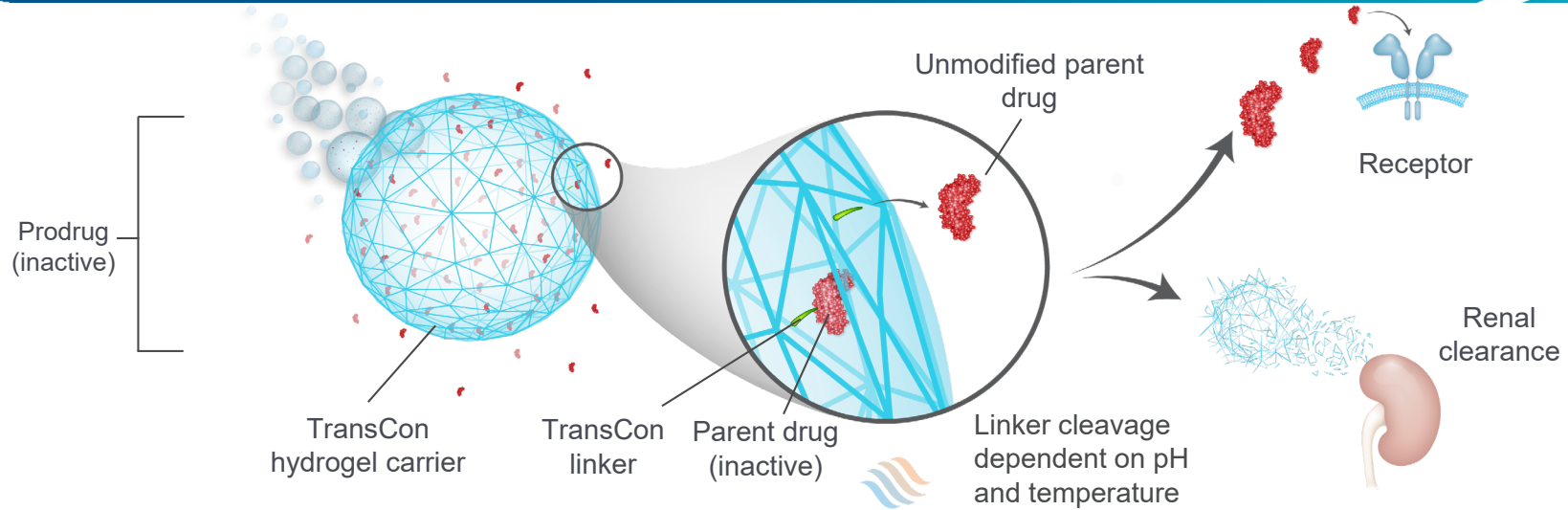


Parent drug is transiently bound to a TransCon linker-soluble carrier moiety, which inactivates and shields parent drug from clearance

Following injection, the linker is designed to autocleave at a specific rate to predictably release unmodified parent drug

Designed to distribute released drug like the parent molecule; linker-carrier is cleared renally

# TransCon Technology: Sustained Localized Release

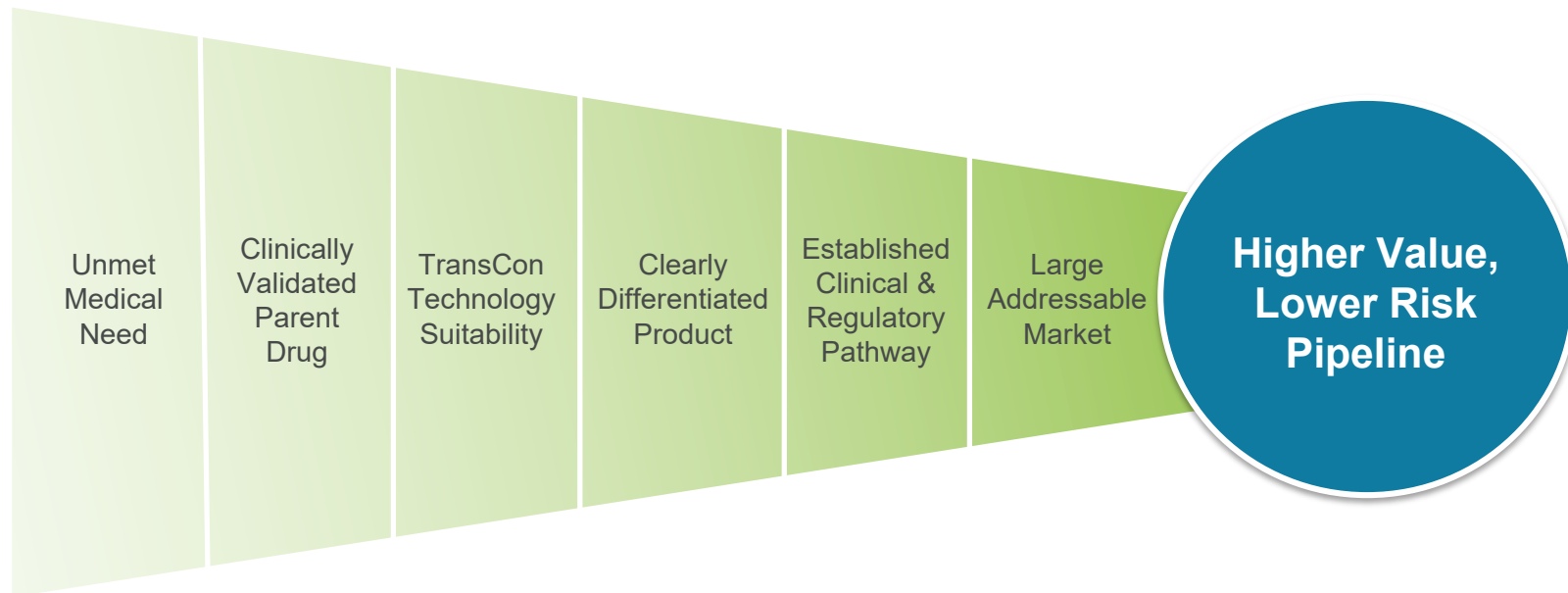


Parent drug is transiently bound to TransCon linker-hydrogel carrier, which inactivates, shields parent drug and prevents clearance

Following injection, the linker is designed to autocleave at a specific rate to predictably release unmodified parent drug

Designed to provide sustained high local drug levels with low systemic exposure; hydrogel degrades into small polymers that are renally cleared

# Ascendis Algorithm for Product Innovation







## TransCon Growth Hormone: Once-Weekly Replacement Therapy

# Growth Hormone Supports Overall Endocrine Health

## BODY COMPOSITION<sup>2,3,4</sup>



ULTIMATE HEIGHT  
ACHIEVEMENT<sup>1</sup>



MENTAL HEALTH<sup>5</sup>



## CARDIOVASCULAR DISEASE<sup>6,7</sup>



FRACTURES<sup>8</sup>

Daily hGH addresses all the symptoms of the disease; long-acting growth hormone products must fully mimic daily hGH to adequately address the totality of the disease

Sources: 1. de Boer, H. et al. 1997; 2. Rutherford, O. M. et al. 1991. 3. Colle, M., J. Auzeir. 1993. 4. Johannsson, Gudmundur, et al. 1999. 5. Stabler, Brian et al. 1996. 6. Leong, Gary M., Gudmundur Johannsson. 2003. 7. Colao, Annamaria et al. 2002. 8. Bex, M, and R Bouillon. 2003

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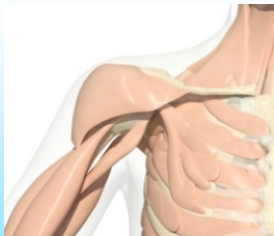
# Impact of hGH Distribution

TransCon hGH is designed to achieve the same distribution in the body as daily growth hormone



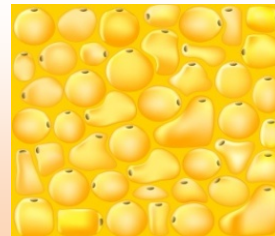
## BONE

Optimal growth achieved *via* direct stimulation of GH receptors in bone and through IGF-1



## MUSCLE

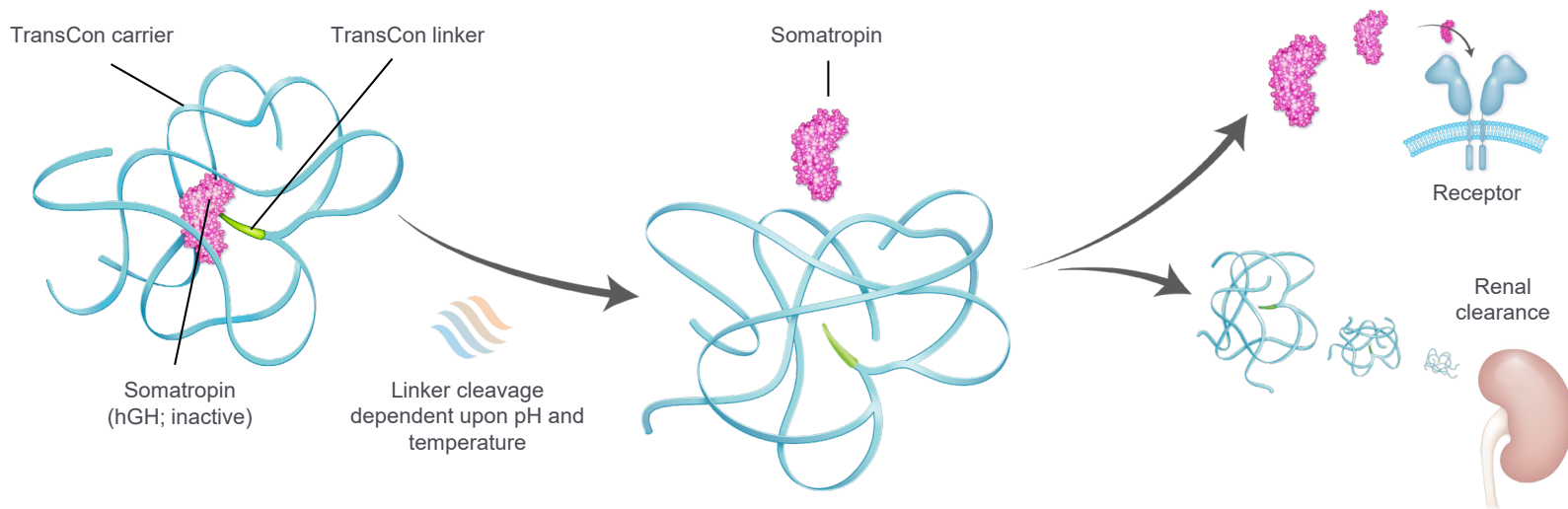
hGH stimulates muscle growth *via* direct stimulation of GH receptors in muscle and through IGF-1



## ADIPOSE TISSUE

hGH directly stimulates the breakdown of fat *counteracting* the adipogenic effect of IGF-1

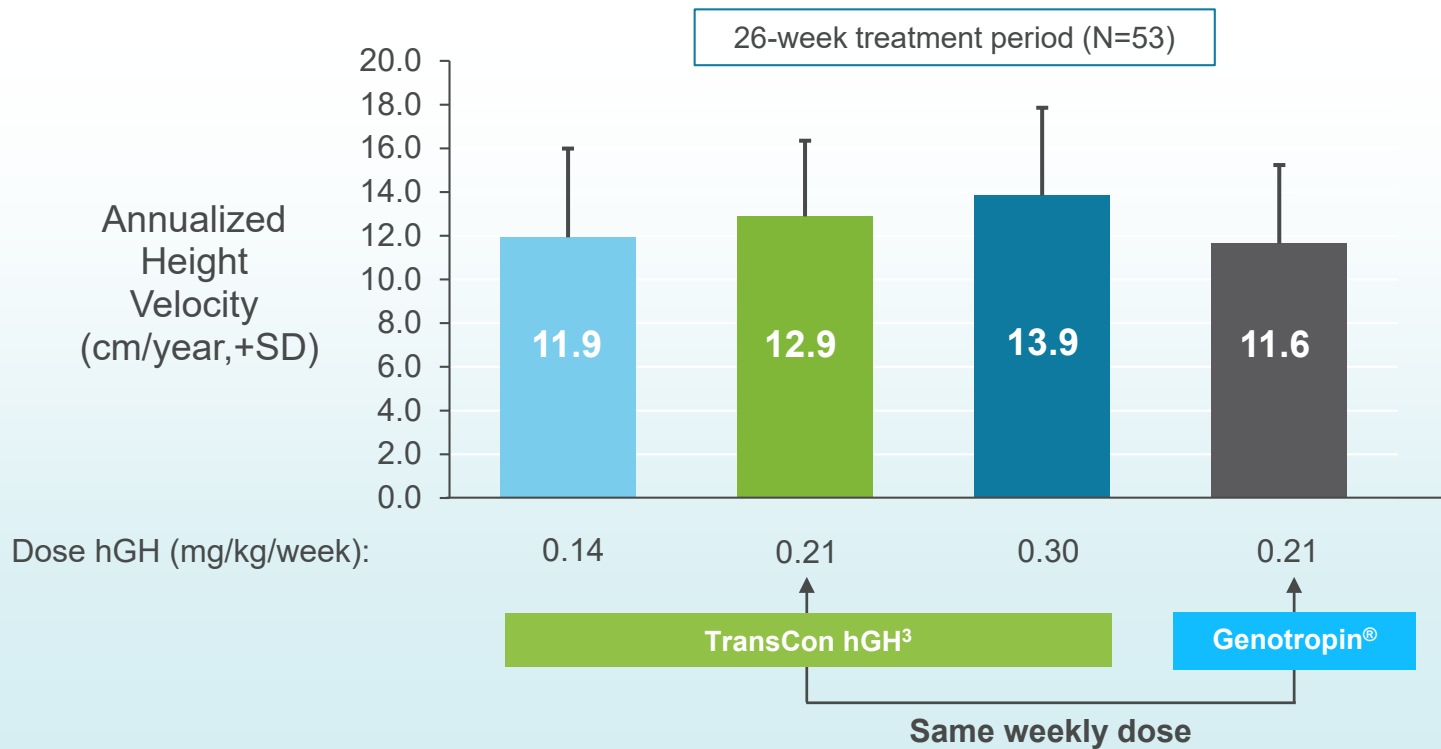
# TransCon hGH (lonapegsomatropin) Design



Once-weekly prodrug releases unmodified hGH designed to mimic daily hGH:

- ✓ Tissue distribution
- ✓ Physiological levels
- ✓ Therapeutic effects: efficacy, safety and tolerability

# Growth Comparable to a Daily hGH in Phase 2<sup>1,2</sup>

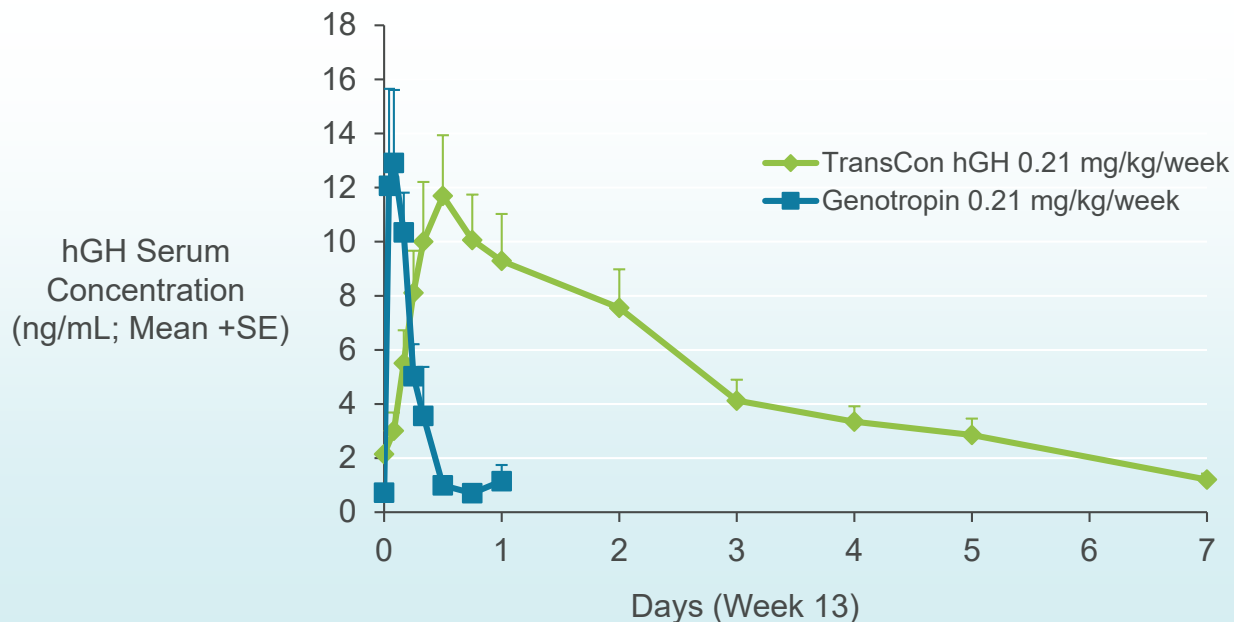


<sup>1</sup> Intergroup differences not statistically significant

<sup>2</sup> J Clin Endocrinol Metab 2017, 102(5): 1673–1682

<sup>3</sup> Conducted with a bioequivalent version of TransCon hGH

# Comparable hGH Levels in Phase 2<sup>1</sup>



Maximum hGH concentration comparable between equivalent weekly doses of TransCon hGH and a daily hGH



# TransCon hGH Phase 3 Program in Pediatric GHD



N=161

- Treatment-naïve subjects



N=146

- Subjects previously treated (n=143) and treatment-naïve (<3 years, n=3)



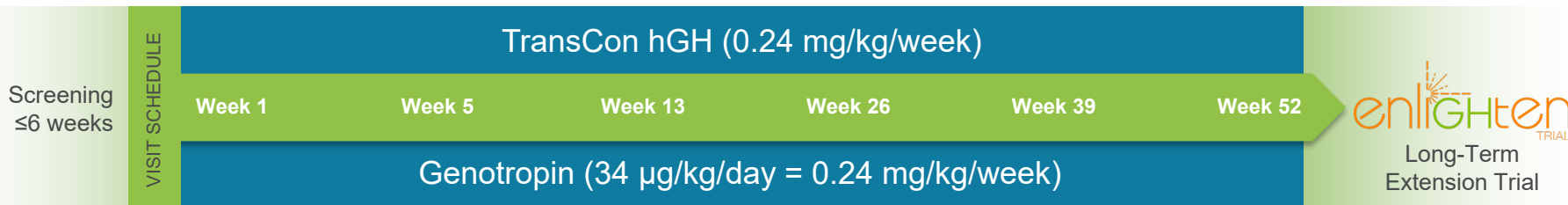
Extension trial  
(N=296)

*2020 Regulatory Filings  
(BLA submitted June 2020;  
MAA planned Q3)*

# Phase 3 heiGHt Trial



161 treatment-naïve children with GHD dosed  
(2:1 randomization)



## Key Inclusion Criteria

- Prepubertal children with GHD
- Height SDS  $\leq -2.0$
- IGF-1 SDS  $\leq -1.0$
- 2 GH stimulation tests (GH  $\leq 10$  ng/mL)
- Bone age  $\geq 6$  months behind chronological

## Key Endpoints

- Annualized height velocity (AHV) at 52 weeks (primary endpoint)
- AHV at earlier time points
- Change in height SDS over 52 weeks
- Change in serum IGF-1/IGFBP-3 levels
- Change in IGF-1 SDS and IGFBP-3 SDS
- Normalization of IGF-1 SDS
- hGH and IGF-1 levels over 168 hours at Week 13 (PK/PD subset)

# Demographics and Baseline Characteristics Comparable Between Arms



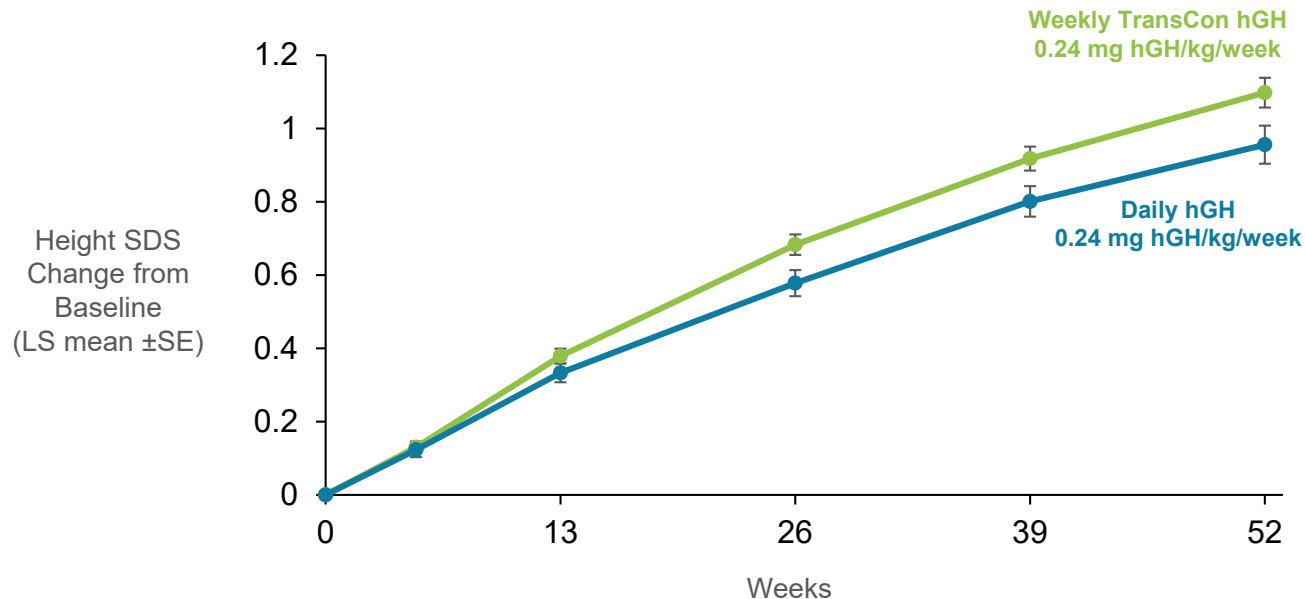
	TransCon hGH (n=105) Mean	Genotropin (n=56) Mean
Age (years)	8.51	8.48
Male (%)	81.9	82.1
Height SDS	-2.89	-3.00
Δ Average Parental Height SDS	-2.32	-2.55
IGF-1 SDS	-2.08	-1.96
Peak Stimulated GH (ng/mL)	5.89	5.48
BMI (kg/m <sup>2</sup> )	16.1	16.5
BMI SDS	-0.32	-0.14
Bone Age (years)	5.84	5.98
Bone Age-to-Chronologic Age (BA/CA)	0.69	0.70
Caucasian (%)	95.2	92.9

# TransCon hGH Met Primary Objective of Non-inferiority and Demonstrated Superiority in AHV at Week 52



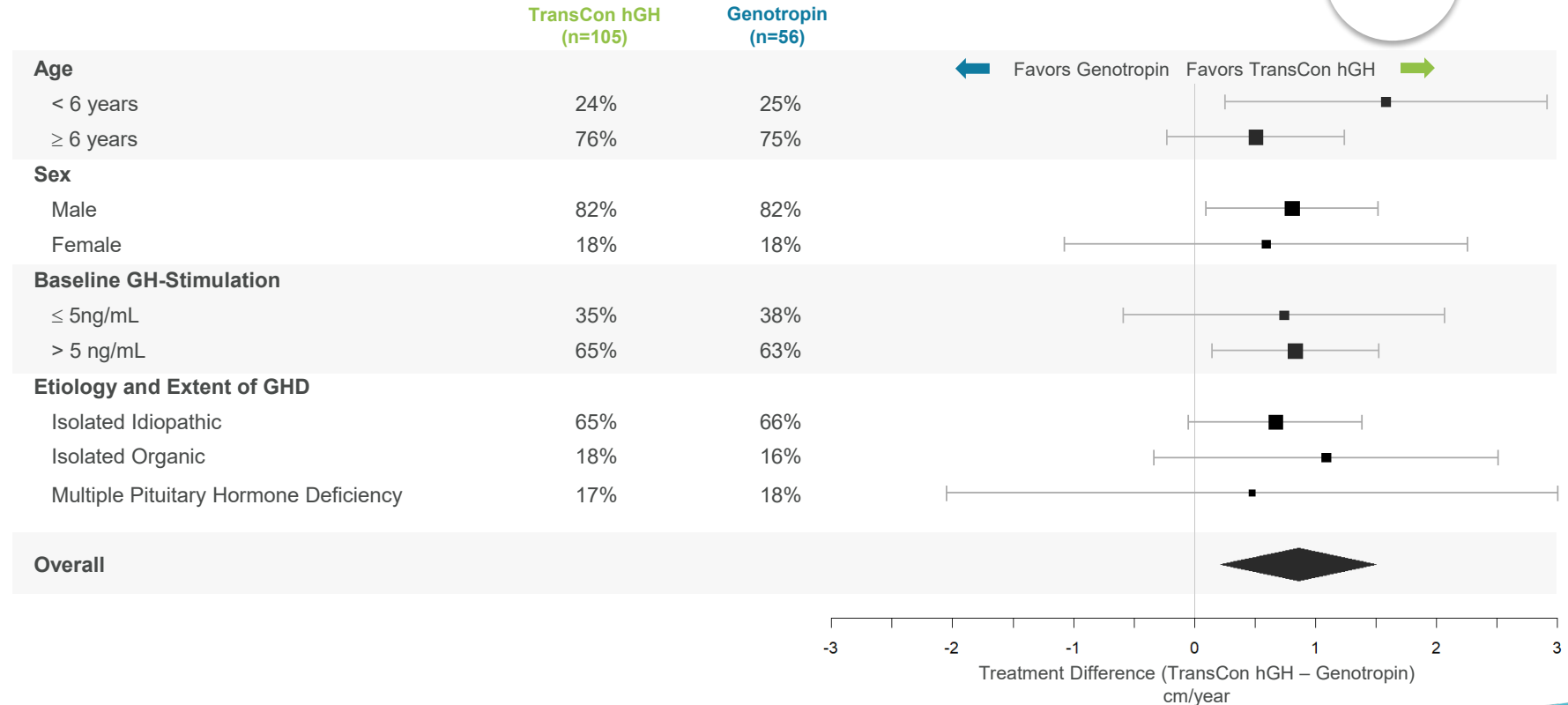
	TransCon hGH 0.24 mg/kg/week (n=105)	Genotropin 0.24 mg/kg/week (n=56)	Estimate of Treatment Difference	P-value
LS Mean AHV at Week 52 (cm/year)	11.2	10.3	0.86	0.0088
Standard Error	0.23	0.30	0.33	
95% Confidence Interval (cm/year)	10.71 – 11.62	9.73 – 10.89	0.22 – 1.50	

# Change in Height SDS Over 52 Weeks for Equivalent Doses of TransCon hGH and Daily Genotropin Demonstrated an Increasing Difference



Statistically significant difference between TransCon hGH and Genotropin from week 26

# AHV Consistently Favors TransCon hGH Across All Subgroups at Week 52





# AHV Poor Responders: Post-hoc Analysis



Poor responders defined as AHV <8.0 cm/year<sup>1</sup>

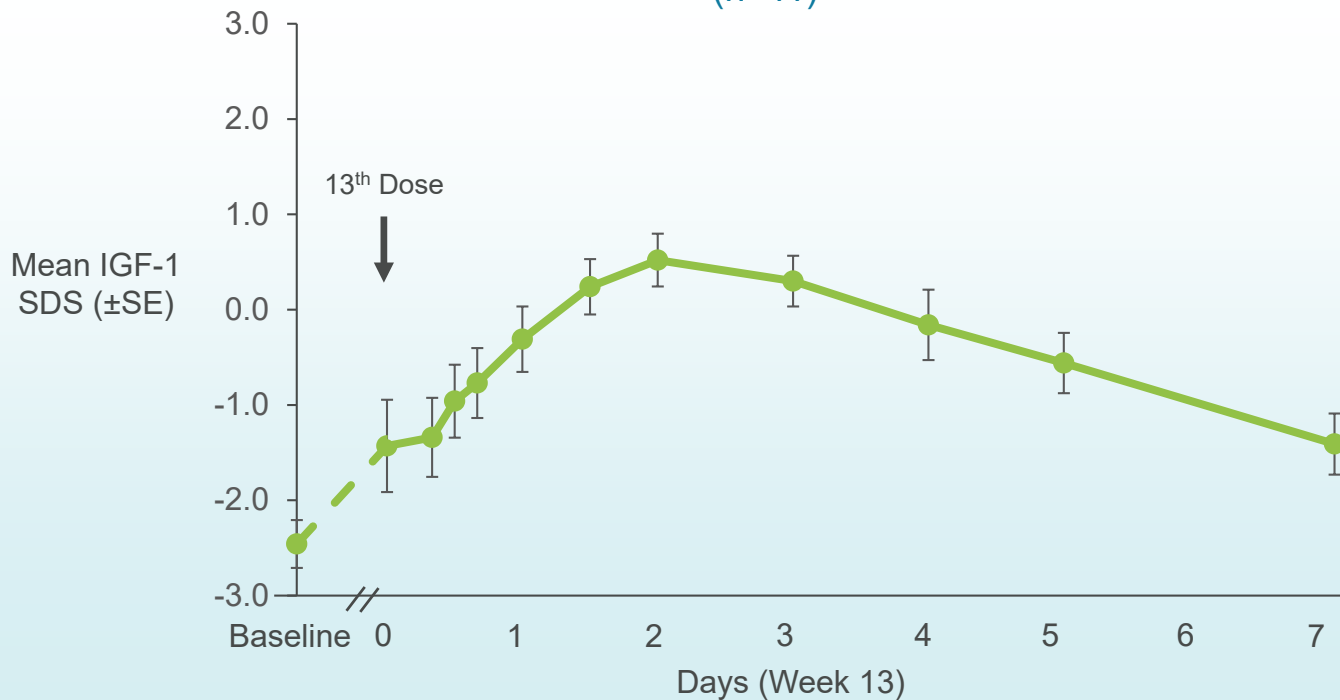
At Week 52 <sup>2</sup>	TransCon hGH (n=104) n (%)	Genotropin (n=55) n (%)
Responder	100 (96.2)	49 (89.1)
Poor Responder	4 (3.8)	6 (10.9)

Incidence of poor responders ~3x lower in TransCon hGH arm compared to daily Genotropin arm

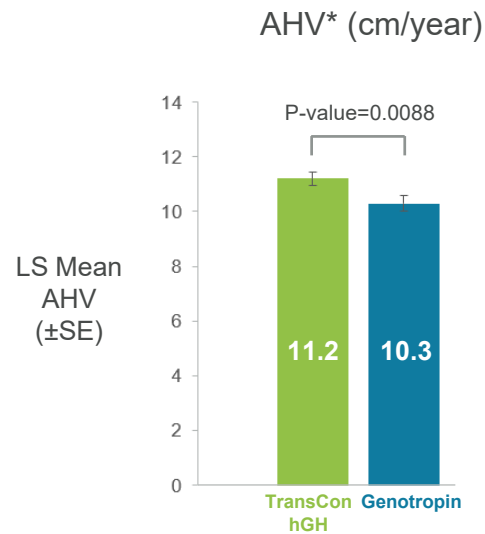
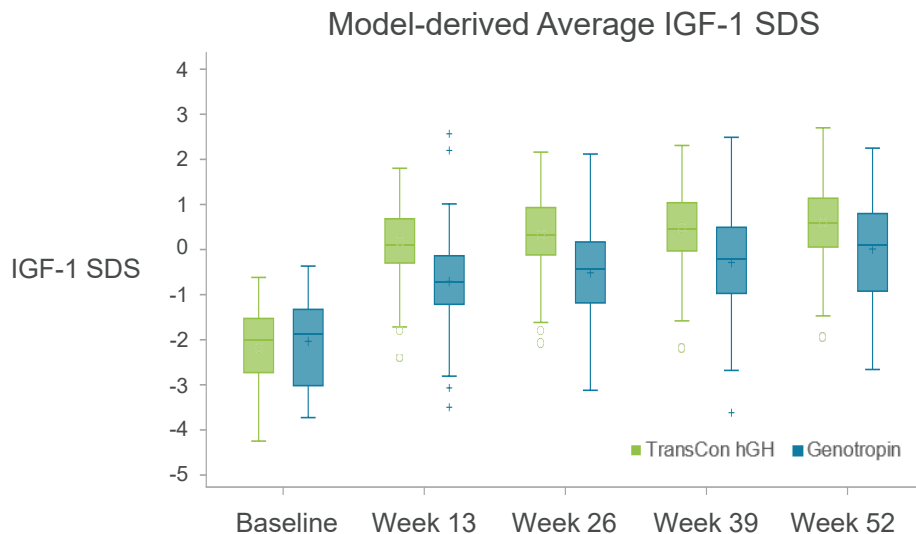
# IGF-1 Profile Over 1 Week



TransCon hGH (0.24 mg/kg/week)  
(n=11)



# AHV Paralleled the Difference in Average IGF-1



TransCon hGH preserved the balance between direct and indirect effects of daily hGH

# Stable Glycemic Parameters



TransCon hGH	Baseline	Week 5	Week 13	Week 26	Week 39	Week 52
HbA1c (%), mean	5.1	5.0	5.2	5.2	5.2	5.2

Genotropin	Baseline	Week 5	Week 13	Week 26	Week 39	Week 52
HbA1c (%), mean	5.0	5.0	5.1	5.1	5.1	5.1

Fasting glucose normal range 70 – 105 mg/dL

- Glycemic parameters were stable and within the normal range
- 2 subjects with high HbA1c (both 6.2%) at baseline remained stable throughout the trial

# Low Incidence of Anti-hGH Binding Antibodies



Anti-hGH Binding Antibodies	TransCon hGH n=105 n (%)	Genotropin n=56 n (%)
<b>Treatment-emergent positive</b>	<b>7 (6.7)</b>	<b>2 (3.6)</b>
Transient, non-neutralizing	7 (6.7)	2 (3.6)
Persistent <sup>1</sup>	0	0
Neutralizing	0	0

# Similar Change in Bone Age Over 52 Weeks



Bone Age	TransCon hGH (n=105) Mean Years	Genotropin (n=56) Mean Years
Baseline	5.84	5.98
Week 52	7.16	7.35
Change from Baseline	1.36	1.35

TransCon hGH demonstrated superior height velocity, despite advancing bone age at the same rate as Genotropin



# BMI SDS of heiGHt Subjects Over 78 Weeks



Mean (SD) BMI SDS	Group A (TransCon hGH/TransCon hGH)	Group B (Genotropin/TransCon hGH)
Baseline	n=105 -0.32 (0.9)	n=56 -0.14 (1.1)
Week 52	n=104 -0.03 (0.8)	n=55 -0.40 (1.0)
Week 78	n=100 0.05 (0.8)	n=54 0.09 (0.9)

Mean BMI SDS remained near 0 over 78 weeks

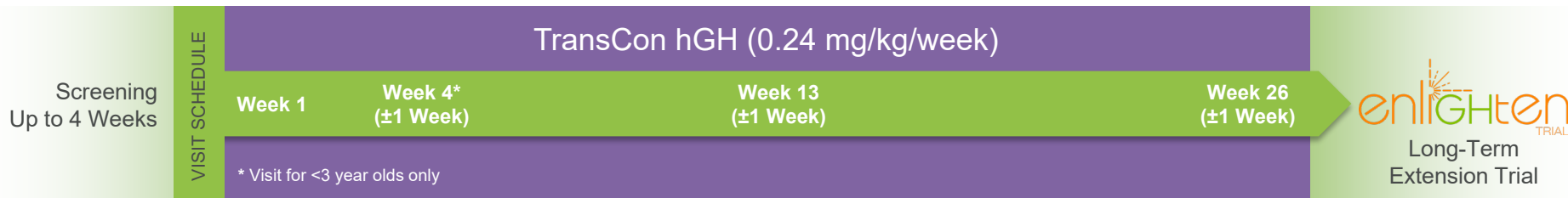


- Treatment with TransCon hGH showed superiority over Genotropin in AHV at 52 weeks
- Treatment difference in height reached statistical significance at Week 26 and onwards
- Difference in AHV paralleled the difference in average IGF-1 SDS
- Bone age advanced at the same rate for TransCon hGH and Genotropin
- Mean BMI SDS remained near 0
- Safety profile of TransCon hGH was comparable to Genotropin
- Similar local injection site tolerability between treatment arms
- Comparable, low incidence of anti-hGH binding antibodies and no neutralizing antibodies

# Phase 3 fliGHt Trial Design



146 children with GHD (143 treatment-experienced)



## Key Inclusion Criteria

- Investigator-determined GHD with supporting biochemical and auxologic criteria
- Age 6 months – 17 years old
  - Tanner stage <5
  - Open epiphyses
  - Treated with commercially-available daily hGH therapy  $\geq 0.20$  mg/kg/week for 13 – 130 weeks
  - Children <3 years could have been treatment-naïve

## Key Endpoints<sup>1</sup>

- Adverse events
- Injection site reactions
- Incidence of anti-hGH antibodies
- Annualized height velocity (AHV)
- Change in height SDS
- Proportion of subjects with IGF-1 SDS (0.0 to +2.0)
- PK/PD in subjects <3 years
- Preference and satisfaction with TransCon hGH

# fliGHt Baseline Demographics



	Baseline Mean (N=146)
Male (%)	75.3
Age (years)	10.6
Age Range (years)	1 to 17
Height SDS	-1.42
BMI (kg/m <sup>2</sup> )	17.5
Δ Average Parental Height SDS	-1.14
IGF-1 SDS	+0.9
IGF-1 SDS Range	-1.9 to +4.0
Caucasian (%)	84.9
Recruited in North America (%)	95.2

# Previous Daily hGH Use



	Baseline (N=146)
Daily hGH Dose Prior to Trial (mg/kg/week), mean (range)	0.29 (0.13 – 0.49)
Treatment-Experienced, n (%)	143 (97.9%)
<6 Months	40 (27.4%)
≥6 to <12 Months	32 (21.9%)
≥12 to <18 Months	28 (19.2%)
≥18 Months	43 (29.5%)
Treatment-Naïve, n (%)	3 (2.1%)

# Summary of Adverse Events



	TransCon hGH (N=146) n (%)
Any Treatment Emergent Adverse Event (TEAE) <sup>a</sup>	83 (56.8)
Pyrexia	17 (11.6)
Nasopharyngitis	14 (9.6)
Upper respiratory tract infection	14 (9.6)
Headache	12 (8.2)
Oropharyngeal pain	8 (5.5)
TEAEs Related to Study Drug	6 (4.1)
Serious Adverse Events (SAEs)	1 (0.7)
SAEs Related to Study Drug	0
TEAEs Leading to Discontinuation of Study Drug	0

- Safety in children <3 years old was consistent with the overall trial population and the known profile of daily hGH
- A low-titer of non-neutralizing anti-hGH binding antibodies were detected in 2.8% of subjects
- No injection-site reactions were reported as AEs

# Mean AHV at Week 26 by Subgroups



	AHV at Week 26 (cm/year)
	TransCon hGH (N=146) Arithmetic Mean
Age	
<3 years	16.2
≥3 and <6 years	10.0
≥6 and <11 for girls; ≥6 and <12 for boys	8.2
≥11 for girls; ≥12 for boys	9.0
Gender	
Male	9.0
Female	9.1
Peak Stimulated GH	
≤5 ng/mL	9.6
>5 ng/mL	8.6

# Key Learnings from TransCon hGH Clinical Trials

- TransCon hGH demonstrated a safety profile comparable to that of a daily hGH
- TransCon hGH demonstrated superior height velocity<sup>1</sup> to a daily hGH through a PK profile of released hGH that may be more efficiently utilized by target tissues
  - Treatment advantage maintained beyond first year
- TransCon hGH data showed predictable linear response to dose titrations
- TransCon hGH data suggest the same mode of action as daily hGH and preservation of the biological balance between direct hGH and IGF-1 effects in target tissues
- TransCon hGH demonstrated consistent safety and efficacy profile following switch from daily hGH across fliGHt and enliGHten trials, including use of auto-injector



# Adverse Event Profile of TransCon hGH in the Phase 3 Program<sup>1</sup>

	heiGHt Trial		fliGHt Trial	enliGHten Trial <sup>2</sup>
	TransCon hGH 0.24 (n=105) n (%)	Genotropin 0.24 (n=56) n (%)	TransCon hGH 0.24 (N=146) n (%)	TransCon hGH 0.24 (N=296) n (%)
Treatment-emergent Adverse Events (TEAEs)	81 (77)	39 (70)	83 (57)	161 (54)
TEAEs Related to Study Drug	12 (11)	10 (18)	6 (4.1)	10 (3.4)
Serious Adverse Events (SAEs)	1 (1.0)	1 (1.8)	1 (0.7) <sup>3</sup>	5 (1.7) <sup>4</sup>
SAEs Related to Study Drug	0	0	0	0
TEAEs Leading to Any Action on Study Drug	2 (1.9)	1 (1.8)	2 (1.4)	5 (1.7)
TEAEs Leading to Discontinuation of Study Drug	0	0	0	0

TransCon hGH had an adverse event profile comparable to daily hGH which was consistent across phase 3 trials

<sup>1</sup> All doses expressed in mg/kg/week

<sup>2</sup> Based on data reported up to September 2019

<sup>3</sup> One subject reported two SAEs; both considered unrelated to study drug

<sup>4</sup> Two subjects reported two SAEs; all considered unrelated to study drug

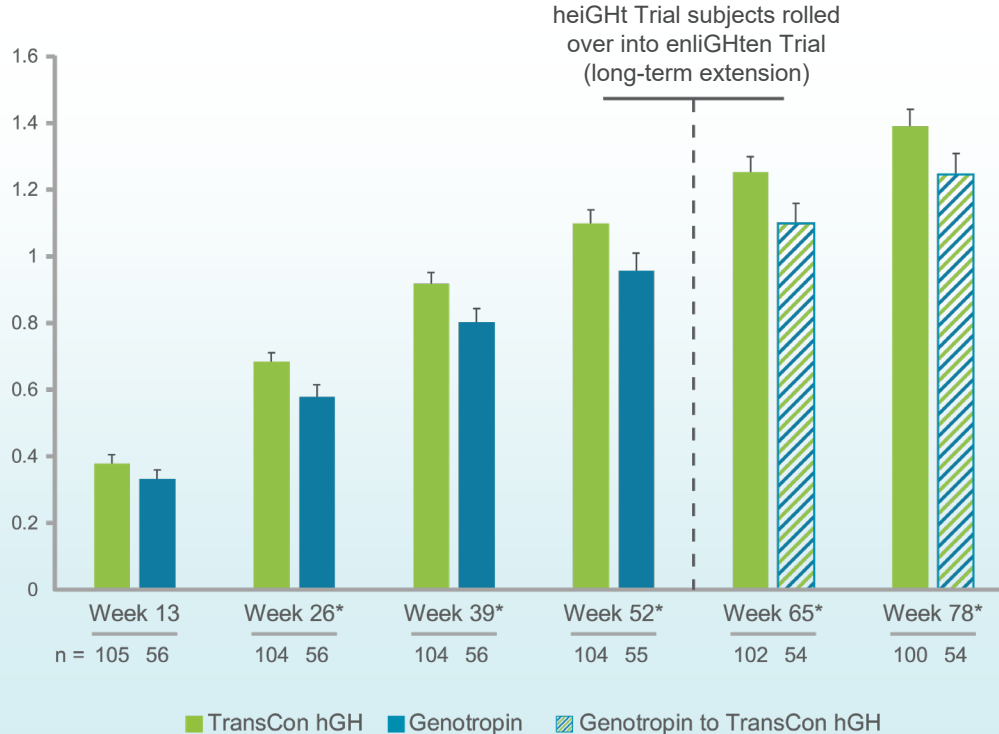
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# Treatment Advantage Maintained Beyond First Year in Subjects Initially Treated with TransCon hGH



Height SDS  
Change from  
Baseline

LS Mean (+SE)



heiGHt subjects treated for 1.5 years with TransCon hGH demonstrated:

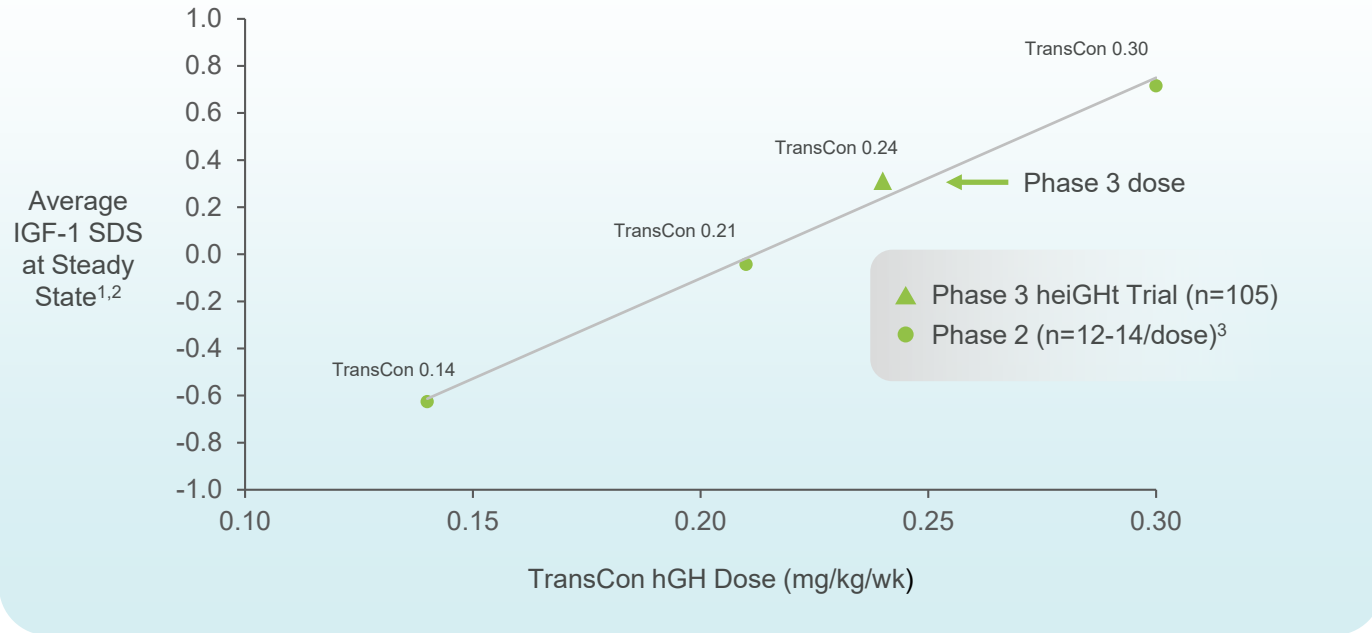
- Superior growth after 52 weeks compared to Genotropin<sup>1</sup>
- Superior growth continued in the enliGHten extension trial

<sup>1</sup> Based on results from phase 3 heiGHt Trial on the primary endpoint of AHV at 52 weeks

\*Treatment difference resulted in a nominal p-value <0.05 ANCOVA model

# Linear Relationship Between Dose and IGF-1 Response Demonstrated in Clinical Program

## Average IGF-1 SDS vs TransCon hGH Dose



**TransCon hGH  
data support  
predictable  
dose titration**

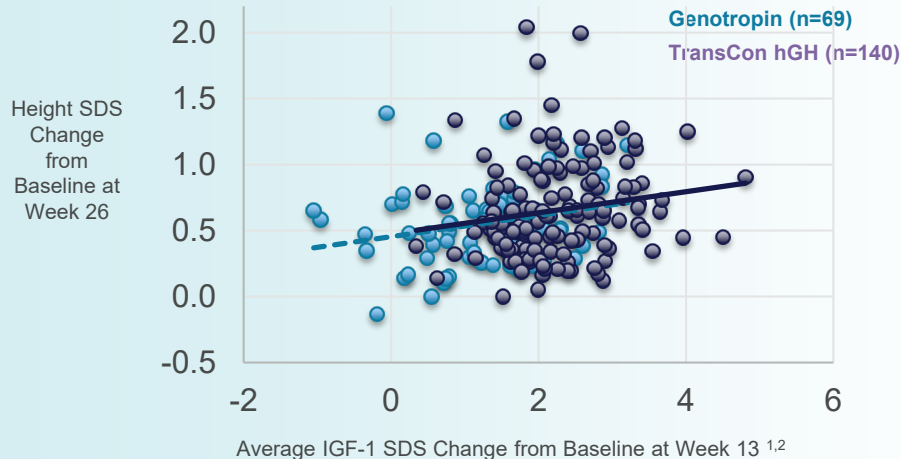
<sup>1</sup> Average IGF-1 at Week 13 was used given availability of measured data over one week for the phase 2 trial

<sup>2</sup> Average IGF-1 during Week 13 for phase 3 heiGHt Trial TransCon hGH subjects is model-derived average

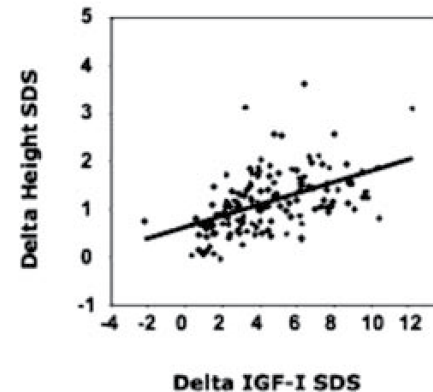
<sup>3</sup> Conducted with an earlier bioequivalent version of TransCon hGH

# Relationship Between Average IGF-1 SDS and Height SDS from Phase 2 and Phase 3 Trials

TransCon hGH subjects from  
phase 2 and phase 3 trials combined



Published two-year data from controlled trial  
with daily hGH in the U.S. (N=172)<sup>3</sup>



Similar slopes for Genotropin and TransCon hGH suggest:

- Similar relationship of height SDS and average IGF-1 SDS
- Preservation of the biological balance between direct hGH and IGF-1 effects

<sup>1</sup> Average IGF-1 at week 13 was used given availability of measured data over one week for the phase 2 trial

<sup>2</sup> Average IGF-1 during week 13 for phase 3 heiGHT Trial TransCon hGH subjects is model-derived average

<sup>3</sup> Cohen et al. J Clin Endocrinol Metab 2007, 92(7): 2480-2486

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# Auto-Injector Designed to Improve Adherence



## Key Features to Enhance Patient Experience

- Room temperature storage
- Small needle, comparable to daily hGH (31G, 4mm)
- Single low-volume (<0.60mL) injection for patients ≤60kg
- Simple operation
- No waste due to empty-all design
- Device lifespan at least 4 years
- Easy to titrate
- Bluetooth® connectivity planned for automatic data capture
- Development of integrated connectivity platform underway

>160 subjects are using Auto-Injector and dual-chamber cartridges (DCCs) in extension trial



# TransCon hGH: Raising the Bar

- Phase 3 heiGHt Trial demonstrated superior height velocity of TransCon hGH in pediatric GHD, with comparable safety and tolerability to a daily hGH
- Received orphan designation for TransCon hGH in US and Europe for GHD
- In pediatric GHD, submitted BLA filing in June 2020 and MAA filing planned Q3 2020
- Create further growth:
  - China: Pediatric GHD phase 3 ongoing\*
  - Global: Submitted IND amendment to initiate adult GHD phase 3 in Q1 2020; enrollment to begin later in 2020
  - Japan: Pediatric phase 3 expected to be initiated Q4 2020
- User-friendly Auto-Injector part of initial BLA/MAA filings
- Commercial manufacturing ongoing
- Commercial leadership team, infrastructure and launch plan in place
- Multiple independent patent filings to provide additional potential protection into 2039



# TransCon PTH: PTH Replacement Therapy for Hypoparathyroidism

# Hypoparathyroidism

## Short-term Symptoms

### Hypocalcemia

*Paresthesias, muscle cramps, tetany, laryngospasm, seizures, coma*

### Brain fog

### Anxiety due to “fear of crash”

### Hypercalcemia

*Nocturia, polyuria, constipation, muscle weakness, coma*

## Patient Burden

**76%**

*Either unable to work or report significant interference with work d/t HP symptoms<sup>1</sup>*

**79%**

*Require hospitalizations or emergency department visits*

**85%**

*Report inability to perform household activities<sup>2</sup>*

**52%**

*Experience brain calcifications (basal ganglia)*

## Long-term Complications<sup>3</sup>

**4-fold**

*Increased risk of renal disease (nephrocalcinosis, nephrosclerosis, kidney stones & renal insufficiency)*

**2-fold**

*Increased risk of depression or bipolar disorder*

**4-fold**

*Increased risk of seizures*

<sup>1</sup> 2019 Ascendis Pharma HP Patient Experience Research

<sup>2</sup> Endo Pract. 2017, 20(7):671-679

<sup>3</sup> J Bone Miner Res 2013, 28: 2570-2576; J Clin Endocrinol Metab 2012, 97(12): 4507-4514; J Bone Miner Res 2013, 28: 2277-2285



## Managing Calcium Levels Remains a Key Challenge

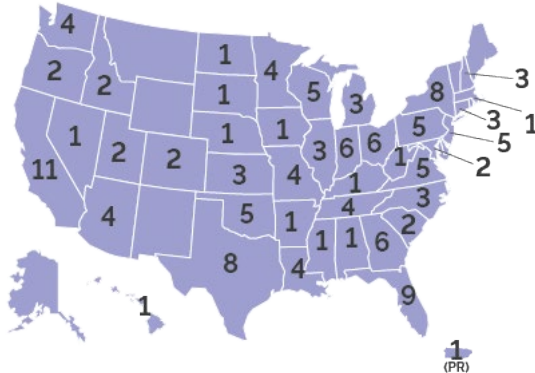
## About the Survey

146 patients with hypopara participated in the survey

**89%** were women and the average age was 51 years

**60%** have lived with hypopara for 5 years or longer

## Participants Across the U.S. (N=146)



- Despite frequent adjustment of medication:
  - 69% had a ‘calcium crash’ at least once in the past year
  - 43% reported calcium crashes weekly or monthly, and 4% daily
  - Approximately 42% visited an ER and/or urgent care facility in the last year
    - Half of these visited two to four times, and another 18% visited the ER and/or urgent care even more

# Majority of Patients Remain Unsatisfied with Current Management and Care for HP<sup>1</sup>

**71%** of Patients  
Reported Difficulty<sup>2</sup>  
in Managing HP

“ *If my calcium level is good, then I might only have paresthesia four or five times a week. If I'm going through a really rough patch...then it will happen daily, several times a day. That's one of the things that can be very frustrating with this disease...it's so poorly controlled.* ”

**64%** of Patients  
Reported Difficulty to  
Find Physicians with  
Sufficient HP Knowledge

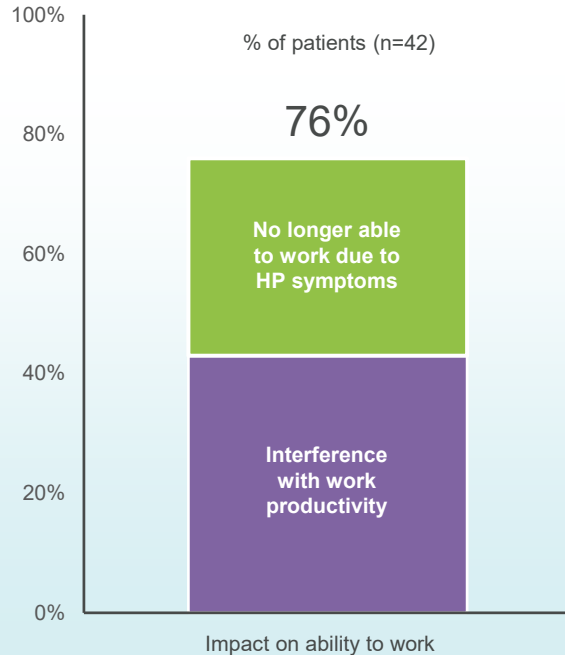
“ *I find that doctors don't know much about this and...I have to educate them. I ordered these booklets from the hypoparathyroidism organization...The endocrinologist that I see he does have some patients that have hypoparathyroidism, but it's not the majority of his practice.* ”

<sup>1</sup> Poster presented at ISPOR 2019 and 2019 Ascendis Pharma HP Patient Experience Research.

<sup>2</sup> Somewhat, A Lot, or Extremely Difficult to Manage Their HP

# Vast Majority of Patients Unable to Work or Less Productive Due to HP Symptoms<sup>1</sup>

## Work-Related Impacts



- Among those currently employed, 90% reported their HP symptoms interfered with work productivity, most often due to:
  - Ability to perform cognitive tasks
  - Absenteeism
  - Interference with ability to perform physical tasks
- 45% of patients experienced the economic impacts of a loss of income due to hypoparathyroidism

# Chronic Hypoparathyroidism: Significant Patient Population

**Estimated Prevalence: ~200k in these 4 regions**

USA

**~70k-112k**

- 2013, Powers et. al., Prevalence and Incidence of Hypoparathyroidism in the United States Using a Large Claims Database, JBMR
- 2011, Clarke et. al., Co-morbid Medical Conditions Associated with Prevalent Hypoparathyroidism: A Population-Based Study

Europe

**~86k-223k**

- 2013, Underbjerg et. al., Cardiovascular and Renal Complications to Postsurgical Hypoparathyroidism: A Danish Nationwide Controlled Historic Follow-up Study
- 2015, The Epidemiology of Nonsurgical Hypoparathyroidism in Denmark: A Nationwide Case Finding Study
- 2016, Astor et. al., Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway

Japan

**~25k-32k**

- 2016, Suzuki et. al., Factors Associated with Neck Hematoma After Thyroidectomy
- 2018, Interview conducted with Japanese HP expert

South Korea

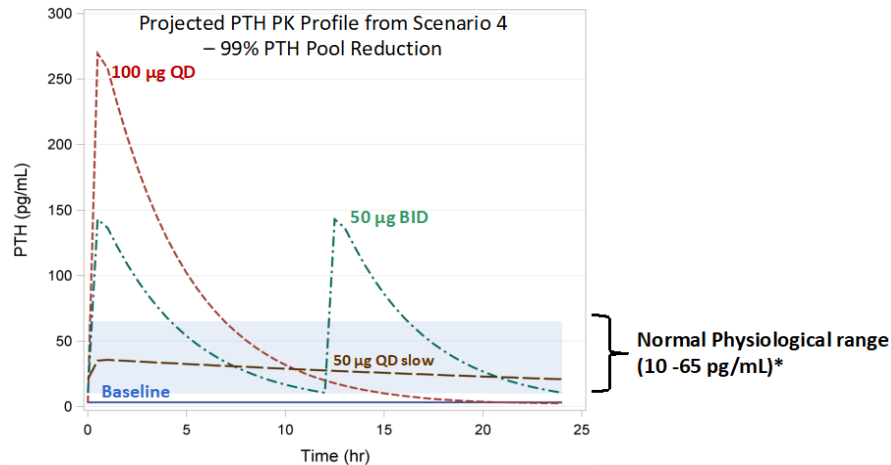
**~12k-13k**

- S. Korean ICD-10 codes
- 2018, Interview conducted with S. Korean HP expert

# Constant Normal Level of PTH is Optimal - FDA Perspective<sup>1,2</sup>

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Altering Regimen (QD to BID) or Release Profile Bring PTH Levels Close to the Physiological Levels



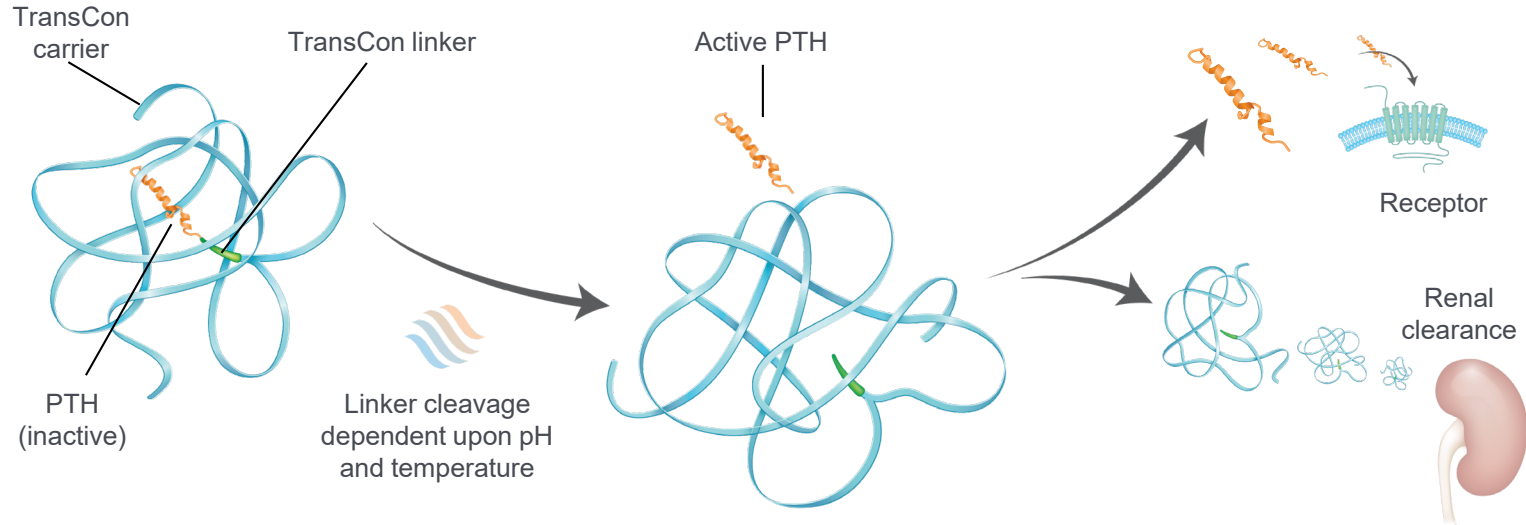
Continuous infusion of PTH demonstrated<sup>3,4</sup>:

- Normalization of serum calcium and phosphate
- Complete removal of current standard of care (vitamin D and calcium supplements)
- Normalization of urinary calcium

<sup>1,2</sup> FDA presentation: Natpara Advisory Committee, September 12, 2014; Clin Pharmacol Ther. 2019 105(3):710

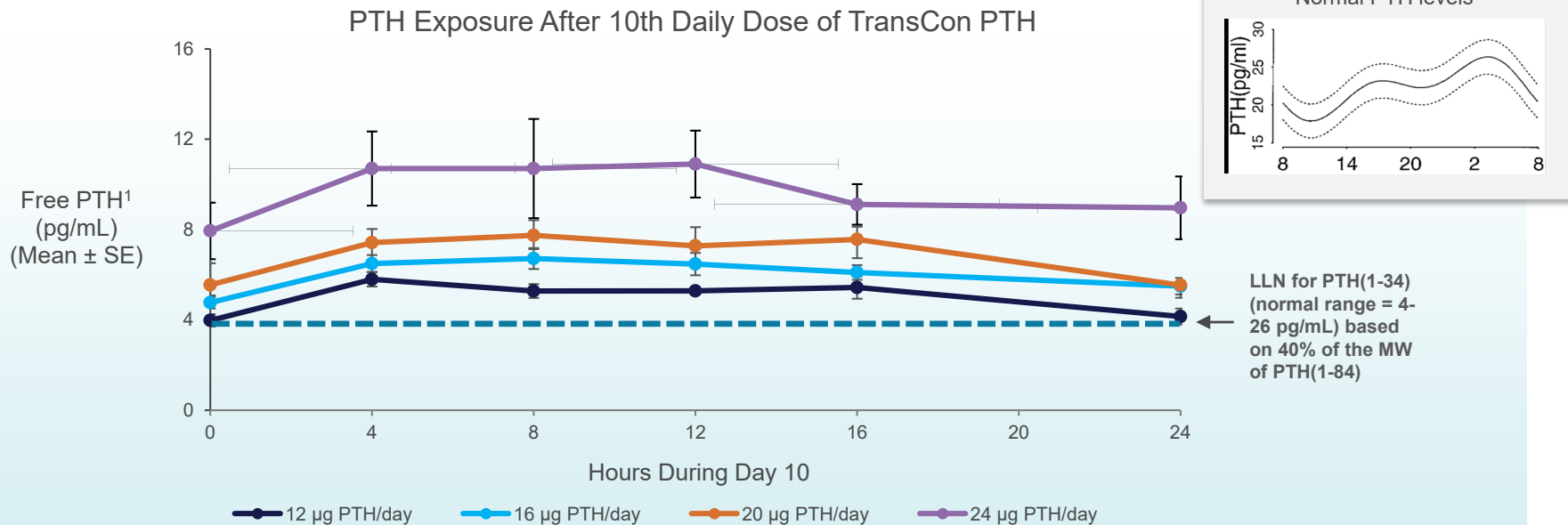
<sup>3,4</sup> J Clin Endo Metab 2012 97(2);391–399; J Pediatr 2014 165(3);556–563

# TransCon PTH Design



- TransCon PTH is a sustained-release prodrug designed to provide stable PTH levels in the physiological range for 24 hours/day
- TransCon PTH designed to normalize blood and urinary calcium levels, serum phosphate and bone turnover

# Phase 1: PK Data Support Infusion-like Profile over 24 Hours



TransCon PTH daily dosing provided a flat infusion-like profile of released PTH at day 10

<sup>1</sup> PTH measured as Free PTH(1-34) and Free PTH(1-33)  
Analyses from TransCon PTH Phase 1 trial; data not shown for doses <12 µg/day, as levels of Free PTH are BLQ.  
Poster presented at ECTS 2019

# TransCon PTH Phase 2 Trial Design



59 adult subjects with HP currently receiving standard of care (active vitamin D + calcium)



## Primary Composite Endpoint (4 weeks)

Proportion of subjects with:

- Normal serum calcium; **and**
- Normal FeCa (or at least 50% decrease from baseline); **and**
- Off active vitamin D; **and**
- Taking ≤1,000 mg/day calcium

## Key Secondary Endpoints (4 weeks)

- Primary composite **and** taking ≤500 mg/day calcium

## Additional Endpoints ≥4 weeks

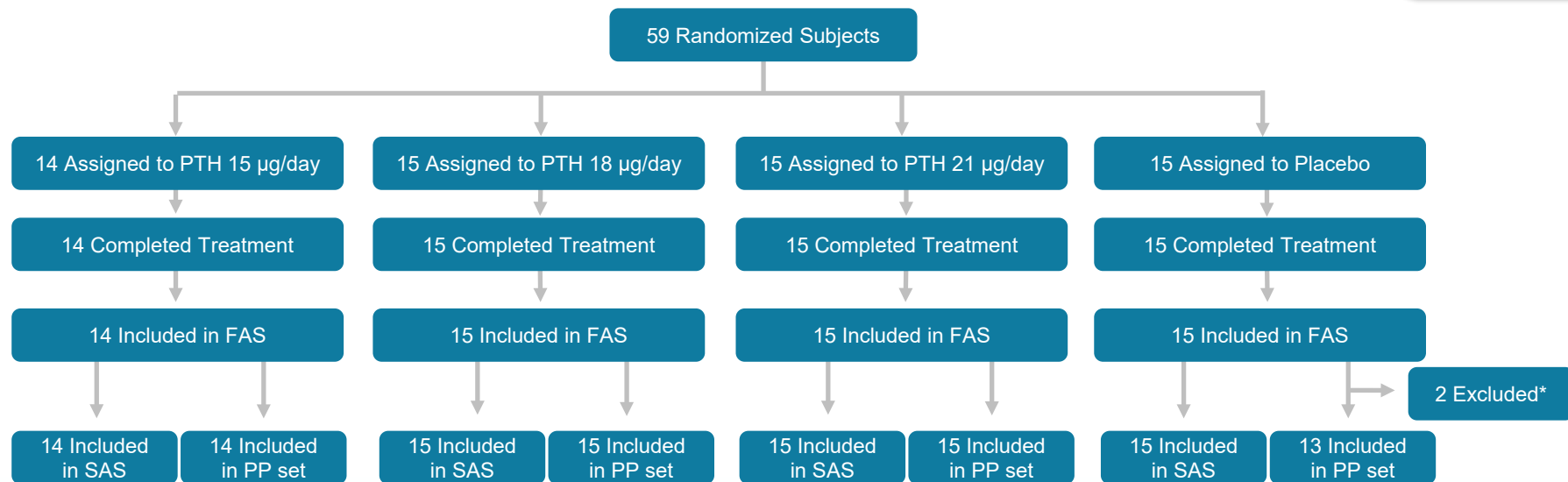
- PRO\* measures (HPES: a disease-specific PRO for HP)
- Nephrolithiasis, nephrocalcinosis, vascular calcification, ER/urgent care visits and hospitalizations
- BMD and TBS by DXA, bone turnover markers, 24-hour urine calcium excretion (in extension only)



# PaTH Forward Top-Line Data from 4-Week Fixed Dose Period

- PaTH Forward top-line data support TransCon PTH as a potential replacement therapy for adult HP
  - TransCon PTH eliminated standard of care (i.e. off active vitamin D and  $\leq 500$  mg per day of calcium supplements) in 100% of subjects in the 21  $\mu\text{g/day}$  arm and in 82% of subjects across all dosage arms
  - Both the 21  $\mu\text{g/day}$  arm and the combined TransCon PTH dosage arms showed a statistically significant response for the primary endpoint compared to placebo at 4 weeks
  - TransCon PTH increased mean serum calcium
  - TransCon PTH reduced mean urinary calcium excretion
  - TransCon PTH reduced mean serum phosphate and calcium-phosphate product
- All doses of TransCon PTH were well-tolerated
  - No serious or severe adverse events at any point
  - No treatment-emergent adverse events (TEAEs) led to discontinuation of study drug
  - Overall incidence of TEAEs comparable between TransCon PTH and placebo
- No drop-outs in blinded period

# PaTH Forward Trial Profile



- Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of randomized treatment
- Per Protocol (PP): Subjects from FAS who met inclusion/exclusion criteria and completed full double-blind trial period
- Safety Analysis Set (SAS): All randomized subjects who received at least 1 dose of randomized treatment

# Demographics and Baseline Characteristics – PP

	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
<b>Age (years) (n)</b>	14	15	15	44	13
Mean (SD)	47 (13)	47 (11)	54 (11)	49 (12)	50 (13)
<b>Age Group (years) – n (%)</b>					
< 30	1 (7.1)	1 (6.7)	0	2 (4.5)	1 (7.7)
≥ 30 - < 65	11 (79)	14 (93)	13 (87)	38 (86)	11 (85)
≥ 65	2 (14)	0	2 (13)	4 (9.1)	1 (7.7)
<b>Sex at Birth n (%)</b>					
Female	12 (86)	12 (80)	12 (80)	36 (82)	10 (77)
<b>Body Mass Index (kg/m<sup>2</sup>) (n)</b>	14	15	15	44	13
Mean (SD)	27 (5.7)	29 (3.1)	26 (4.6)	27 (4.6)	28 (3.8)
<b>Menopausal Status – n (%)</b>	12	12	12	36	10
Postmenopausal	4 (33)	4 (33)	5 (42)	13 (36)	3 (30)

# Demographics and Baseline Characteristics – PP

	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
<b>Race – n (%)</b>					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	2 (13)	2 (4.5)	0
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	14 (100)	12 (80)	13 (87)	39 (89)	13 (100)
Unknown	0	0	0	0	0
Other	0	3 (20)	0	3 (6.8)	0
<b>Geographic Region – n (%)</b>					
North America	7 (50)	12 (80)	10 (67)	29 (66)	7 (54)
Europe	7 (50)	3 (20)	5 (33)	15 (34)	6 (46)

# HP Disease Characteristics and History – PP

	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
<b>Cause of Hypoparathyroidism (HP)</b>					
Acquired from neck surgery	10 (71)	12 (80)	12 (80)	34 (77)	11 (85)
Autoimmune disease	1 (7.1)	0	0	1 (2.3)	0
Idiopathic disease	3 (21)	3 (20)	3 (20)	9 (20)	2 (15)
<b>Duration of HP (Years) (n)</b>	14	15	15	44	13
Mean	12	9.3	12	11	13
Min, Max	1, 39	2, 29	3, 25	1, 39	3, 30
<b>Renal Insufficiency History</b>	1 (7.1)	3 (20)	1 (6.7)	5 (11)	0
<b>Kidney Stones History</b>	2 (14)	1 (6.7)	1 (6.7)	4 (9.1)	4 (31)
<b>Ectopic Calcifications History</b>	0	0	1 (6.7)	1 (2.3)	0
<b>Vascular Calcifications History</b>	0	0	0	0	0
<b>Brain Calcification History</b>	0	0	0	0	0
<b>Cataract History</b>	0	0	0	0	0
<b>Seizure History</b>	1 (7.1)	0	0	1 (2.3)	1 (7.7)

# Baseline HP Supplements – PP

HP Supplements at Baseline collected by eDiary/ Total Daily Dose (TDD)	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
<b>Calcium /TDD (mg) (n)</b>	14	14	15	43	13
Mean	1643	2395	2334	2129	1636
Min, Max	500, 4000	900, 8000	500, 4500	500, 8000	800, 3200
<b>Calcium Category, n (%)</b>					
≤ 2000 mg TDD	11 (79)	9 (60)	6 (40)	26 (59)	9 (69)
> 2000 mg TDD	3 (21)	5 (33)	9 (60)	17 (39)	4 (31)
<b>Calcitriol (Active Vitamin D) /TDD (µg) (n)</b>	10	11	13	34	8
Mean	1.025	0.750	0.750	0.831	0.719
Min, Max	0.50, 3.00	0.50, 1.25	0.50, 2.00	0.50, 3.00	0.50, 1.00
<b>Alfacalcidol (Active Vitamin D) /TDD (µg) (n)</b>	4	3	2	9	4
Mean	2.75	2.00	2.00	2.33	2.50
Min, Max	2.0, 4.0	1.0, 3.0	1.0, 3.0	1.0, 4.0	1.0, 4.0

# Baseline of Spot FECa & Albumin-Adjusted sCa – PP

Lab Summary at Baseline	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
<b>Albumin-Adjusted sCa (mg/dL) (n)</b>	14	15	15	44	13
Mean (SD)	8.6 (0.49)	9.1 (1.3)	8.7 (0.62)	8.8 (0.91)	8.9 (0.39)
<b>Spot AM FECa (%) (n)</b>	14	15	15	44	13
Mean (SD)	2.5 (1.4)	3.3 (1.5)	2.4(1.2)	2.8 (1.4)	2.3 (0.76)
<b>Spot AM FECa normal (<math>\leq 2\%</math>) at baseline</b>	7 (50%)	4 (27%)	8 (53%)	19 (43%)	5 (39%)

# Treatment-Emergent Adverse Event Summary – SAS

	PTH 15 µg/day (N=14) n (%)	PTH 18 µg/day (N=15) n (%)	PTH 21 µg/day (N=15) n (%)	Total PTH (N=44) n (%)	Placebo (N=15) n (%)
TEAEs	6 (43)	3 (20)	8 (53)	17 (39)	5 (33)
Serious TEAE	0	0	0	0	0
Severity*					
Severe TEAE	0	0	0	0	0
Moderate TEAE	1 (7.1)	1 (6.7)	1 (6.7)	3 (6.8)	3 (20)
Mild TEAE	5 (36)	2 (13)	7 (47)	14 (32)	2 (13)
Related TEAE	3 (21)	1 (6.7)	5 (33)	9 (20)	1 (6.7)
Serious Related TEAE	0	0	0	0	0
TEAE Related to Hyper- or Hypocalcaemia Leading to ER/Urgent Care Visit and/or Hospitalization	0	0	0	0	0
TEAE Leading to Discontinuation of Study Drug	0	0	0	0	0
TEAE Leading to Discontinuation of Trial	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0



# Treatment-Emergent Adverse Events of Interest – SAS

Preferred Term	PTH 15 µg/day (N=14) n (%)	PTH 18 µg/day (N=15) n (%)	PTH 21 µg/day (N=15) n (%)	Total PTH (N=44) n (%)	Placebo (N=15) n (%)
<b>TEAEs</b>	6 (43)	3 (20)	8 (53)	17 (39)	5 (33)
Headache	3 (21)	1 (6.7)	2 (13)	6 (14)	0
Nausea	2 (14)	1 (6.7)	1 (6.7)	4 (9.1)	1 (6.7)
Fatigue	0	1 (6.7)	1 (6.7)	2 (4.5)	0
Injection site haemorrhage	1 (7.1)	0	1 (6.7)	2 (4.5)	0
Injection site pain	1 (7.1)	0	1 (6.7)	2 (4.5)	0
Thirst	0	1 (6.7)	1 (6.7)	2 (4.5)	0
Urinary tract infection	1 (7.1)	0	1 (6.7)	2 (4.5)	0
Hypertension	1 (7.1)	1 (6.7)	0	2 (4.5)	0
Hypercalcaemia	0	0	2 (13)	2 (4.5)	0
Hypocalcaemia	0	0	0	0	1 (6.7)

# PaTH Forward 4-Week Fixed Dose Safety Summary

- All doses of TransCon PTH were well-tolerated
- No drop-outs during 4-week blinded period
- No serious or severe TEAEs were reported
- No TEAEs leading to discontinuation of study drug
- Overall incidence of TEAEs comparable between TransCon PTH and placebo
- TEAEs in TransCon arms reflect known PTH pharmacology
- Injections were well-tolerated using pen injector planned for commercial presentation

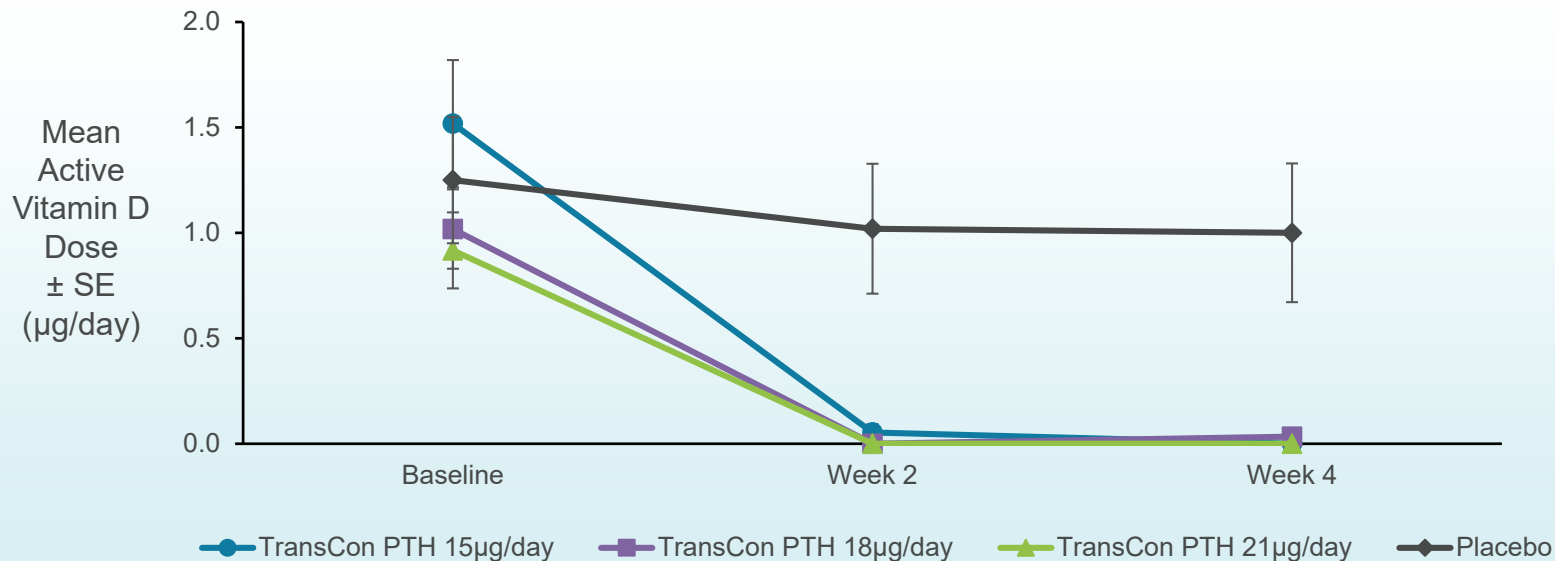
Titration algorithm to eliminate standard of care demonstrated no hypocalcaemic AEs

# Elimination of Standard of Care – PP

Number of Subjects Meeting Each Component	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
Not taking active vitamin D supplements	14 (100%)	14 (93%)	15 (100%)	43 (98%)	4 (31%)
Taking ≤1000 mg/day of calcium supplements	13 (93%)	13 (87%)	15 (100%)	41 (93%)	6 (46%)
Taking ≤500 mg/day of calcium supplements	12 (86%)	9 (60%)	15 (100%)	36 (82%)	2 (15%)
Taking 0 mg/day of calcium supplements	7 (50%)	7 (47%)	8 (53%)	22 (50%)	0
Not taking active vitamin D and 0 mg/day of calcium supplements	7 (50%)	7 (47%)	8 (53%)	22 (50%)	0
Not taking active vitamin D and ≤500 mg/day of calcium supplements	12 (86%)	9 (60%)	15 (100%)	36 (82%)	2 (15%)

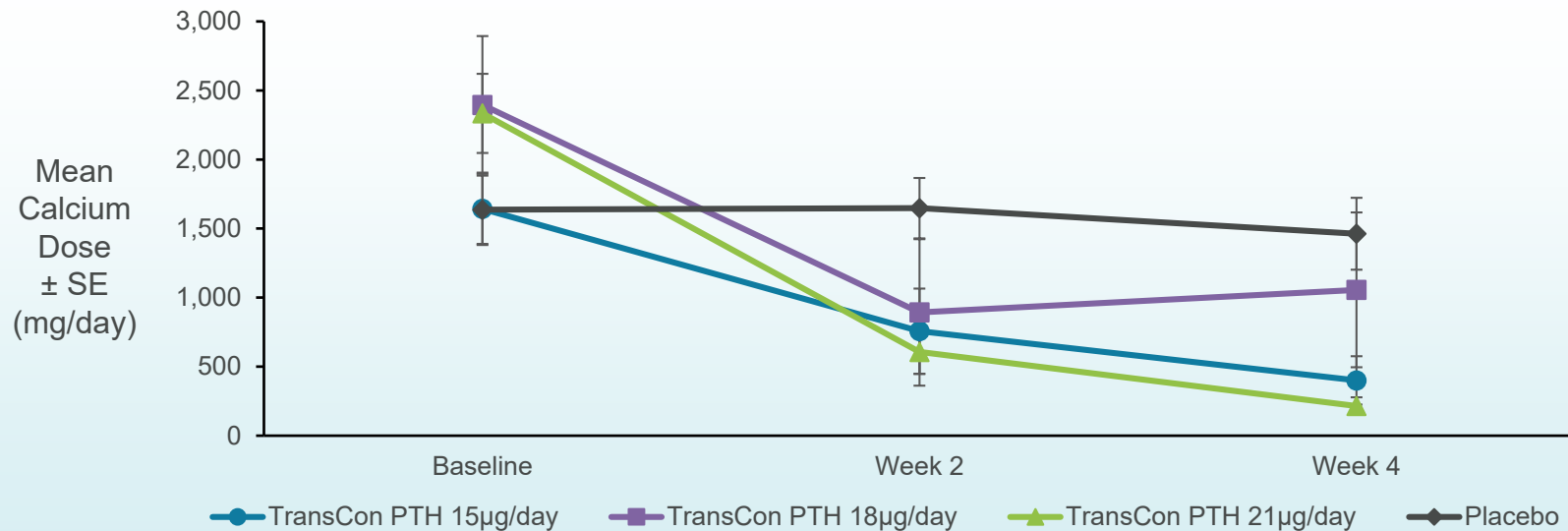
100% of subjects in the 21 µg/day arm and 82% of all subjects across all TransCon PTH dosage arms were able to eliminate standard of care\*

# Mean Active Vitamin D Dose by Visit – PP



TransCon PTH enabled discontinuation of active vitamin D at week 2

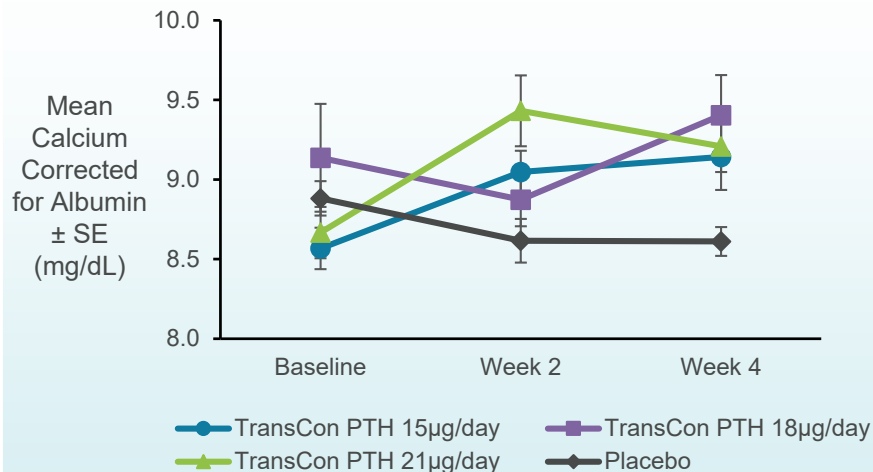
# Mean Calcium Supplement Dose by Visit – PP



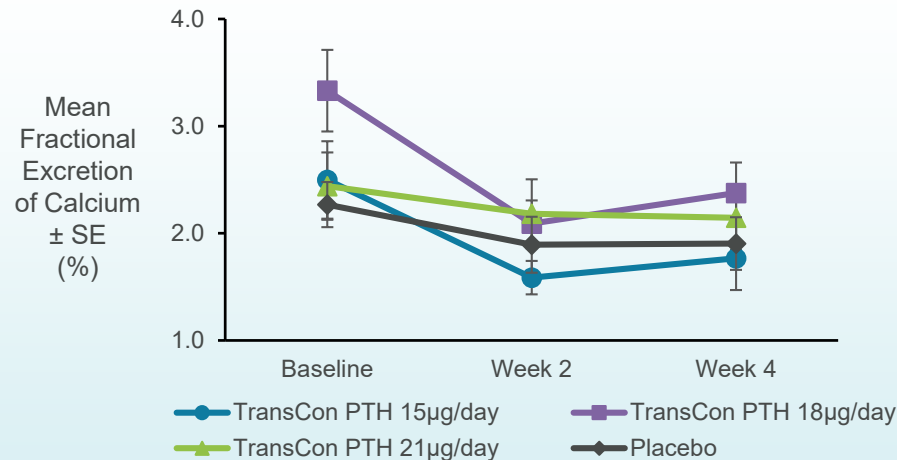
TransCon PTH enabled continuous calcium supplement reduction over 4-week study period

# Mean Serum Calcium and Spot FECa by Visit – PP

## Mean Serum Calcium

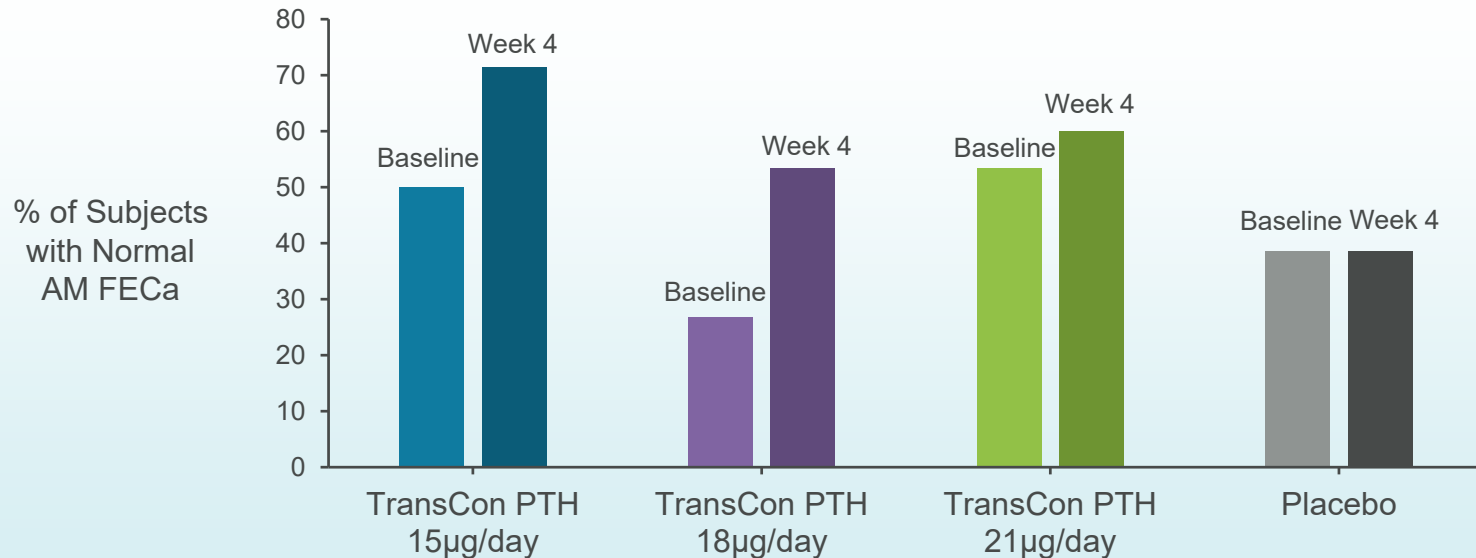


## Mean Spot FECa



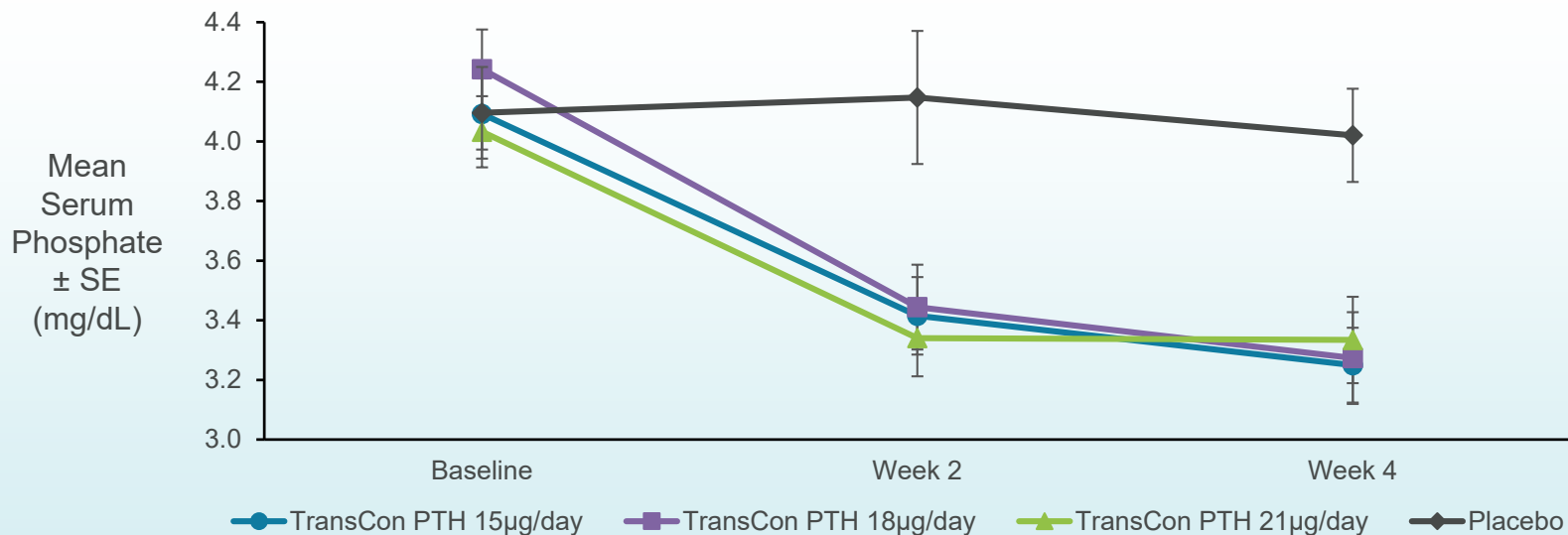
TransCon PTH subjects exhibited reduced FECa, despite increased serum calcium  
For placebo subjects, FECa followed serum calcium levels

# TransCon PTH Increased Number of FECa Responders – PP



By week 4 of treatment, TransCon PTH had normalized an additional 8 subjects compared to none on placebo

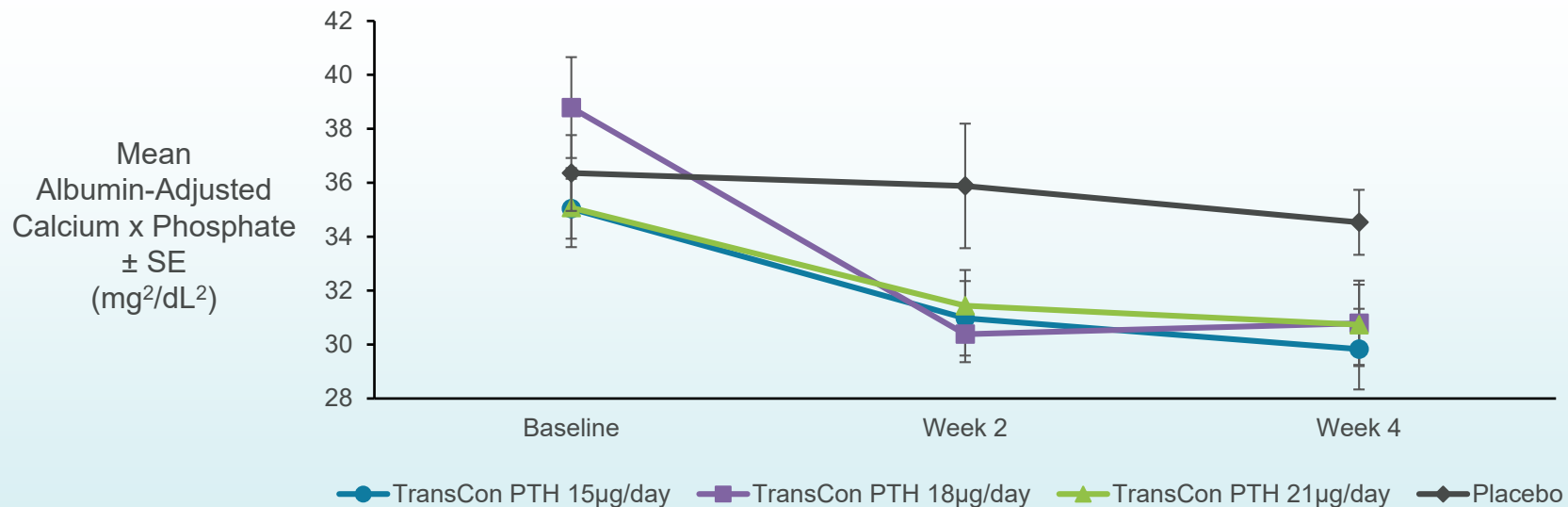
# Mean Serum Phosphate by Visit – PP



TransCon PTH subjects demonstrated consistent, sustained reductions in serum phosphate



# Mean Calcium-Phosphate Product by Visit – PP



TransCon PTH demonstrated consistent, sustained reductions in calcium-phosphate product

# Primary Composite Endpoint at Week 4 – PP

	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
Number of Subjects Meeting Primary Composite Endpoint at Week 4 with Fixed Dosing	7	6	9	22	2
Proportion (95% CI)	50 (23, 77)	40 (16, 68)	60 (32, 84)	50 (35, 65)	15 (1.9, 45)
<b>P-value</b>	0.10	0.22	0.02	0.03	
Number of Subjects Meeting Each Component:					
<b>Serum calcium within the normal range, n (%)</b>	12 (86%)	12 (80%)	14 (93%)	38 (86%)	12 (92%)
Below lower limit of normal (<8.3 mg/dL)	2	1	0	3	1
Above upper limit of normal (>10.6 mg/dL)	0	2	1	3	0
<b>Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, n (%)</b>	10 (71%)	8 (53%)	9 (60%)	27 (61%)	5 (38%)
<b>Not taking active vitamin D supplements, n (%)</b>	14 (100%)	14 (93%)	15 (100%)	43 (98%)	4 (31%)
<b>Taking ≤1000 mg/day of calcium supplements, n (%)</b>	13 (93%)	13 (87%)	15 (100%)	41 (93%)	6 (46%)

The 21 µg/day arm and the combined TransCon PTH dosage arms showed a statistically significant response compared to placebo at week 4

# Key Secondary Composite Endpoint at Week 4 – PP

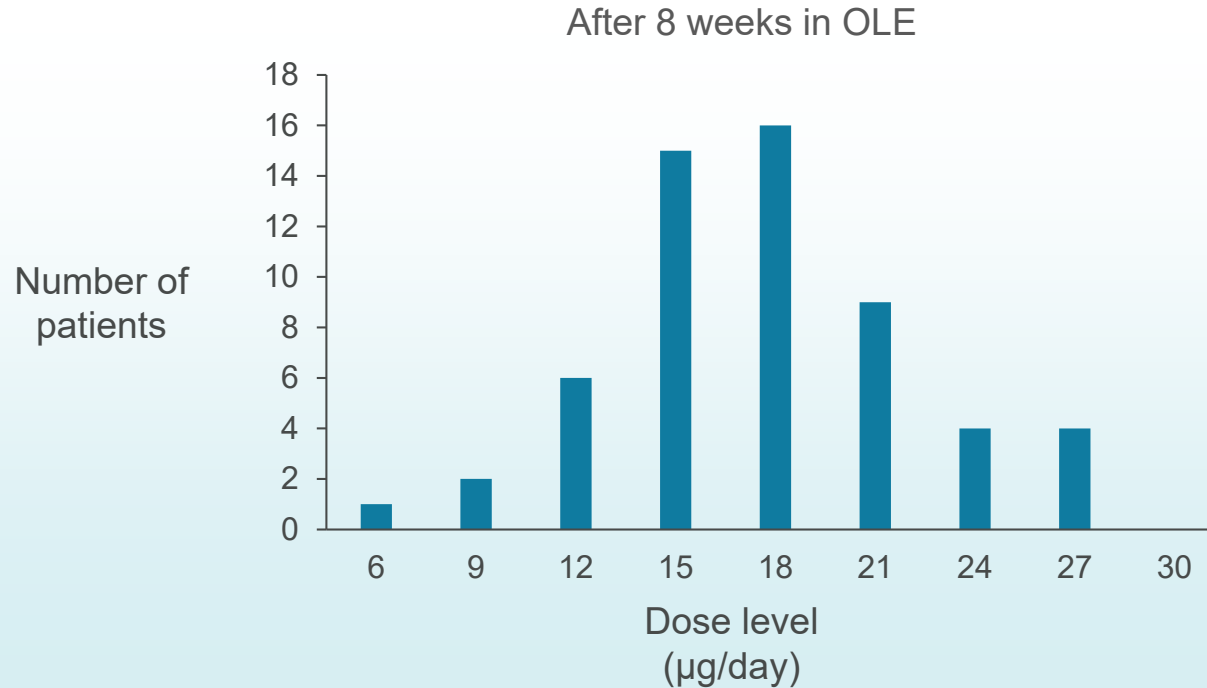
	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
Number of Subjects Meeting Key Secondary Composite Endpoint at Week 4 with Fixed Dosing	7	4	9	20	2
Proportion (95% CI)	50 (23, 77)	27 (7.8, 55)	60 (32, 84)	45 (30, 61)	15 (1.9, 45)
<b>P-value</b>	0.10	0.65	0.02	0.06	
Number of Subjects Meeting Each Component:					
<b>Serum calcium within the normal range, n (%)</b>	12 (86%)	12 (80%)	14 (93%)	38 (86%)	12 (92%)
Below lower limit of normal (<8.3 mg/dL)	2	1	0	3	1
Above upper limit of normal (>10.6 mg/dL)	0	2	1	3	0
<b>Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, n (%)</b>	10 (71%)	8 (53%)	9 (60%)	27 (61%)	5 (38%)
<b>Not taking active vitamin D supplements</b>	14 (100%)	14 (93%)	15 (100%)	43 (98%)	4 (31%)
<b>Taking ≤500 mg/day of calcium supplements</b>	12 (86%)	9 (60%)	15 (100%)	36 (82%)	2 (15%)

The 21 µg/day arm showed a statistically significant response compared to placebo at week 4

# Open-label Extension (OLE) Trial

- Subjects from fixed-dose PaTH Forward Trial rolled over to the open-label extension which enabled individually optimized TransCon PTH dosing (6-30 µg/day) to evaluate long-term safety and efficacy
- 58 out of 59 randomized subjects currently receiving TransCon PTH in the open-label extension
  - Both placebo responders continue in the open-label extension
  - One subject (randomized to placebo) withdrew for reasons unrelated to safety or efficacy of the study drug
- Long-term data from open-label extension evaluates a composite endpoint. Evaluating proportion of subjects with:
  - Normal serum calcium; **and**
  - Off active vitamin D; **and**
  - Taking ≤500 mg/day calcium; **and**
  - Normal 24-hour urine calcium excretion (or at least 50% decrease from baseline)

# Distribution of Doses\* in Phase 2 Open-label Extension



# Simple Pen Injector in Phase 2

## Key Features

- Simple operation
- Three multi-use pens with three different strengths (6, 9, 12 µg; 15, 18, 21 µg; 24, 27, 30 µg)
- Ready-to-use liquid formulation, room temp stability for 14 days
- Low injection volume ( $\leq 0.1$  mL)
- Small (31G), short (5 mm) safety pen needle



Pen injector  
planned for  
commercial  
launch being  
used in phase 2

PaTHforward  
TRIAL

# TransCon PTH: A Potential 24-hour PTH Replacement Therapy

- Phase 1 and phase 2 data support profile of TransCon PTH as a potential 24-hour PTH replacement therapy for HP
  - PaTH Forward data demonstrate potential for TransCon PTH to replace standard of care
- Report PaTH Forward open-label extension six-month data in Q3 2020
- Submit proposed PRO instrument for FDA review in Q3 2020
- Carcinogenicity study waiver granted in the US and EU
- On track to submit regulatory filings to initiate a global phase 3 trial in North America, Europe and Asia in Q4 2020:
  - Ethnobridging study showed comparable PK profile between Japanese and non-Japanese populations, enabling inclusion of Japan
- Received orphan designation in US in 2018
- Disease burden and PaTH Forward results validate significant unmet need



# TransCon CNP: The New Frontier of Growth Biology

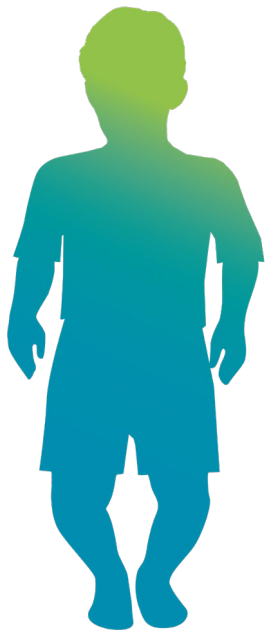


# TransCon CNP: The New Frontier of Growth Biology

- C-type natriuretic peptide (CNP) is a promising therapeutic pathway for treating growth failure and dwarfism
  - Inhibits the overactive signalling resulting from both ligand-dependent and independent signalling through the mutated FGFR3 receptor causing achondroplasia
- Due to its very short half-life (2-3 minutes), CNP has historically not been a druggable target, as prolonged exposure is required for improved growth
- Phase 1 data support the TransCon CNP Target Product Profile

TransCon CNP may provide benefit in several growth disorders — as monotherapy, and potentially in combination with TransCon hGH

# Achondroplasia: High Morbidity



Up to **85%** of patients require intervention for obstructive sleep apnea and respiratory insufficiency

**25%** of children have hearing loss increasing to > 50% in adulthood

**22%** have osteotomy

**15-30%** have fixed kyphotic deformity

Up to **28%** require cervicomedullary decompression by age 4

**10%** of children have neurological signs of spinal stenosis

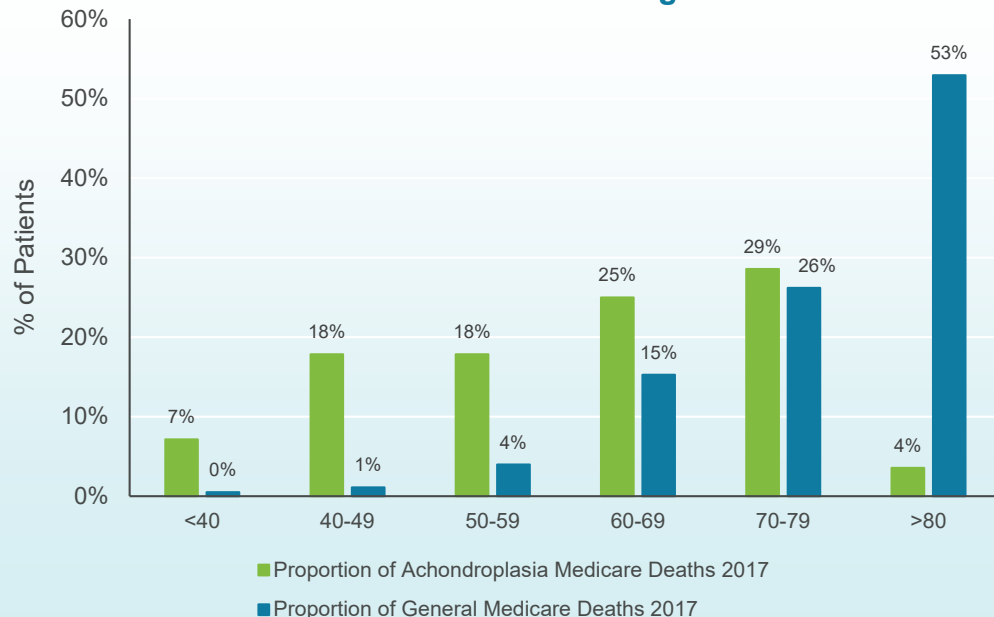
**80%** of adults have clinical signs and symptoms related to spinal stenosis

# Achondroplasia: Higher Mortality

Preliminary analysis shows among achondroplasia patients a median age of death of 60 years – consistent with the published literature

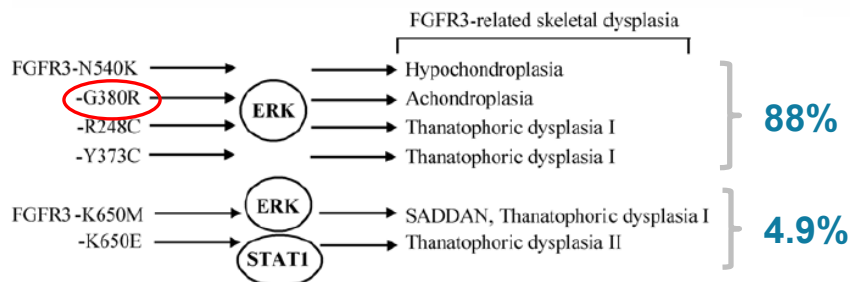
Markedly higher rates of death in these patients compared to the overall Medicare population, especially among patients <70 years

Age of Death for Achondroplasia vs General Medicare Patients Passing in 2017



# Achondroplasia: Autosomal Dominant Mutation in *FGFR3*

## Mutations leading to different Skeletal Dysplasias<sup>1</sup>



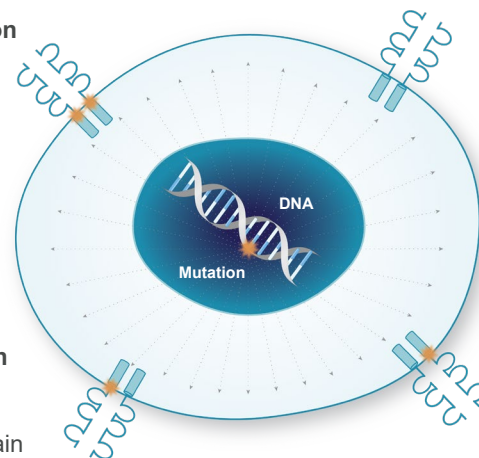
## Different Conformations of the *FGFR3* G380R mutated dimer<sup>2</sup>

### Double mutation

2.5 increase in activation in absence of ligand

### Single mutation

Activation in absence of ligand uncertain

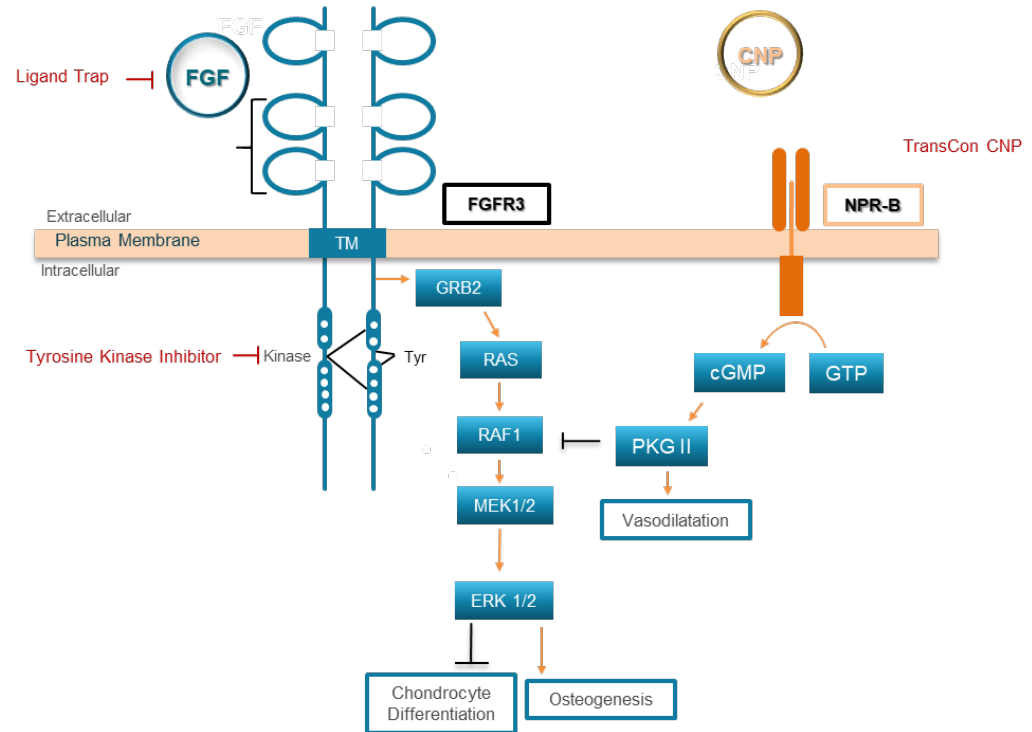


Downstream inhibition required to inhibit ligand-independent signaling

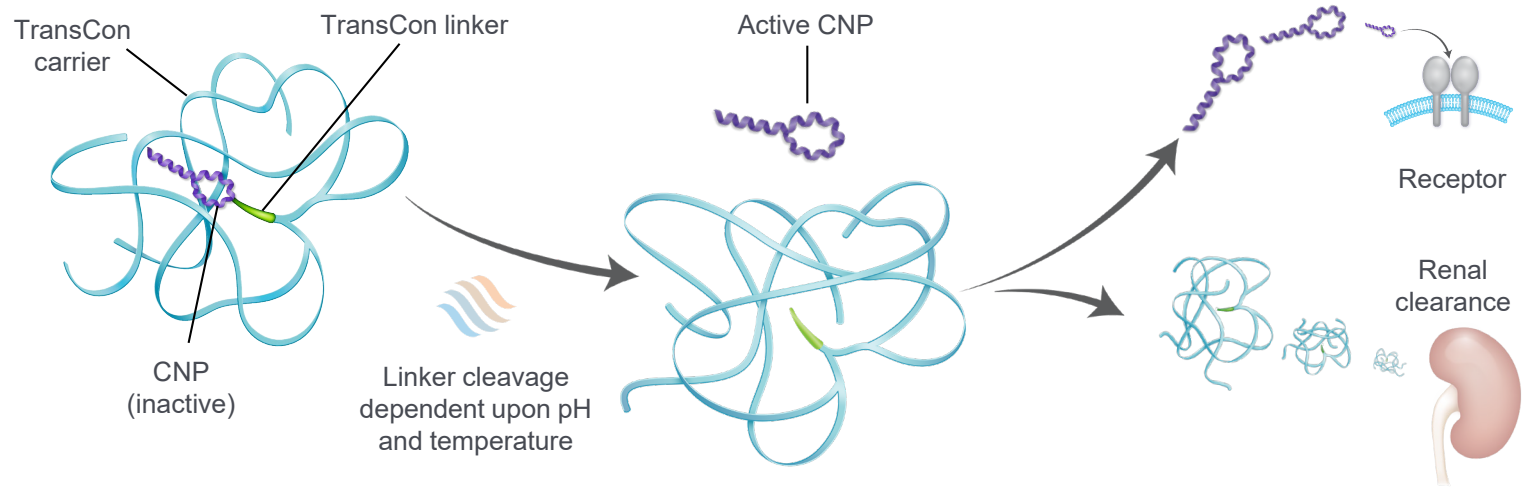
# Achondroplasia Signaling Defect is Well Understood<sup>1</sup>

TransCon CNP continuously inhibits abnormal FGFR3 signaling, restoring proliferation and differentiation of chondrocytes to rebalance bone growth

CNP does not alter the function of FGF receptors or change endogenous levels of FGF ligands, reducing the risk of interfering with normal FGF biology



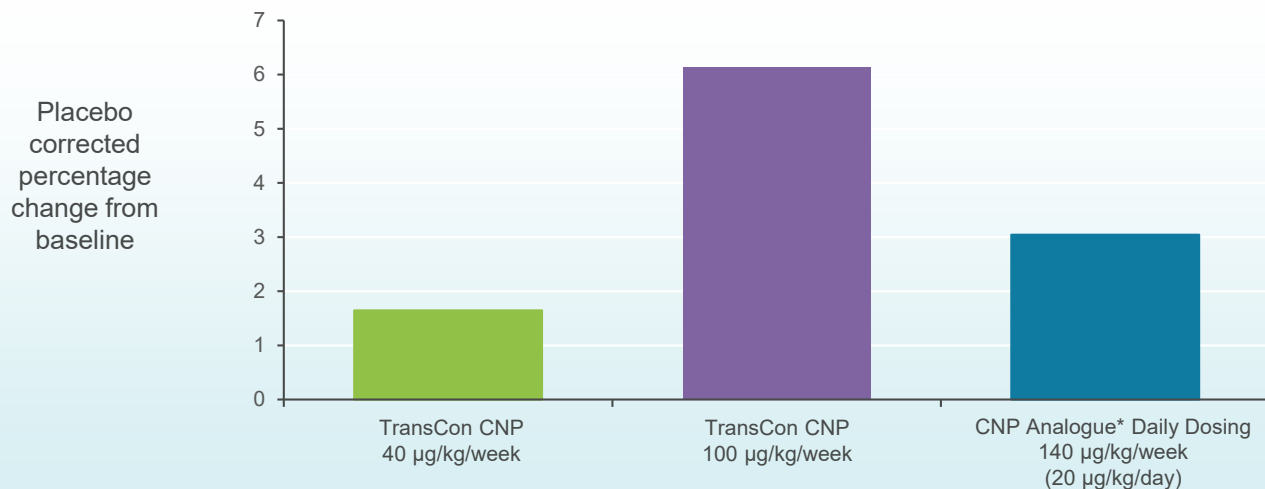
# TransCon CNP Design



- TransCon technology is designed to provide effective shielding of CNP:
  - From neutral endopeptidase degradation in subcutaneous tissue and blood compartment
  - Minimize binding of TransCon CNP to the NPR-C receptor
  - Reduce binding of TransCon CNP to the NPR-B receptor in vasculature to avoid hypotension
- CNP liberated from TransCon CNP maintains small enough size to allow penetration into growth plates

# Juvenile Healthy Monkey Growth Study

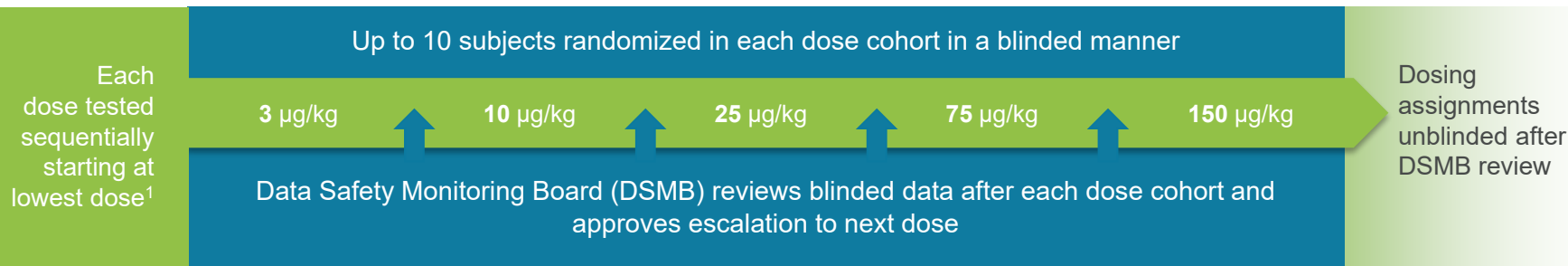
## Tibial growth at 6 months (n=4/group)



- Demonstrated dose-proportional tibial linear growth; ulnar growth consistent
- TransCon CNP induced a more robust growth response compared to daily administration of CNP, despite being administered at a 40% lower dose

# Phase 1 Trial Design

## 45 healthy adult male subjects TransCon CNP vs. placebo (4:1 randomization)



### Primary Endpoint

- Frequency of adverse events (AEs) reported after administration of TransCon CNP

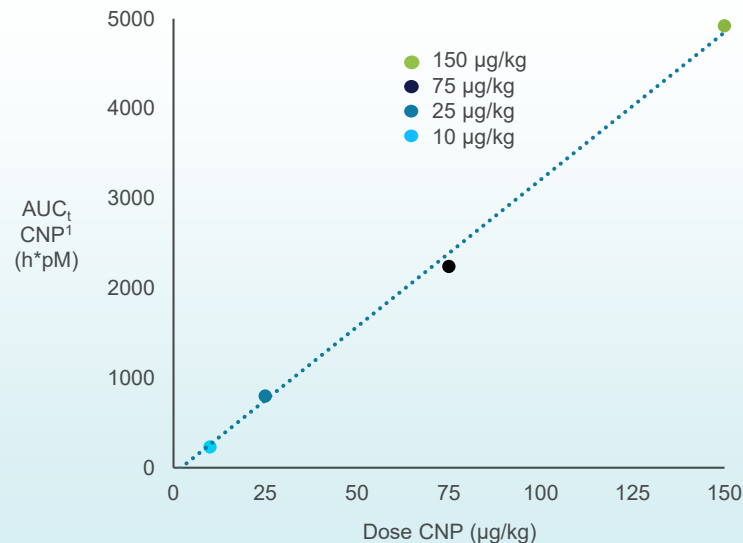
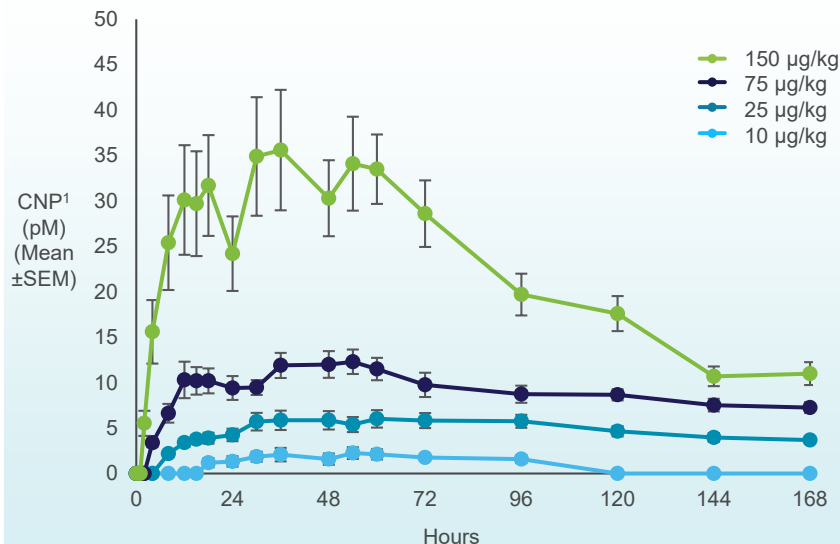
### Secondary/Exploratory Endpoints

- Safety parameters and local tolerability assessment
- Pharmacokinetic parameters
- Other exploratory endpoints



# Dose Proportional CNP Exposure For 1 Week

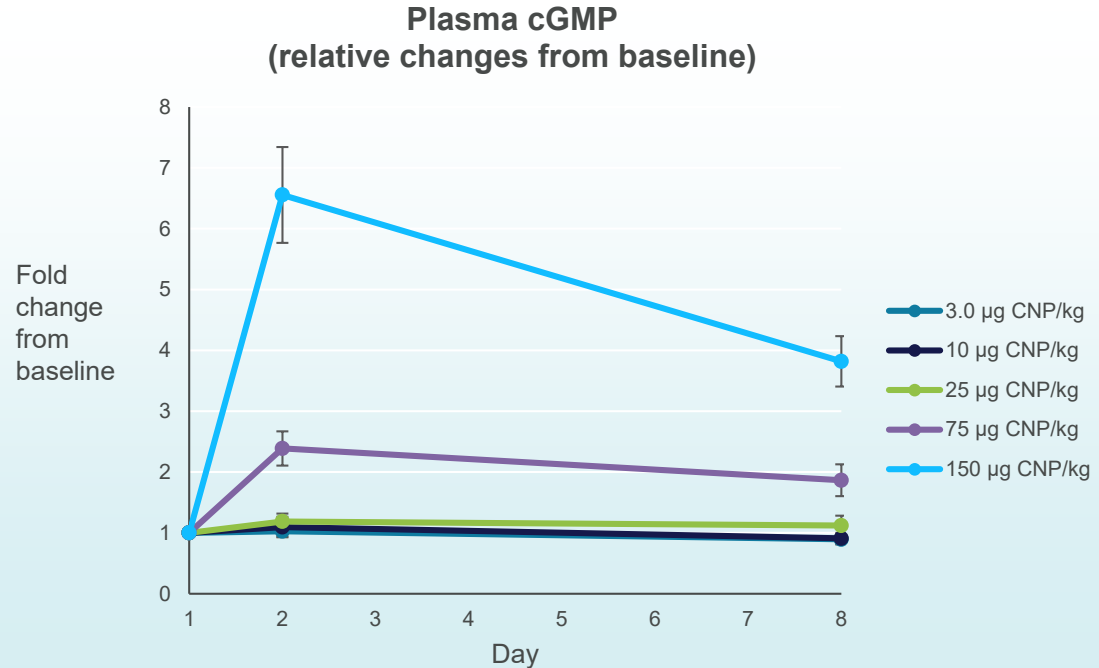
TransCon CNP 10, 25, 75 and 150 µg/kg (n=5-8/group)



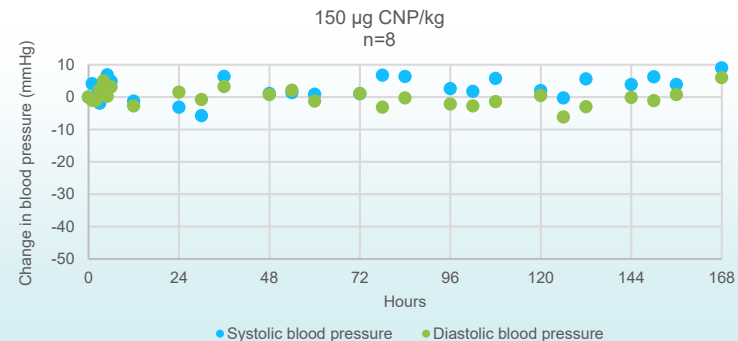
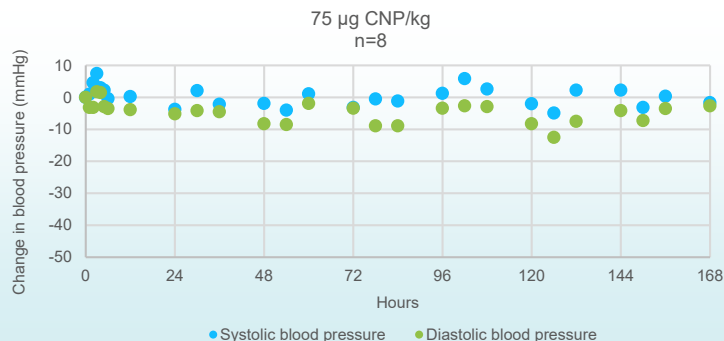
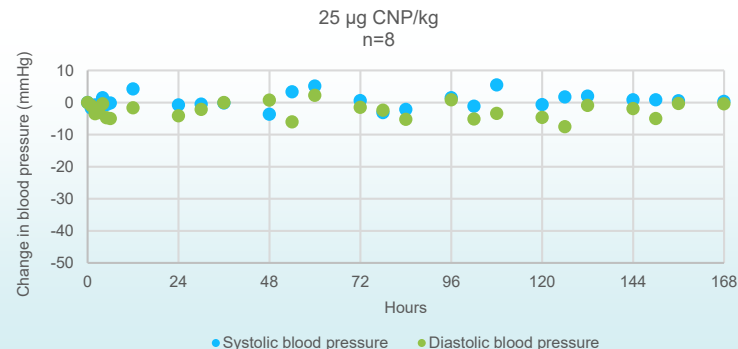
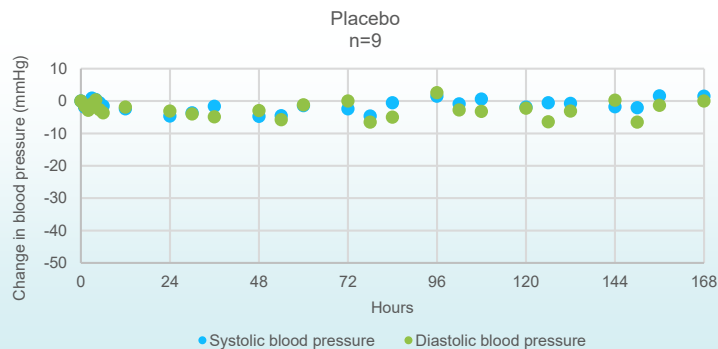
- Dose proportional increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP  $t_{1/2}$  of approximately 120 hours (native CNP  $t_{1/2}$  of 2-3 minutes)

# Dose Dependent cGMP<sup>1</sup> Response Demonstrated Receptor Engagement For 7 Days

- cGMP is a secondary messenger of NPR-B activation by CNP
- cGMP levels correlate with TransCon CNP PK profile



# Mean Resting Blood Pressure Unchanged from Predose<sup>1</sup>



● Change in systolic blood pressure ● Change in diastolic blood pressure

# TransCon CNP: Safety Profile in Phase 1



No serious AEs were reported in the trial



TransCon CNP was generally well tolerated at doses up to 150 µg/kg



No anti-CNP antibodies detected in any subjects



Mean resting blood pressure and heart rate were unchanged from pre-dose at all time points, in all cohorts

Mean orthostatic changes in vital signs appear unrelated to TransCon CNP exposure; consistent between placebo and TransCon CNP cohorts



Injections were well tolerated in all dose cohorts

# ACHieve Ongoing and Enrolling



- A global natural history study of ~200 children <8 years with achondroplasia (ACH):
  - Over 50 subjects enrolled
- Evaluates height velocity, body proportionality and comorbidities
- Establishes relationships with study sites worldwide, paving the way for potential future TransCon CNP clinical trials
- Twenty sites selected and site qualification ongoing:
  - Australia, Austria, Canada, China, Germany, Ireland, Italy, New Zealand, Portugal, Spain, Switzerland, UK, and US



# TransCon CNP: Phase 2 Trial Design



Up to 60 children (ages 2 – 10 years) with achondroplasia

TransCon CNP  
vs. placebo (3:1  
randomization)

12 subjects randomized in each dose cohort in a blinded manner

6 µg/kg

20 µg/kg

50 µg/kg

100 µg/kg

>100 µg/kg<sup>1</sup>

Data Monitoring Committee reviews blinded data after each dose cohort

Extension  
trial to  
evaluate  
safety and  
efficacy

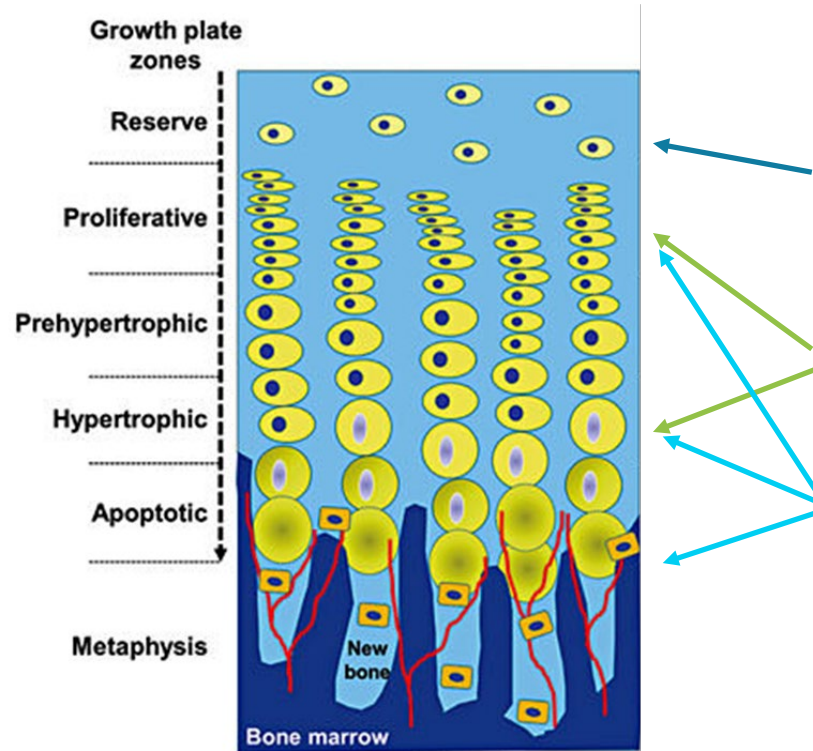
## Primary Endpoint

- Annualized height velocity, as measured after 12 months of weekly TransCon CNP treatment

## Key Secondary/Additional Endpoints

- Change in body proportionality (upper to lower body segment ratio), as measured after 12 months of weekly TransCon CNP treatment
- Change in body mass index (BMI), as measured after 12 months of weekly TransCon CNP treatment
- Patient reported outcome (PRO) measures

# Growth Biology: Rationale for Combination Effects of Different Pathways



Williams GR, Eur Thyroid J 2013;2:3

**hGH** acts directly on pre-chondrocytes in the growth plate, driving differentiation into chondrocytes required for sustained growth. hGH also stimulates local production of IGF-1

**IGF-1** stimulates chondrocyte proliferation, hypertrophy and survival

**CNP** stimulates chondrocyte proliferation, hypertrophy, differentiation, and increases in extracellular matrix formation

# TransCon CNP: Pursuing New Frontier of Growth Biology

- C-type natriuretic peptide (CNP) pathway has demonstrated clinical proof of concept
  - Short half-life of native CNP (2-3 minutes) limits therapeutic use
- TransCon CNP provides continuous CNP exposure 24 hours a day, seven days a week to balance constantly activated FGFR3 pathway, aiming to restore normal growth
- In phase 1, TransCon CNP demonstrated effective CNP  $t_{1/2}$  of approximately 120 hours
  - No serious AEs, no impact on resting blood pressure or heart rate, no downregulation of endogenous CNP production; no anti-CNP antibodies
- ACHieve natural history study and ACcomplishH phase 2 trial (ages 2 – 10 years) initiated, with escalation of sequential dose cohorts in ACcomplishH throughout 2020
- Expansion of clinical program in China through VISEN Pharmaceuticals
  - ACHieve initiated; ACcomplishH China expected to be initiated Q4 2020
- Received orphan designation in US in 2019
- Potential for significant impact on patients' lives, including height and comorbidities





# Oncology

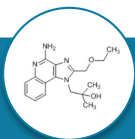
# Vision in Oncology

- Create best-in-class oncology therapies by applying systemic and intratumoral TransCon technologies for clinically validated pathways
- Improve outcomes upon validated mechanisms that are currently limited by suboptimal efficacy and systemic toxicity
  - Apply Ascendis' unique algorithm for product innovation to oncology development
- Build a diversified high-value pipeline addressing multiple indications
  - Expect to file first IND or similar for TLR7/8 Agonist in Q4 2020, followed by IL-2  $\beta/\gamma$  in 2021
- Enable rapid path to global commercialization, including through mutually-beneficial collaborations as needed

# Potential to Impact Efficacy, Safety and Practicality of Both Systemic and Intratumoral Cancer Treatments

- Applying TransCon technologies to clinically validated mechanisms to develop differentiated and potentially best-in-class products
  - Large number of validated oncology targets with known limitations
  - Applicable for diverse drug classes and mechanisms of action
  - Enable both systemic and intratumoral (IT) approaches

## Advancing a diversified high-value pipeline



TransCon TLR7/8  
Agonist

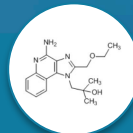


TransCon  
IL-2  $\beta/\gamma$



TransCon  
VEGF-TKI

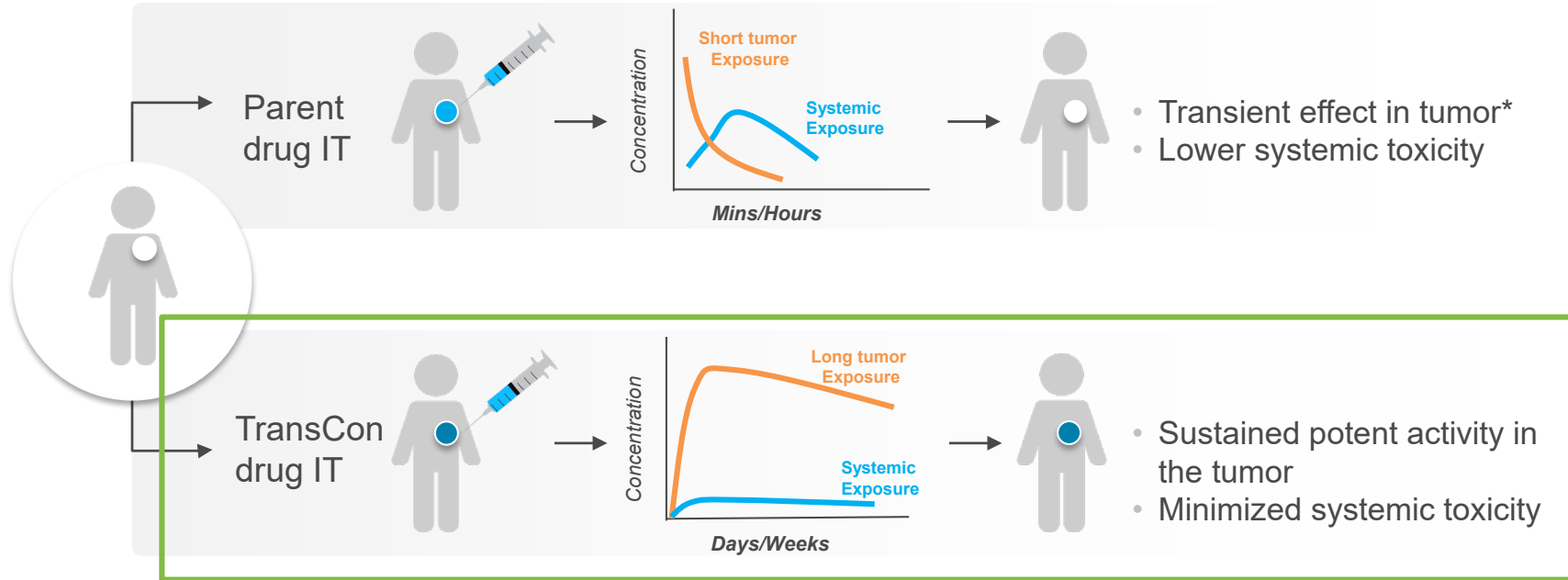
# Oncology Product Candidate



TransCon TLR7/8  
Agonist

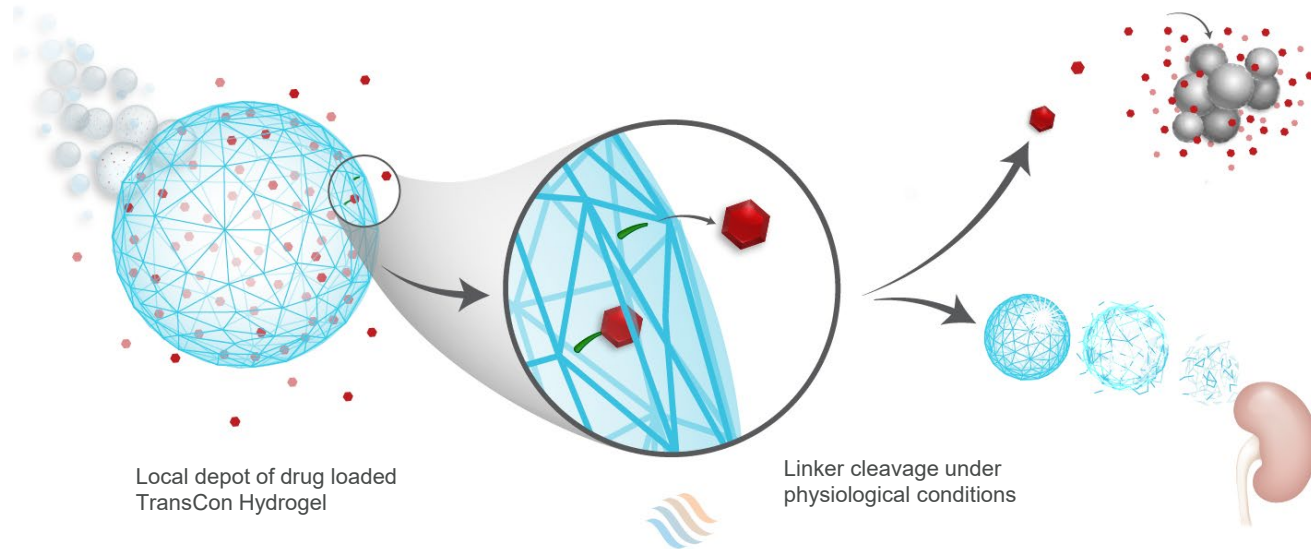
# Potential to Transform Efficacy, Safety and Practicality of Intratumoral Treatments

TransCon expected to provide weeks of drug exposure in the tumor, with minimal systemic toxicity



\* Example: STING agonist “plasma half-life ranging from 8 to 28 min” (Meric-Bernstam, ASCO, 2019)

# Resiquimod Loaded onto TransCon Hydrogel for Intratumoral Sustained Delivery

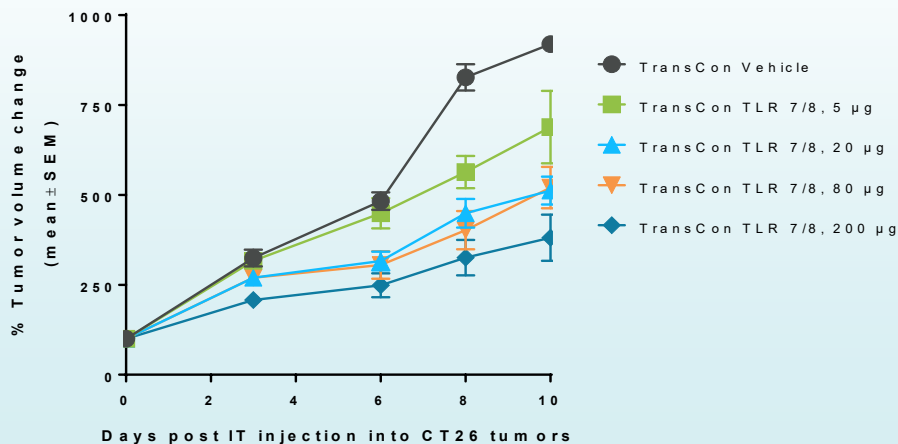


- Resiquimod transiently conjugated to TransCon Hydrogel carrier, designed to provide sustained local release of unmodified parent drug
- Designed to provide sustained activation of tumoral myeloid lineages driving tumor antigen release/presentation and induction of immune stimulatory cytokines

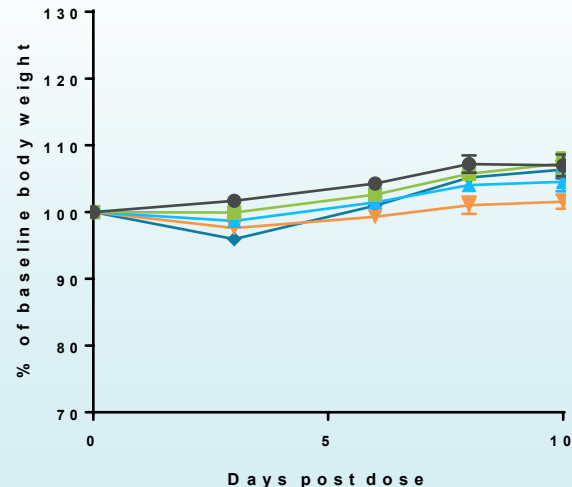
# Dose-dependent Tumor Growth Inhibition Following a Single IT Injection of TransCon TLR7/8 Agonist

## Single IT Dosing

Tumor Growth:  
Dose-dependent Inhibition



Body Weights:  
All Doses Well Tolerated

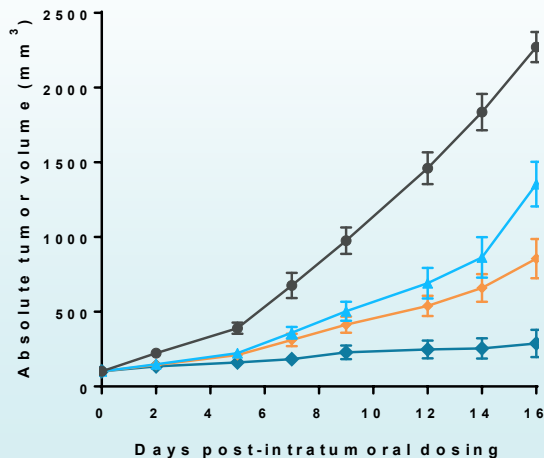


*Consistent with MOA, local inflammation and some tumor ulcerations observed*

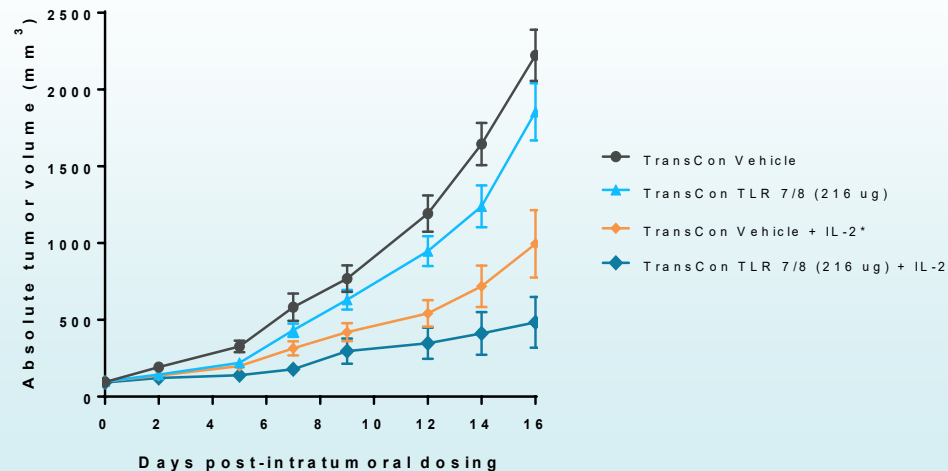
# Single-dose of TransCon TLR7/8 Agonist Triggered Abscopal Anti-Tumor Inhibition and Enhanced Anti-tumor Effects of IL-2

## Single IT Dosing

Injected Tumor



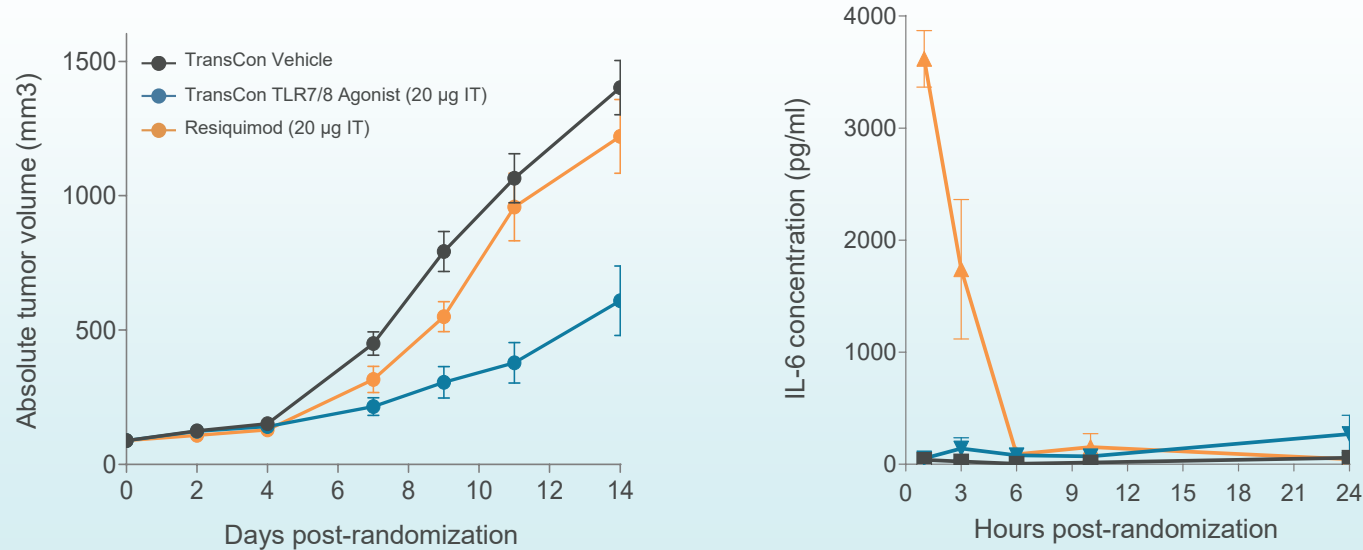
Non-injected Tumor





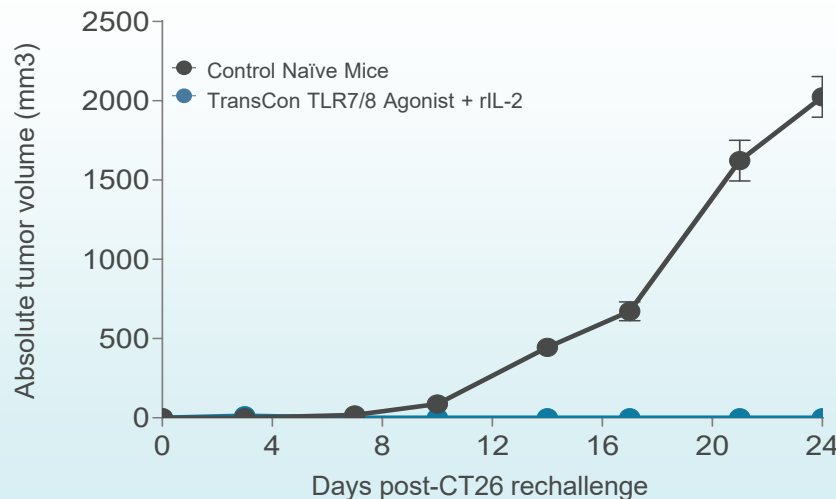
# A Single Dose of TransCon TLR7/8 Agonist Mediated Potent Tumor Growth Inhibition with Minimal Systemic Cytokine Release

Tumor Growth Inhibition (CT26) with Low Systemic Cytokine Induction



# A Single Dose of TransCon TLR7/8 Agonist with IL-2 Treatment Induced Immunological Memory and Prevented Tumor Growth Upon Rechallenge

CT26 Rechallenge, 2 Months After TransCon TLR7/8 Agonist and IL-2 Treatment



Three out of seven mice treated with TransCon TLR7/8 Agonist + IL-2 experienced complete regressions in injected and non-injected tumors. The mice were rechallenged with CT26 tumor cells two months after treatment and observed for tumor growth. Naïve mice were used as controls. Tumor volumes are represented as mean  $\pm$  SEM.

# TransCon TLR7/8 Agonist - Summary

- Offers a new treatment paradigm for intratumoral sustained delivery with potential for superior efficacy and safety
  - Single intratumoral dose potentially provides exposure for weeks/months
  - Dramatically altered ratio of anti-tumor vs systemic effects when compared to equimolar dose of parent drug
  - Complete tumor regressions, including abscopal effects, and immunological memory against rechallenge observed
  - Well tolerated in cynomolgus monkeys at all doses tested, up to 250 µg/animal
  - Potential to enable efficacy with dosing interval of months

# Oncology Product Candidate



TransCon  
IL-2  $\beta/\gamma$

# IL-2: Validated Cytokine with Suboptimal Receptor Binding *and* PK Properties

## Suboptimal receptor binding

- Two receptors: IL-2R $\alpha/\beta/\gamma$  and IL-2R $\beta/\gamma$
- $\alpha/\beta/\gamma$  receptor activates Tregs and endothelial cells, reducing efficacy and increasing risk of capillary leak syndrome

## Suboptimal PK

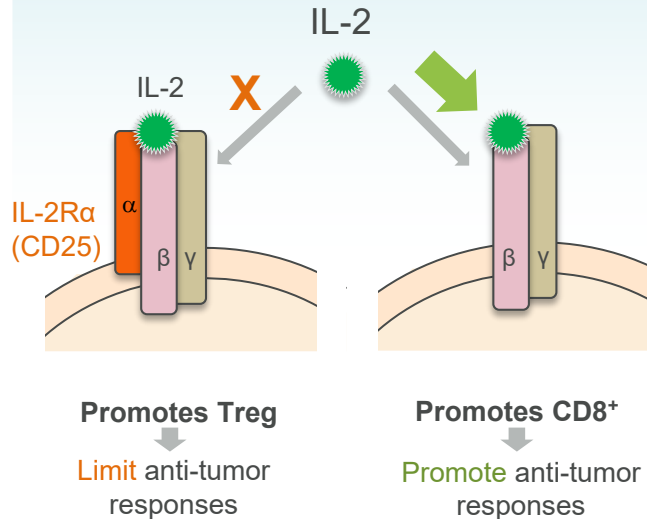
- Short half life of IL-2 (~1.5 h)
- High C<sub>max</sub> and pulsatile dosing drive adverse events

- Several IL-2 approaches in development
- To our knowledge, none have fully solved both shortcomings of IL-2

# Next Generation IL-2: Designed for Desired Receptor Binding and Exposure

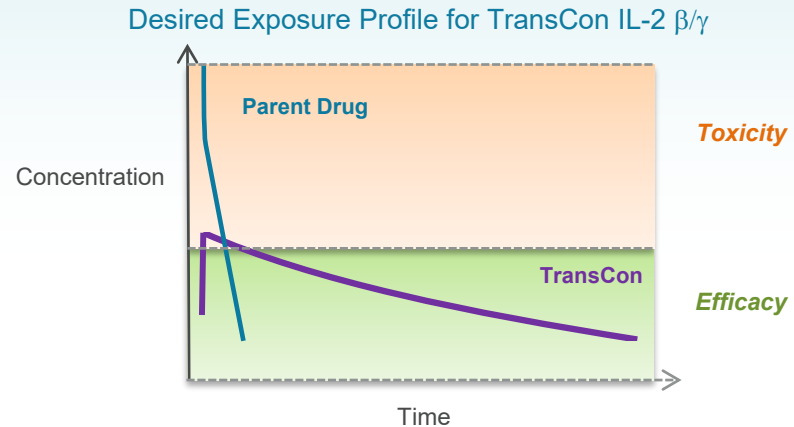
1)

Prevent IL-2R $\alpha$  binding to selectively activate IL-2R $\beta/\gamma$



2)

Generate a product with long-lasting exposure avoiding high C<sub>max</sub>

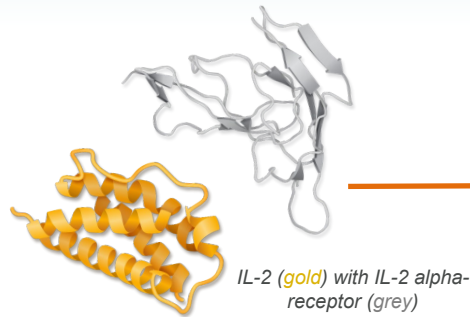


# Design of TransCon IL-2 $\beta/\gamma$ :

## 1) Designed for Desired Receptor Binding

### Generation of IL-2 Variant

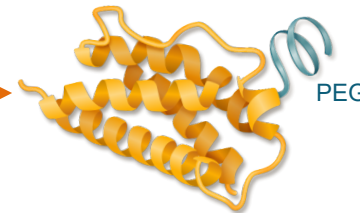
Introduction of cysteine at  $\alpha$ -binding site of IL-2 (aldesleukin)



### Blocking IL-2R $\alpha$ -binding

Site-selective permanent PEG conjugation (5kDa) of introduced cysteine

Permanent PEG attachment  
at  $\alpha$ -binding site

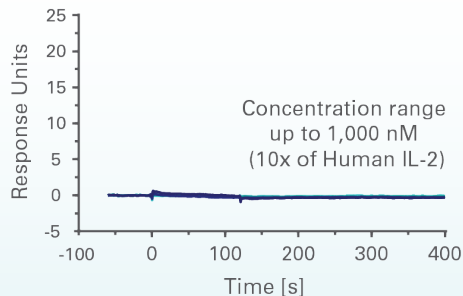


Optimized IL-2  $\beta/\gamma$  receptor selectivity and potency by permanent site-selective PEG conjugation at IL-2R $\alpha$ -binding site

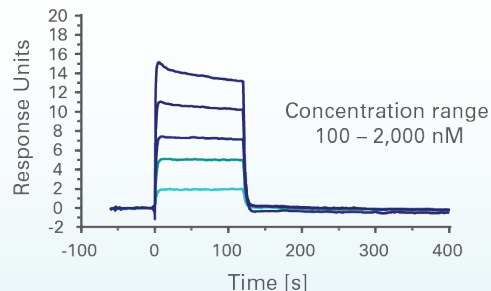
# Receptor Selectivity Demonstrated in Binding Assays

## Binding to IL-2R $\alpha$ -chain

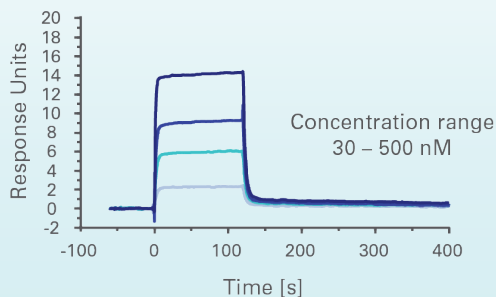
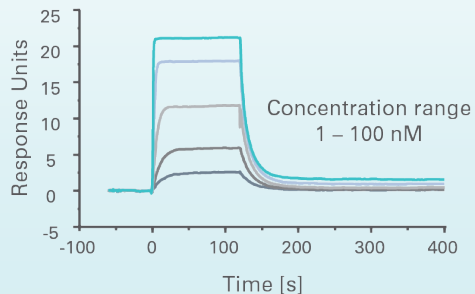
IL-2  $\beta/\gamma$



## Binding to IL-2R $\beta$ -chain



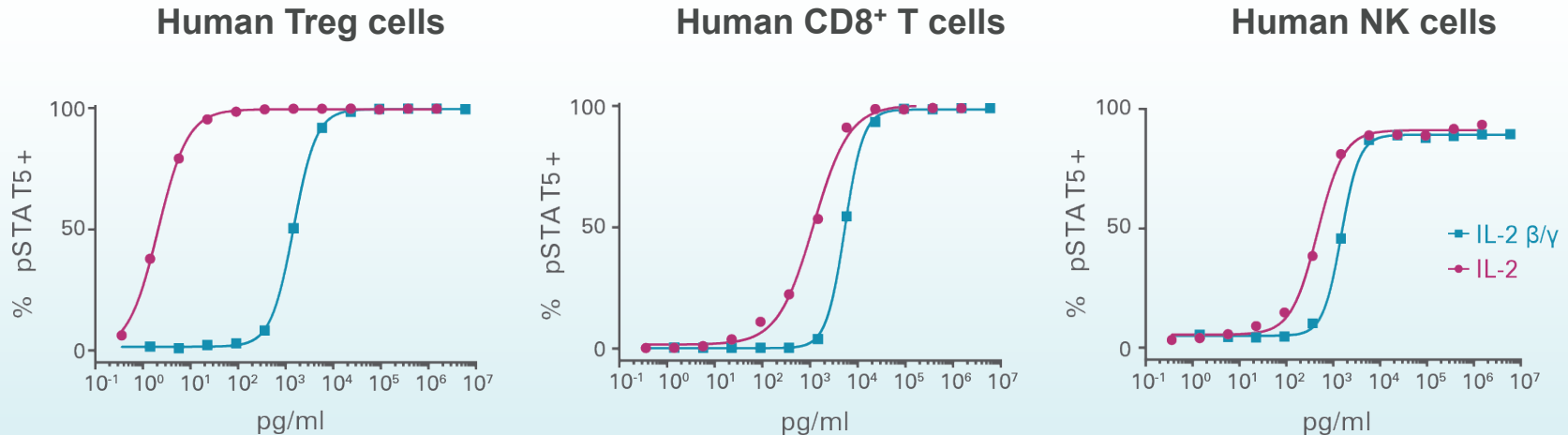
Human IL-2



IL-2  $\beta/\gamma$  demonstrated strong receptor bias with reduced IL-2R $\alpha$  binding and well-retained IL-2R $\beta$  binding



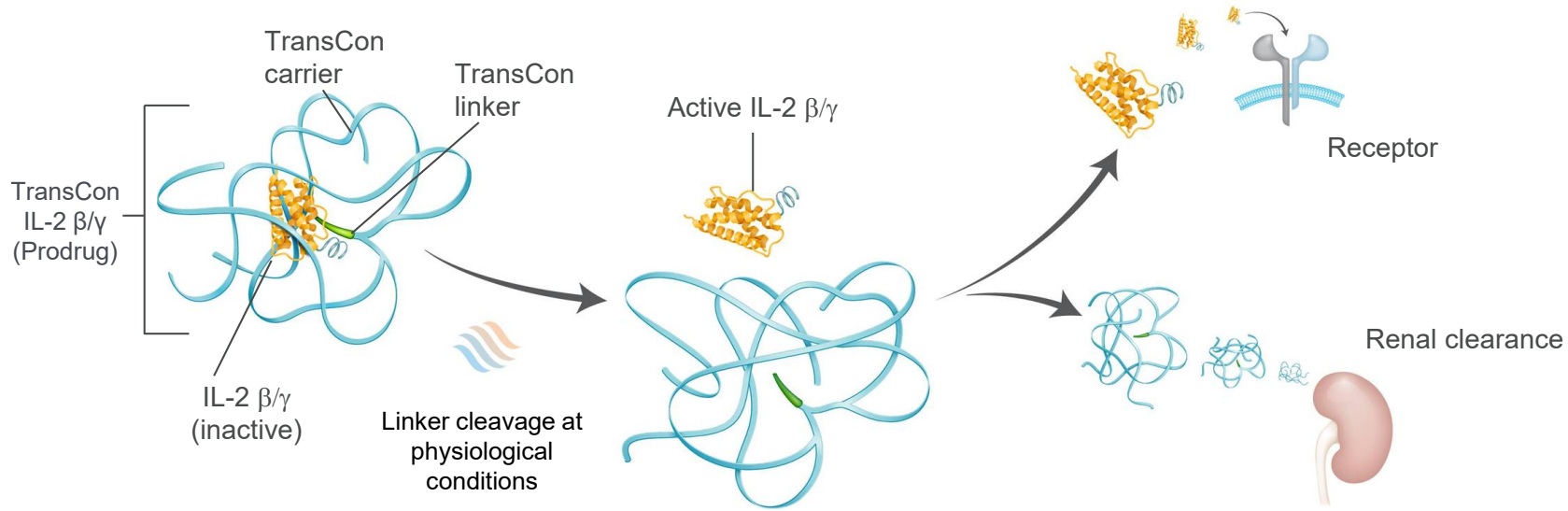
# Receptor Selectivity Confirmed in Primary Human Cells



Substantially reduced potency on primary human Treg cells compared to rhIL-2  
with minimal potency loss on CD8<sup>+</sup> T cells and NK cells

# Design of TransCon IL-2 $\beta/\gamma$ :

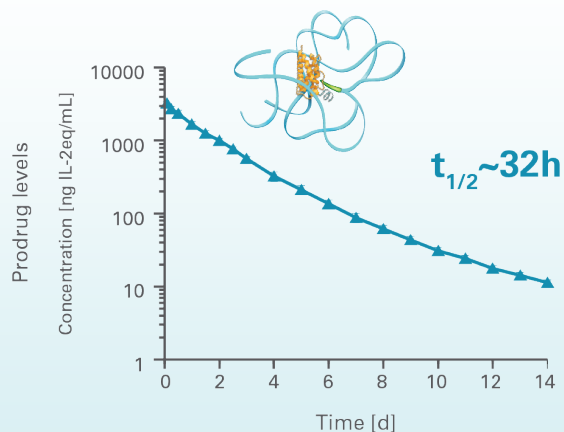
## 2) TransCon Technology to Optimize Exposure



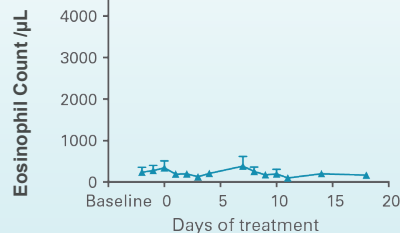
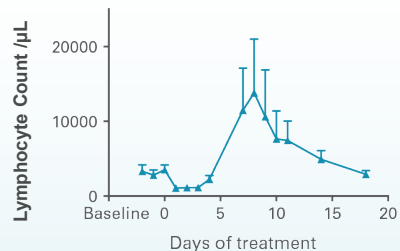
Sustained, long-lasting exposure utilizing the TransCon hGH linker and carrier, expected to support every 3 week dosing

# Single Dose TransCon IL-2 $\beta/\gamma$ Induced Robust Lymphocyte but Minimal Eosinophil Expansion in NHP\* When Compared to Aldesleukin

TransCon IL-2  $\beta/\gamma$  prodrug  
plasma PK

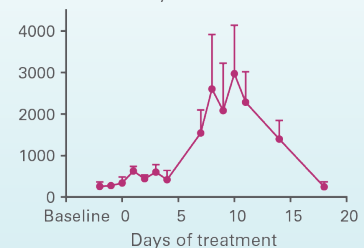
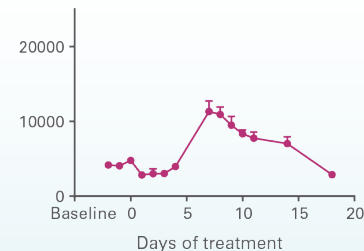


TransCon IL-2  $\beta/\gamma$   
(single 1mg dose)



1mg dose /animal;  
average animal weight 8.2 kg (7.8–8.8 kg)

Aldesleukin  
(0.4 mg/day x 5 days)



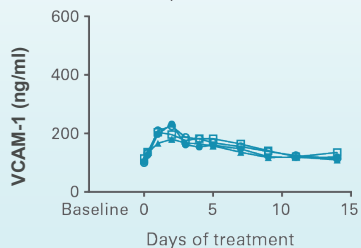
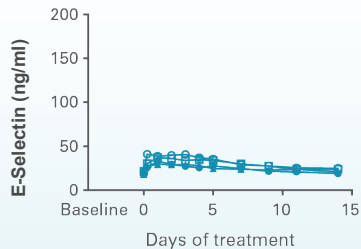
0.4 mg daily dose /animal;  
average animal weight 9.2 kg (7.7–10.6 kg)

Single dose provided >3-fold and prolonged enhancement of lymphocyte counts supporting Q3W dosing

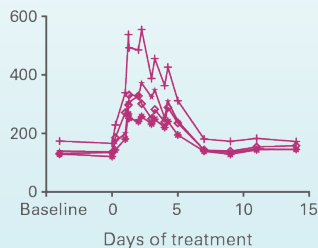
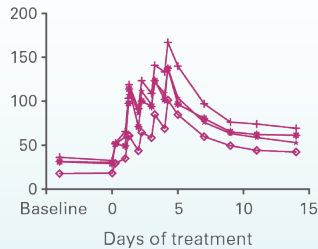
# Single Dose TransCon IL-2 $\beta/\gamma$ Induced Minimal Endothelial Cell Injury and Systemic Inflammation Markers in NHP When Compared to Aldesleukin

## Endothelial cell injury markers

**TransCon IL-2  $\beta/\gamma$   
(single 1mg dose)**

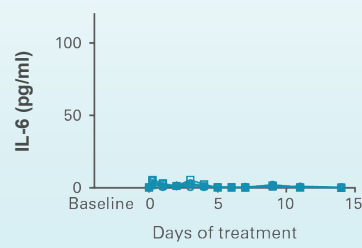
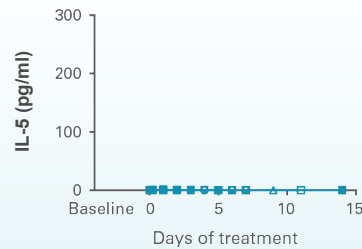


**Aldesleukin  
(0.4 mg/day x 5)**



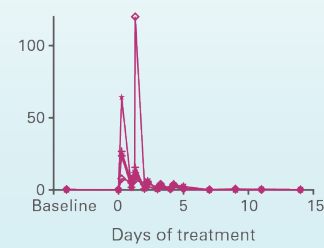
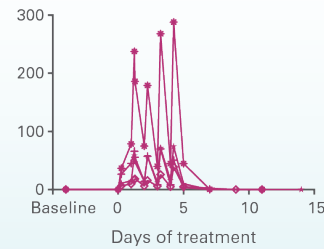
## Systemic inflammation markers

**TransCon IL-2  $\beta/\gamma$   
(single 1mg dose)**



Minimal IL-5 = Minimal eosinophil induction

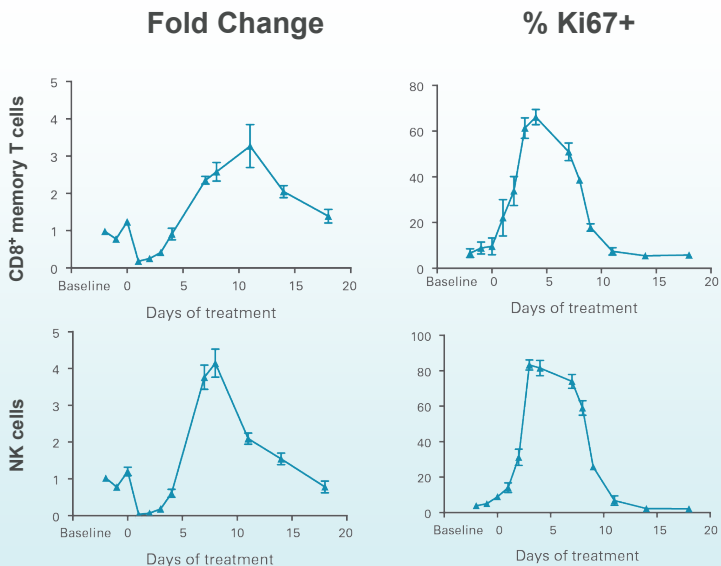
**Aldesleukin  
(0.4 mg/day x 5)**



Well tolerated in vivo with minimal induction of markers of endothelial cell injury or systemic inflammation, suggesting low risk of vascular leak syndrome (VLS)

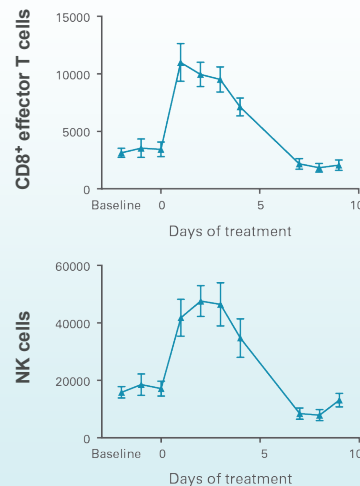
# Single Dose TransCon IL-2 $\beta/\gamma$ Induced Robust CD8<sup>+</sup> T Cell and NK Cell Expansion and Activation in NHP

## CD8<sup>+</sup> T cell and NK cell expansion



## CD8<sup>+</sup> T cell and NK cell activation

### Granzyme B MFI



Expansion and activation of effector function observed in multiple cytotoxic lymphocyte subsets

# TransCon IL-2 $\beta/\gamma$ – Potential Best-in-Class IL-2 Molecule

- Demonstrated sustained release of a novel IL-2 variant (IL-2  $\beta/\gamma$ ) with selective binding and activation of IL-2R $\beta/\gamma$
- Potential for best-in-class IL-2 molecule across multiple tumor types
  - Potent expansion and activation of lymphocyte counts in vivo
  - Low activation of eosinophils and Treg cells observed in NHP
  - Minimal signs of systemic inflammation or endothelial cell damage, suggesting low risk of VLS
  - Single dose provided >3-fold and prolonged enhancement of lymphocyte counts
  - Long half-life (~32 hours) and pharmacodynamic effect expected to support dosing every 3 weeks in patients
- No dose limiting toxicities observed in NHP; MTD not reached
- TransCon IL-2  $\beta/\gamma$  has potential to become a backbone agent in oncology

# Oncology Product Candidate



TransCon  
VEGF-TKI

# Opportunity for TransCon VEGF-TKI

## Efficacy

- Better tolerated approaches are needed to enable sufficient tumor exposure and new combination approaches

## Safety

- Lower systemic exposure expected to enable aggressive multiagent therapies

## New Indications

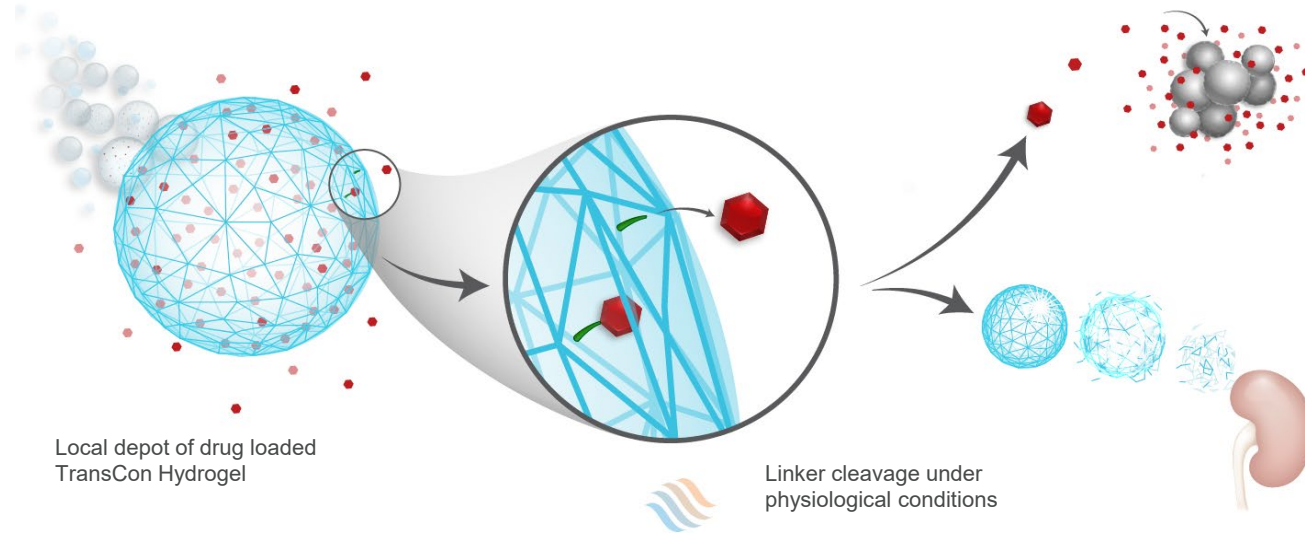
- Patients on poorly tolerated combos
- Enable intratumoral mechanisms not achievable via oral route
- CNS tumors

## TransCon VEGF-TKI

***Tumor-localized, sustained release*** aiming for mechanisms and efficacy not achievable by oral alternatives



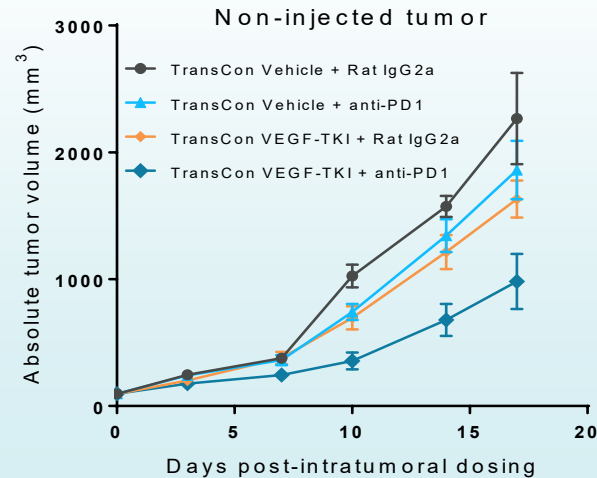
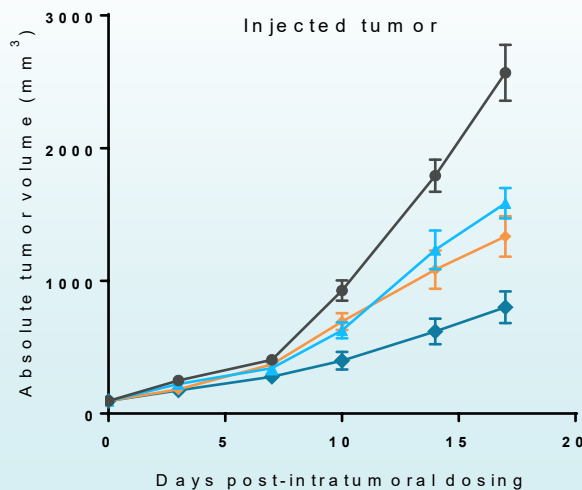
# TransCon VEGF-TKI: Axitinib Loaded onto TransCon Hydrogel for Intratumoral Sustained Delivery



- Axitinib transiently conjugated to TransCon hydrogel carrier, designed to provide sustained release of unmodified axitinib
- Designed to provide sustained modulation of the tumor microenvironment with potential for direct anti-tumor effects

# Single Dose of TransCon VEGF-TKI Allowed for Combination Benefits with anti-PD-1 in Injected and Non-injected Tumors

Anti-tumor Activity and Combination Benefits with Anti-PD1 in Injected and Non-injected tumors (MC38 model)



# TransCon VEGF-TKI – Summary

- New approach to modulation of tumor microenvironments, with the potential for direct anti-tumor effects
  - TransCon Hydrogels generated for sustained release of axitinib
  - Potent anti-tumor effects in mice observed, including combination benefits with checkpoint blockade
  - Slow intratumoral release expected to enable mechanisms not achievable by oral administration
  - Potential to enable combinations with aggressive therapeutic regimens in multiple indications, including CNS tumors

# Oncology Summary

- Best-in-class potential using systemic and intratumoral TransCon technologies
  - Preclinical anti-tumor proof-of-concept demonstrated with small molecules, cytokines and antibodies
  - TransCon intratumoral technologies acceptance into the FDA's Emerging Technology Program
- Differentiated product candidates with potential in multiple indications
  - TransCon IL-2  $\beta/\gamma$
  - TransCon TLR7/8 Agonist
  - TransCon VEGF-TKI
- Potent anti-tumor effects of TransCon oncology candidates demonstrated in preclinical studies
- First IND or similar expected to be filed for TransCon TLR7/8 in Q4 2020, followed by TransCon IL-2  $\beta/\gamma$  in 2021
- Over 20 patents and applications in support of TransCon oncology candidates

# Selected 2020 Expected Milestones

## Q1 2020

✓ Initiate global phase 3 trial for AGHD

✓ Top-line data phase 2 trial - end of March<sup>1</sup>

## Q2 2020

✓ Submit US BLA filing for PGHD

## Q3 2020

Six-month data from phase 2 open-label extension

Submit EU MAA filing for PGHD

## Q4 2020

Initiate phase 3 trial for PGHD in Japan

Initiate global adult HP phase 3 trial

Initiate phase 2 trial for ACH in China<sup>2</sup>

Submit IND or similar for TransCon TLR7/8 Agonist

● TransCon hGH

● TransCon CNP

● TransCon PTH

● Oncology

<sup>1</sup> Results timing +/- two weeks

<sup>2</sup> Conducted through strategic investment in VISEN Pharmaceuticals