

# Ascendis Pharma A/S

January 2020

# Cautionary Note On Forward-Looking Statements

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, such as statements regarding our future results of operations and financial position, including our business strategy, prospective products, availability of funding, clinical trial results, product approvals and regulatory pathways, collaborations, timing and likelihood of success, plans and objectives of management for future operations, and future results of current and anticipated products, are forward-looking statements. These forward-looking statements are based on our current expectations and beliefs, as well as assumptions concerning future events. These statements involve known and unknown risks, uncertainties and other factors that could cause our actual results to differ materially from the results discussed in the forward-looking statements. These risks, uncertainties and other factors are more fully described in our reports filed with or submitted to the Securities and Exchange Commission, including, without limitation, our most recent Annual Report on Form 20-F filed with the SEC on April 3, 2019 particularly in the sections titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations”. In light of the significant uncertainties in our forward-looking statements, you should not place undue reliance on these statements or regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

Any forward-looking statement made by us in this presentation speaks only as of the date of this presentation and represents our estimates and assumptions only as of the date of this presentation. Except as required by law, we assume no obligation to update these statements publicly, whether as a result of new information, future events or otherwise after the date of this presentation.

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

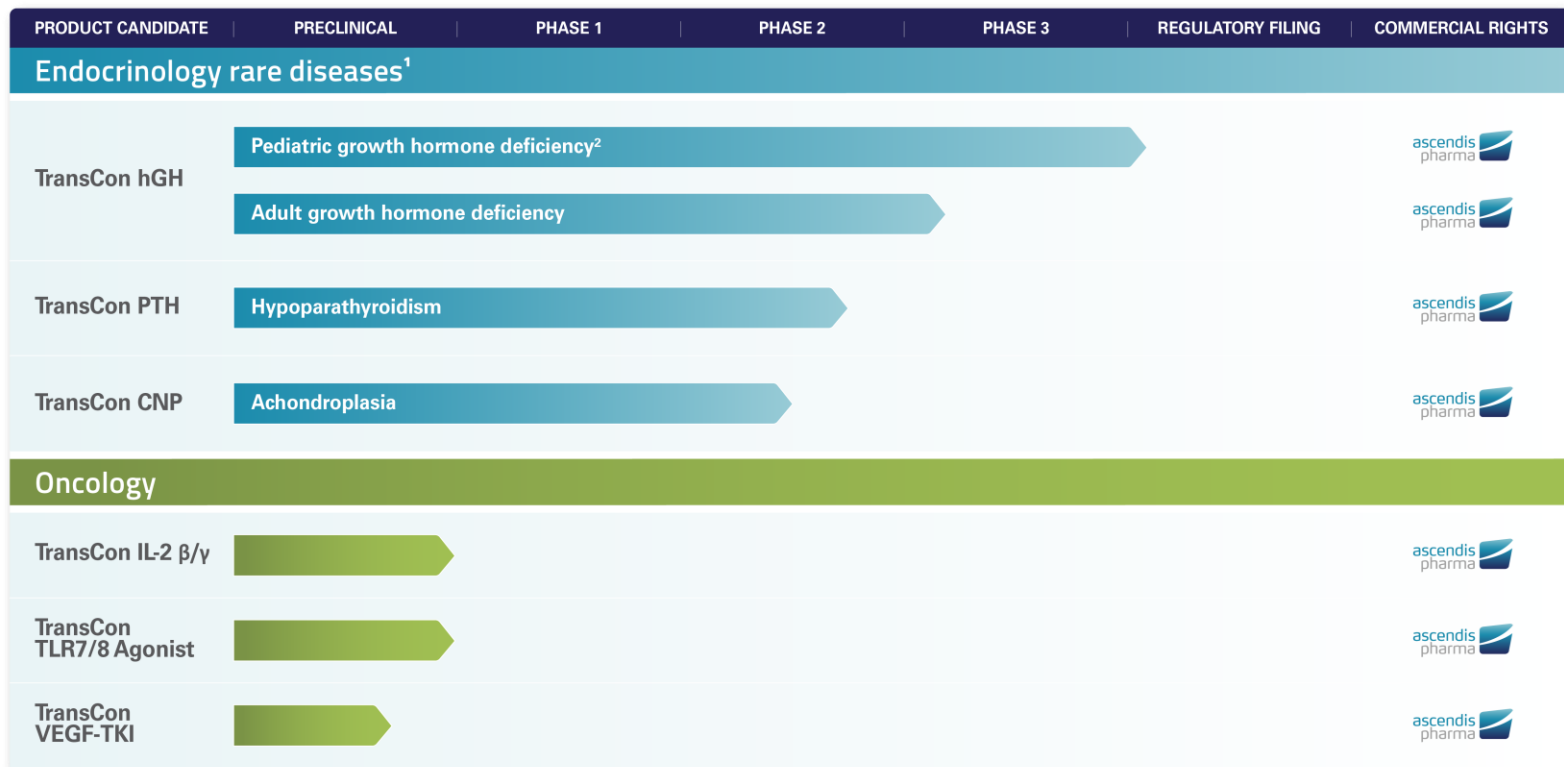
- Create best-in-class products addressing unmet medical needs by applying TransCon™ technologies to parent drugs with clinical proof-of-concept
- Endocrinology rare disease internal pipeline and expected 2020 milestones
  - TransCon hGH for pediatric GH deficiency: BLA and MAA filings expected Q2 and Q4
  - TransCon PTH for hypoparathyroidism: Phase 2 top-line data end March<sup>1</sup>; long-term data Q3
  - TransCon CNP for achondroplasia: Phase 2 ACcomplish dose escalation and initiate second trial in China<sup>2</sup> Q4
- Build leading positions for each endocrinology rare disease product with commercial focus on maximizing global reach
  - Partnership with VISEN Pharmaceuticals for endocrinology rare disease products in China
- Oncology pipeline in development with highly differentiated product candidates
  - First IND filing or equivalent expected in 2020
- As of September 30, 2019, cash and cash equivalents of ~€659 million

# 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
- Create further growth of 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
- In Oncology, create a high value pipeline with one IND or equivalent filing each year
- Creation of a third independent therapeutic area with a diversified pipeline

# Diverse Pipeline of Independent Product Candidates

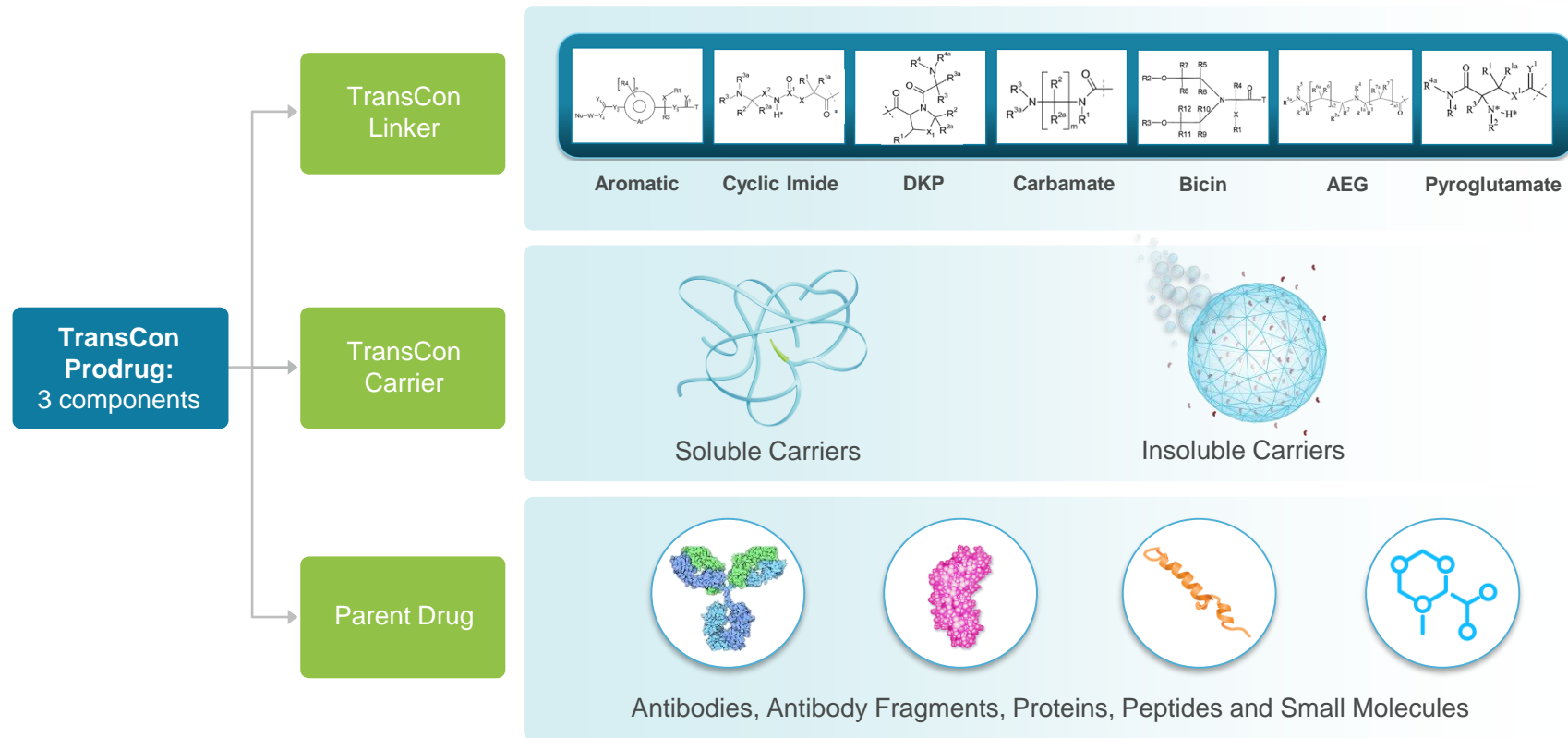


<sup>1</sup> Excludes rights granted to VISEN Pharmaceuticals in Greater China

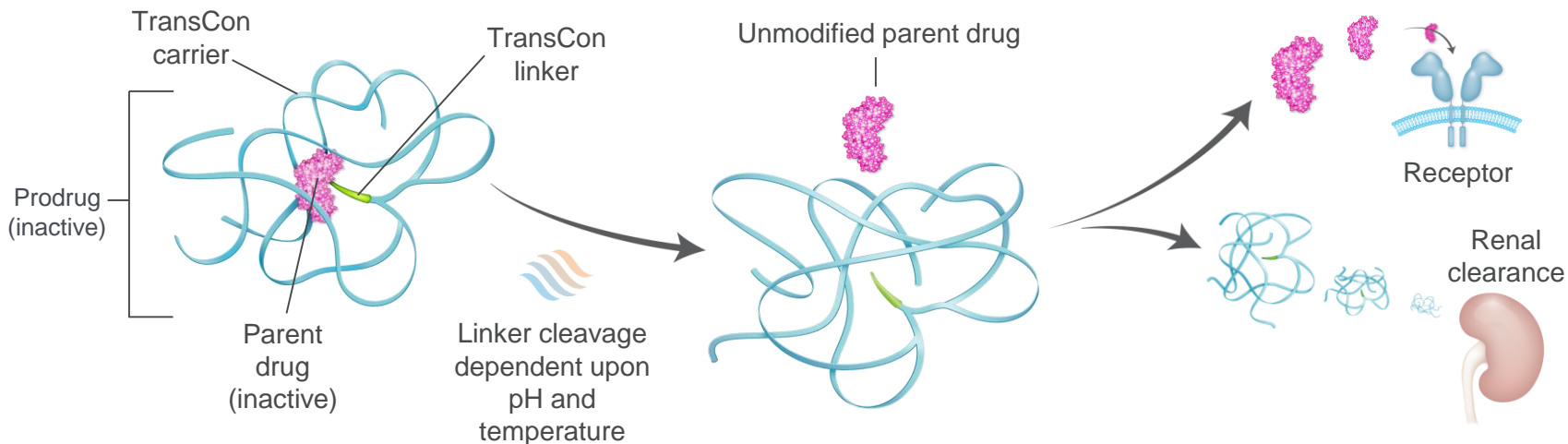
<sup>2</sup> In phase 3 development for pediatric growth hormone deficiency in Greater China through strategic investment in VISEN Pharmaceuticals

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# Transient Conjugation: Flexible and Versatile Platform



# TransCon Technology: Sustained Systemic Delivery

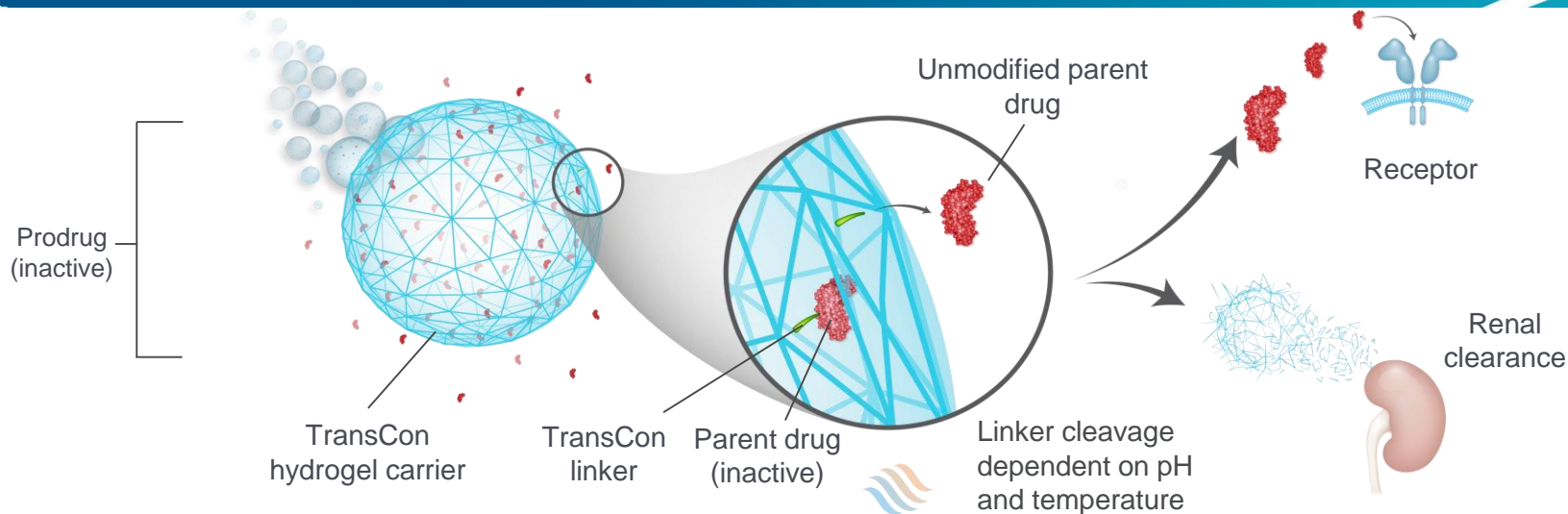


Parent drug is transiently bound to a TransCon linker-soluble carrier moiety, which inactivates and shields parent drug from clearance

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 Delivery



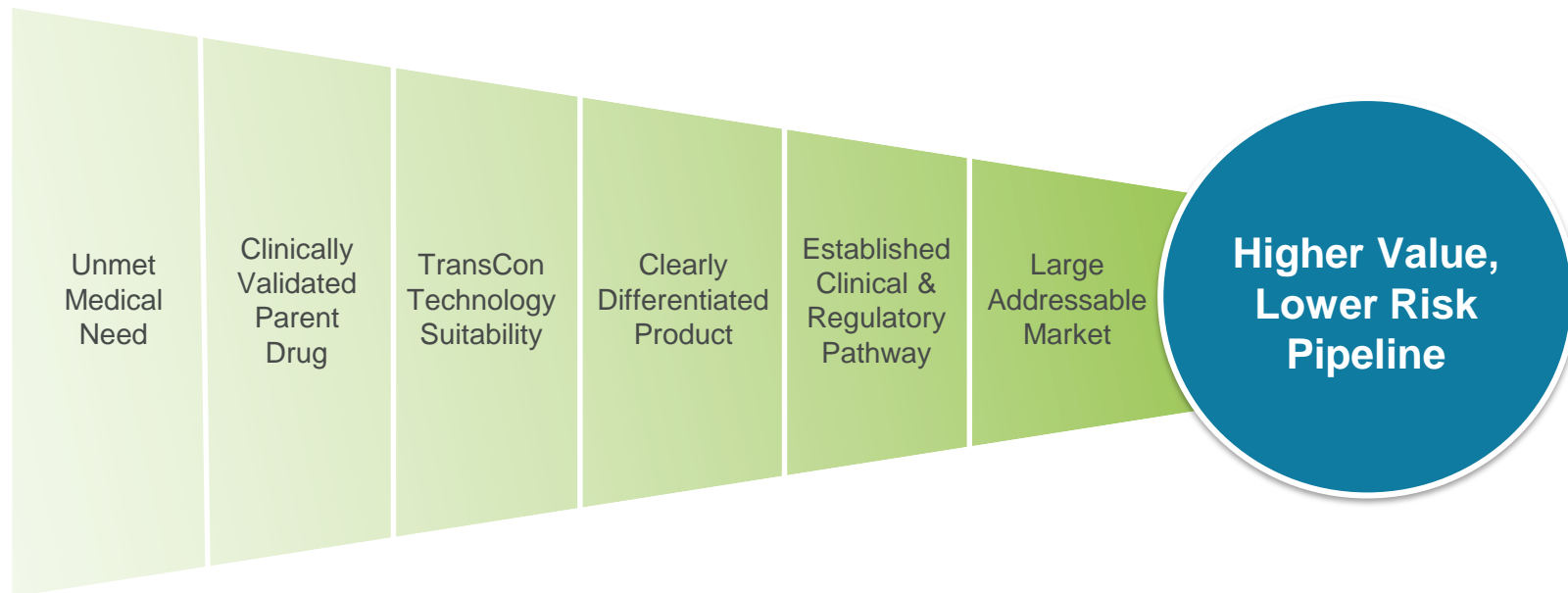
Parent drug is transiently bound to TransCon linker-hydrogel carrier, which inactivates, shields parent drug and prevents clearance

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>



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



MENTAL HEALTH<sup>5</sup>



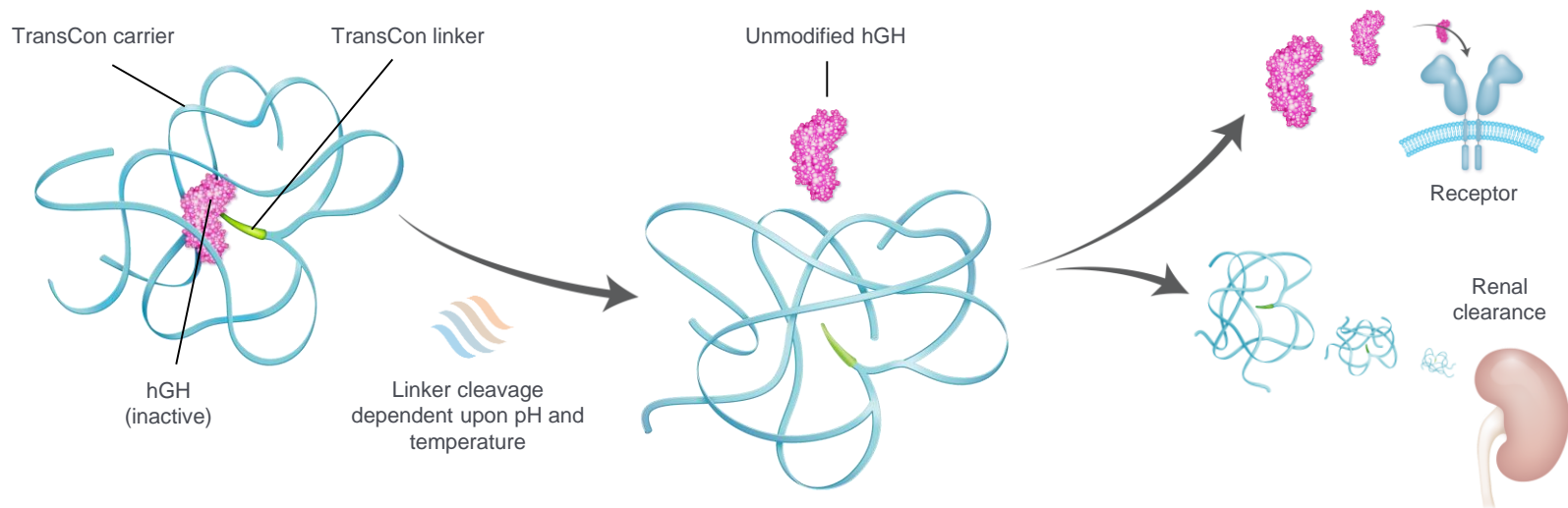
FRACTURES<sup>8</sup>

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

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

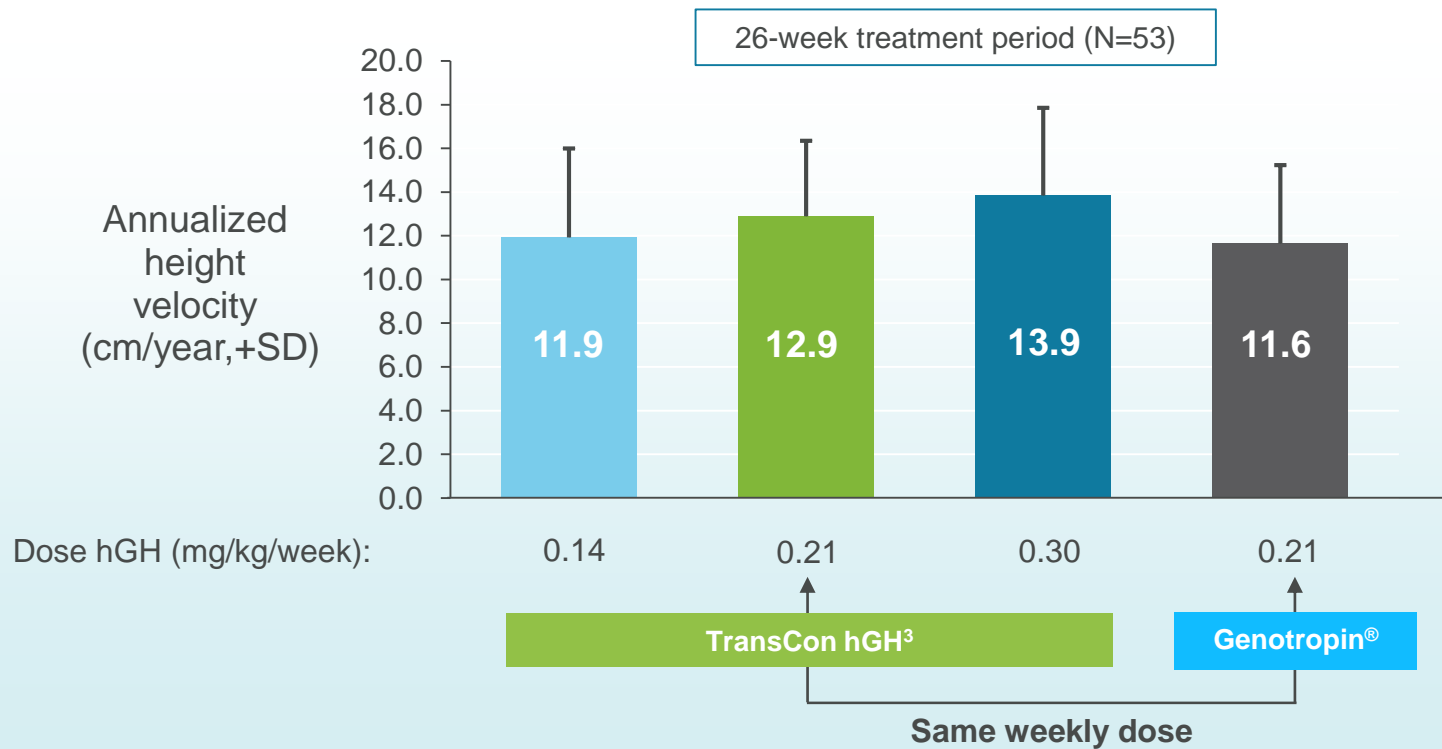
# TransCon hGH Design



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

# TransCon hGH Phase 3 Program in Pediatric GHD

 height  
TRIAL

N=161

- Treatment-naïve subjects

 flight  
TRIAL

N=146

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

 enlighten  
TRIAL

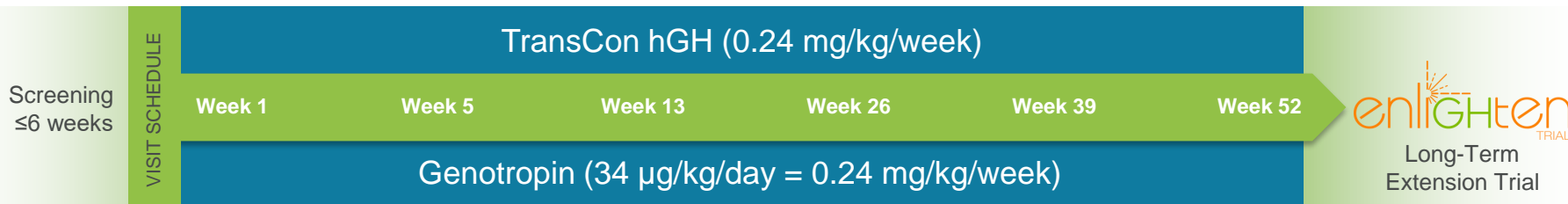
Extension trial  
(N=296)

*Expected  
Regulatory filings  
(BLA Q2 2020,  
MAA Q4 2020)*

# Phase 3 heiGHt Trial



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



## Objective

- Demonstrate non-inferiority

## 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
$\Delta$ 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

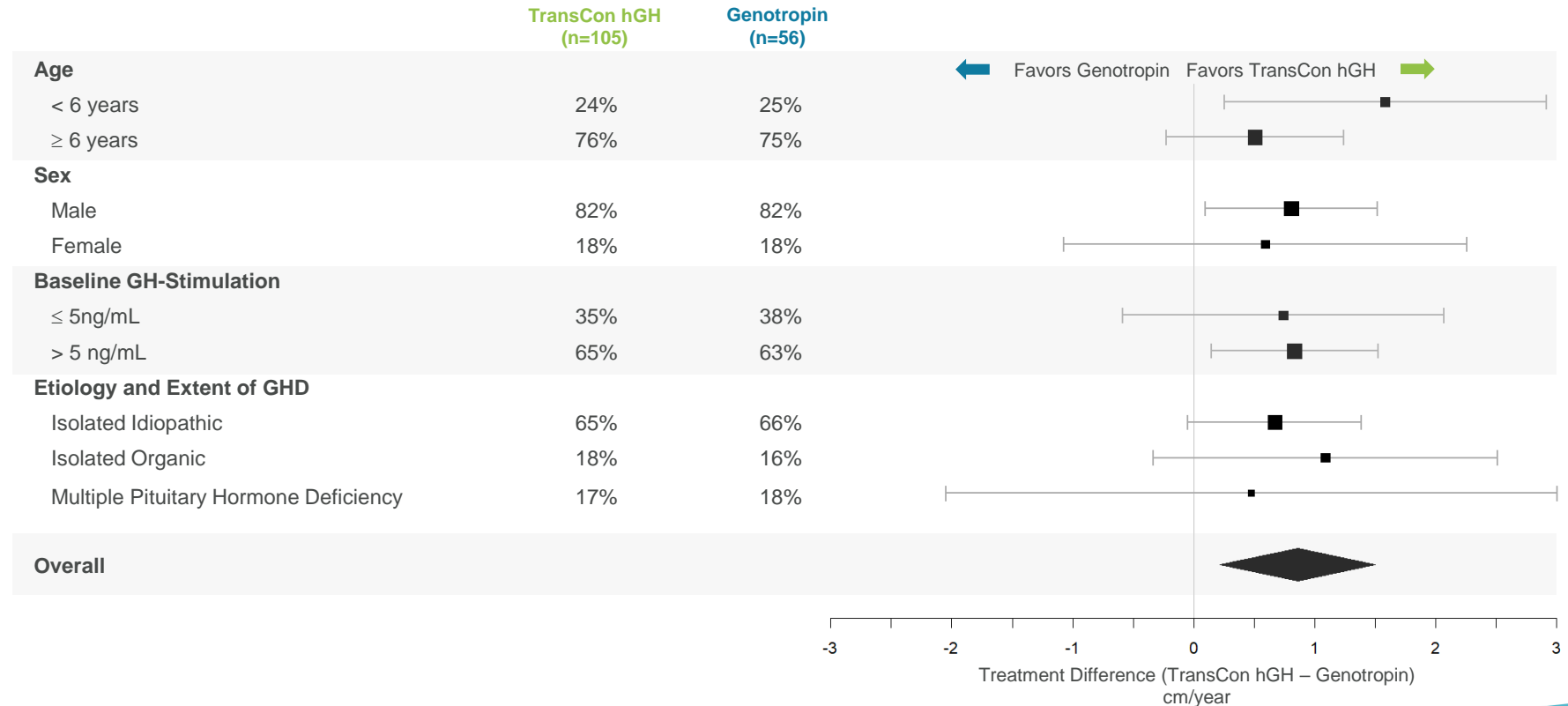


# TransCon hGH Met Primary Objective of Non-inferiority and Demonstrated Superiority in AHV at Week 52



	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	

# 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>

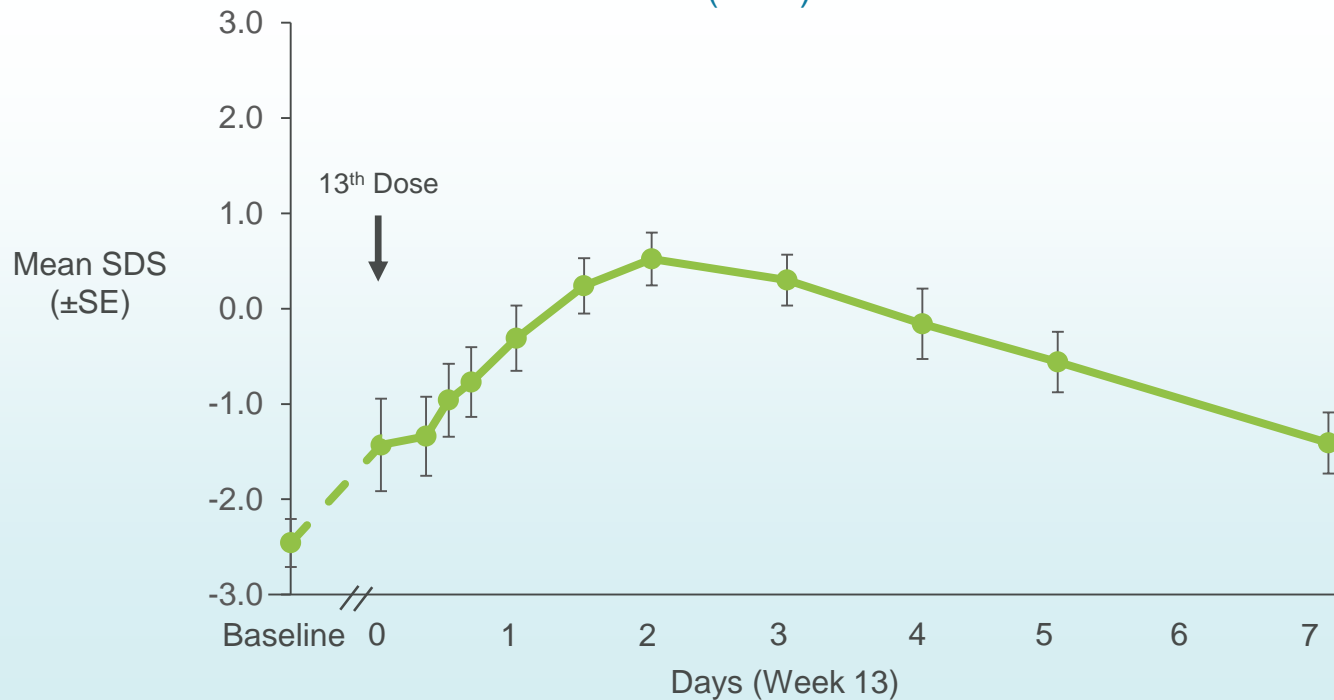
At Week 52 <sup>2</sup>	TransCon hGH (n=104) n (%)	Genotropin (n=55) n (%)
Responder	100 (96.2)	49 (89.1)
Poor Responder	4 (3.8)	6 (10.9)

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

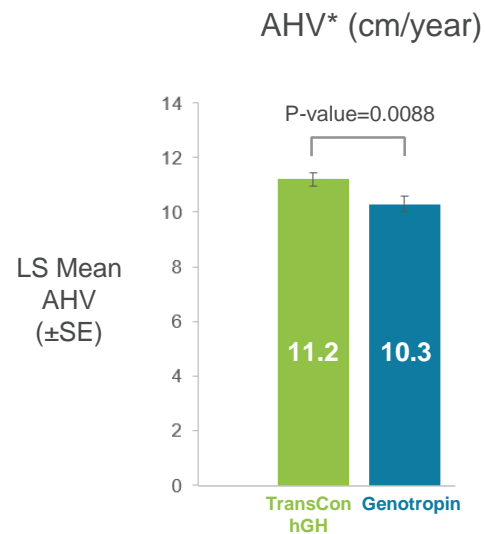
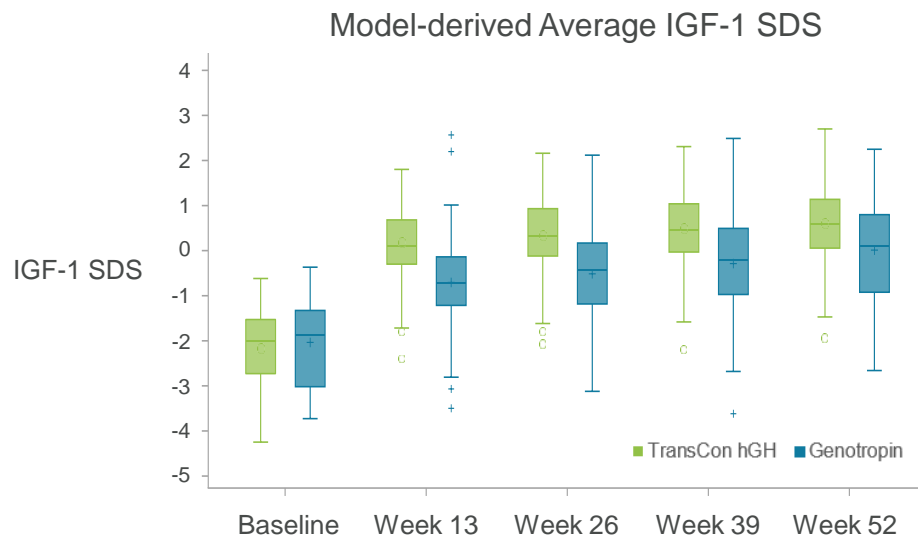
# IGF-1 Profile Over 1 Week



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



# AHV Paralleled the Difference in Average IGF-1

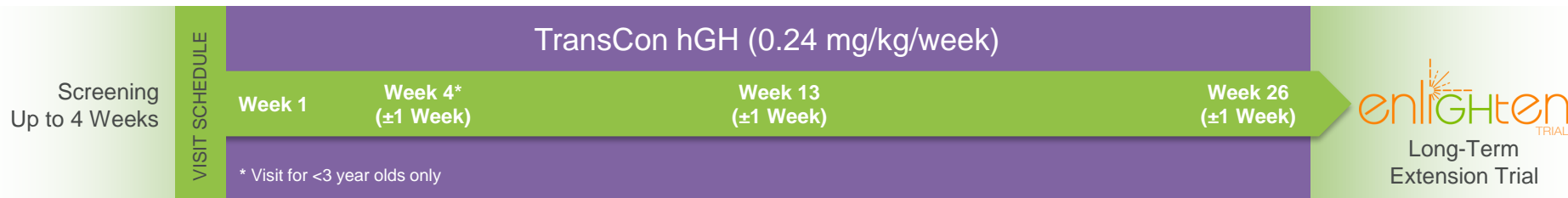


TransCon hGH preserved the balance between direct and indirect effects of daily hGH

# 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%)



# 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 an adverse event and immunogenicity 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
- 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

# 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

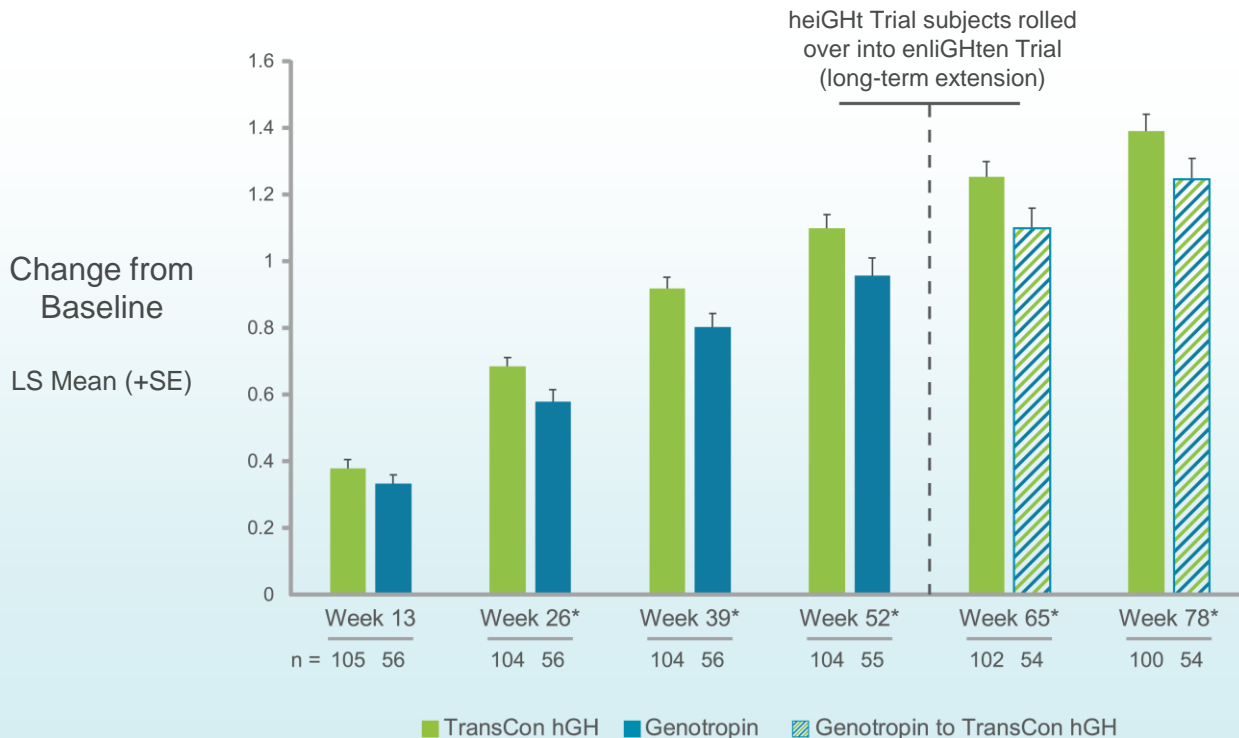
<sup>2</sup> Based on data reported up to September 2019

<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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# TransCon hGH Sustained Improvement in Height SDS



heiGHt subjects treated for 1.5 years with TransCon hGH demonstrated:

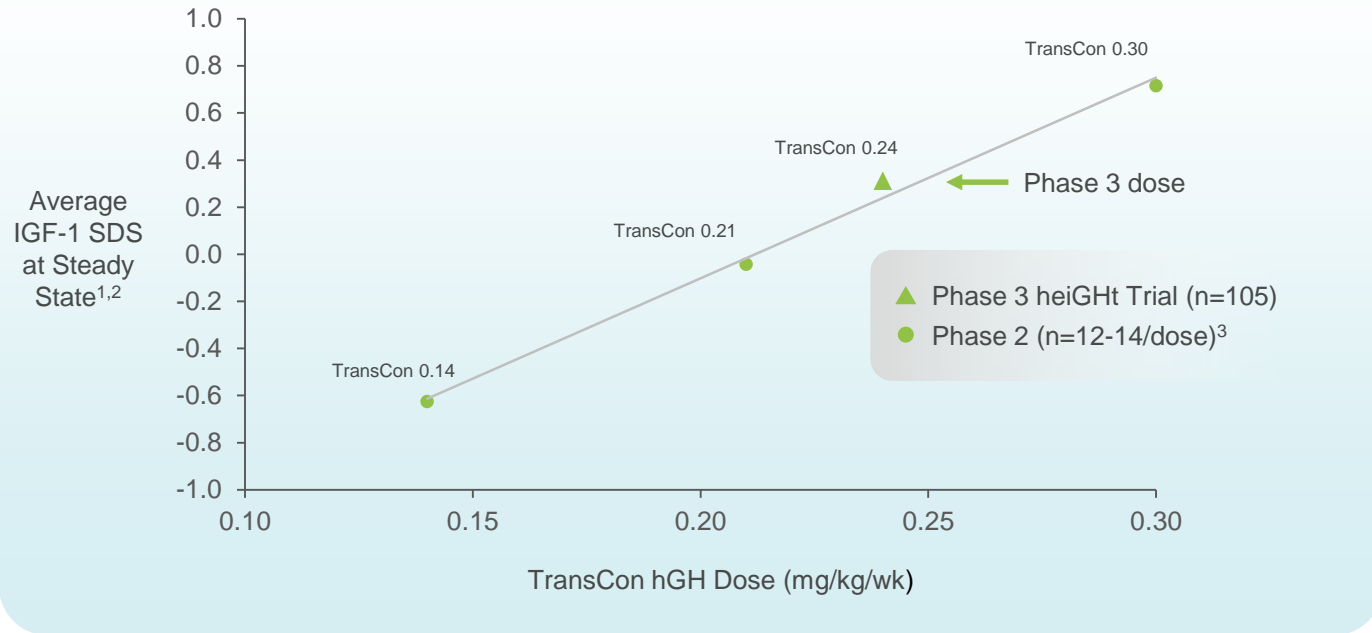
- Superior growth after 52 weeks compared to Genotropin<sup>1</sup>
- Superior growth continued in the enLiGHten extension trial

<sup>1</sup> Based on results from phase 3 heiGHt Trial at 52 week endpoint

\*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**

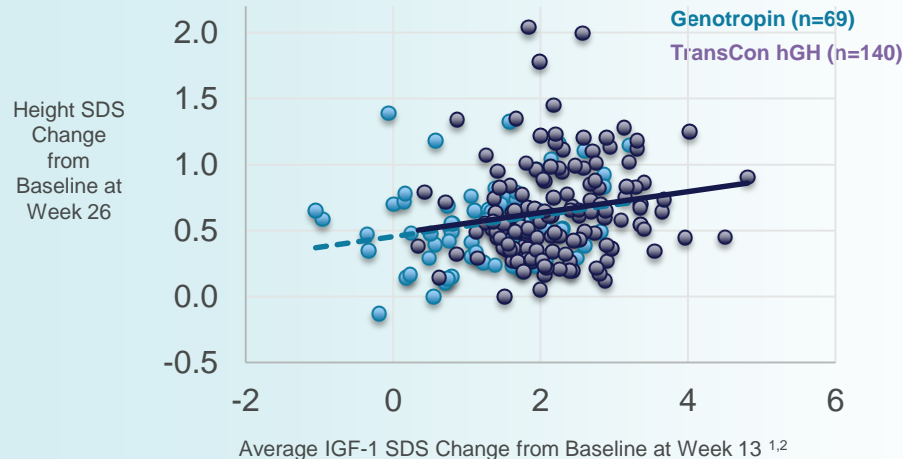
<sup>1</sup> Average IGF-1 at Week 13 was used given availability of measured data over one week for the phase 2 trial

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

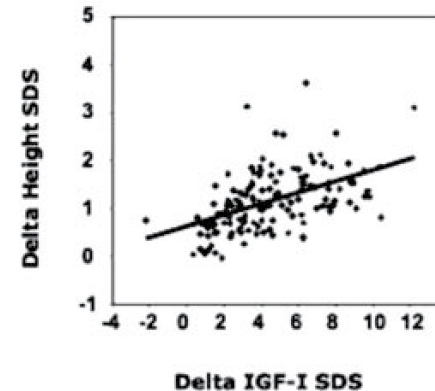
<sup>3</sup> Conducted with an earlier bioequivalent version of TransCon hGH

# 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 heiGH 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 enabled for automatic data capture
- Development of integrated connectivity platform underway

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



# Global Clinical Reach

Region	US	EU	Japan	South Korea	China
Nonclinical packet acceptable for regulatory filing					
Regulatory concurrence with proposed clinical development plan			Planned phase 3 initiation Q4 2020* (40 subjects)		Phase 3 initiated 2019** (75 subjects)



# On-track towards Filing TransCon hGH BLA Q2 and MAA Q4

- Completed both the fliGHt and heiGHt Trials, including rollover into enliGHten, and completed two-year follow-up for 46 subjects on TransCon hGH
- Completed manufacturing of PPQ batches and development of the auto-injector
- Proprietary Auto-Injector and DCCs introduced in phase 3 enliGHten Trial; met objective of collecting required usability data to support auto-injector as part of initial BLA submission
- Two pre-BLA meetings held with FDA related to Chemistry, Manufacturing and Controls (CMC), and for clinical/non-clinical packages
- In Europe, received orphan designation for TransCon hGH and Conformité Européenne (CE) mark for Auto-Injector

# TransCon hGH: Raising the Bar

- Phase 3 heiGHt Trial demonstrated superior height velocity of TransCon hGH in pediatric GHD, with comparable safety and tolerability as compared to a daily hGH
- BLA filing expected Q2 2020 and MAA filing expected Q4 2020
- Create further growth:
  - China: Pediatric GHD phase 3 initiated
  - Global: Adult GHD phase 3 expected to be initiated Q1 2020
  - Japan: Pediatric phase 3 expected to be initiated Q4 2020
- Easy-to-use 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: Severe Short-term Complications

## Debilitating Symptoms

### Hypocalcemia

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

### Brain fog

### Anxiety due to “fear of crash”

### Hypercalcemia

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

## Short-term Complications

## Reduced QOL

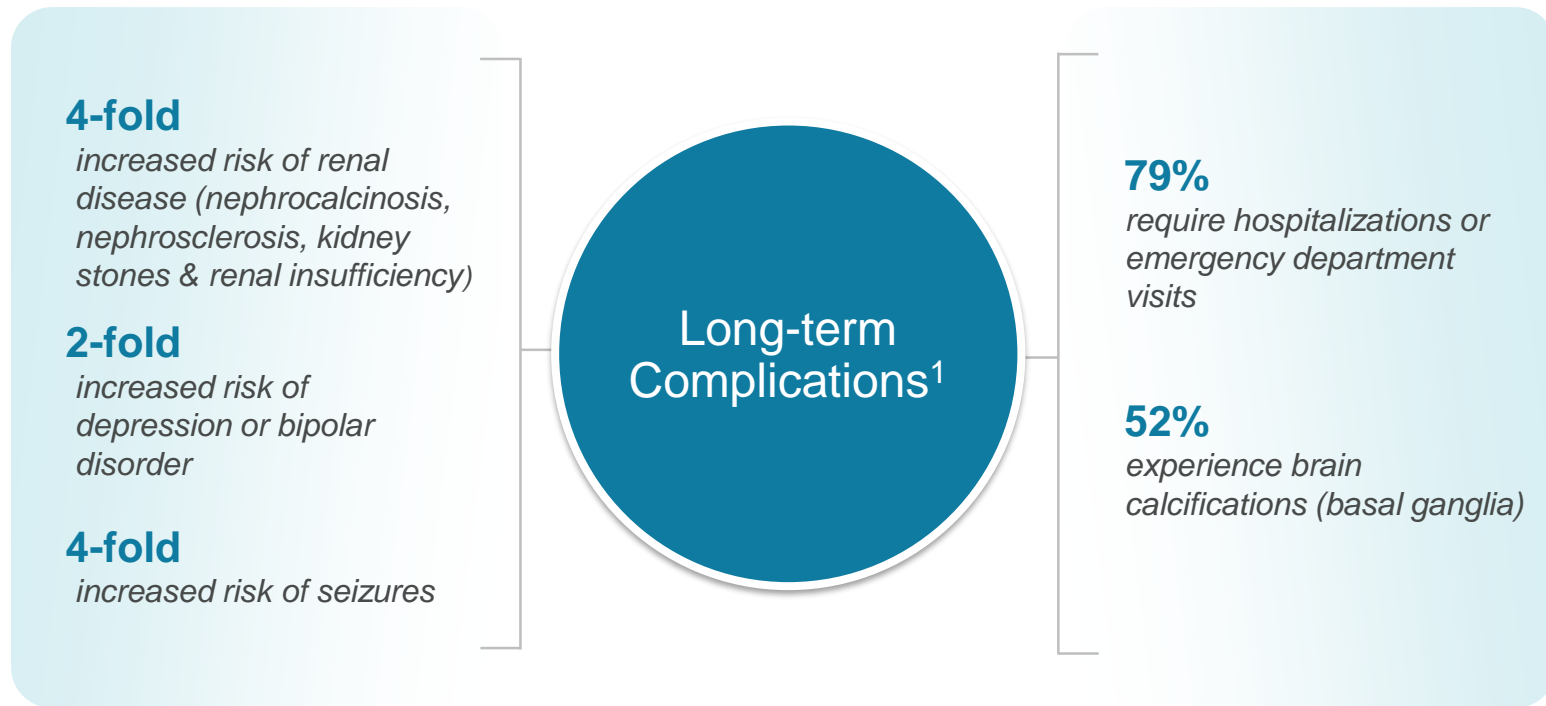
**85%**

*Report inability to perform household activities<sup>1</sup>*

**76%**

*Either unable to work or report significant interference with work d/t HP symptoms<sup>2</sup>*

# Hypoparathyroidism: Severe Long-term Complications



# 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

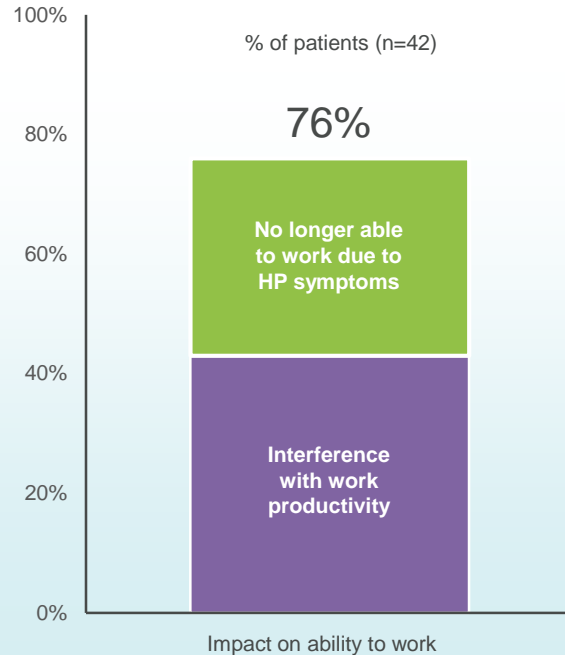
“ *I find that doctors don't know much about this and...I have to educate them. I ordered these booklets from the hypoparathyroidism organization...The endocrinologist that I see he does have some patients that have hypoparathyroidism, but it's not the majority of his practice.* ”

<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

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

# 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**

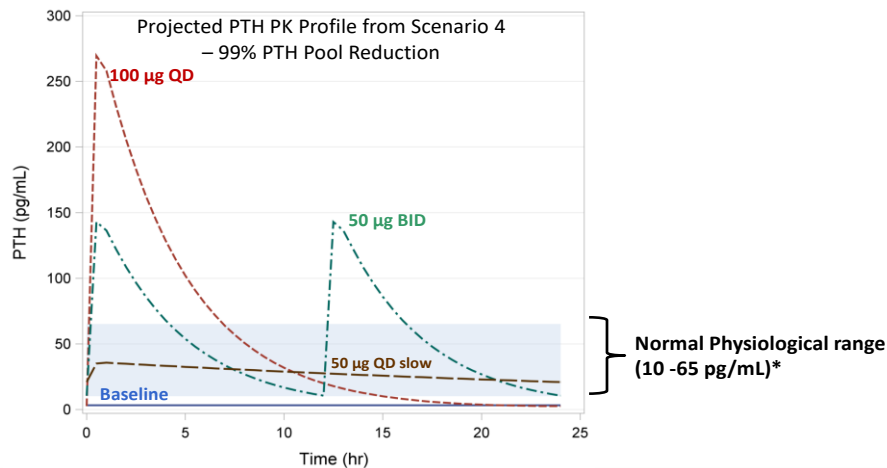
- S. Korean ICD-10 codes
- 2018, Interview conducted with S. Korean HP expert



# 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



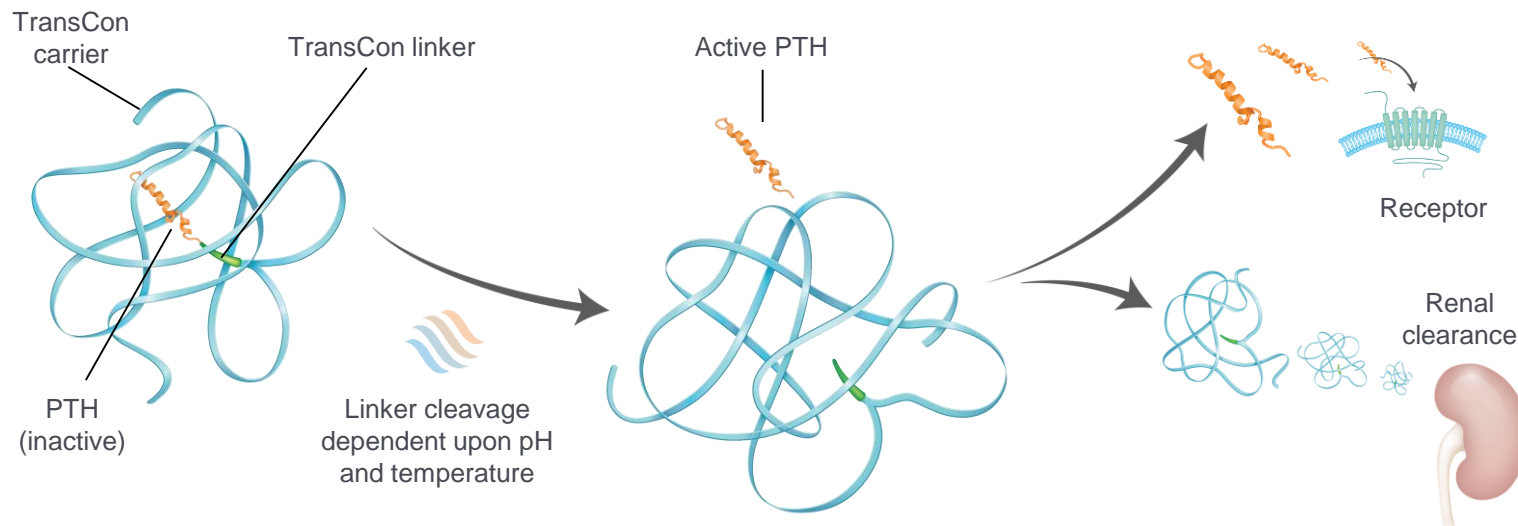
Continuous infusion of PTH demonstrated<sup>3,4</sup>:

- 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

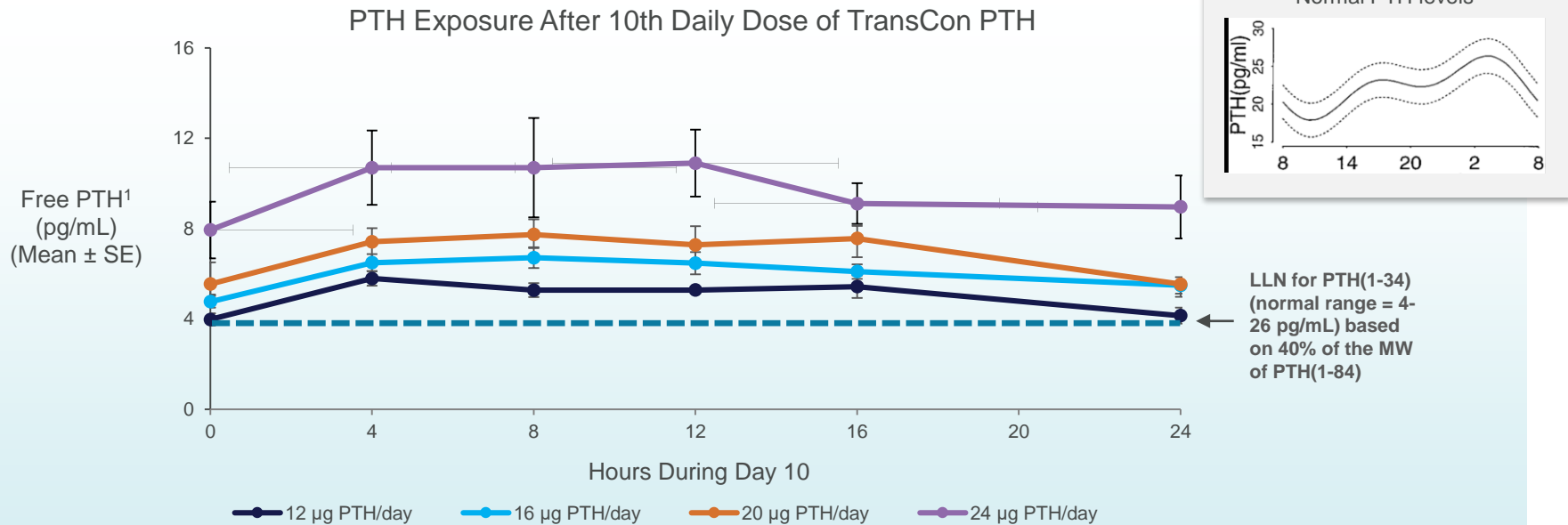
<sup>3,4</sup> J Clin Endo Metab 2012 97(2);391–399; J Pediatr 2014 165(3);556-563

# 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

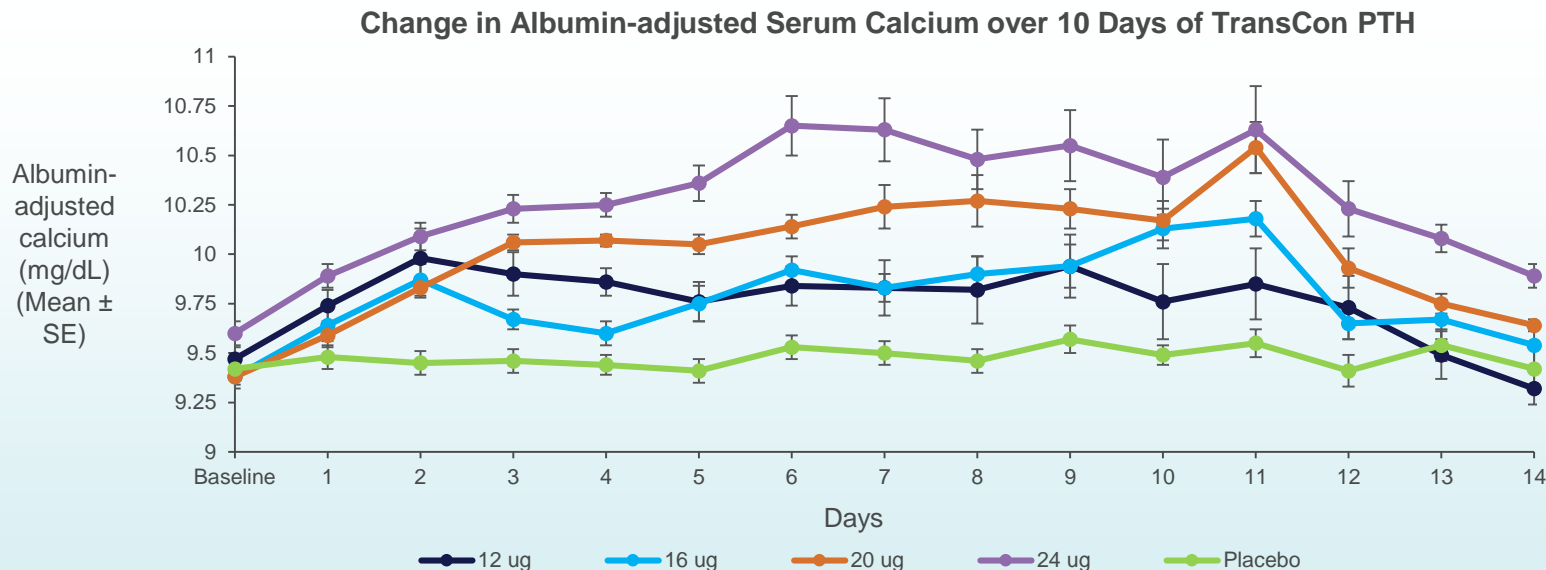
# Phase 1: PK Data Support Infusion-like Profile over 24 Hours



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

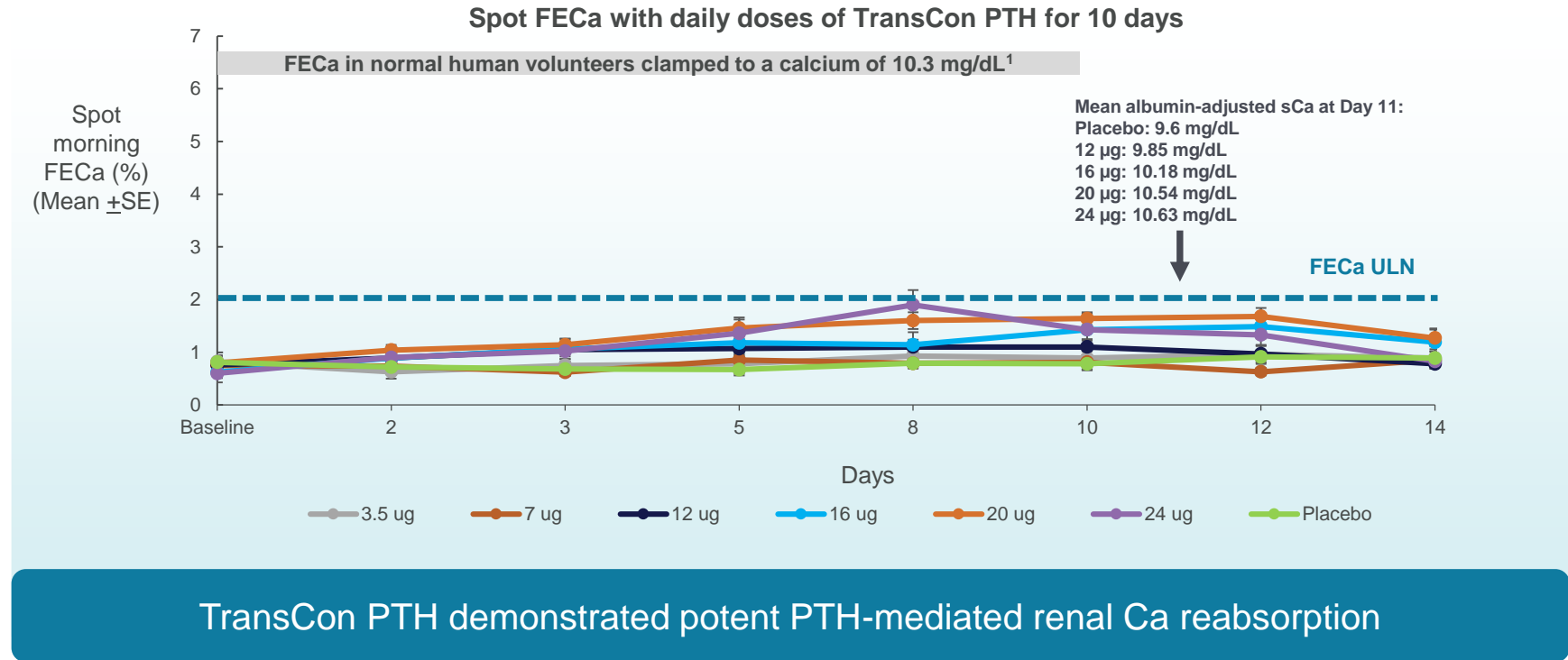
<sup>1</sup> PTH measured as Free PTH(1-34) and Free PTH(1-33)  
Analyses from TransCon PTH Phase 1 trial; data not shown for doses <12 µg/day, as levels of Free PTH are BLQ.  
Poster presented at ECTS 2019

# Dose-Dependent Increase of Serum Calcium



TransCon PTH daily dosing for 10 days provided dose-dependent increase of serum calcium, with more stable calcium levels over the day

# Control of Urinary Calcium Despite Mild Hypercalcemia with Multiple Doses



# Phase 1: Adverse Event and Immunogenicity Summary

- Generally well-tolerated
- 2 placebo subjects (vs. 0 active subjects) discontinued due to SAEs
- 4 subjects experienced SAEs, all of which were unrelated to study drug or placebo
  - SAD: 1 placebo subject (“bacteremia”) (withdrew)  
1 active (12 µg) subject (“catheter site phlebitis”)
  - MAD: 1 placebo subject (“catheter site phlebitis”) (withdrew)  
1 active (12 µg/day) subject (“post-viral neutropenia”)
- No PTH antibodies were seen
- Dose-limiting toxicity (DLT) was not reached in the highest SAD cohort (124 µg)
- DLT (vasodilatory AEs) was reached in the highest MAD cohort (24 µg/day), in 4/8 (50%) active vs 2/2 (100%) placebo subjects

# TransCon PTH Phase 2 Trial Design



~40 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)

# Expanded Phase 2 Trial and Open-label Extension Trial

- Implemented addendum to protocol to expand and expedite enrollment in the U.S. for subjects affected by the NATPARA<sup>®</sup> recall
- Subjects from fixed-dose PaTH Forward Trial roll over to the open-label extension with individually optimized TransCon PTH dosing to evaluate long-term safety and efficacy
- 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  $\leq 500$  mg/day calcium; **and**
  - Normal 24-hour urine calcium excretion (or at least 50% decrease from baseline)



# PaTH Forward Update

- Sites in Canada, Denmark, Germany, Italy, Norway and U.S.
  - Addendum implemented in the U.S.
- Screening completed with expected enrollment of ~55 subjects
- To date, no dropouts in the double-blind portion of PaTH Forward
- Preliminary data on first 8 subjects completing 4 weeks follow-up in open-label extension<sup>1</sup>
  - All subjects are completely off current standard of care
  - 8 of 8 subjects no longer require active vitamin D
  - 7 of 8 subjects no longer require calcium supplements (one subject taking < 500 mg calcium)
- Top-line phase 2 data expected by end of March 2020<sup>2</sup>
- Six-month data from open-label extension expected Q3 2020

# 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: Developing a “True” Replacement Therapy

- Phase 1 data support infusion-like profile of TransCon PTH as a “true” replacement therapy for HP, building on established approach to treat short-term symptoms and long term complications
- Screening completed for PaTH Forward phase 2 trial in adult HP subjects with simple ready-to-use injector pens; top-line data expected Q1 2020, followed by long-term extension trial data Q3 2020
- Carcinogenicity study waiver granted in the U.S. and EU
- TransCon PTH Phase 2 trial expanded to allow easier and faster enrollment of subjects previously treated with NATPARA®
  - Maximizing enrollment to demonstrate substantial evidence of effectiveness
- On track to initiate global phase 3 trial in North America, Europe and Asia Q4 2020
- Disease burden validates potential market opportunity for TransCon PTH



# 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

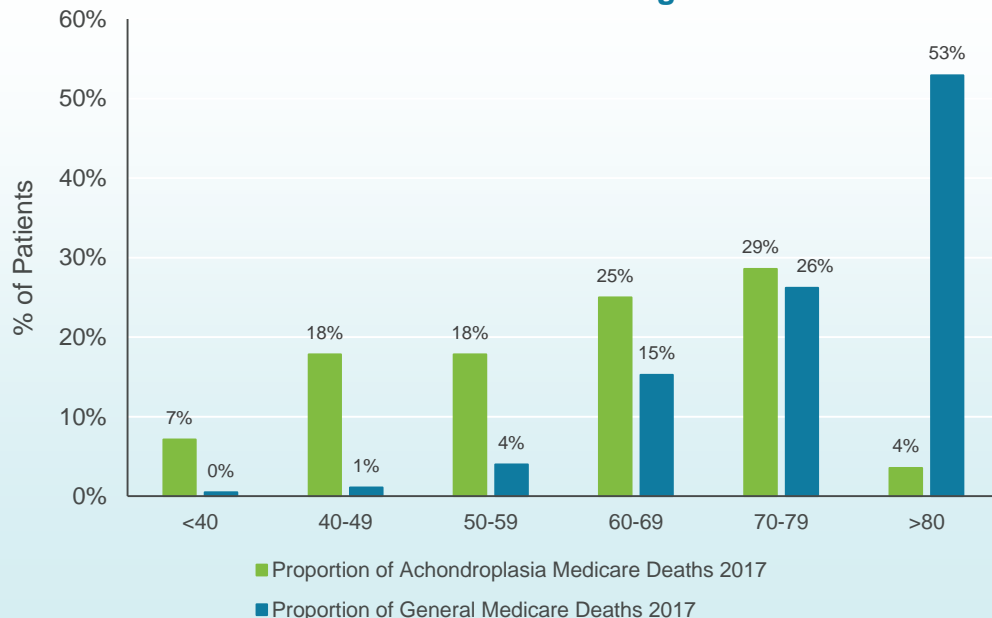
**80%** of adults have clinical signs and symptoms related to spinal stenosis

# Achondroplasia: Higher Mortality

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

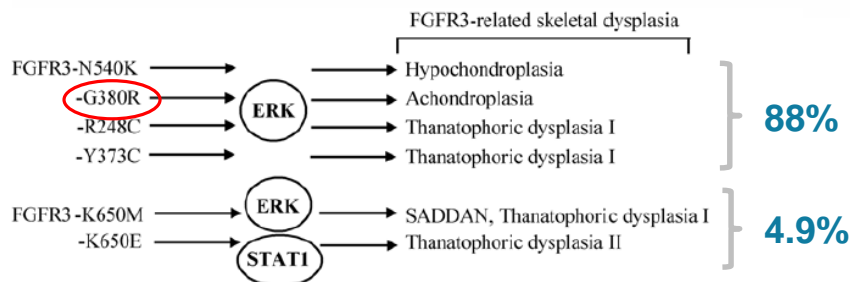
Markedly higher rates of death in these patients compared to the overall Medicare population, especially among patients <70 years

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

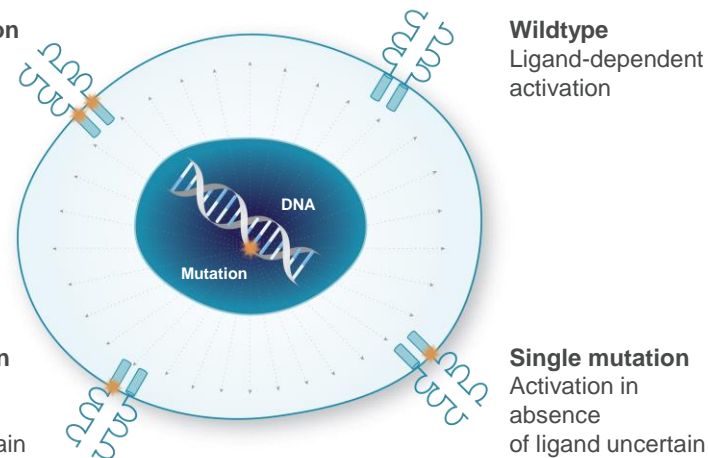
2.5 increase in activation in absence of ligand

### Single mutation

Activation in absence of ligand uncertain

### Wildtype

Ligand-dependent activation



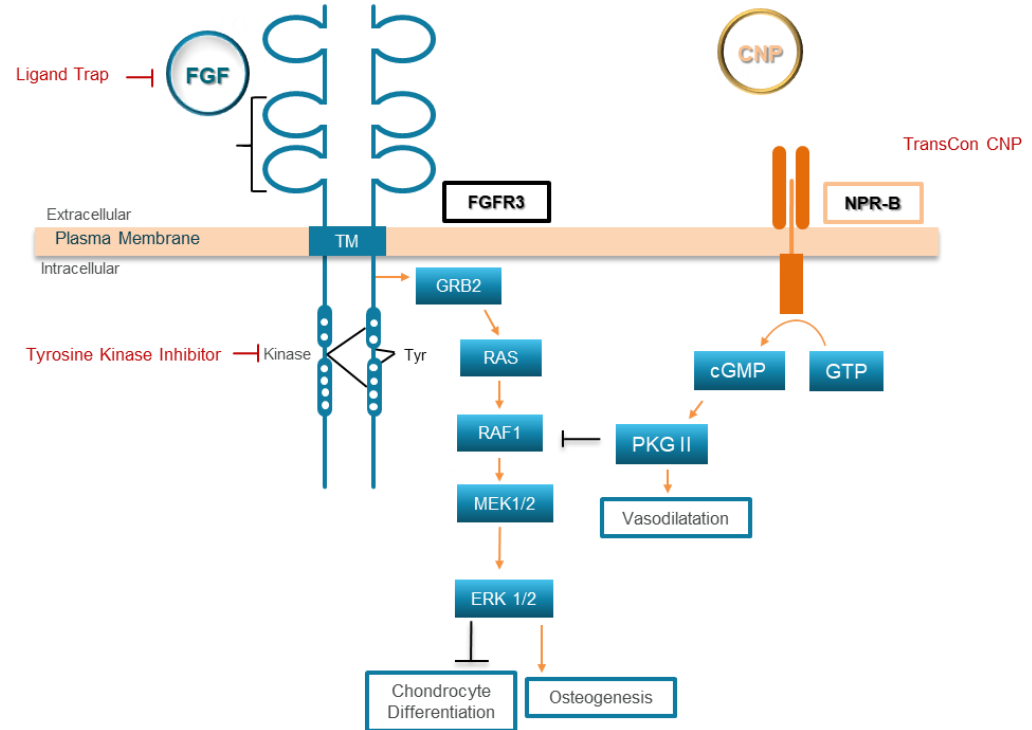
Downstream inhibition required to inhibit ligand-independent signaling



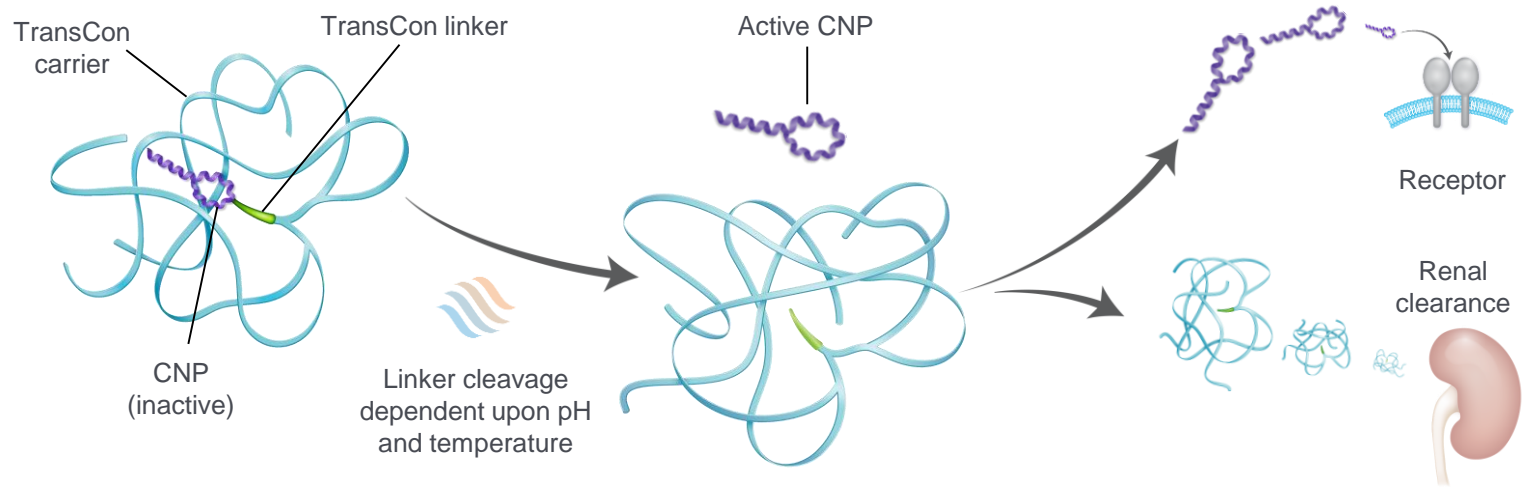
# Achondroplasia Signaling Defect is Well Understood<sup>1</sup>

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



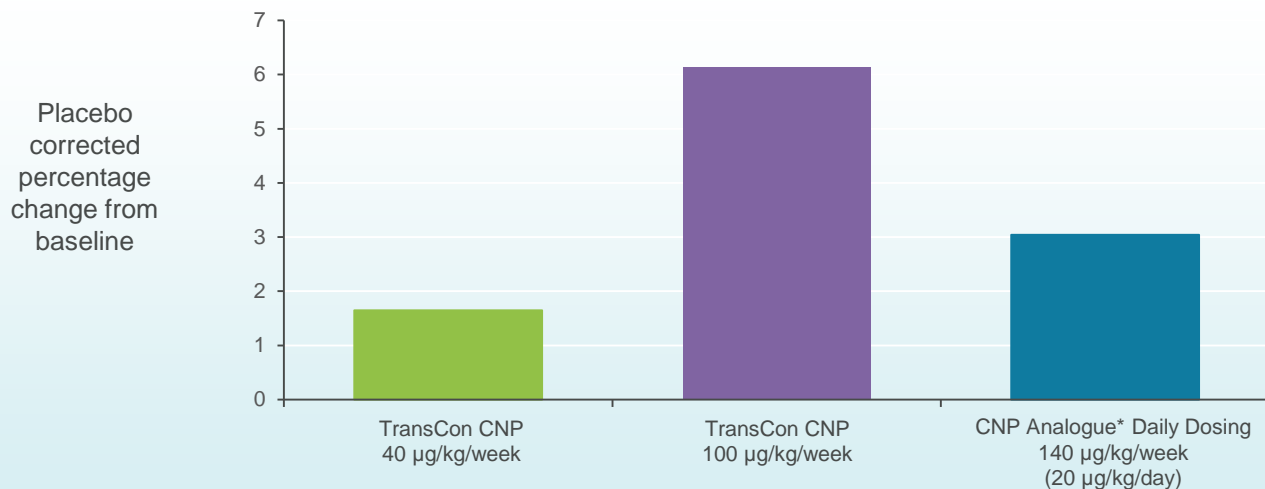
# TransCon CNP Design



- 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

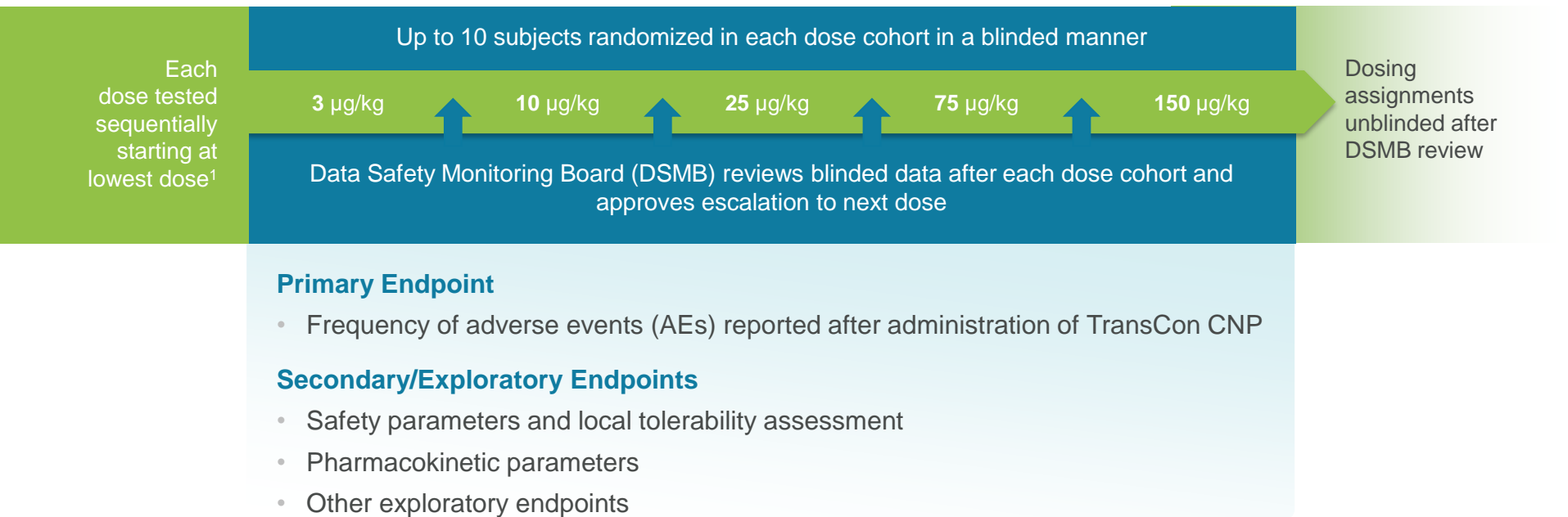
## Tibial growth at 6 months (n=4/group)



- 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

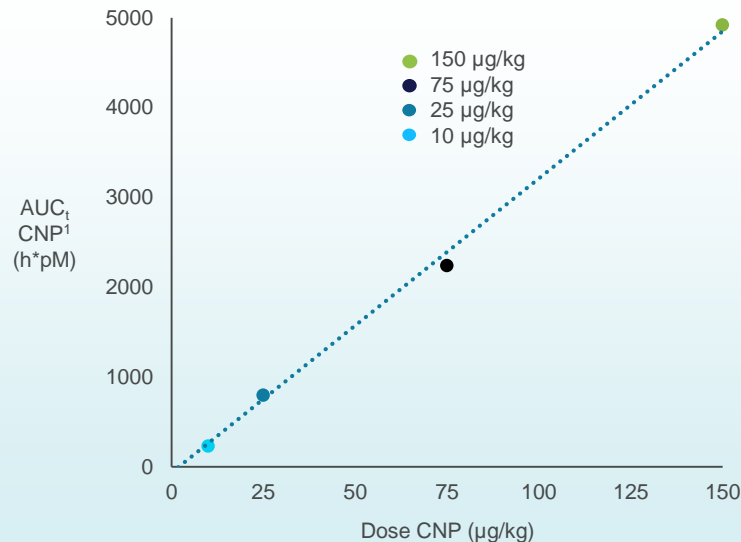
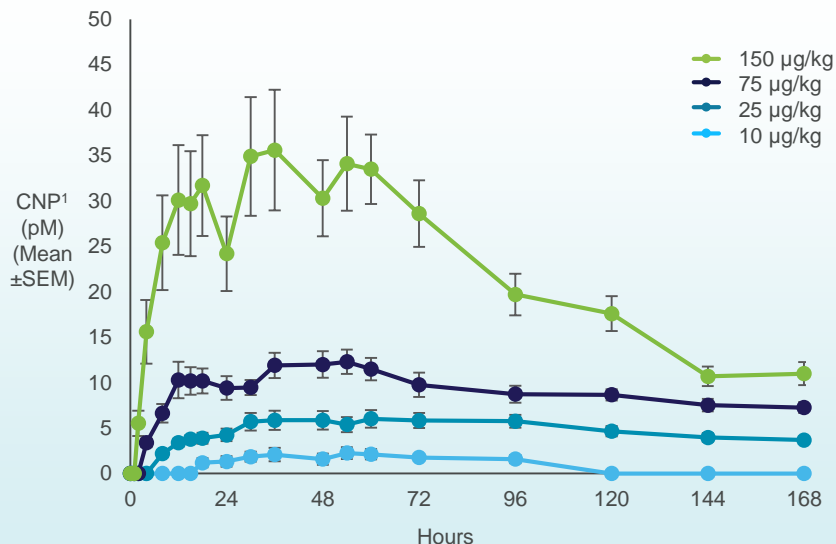
# Phase 1 Trial Design

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



# Dose Proportional CNP Exposure For 1 Week

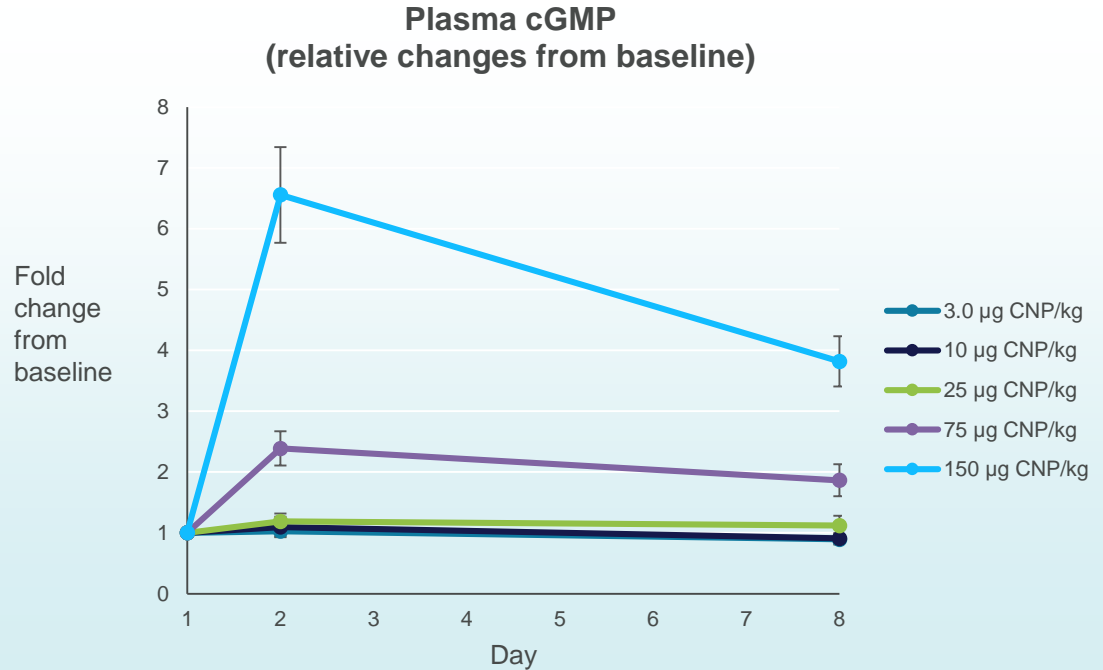
TransCon CNP 10, 25, 75 and 150 µg/kg (n=5-8/group)



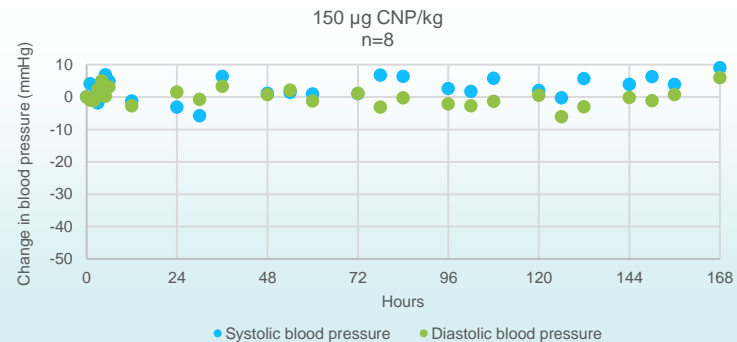
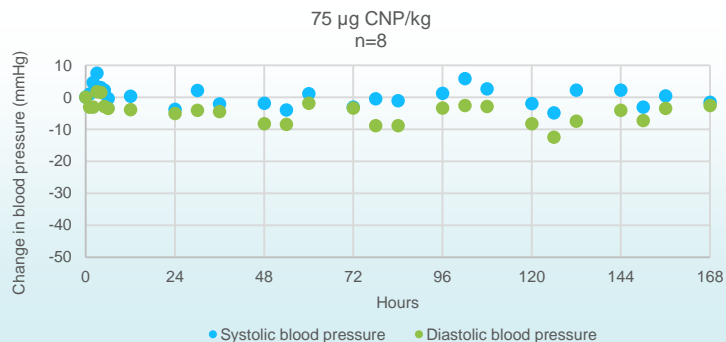
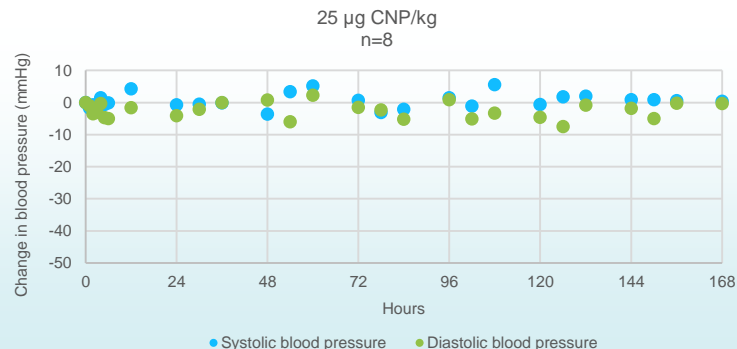
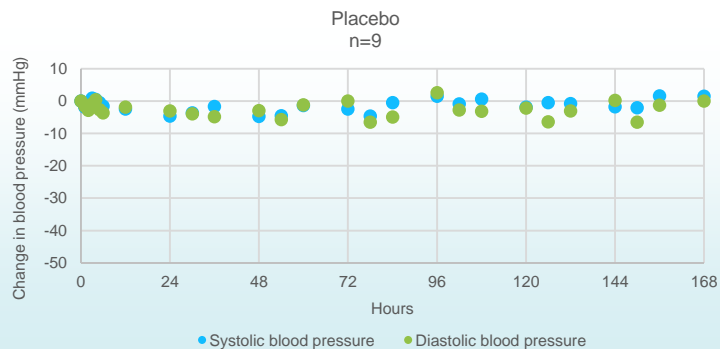
- Dose proportional increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP  $t_{1/2}$  of approximately 120 hours (native CNP  $t_{1/2}$  of 2-3 minutes)

# 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: Adverse Event and Immunogenicity Profile



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 30 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

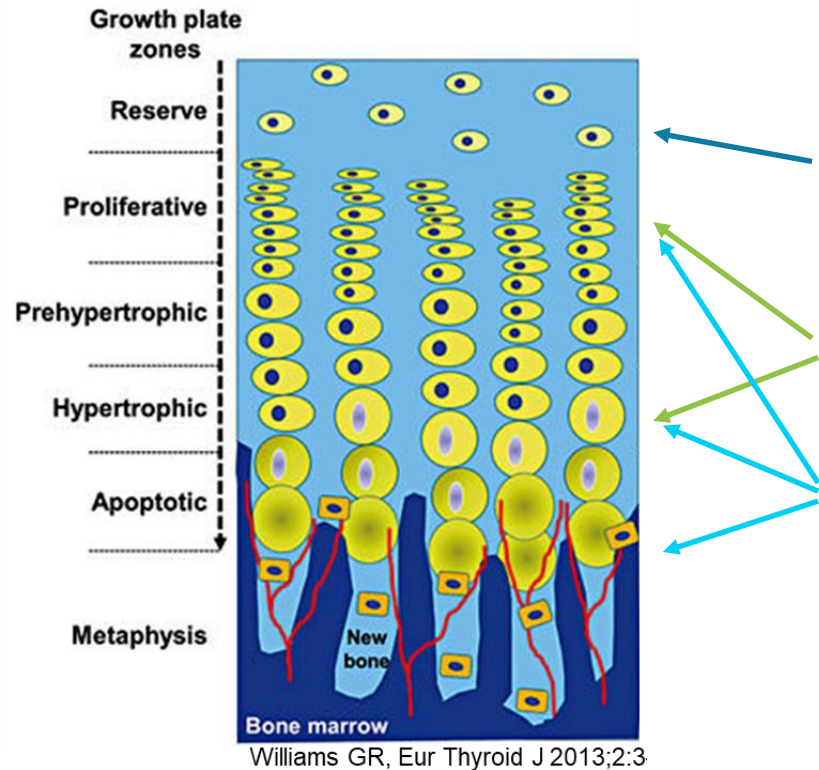
## Primary Endpoint

- 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



**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
- 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 equivalent Q4 2020
- Enable rapid path to global commercialization, including through mutually-beneficial collaborations as needed

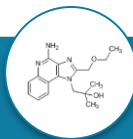
# Potential to Impact Efficacy, Safety and Practicality of Both Systemic and Intratumoral Cancer Treatments

- 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  
IL-2  $\beta/\gamma$



TransCon TLR 7/8  
Agonist



TransCon  
VEGF-TKI

# 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

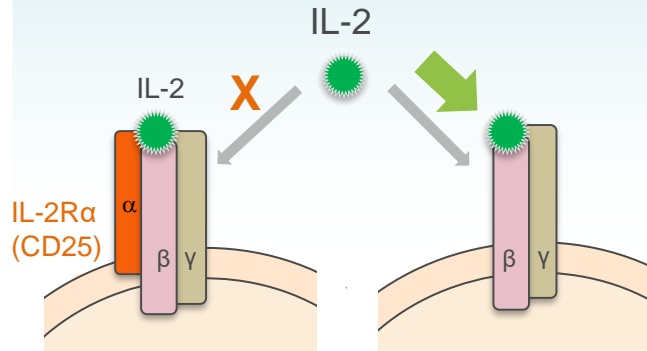
- Short half life of IL-2 (~1.5 h)
- High C<sub>max</sub> and pulsatile dosing drive adverse events

- 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 $\beta/\gamma$



Promotes Treg

Limit anti-tumor responses

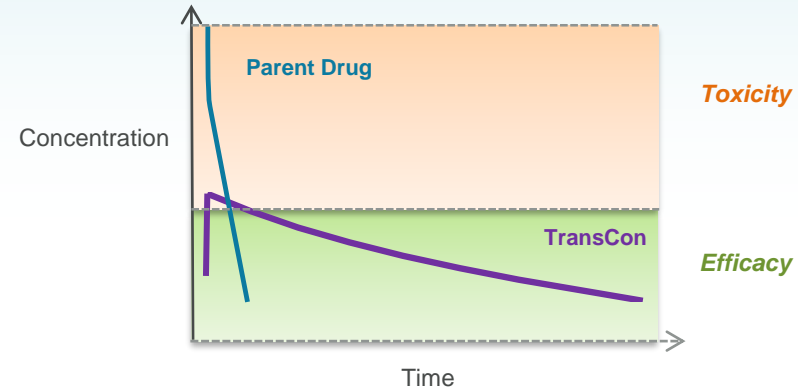
Promotes CD8<sup>+</sup>

Promote anti-tumor responses

2)

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

Desired Exposure Profile for TransCon IL-2  $\beta/\gamma$

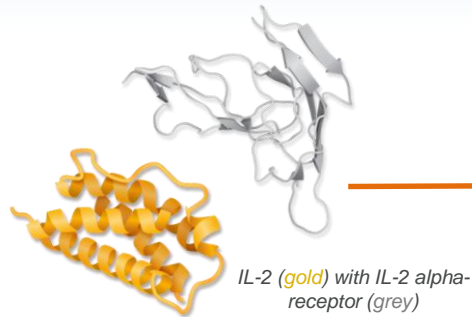


# Design of TransCon IL-2 $\beta/\gamma$ :

## 1) Designed for Desired Receptor Binding

### Generation of IL-2 Variant

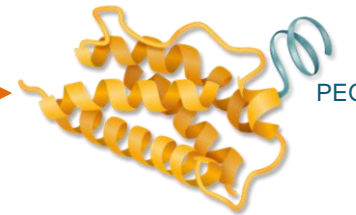
Introduction of cysteine at  $\alpha$ -binding site of IL-2 (aldesleukin)



### Blocking $\alpha$ -binding

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

Permanent PEG attachment  
at  $\alpha$ -binding site

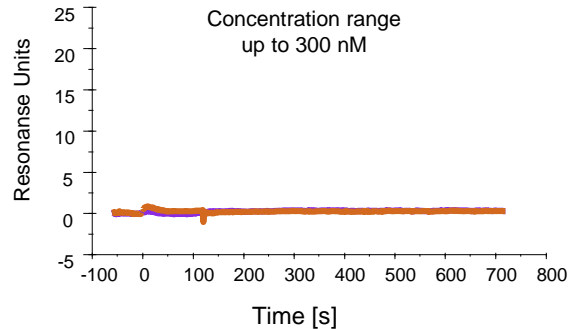


Optimized IL-2  $\beta/\gamma$  receptor selectivity and potency by permanent site-selective PEG conjugation at IL-2R $\alpha$ -binding site

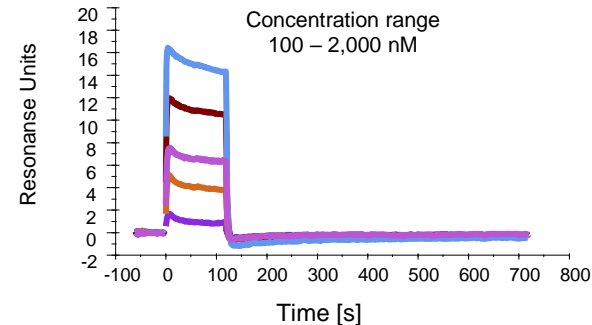
# Permanently PEGylated IL-2 $\beta/\gamma$ Demonstrated Low Binding to IL-2R $\alpha$ , while Retaining Binding to IL-2R $\beta$

IL-2  $\beta/\gamma$

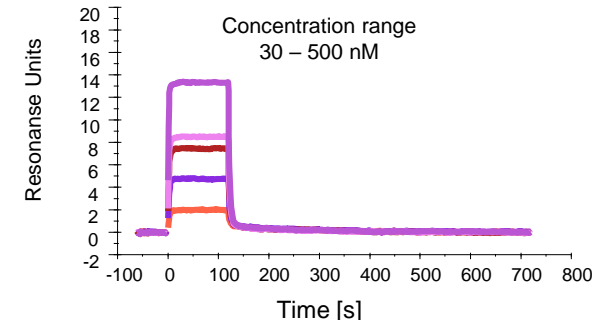
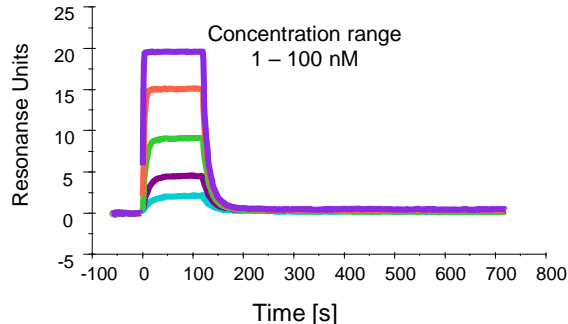
## Binding to IL-2R $\alpha$ -chain



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

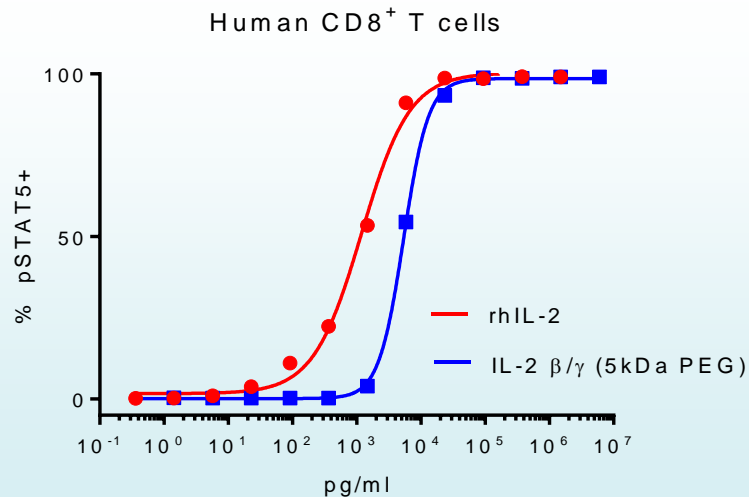
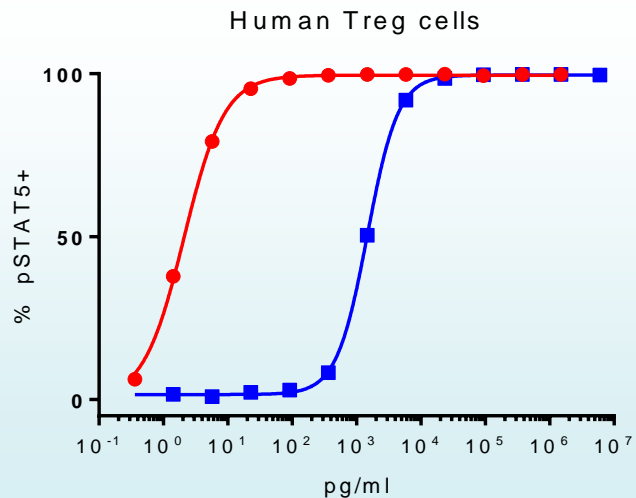


Wild-type  
IL-2  
(aldesleukin seq)



Receptor selectivity confirmed in cell-based assays, including primary human Tregs and CD8<sup>+</sup> T cells

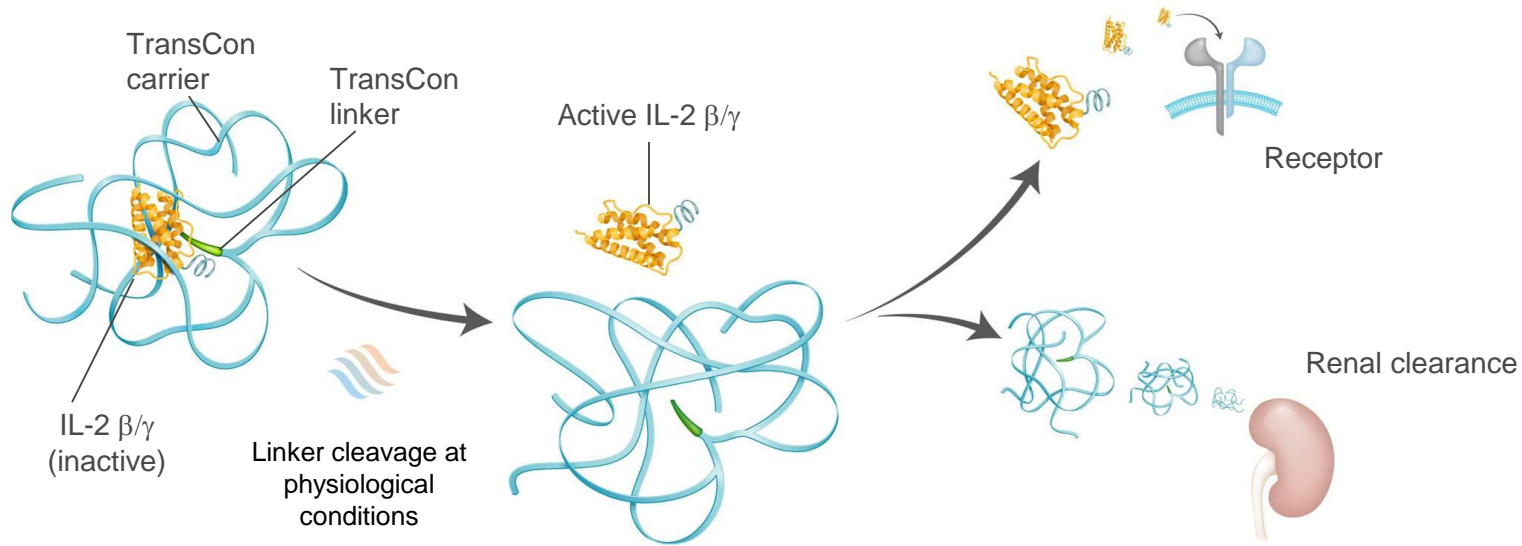
# IL-2 $\beta/\gamma$ – Desired Receptor Selectivity Demonstrated



~770-fold reduced potency on primary human Treg cells compared to rhIL-2  
while only ~4-fold loss in potency on CD8<sup>+</sup> T cells and NK cells

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

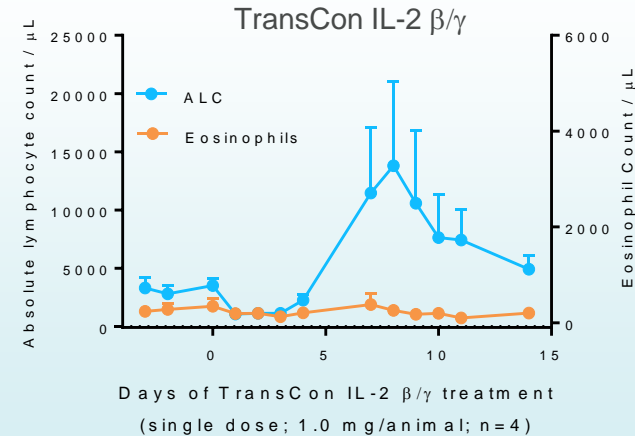
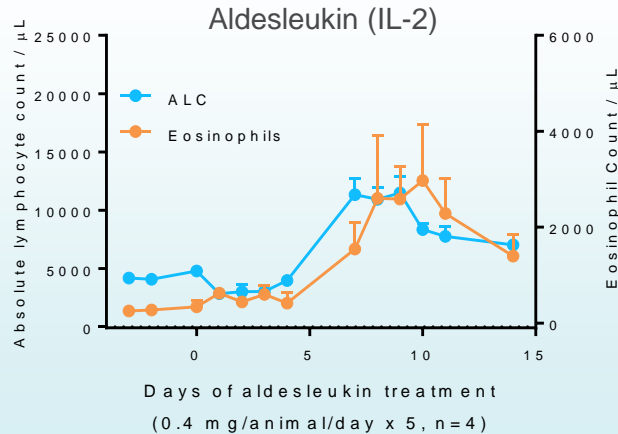
## 2) TransCon Technology to Optimize Exposure



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

# TransCon IL-2 $\beta/\gamma$ – Prolonged Activity and Receptor Selectivity Demonstrated in Cynomolgus Monkeys

A single 1 mg dose/animal (~0.1 mg/kg) TransCon IL-2  $\beta/\gamma$  resulted in >3-fold enhancement of Lymphocyte Counts, Minimal Effect on Eosinophils Compared to Aldesleukin in Cynomolgus Monkeys



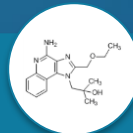
- Single dose provided >3-fold and prolonged enhancement of lymphocyte counts supporting Q3W dosing
- Well tolerated in monkeys with low risk of vascular leak syndrome; minimal effect on eosinophils<sup>1</sup>
- Monotherapy and combination anti-tumor activity observed in mice

# TransCon IL-2 $\beta/\gamma$ - Summary

- Designed to fully solve the limitations of IL-2
  - Optimized receptor binding and exposure
  - Selective activation of IL-2R $\beta/\gamma$  observed
- Potential for best-in-class IL-2 molecule across multiple tumor types
  - Potent expansion and activation of CD8<sup>+</sup> T cells and NK cells *in vivo*
  - Monotherapy and combination anti-tumor activity observed in mice
  - Prolonged lymphocyte expansion in cynomolgus monkeys observed
  - Single dose provided >3-fold and prolonged enhancement of lymphocyte counts supporting Q3W dosing
  - Receptor selectivity with low activation of eosinophils and Treg cells observed in monkeys; no dose limiting toxicity



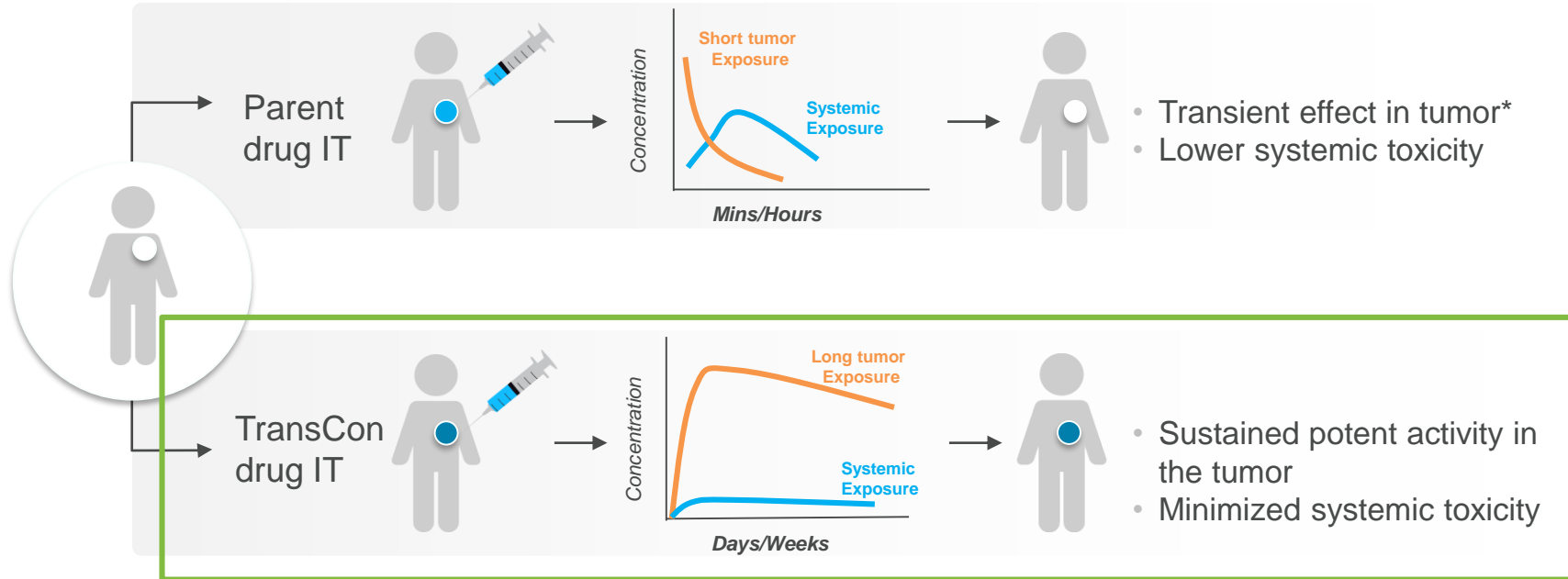
# Oncology Product Candidate



TransCon TLR 7/8  
Agonist

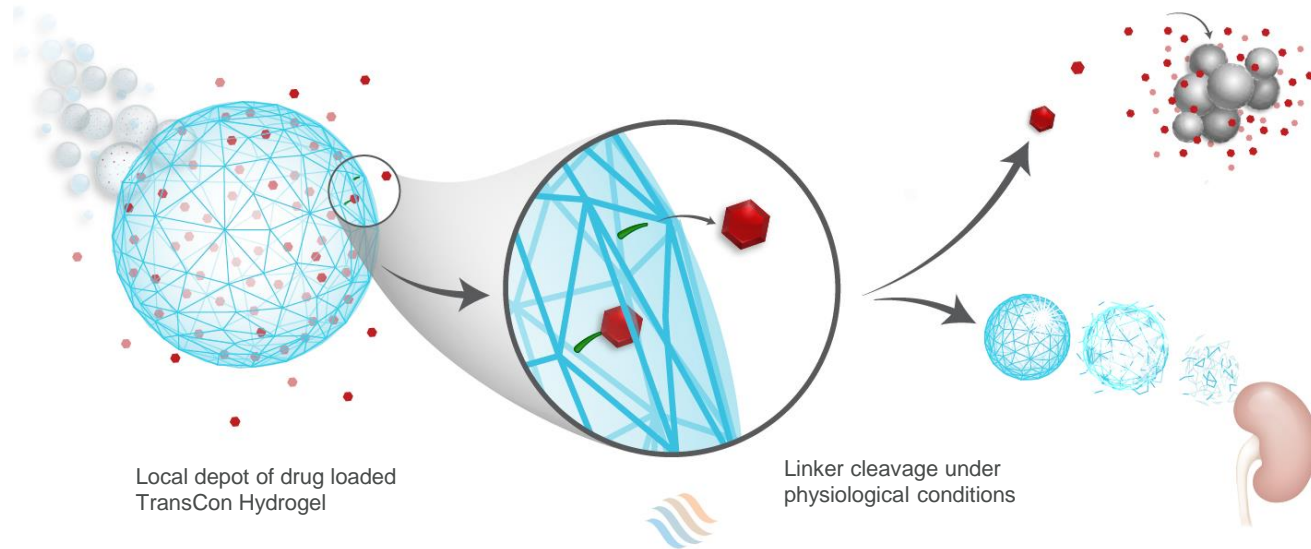
# Potential to Transform Efficacy, Safety and Practicality of Intratumoral Treatments

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

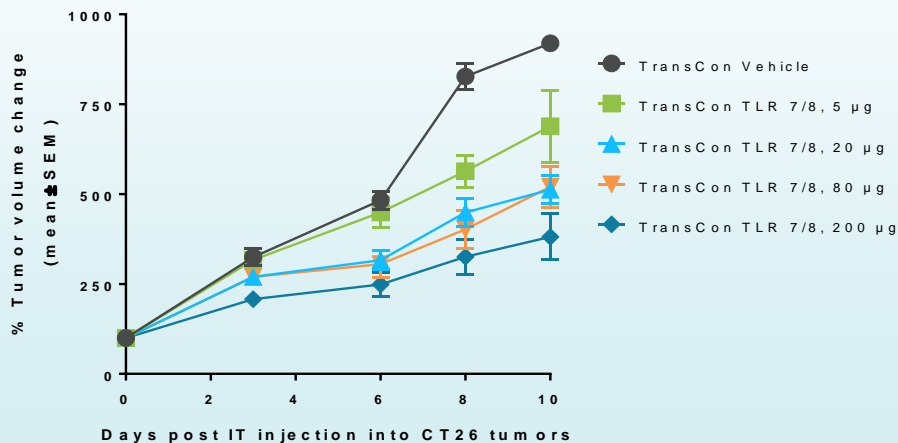


- Resiquimod transiently conjugated to TransCon Hydrogel carrier, designed to provide sustained local release of unmodified parent drug
- Designed to provide sustained activation of tumoral myeloid lineages driving tumor antigen release/presentation and induction of immune stimulatory cytokines

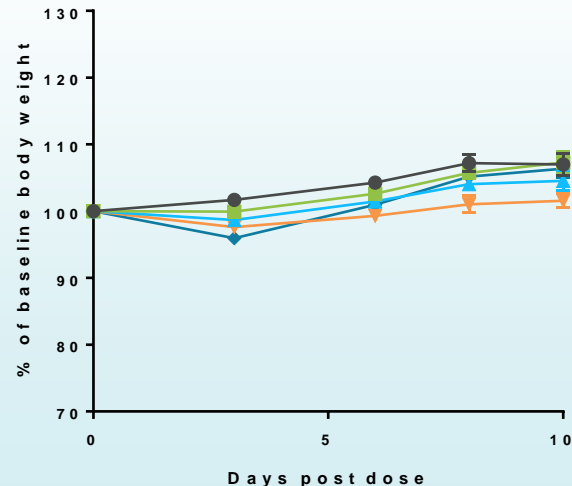
# Dose-dependent Tumor Growth Inhibition Following a Single IT Injection of TransCon TLR 7/8 Agonist

## Single IT Dosing

Tumor Growth:  
Dose-dependent Inhibition



Body Weights:  
All Doses Well Tolerated

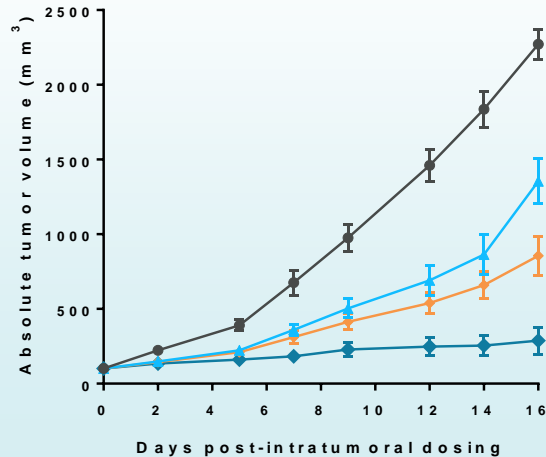


*Consistent with MOA, local inflammation and some tumor ulcerations observed*

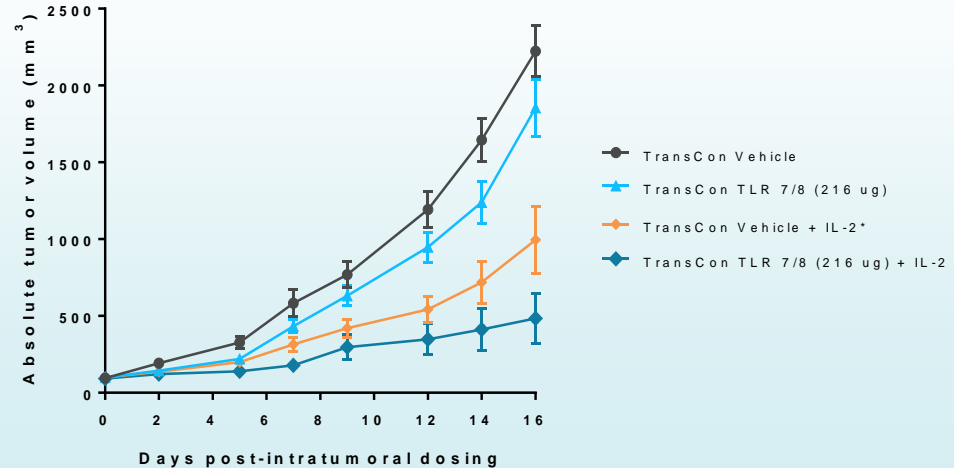
# Single-dose of TransCon TLR7/8 Agonist Triggered Abscopal Anti-Tumor Inhibition and Enhanced Anti-tumor Effects of IL-2

## Single IT Dosing

Injected Tumor

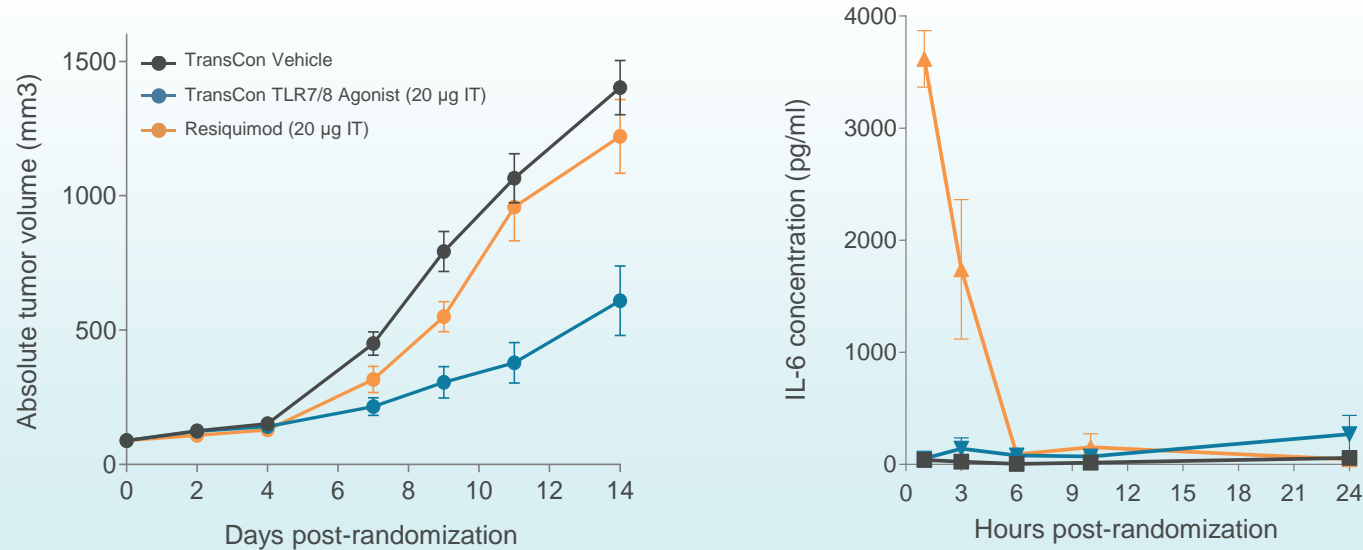


Non-injected Tumor



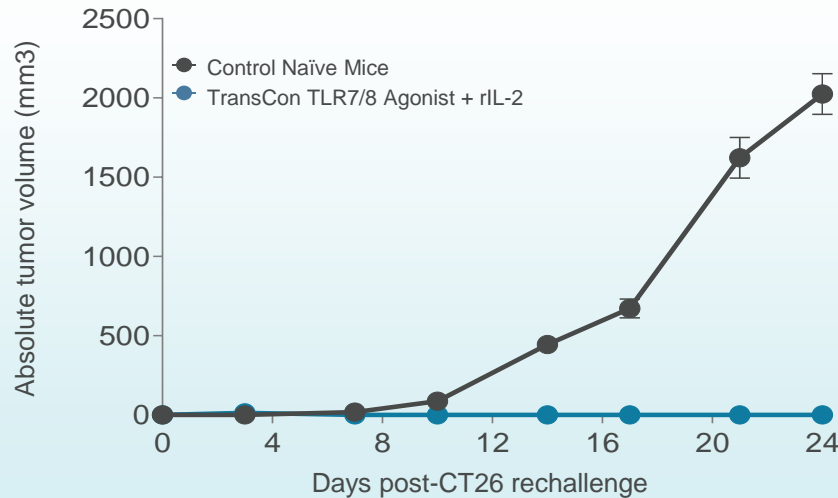
# A Single Dose of TransCon TLR7/8 Agonist Mediated Potent Tumor Growth Inhibition with Minimal Systemic Cytokine Release

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 Grow 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 TLR 7/8 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 ug/animal
  - Potential to enable efficacy with dosing interval of months



# 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

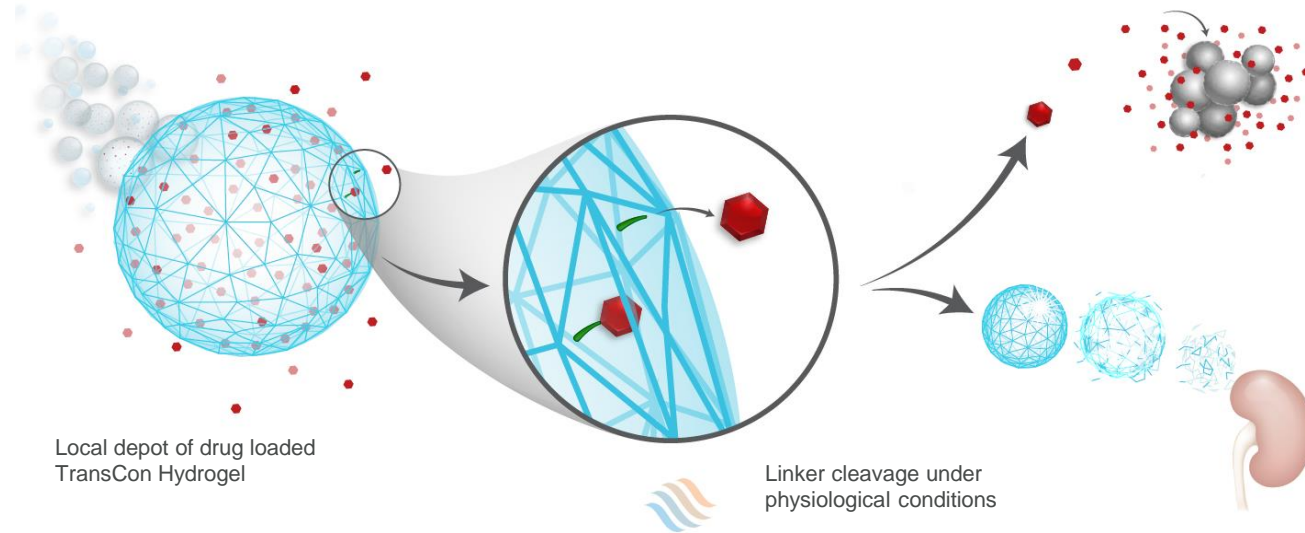
## New Indications

- 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

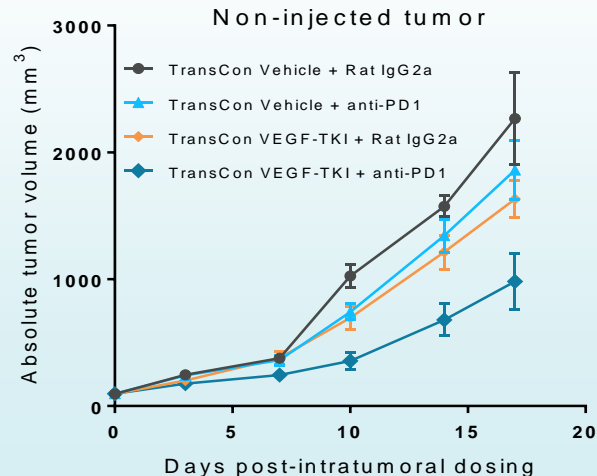
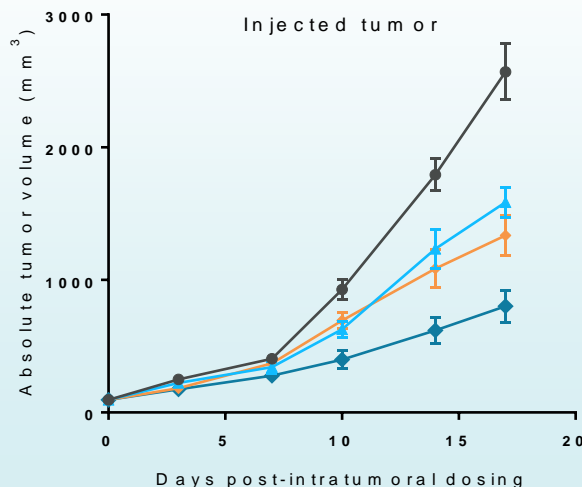
# TransCon VEGF-TKI: Axitinib Loaded onto TransCon Hydrogel for Intratumoral Sustained Delivery



- 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 equivalent expected to be filed Q4 2020
- Over 20 patents and applications in support of TransCon oncology candidates

# Selected 2020 Expected Milestones



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

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