# Ascendis Pharma A/S

April 2019

# 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 March 28, 2018, 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.

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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
  - Unique algorithm for product innovation has resulted in clinical validation of 3 out of 3 product candidates within the endocrinology rare disease area
- Endocrinology rare disease internal pipeline and expected near-term milestones
  - TransCon hGH for pediatric GH deficiency: Phase 3 demonstrated superiority of TransCon hGH
  - TransCon PTH for hypoparathyroidism: Phase 2 top-line data Q4 2019
  - TransCon CNP for achondroplasia: Phase 2 initiation Q3 2019
- Build leading positions for each endocrinology rare disease product with commercial focus on the U.S. and select European markets
  - Partnership with VISEN Pharmaceuticals for commercialization of endocrinology rare disease products in China
- Established high-value collaborations with Roche/Genentech in ophthalmology and Sanofi in diabetes
- As of December 31, 2018, pro forma cash and cash equivalents of ~€755 million[1]



[1] Includes net proceeds from a follow-on offering in March 2019, based on exchange rates as of the date of the offering.



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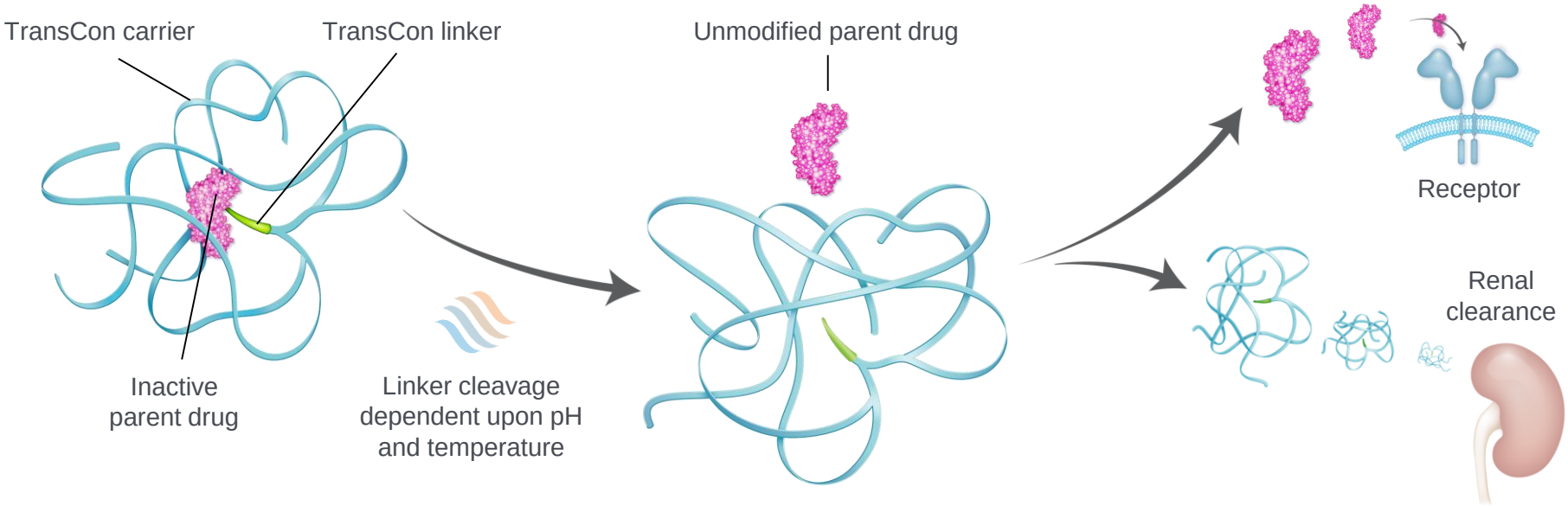
# TransCon Technology: Sustained Systemic Delivery

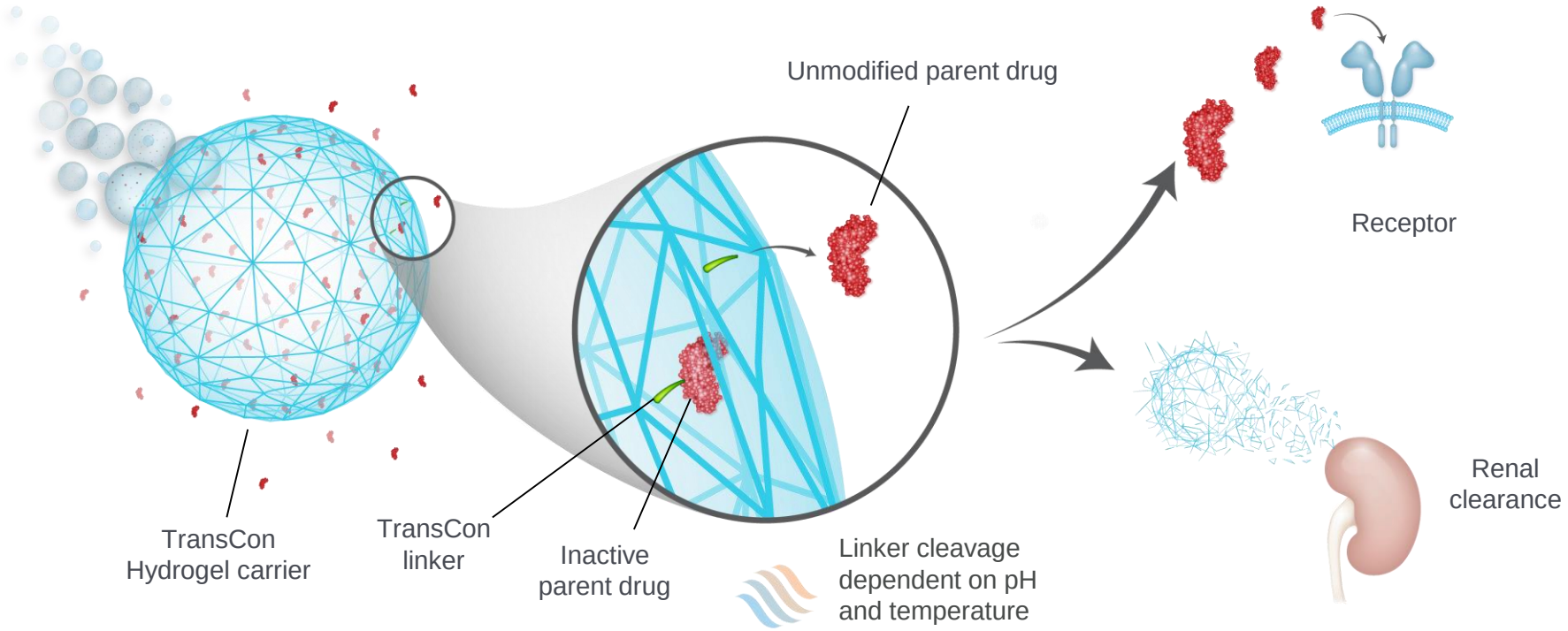



Parent drug is transiently bound to a TransCon linker-soluble carrier moiety, which inactivates and shields parent drug from clearance

Following injection, the linker is designed to autohydrolyze at specific rates to predictably release unmodified parent drug

Designed to distribute parent drug like the endogenous compound; linker-carrier is cleared renally

# TransCon Technology: Sustained Localized Delivery



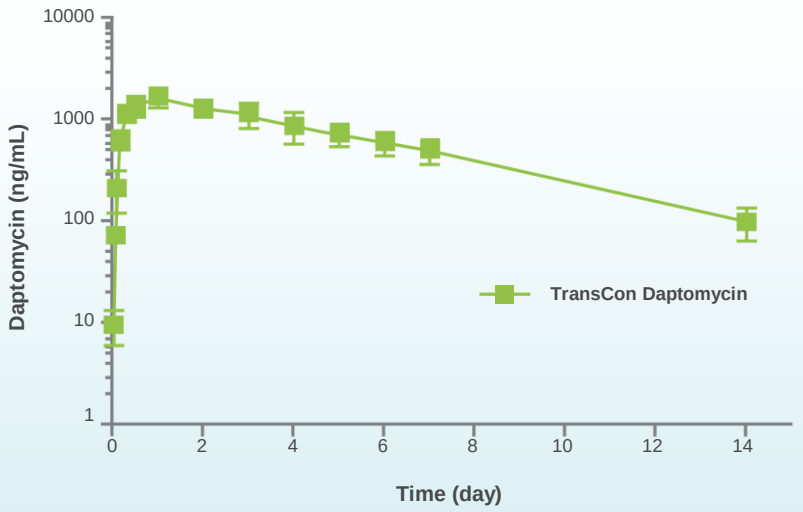

Parent drug is transiently bound to TransCon linker-hydrogel carrier, which inactivates, shields parent drug and prevents clearance

Following injection, the linker is designed to autohydrolyze at specific rates 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 following drug release

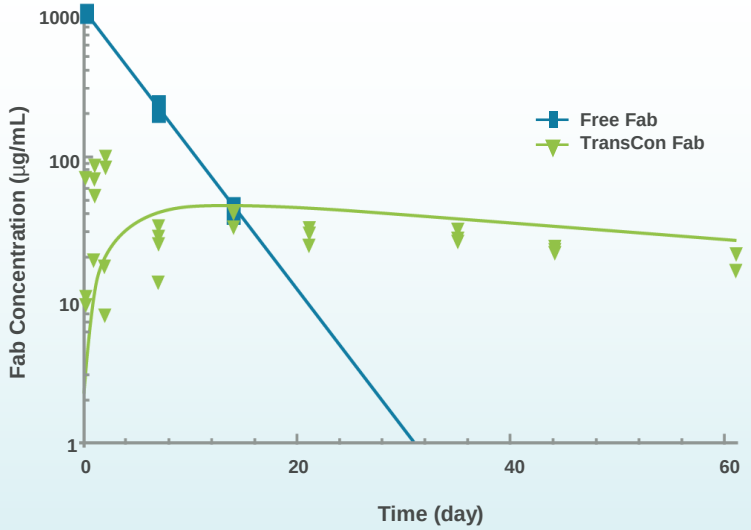
# Sustained Localized Delivery: Validated Across Multiple Drugs and Administration Sites

## Small Molecules
*Intra-articular administration*




Plasma PK of Daptomycin following intra-articular administration in rabbits. TransCon Daptomycin half-life was ~3 days.

## Antibody Fragments (Fab)
*Intra-vitreous administration*[1]



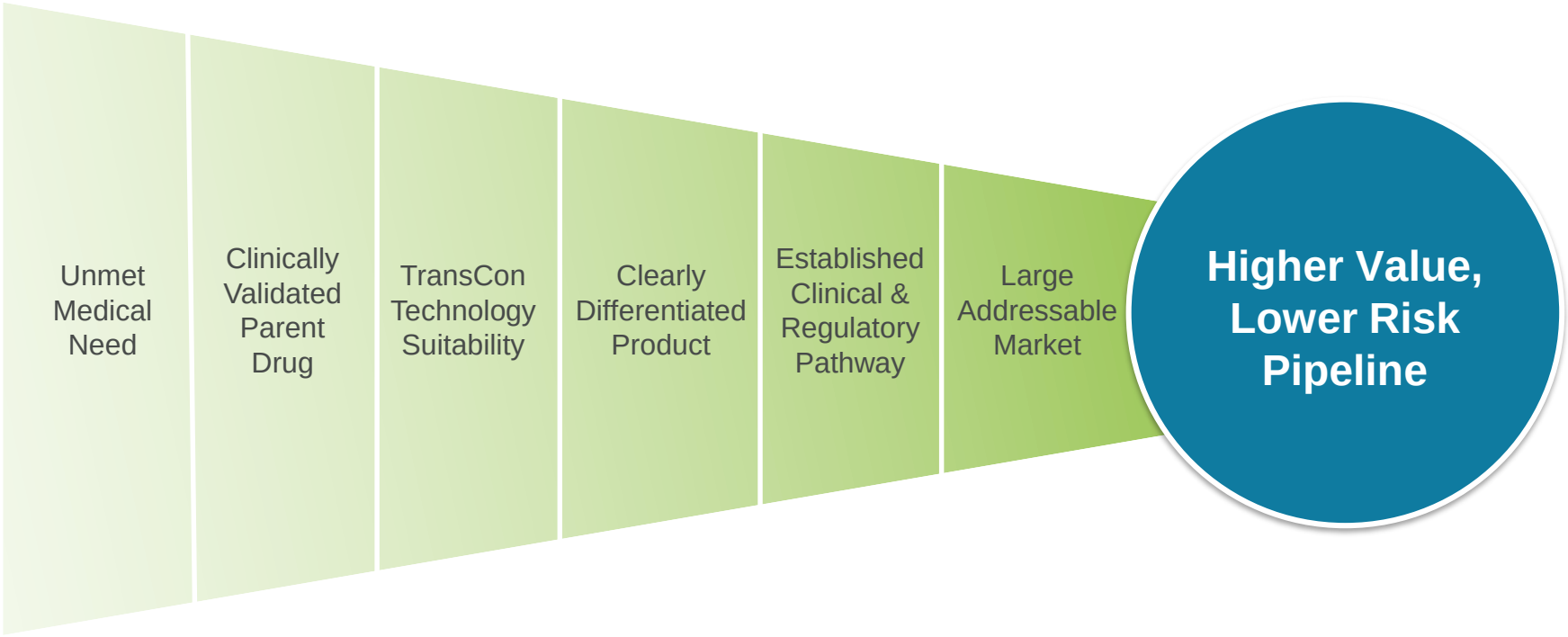

Vitreal PK of Fab following intra-vitreous administration in rabbits. TransCon Fab half-life was ~53 days compared to free Fab half-life of ~3.2 days.

- Excellent local tolerability of TransCon hydrogel carrier
- Sustained high local concentration with low systemic exposure



[1] Patent WO2018175788

# Ascendis Algorithm for Product Innovation




Our unique algorithm for product innovation has resulted in clinical validation of 3 out of 3 product candidates in Endocrinology Rare Disease

# Building a Leading Company in Rare Diseases

## Internal Endocrinology Pipeline

| PRODUCT CANDIDATE | PRECLINICAL | PHASE 1 | PHASE 2 | PHASE 3 | POTENTIAL WW MARKET[1] | COMMERCIAL RIGHTS[2] |
|---|---|---|---|---|---|---|
| **TransCon hGH** | Pediatric Growth Hormone Deficiency | | | | > $3 billion[3] | ascendis pharma |
| | Adult Growth Hormone Deficiency | | | | | |
| **TransCon PTH** | Hypoparathyroidism | | | | > $2 billion[4] | ascendis pharma |
| **TransCon CNP** | Achondroplasia | | | | > $1 billion | ascendis pharma |

## Strategic Collaborations

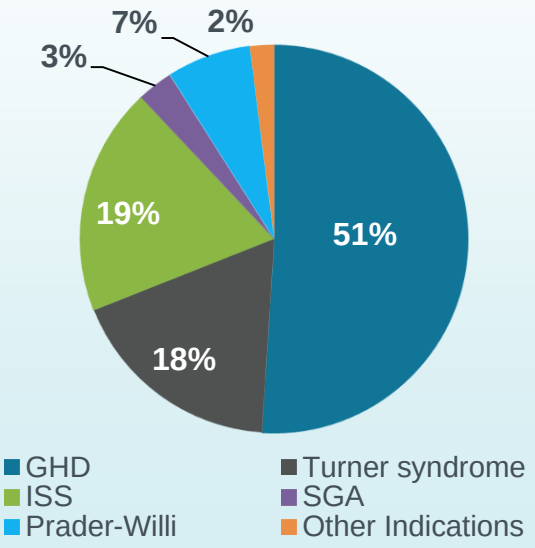
| PRODUCT CANDIDATE | PRIMARY INDICATION | DEVELOPMENT STAGE | POTENTIAL WW MARKET[1] | WW COMMERCIAL RIGHTS |
|---|---|---|---|---|
| **TransCon Anti-VEGF** | Ophthalmology | Not disclosed | >$7 billion | Genentech |
| **TransCon Peptides** | Diabetes | Not disclosed | >$1 billion | SANOFI |

[1] Based on market data and Company estimates
[2] Excludes rights granted to VISEN Pharmaceuticals in Greater China
[3] Includes all indications
[4] Based on treatment of ~25% of the U.S. patient population of ~80,000 patients.

# TransCon Growth Hormone: **Once-Weekly Replacement Therapy**

# The Growth Hormone Market[1]

- ~$3.5 billion in worldwide rhGH[2] sales and growing (2.4% CAGR)[3]
- Fragmented market with same undifferentiated hGH molecule competing on differentiated formulations, devices, services and access strategies
- Pediatric indications comprise ~90% of the market
- Indications for growth hormone treatment include:
  - Growth Hormone Deficiency (GHD) ~50% of market
  - Turner syndrome
  - Idiopathic short stature (ISS)
  - Prader-Willi syndrome
  - Small for gestational age (SGA)




**Well-established market primed for disruption by a long-acting growth hormone product**

[1] Based on company research
[2] Recombinant human growth hormone; subsequently referred to in this presentation as hGH
[3] Compounded Annual Rate of Growth based on 2010-2014 data

# Clinical Implications of Untreated GHD

## BODY COMPOSITION

Increased fat mass, decreased muscle mass, and decreased bone density have been shown to occur soon after treatment discontinuation.[2,3,4]

## CARDIOVASCULAR DISEASE

Early discontinuation of GH treatment may induce impairment of patients' lipid profiles and cardiac structure and performance, leading to increased risk for CV disease.[6,7]

## ULTIMATE HEIGHT ACHIEVEMENT

Adults who had child-onset GHD may not achieve full height potential if treatment is stopped prior to adulthood.[1]

## MENTAL HEALTH

A high incidence of psychiatric disorders, usually accompanied by poor life quality, is associated with adults who were GHD as children.[5]

## FRACTURES

Adult peak bone mass is considerably lower, and rates of fractures are significantly higher among adults with GHD who were not treated as children.[8]

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. Auzerie.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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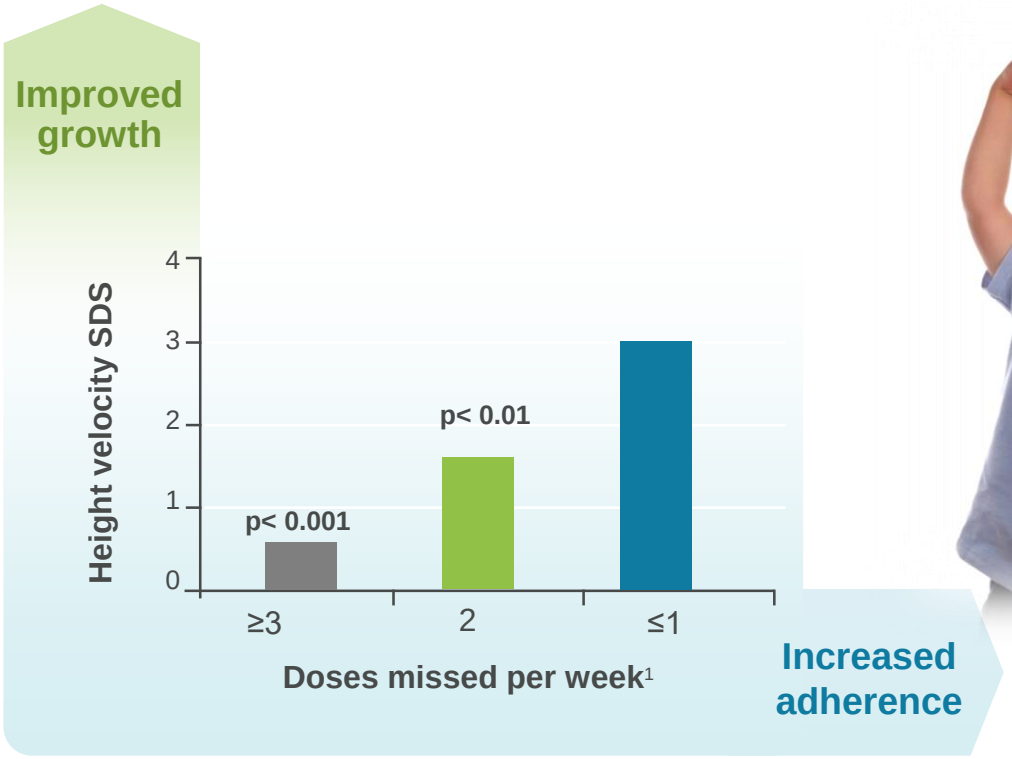
# Daily Growth Hormone: The Problem

Poor adherence with daily hGH therapy is associated with reduced height velocity and impaired quality of life[1]




Reduced frequency of administration is associated with better adherence[2]

In the 1st year, two of three patients miss >1 injection on average per week[1]



[1] PLoS ONE 2011, 6(1): e16223
[2] Clinical Therapeutics 2008, 30(2): 307-316



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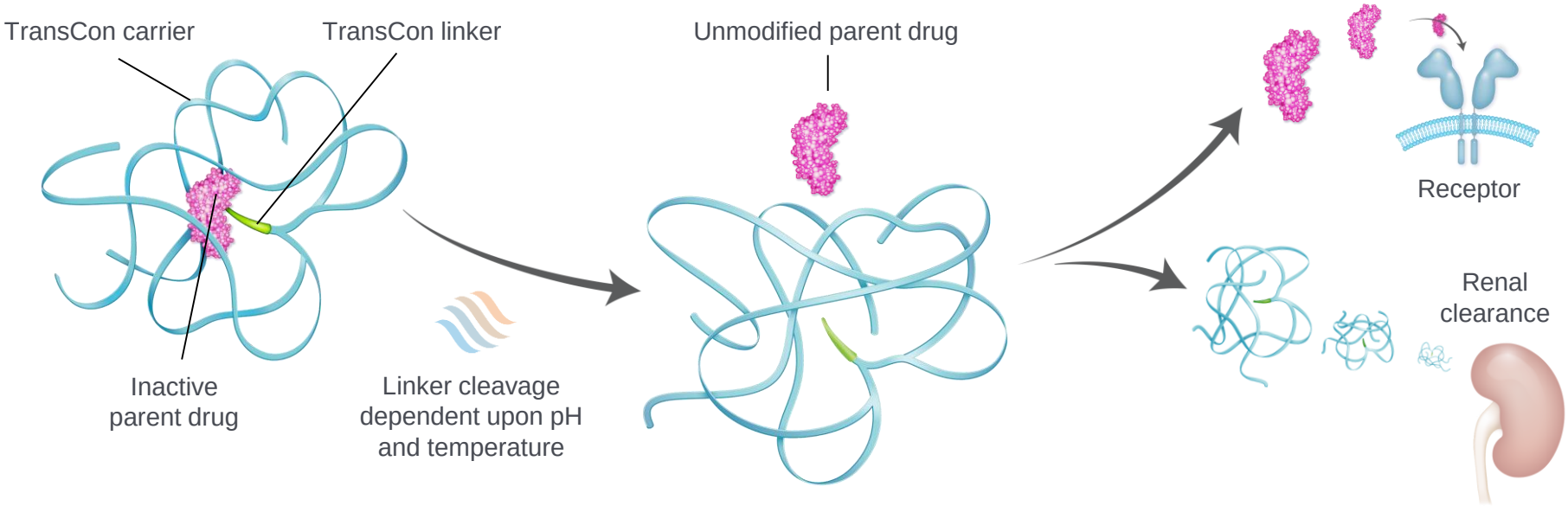
# TransCon hGH Design




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

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

# TransCon Growth Hormone Target Product Profile

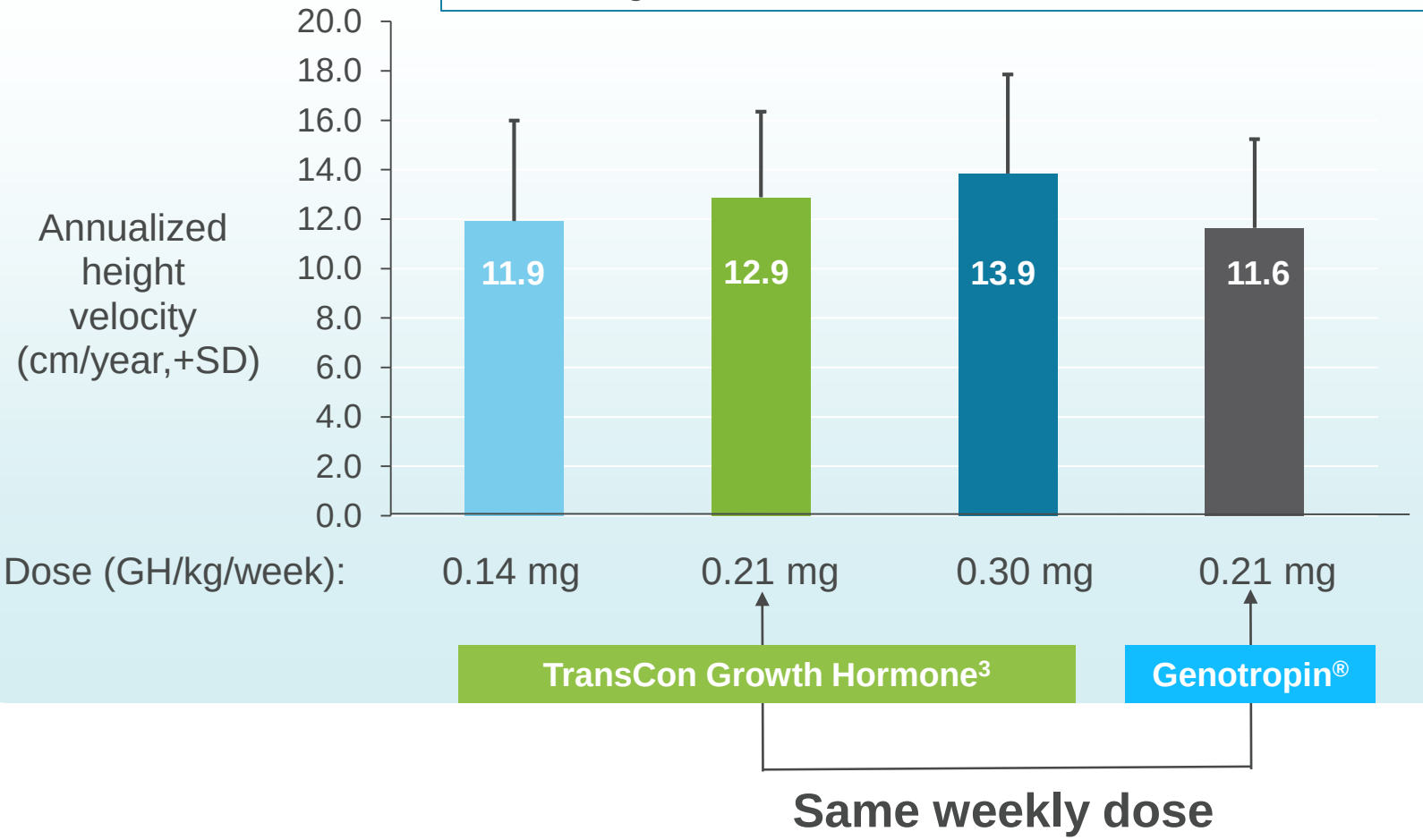
- Efficacy
- Safety (including immunogenicity)
- Tolerability

**Comparable to Daily Growth Hormone**

- Weekly subcutaneous administration
- Small injection volume (31G needle)
- Room temperature storage
- Device
  - Easy to use
  - Automatic data capture
  - Empty-all design

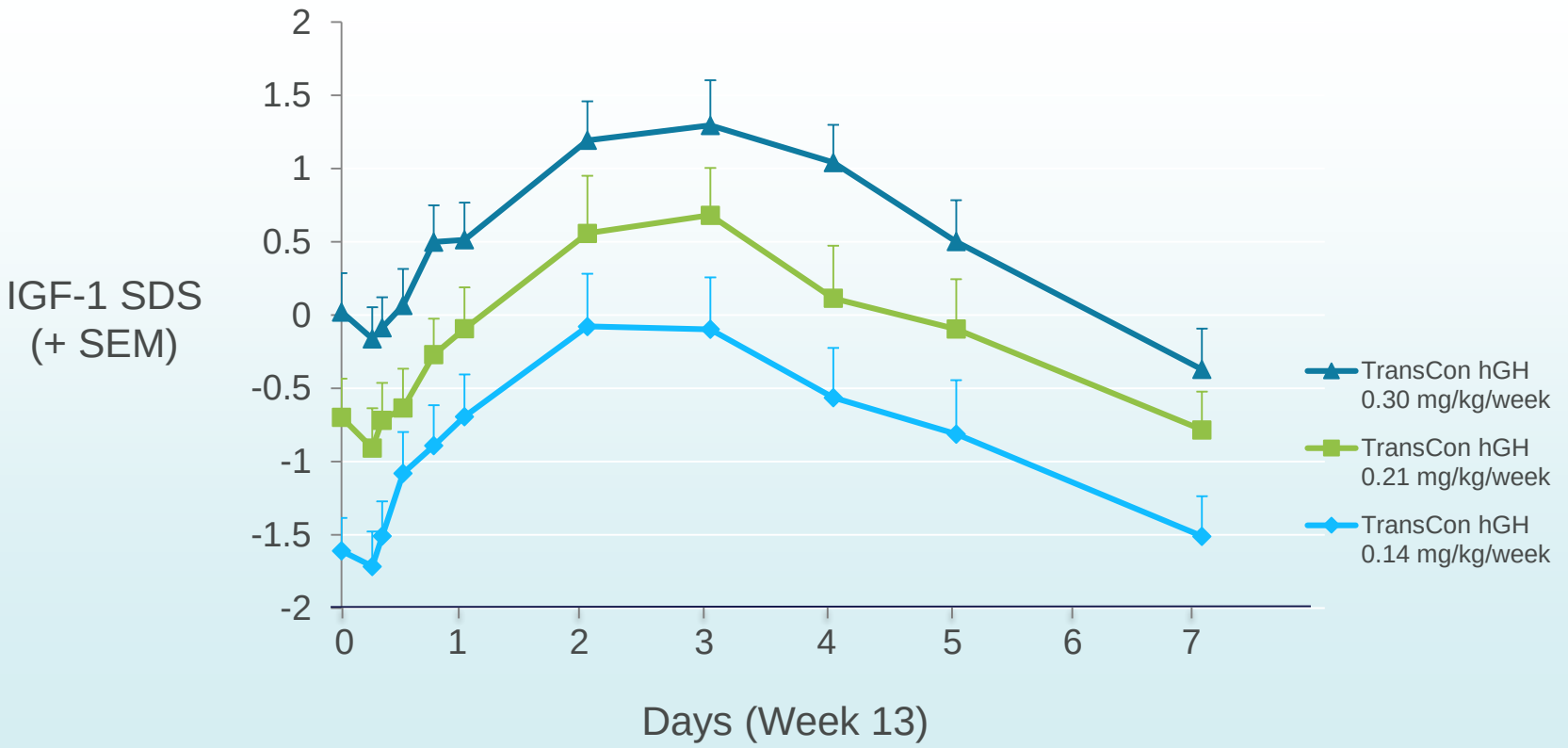
# Growth Comparable to a Daily hGH in Phase 2[1,2]

- 26-week treatment period
- Thorough PK/PD assessments at weeks 1 and 13




[1] Intergroup differences not statistically significant
[2] J Clin Endocrinol Metab 2017, 102(5): 1673–1682
[3] Conducted with a previous lower strength version of TransCon hGH

# Dose Proportional IGF-1 Response in Phase 2[1]

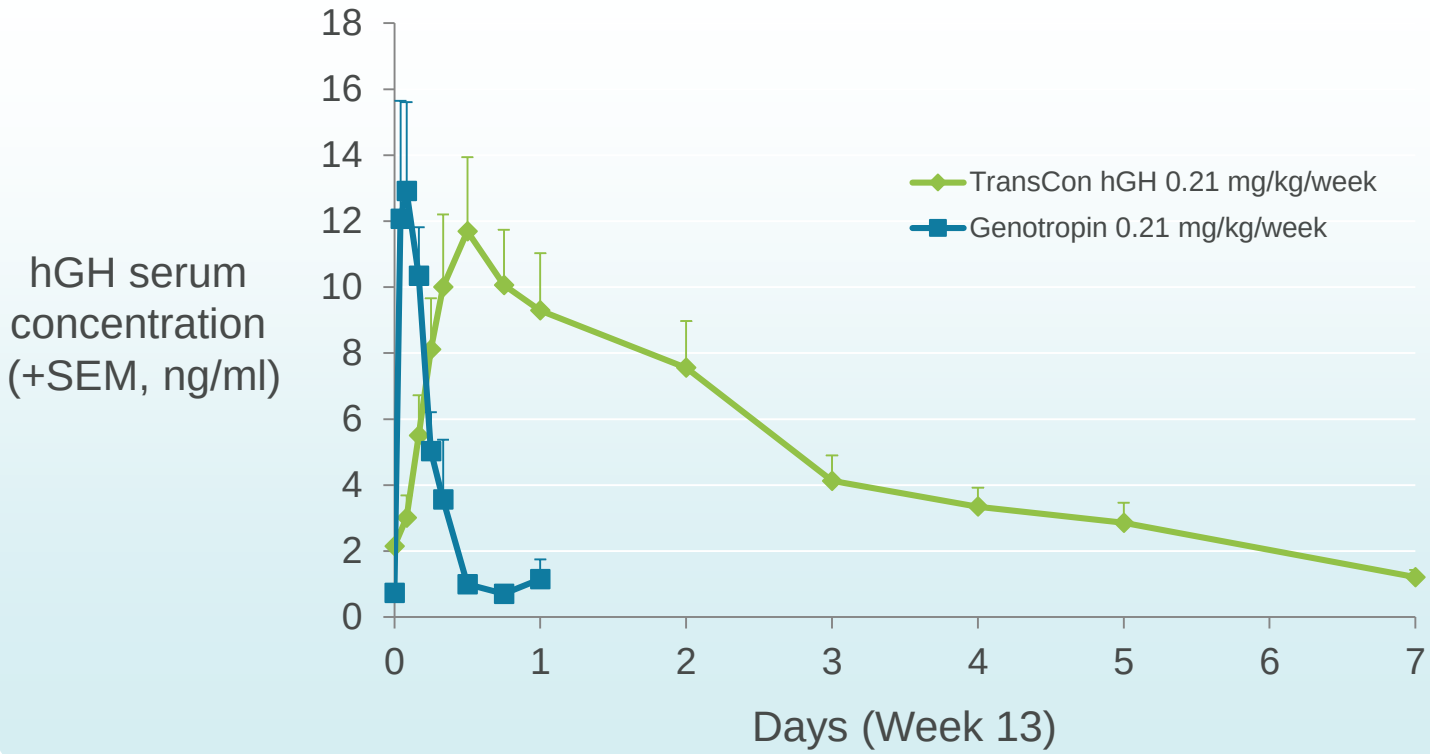



Transient values greater than +2.0 observed in a small number of patients primarily at the highest dose level



[1] J Clin Endocrinol Metab 2017, 102(5): 1673–1682

# Comparable hGH Levels in Phase 2[1]




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



[1] J Clin Endocrinol Metab 2017, 102(5): 1673–1682

# Comparable Safety to a Daily hGH in Phase 2[1]

**No serious adverse events related to study drug**

- Adverse events consistent with daily hGH therapy observed and not different between cohorts

**Immunogenic profile comparable to a daily hGH**

- No occurrence of neutralizing antibodies
- Low incidence of low-titer non-neutralizing antibodies

**Injection site tolerability comparable to a daily hGH**

- >1100 TransCon hGH injections administered
- No reports of lipoatrophy or nodule formation



[1] J Clin Endocrinol Metab 2017, 102(5): 1673–1682

# TransCon hGH Phase 3 Program


- Top-line data reported Q1 2019


- Switch trial (n=146)
- Fully enrolled
- Data expected Q2 2019

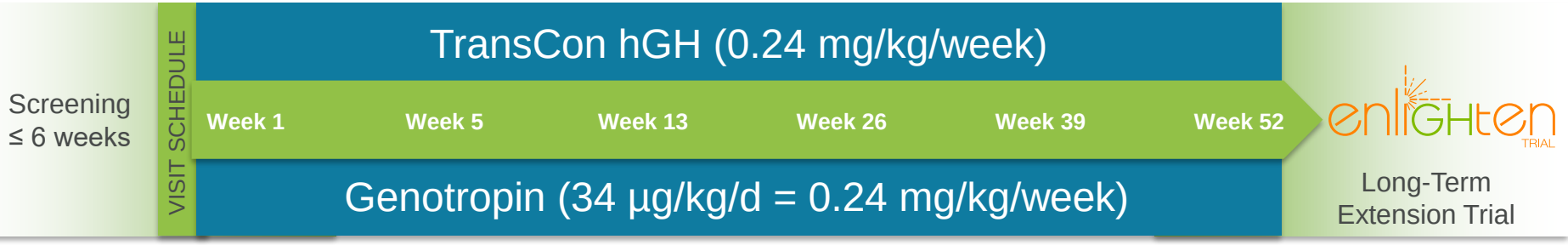

Extension trial (n~300)

*Regulatory Filings*

- FDA and EMA support size and scope of program for pediatric GHD filing
- Database lock for filing package expected Q3 2019

# Phase 3 heiGHt Trial

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




## Key Inclusion Criteria

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

## Key Endpoints

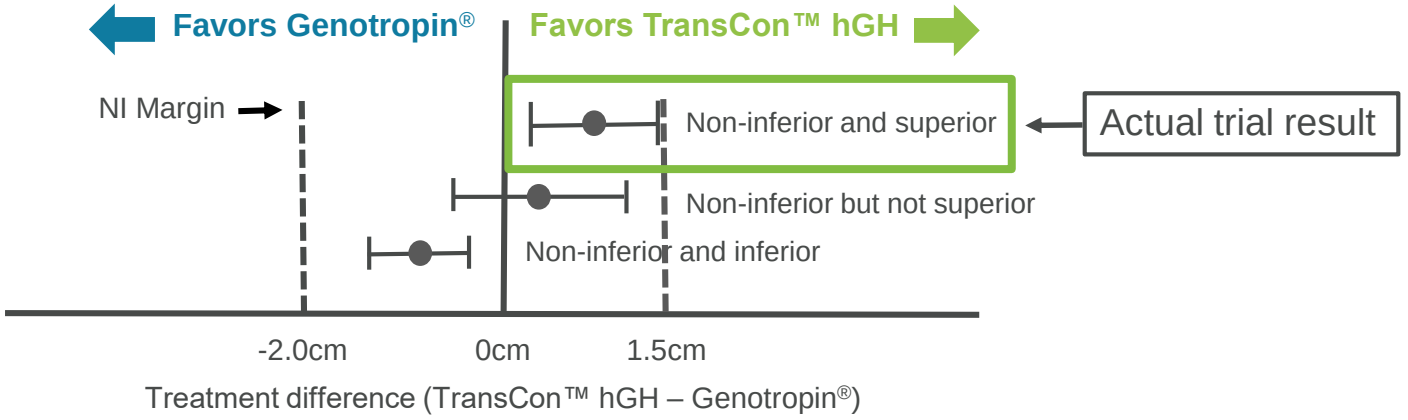
- Annualized height velocity at 52 weeks (primary endpoint)
- Annualized HV at earlier time points
- Change in HT SDS over 52 weeks
- Change in serum IGF-1/IGFBP-3 levels
- Change in IGF-1 SDS and IGFBP-3 SDS
- Normalization of IGF-1 SDS

# Demographics and Baseline Characteristics Comparable Between Arms

| | TransCon™ hGH (N=105) Mean | Genotropin® (N=56) Mean | Total (N=161) Mean |
|---|---|---|---|
| Age (years) | 8.51 | 8.48 | 8.50 |
| Bone Age (years) | 5.84 | 5.98 | 5.88 |
| Height SDS | -2.89 | -3.00 | -2.93 |
| BMI SDS | -0.32 | -0.14 | -0.25 |
| Delta Mid-Parental Height SDS | -2.32 | -2.55 | -2.40 |
| IGF-1 SDS | -2.08 | -1.96 | -2.04 |
| Peak GH (ng/mL) | 5.89 | 5.48 | 5.75 |
| Caucasian (%, in race) | 95.2 | 92.9 | 94.4 |
| Male (%) | 81.9 | 82.1 | 82.0 |

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

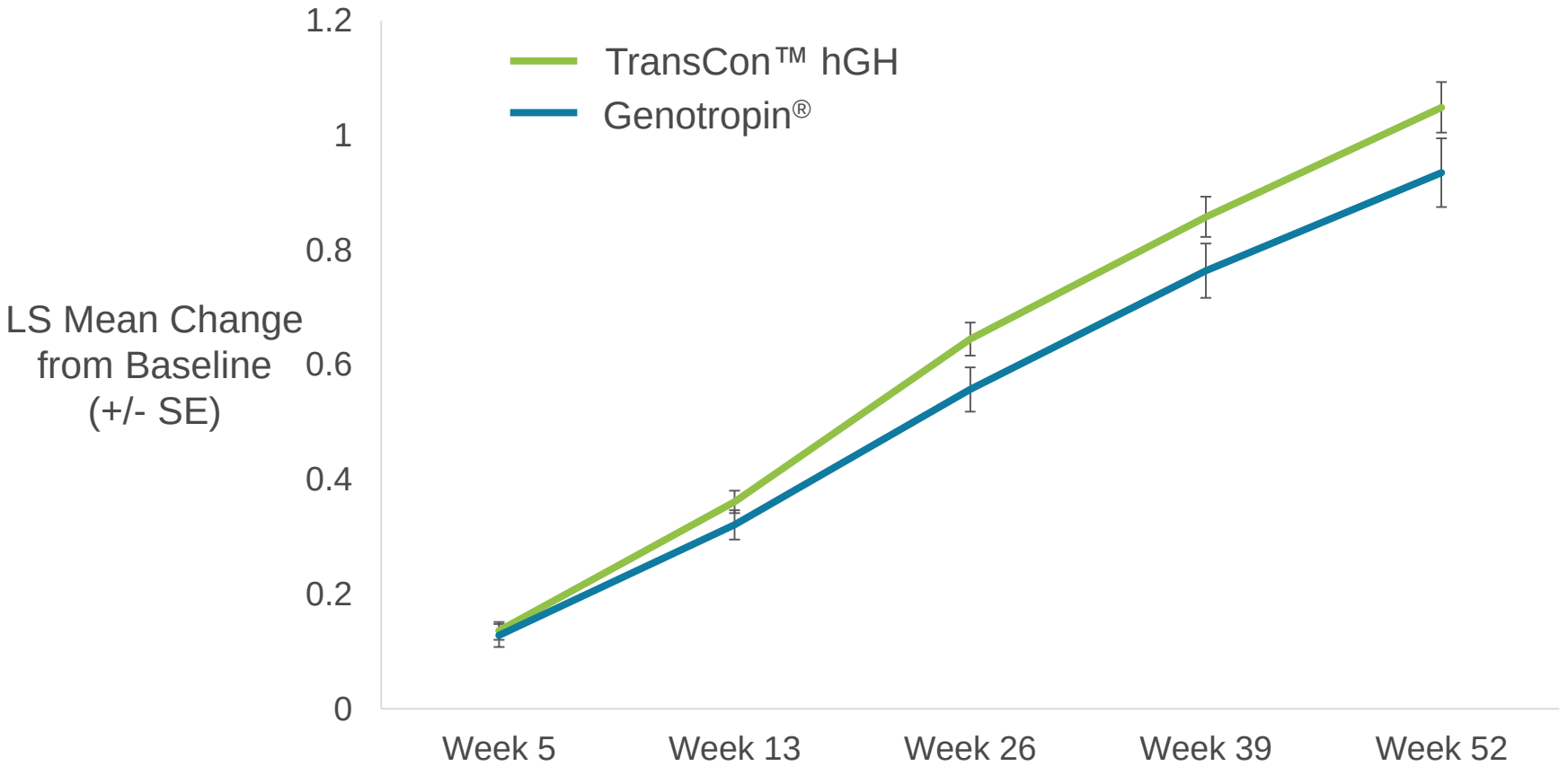
| | TransCon™ hGH (N=105) | Genotropin® (N=56) | Estimate of Treatment Difference | P-value |
|---|---|---|---|---|
| LS Mean AHV at Week 52 (cm/year) | 11. 2 | 10.3 | 0.86 | **0.0088** |
| Standard Error | 0.23 | 0.30 | 0.33 | |
| 95% Confidence Interval (cm/year) | 10.71 – 11.62 | 9.73 – 10.89 | 0.22 – 1.50 | |






ANCOVA model was applied after missing data were imputed by multiple imputation method.
Top-line results from phase 3 heiGHt Trial.

# Change in Height SDS






ANCOVA model.
Top-line results from phase 3 heiGHt Trial.

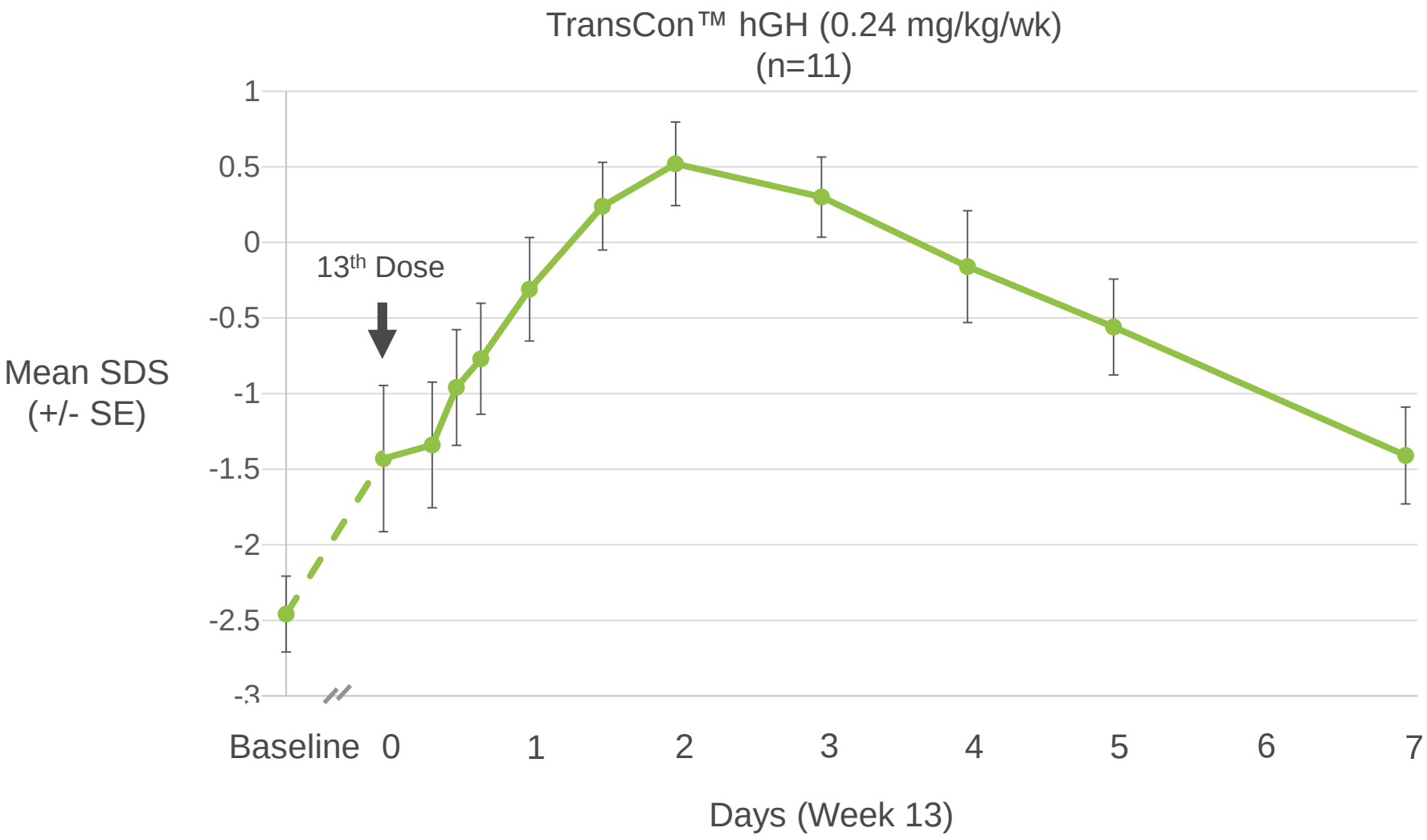
# Lower Incidence of Poor-Responders with TransCon™ hGH

Poor-responders defined as AHV < 8.0 cm/year

| At Week 52 | TransCon™ hGH (N=104)* n (%) | Genotropin® (N=55)* n (%) |
|---|---|---|
| Responder | 100 (96.2) | 49 (89.1) |
| Poor-Responder | 4 (3.8) | 6 (10.9) |

* Excludes one subject/group with missing Week 52 data (98.8% subjects completed study)

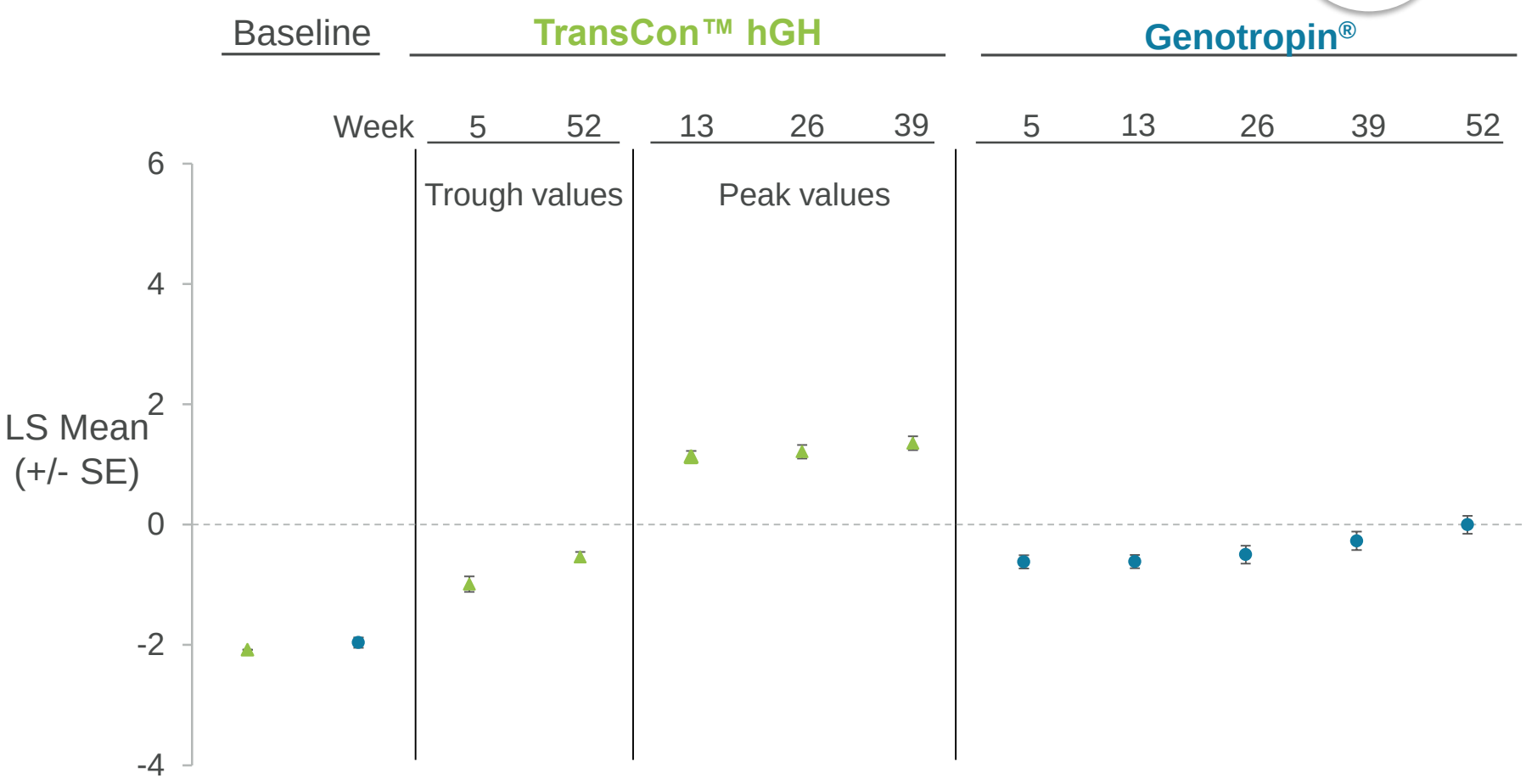
# IGF-1 Profile Over 1 Week of Testing






Top-line results from phase 3 heiGHt Trial.

# IGF-1 SDS Over 52 Weeks (N = 161)




Estimated mean IGF-1 SDS of +0.4 (average trough to peak) for TransCon™ hGH compared to an approximate average IGF-1 SDS of 0.0 for Genotropin® may reflect the different AHV

# Summary of Adverse Events: Safety Population

| | TransCon™ hGH N = 105 n (%) | Genotropin® N = 56 n (%) | Total N = 161 n (%) |
|---|---|---|---|
| Treatment-emergent Adverse Events (TEAE) | 81 (77.1%) | 39 (69.6%) | 120 (74.5%) |
| TEAEs Related to Study Drug | 12 (11.4%) | 10 (17.9%) | 22 (13.7%) |
| Serious Adverse Events (AEs) | 1 (1.0%) | 1 (1.8%) | 2 (1.2%) |
| Serious AEs Related to Study Drug | 0 | 0 | 0 |
| TEAEs Leading to Any Action on Study Drug | 2 (1.9%) | 1 (1.8%) | 3 (1.9%) |
| TEAEs Leading to Discontinuation of Study Drug | 0 | 0 | 0 |

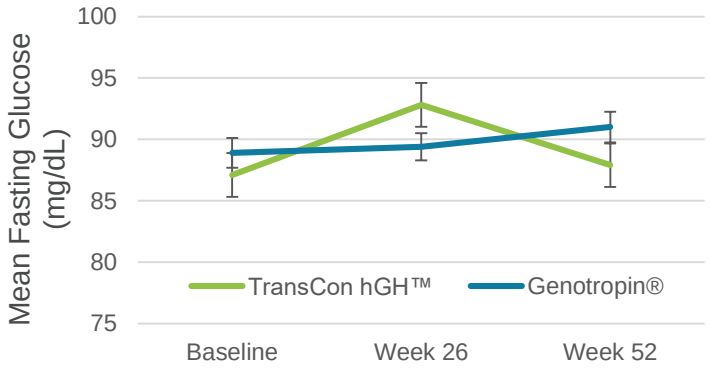
- Adverse events for TransCon™ hGH consistent with the type and frequency observed with Genotropin®
- No serious adverse events related to study drug in either arm
- No treatment-emergent adverse events led to discontinuation of study drug in either arm

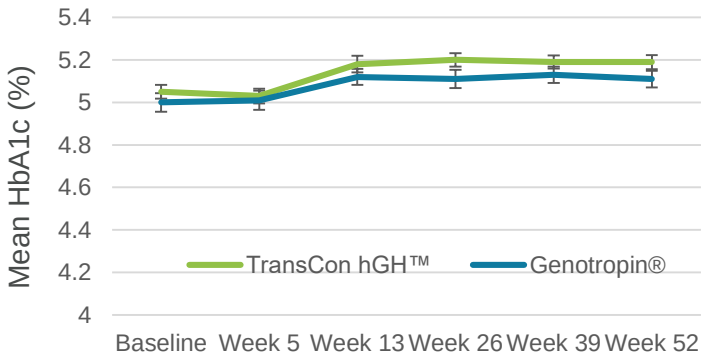

Top-line results from phase 3 heiGHt Trial.

# Preliminary Safety Analyses

- No neutralizing antibodies detected, and transient low level (< 10%) of low-titer non-neutralizing antibodies was similar between the two arms

- Mean fasting glucose and hemoglobin A1c values were stable and within the normal range for both arms




- Two subjects in each treatment arm experienced mild injection site reactions that were considered adverse events

# Summary

- AHV was significantly higher (p=0.0088) with TransCon™ hGH (11.2 cm) compared to daily Genotropin® (10.3 cm)
- The incidence of poor responders was ~3x lower in the TransCon hGH arm compared to the daily Genotropin® arm
- IGF-1 SDS levels were modestly higher with TransCon™ hGH than with Genotropin®, reflecting the higher observed AHV in the TransCon™ hGH arm
- No neutralizing antibodies were detected, and the low level (<10 percent) of low-titer non-neutralizing antibodies was similar between groups
- No serious adverse events related to study drug and no treatment-emergent adverse events leading to discontinuation of study drug were observed in either arm

# Conclusions

- Treatment with TransCon™ hGH achieved the primary objective of non-inferiority in AHV at 52 weeks, and further showed superiority over Genotropin®
- AHV was greater for TransCon™ hGH than for the daily hGH at each visit, with the treatment difference reaching statistical significance at week 26 onward
- IGF-1 SDS scores were generally within the normal range following treatment for both groups
- Safety profile of TransCon™ hGH was consistent with daily Genotropin®

# Auto-Injector Designed to Improve Adherence

## Key Features

- Simple operation with few user steps
- Single low-volume (<0.60 mL) injection for patients ≤60kg
- Small needle, comparable to daily hGH (31G, 4mm)
- Room temperature storage
- No waste due to empty-all design
- Bluetooth® connectivity enabled for automatic data capture
- Device lifetime at least 4 years

Auto-injector introduction during extension study and for commercial launch

# Integrating with a Connected Healthcare Platform

Automated Data Capture of Dose and Injection Time


Data Analysis

TransCon hGH Auto-Injector

**Improve Adherence Through Feedback & Intervention**

Secure Cloud-Based Central Database

# TransCon hGH: Highlights

- Potential best-in and first-in-class long-acting hGH in pediatric GHD
- heIGHt TRIAL phase 3 top-line data demonstrated superiority of TransCon hGH
- fliGHt TRIAL top-line data expected Q2 2019
- Introduction of auto-injector into enlIGHten TRIAL Trial expected Q2 2019
- Clinical database lock for filing package expected Q3 2019
- Improving adherence through integrated automatic data capture and connected healthcare system
- Commercial-scale manufacturing and supply chain established
- Multiple patent filings provide potential protection, with auto-injector, into 2038





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# TransCon PTH:
## PTH Replacement Therapy for Hypoparathyroidism

# Hypoparathyroidism: Serious Unmet Medical Need

- Parathyroid hormone (PTH) regulates calcium/phosphate homeostasis
- Hypoparathyroidism (HP) is a rare disease characterized by deficient or absent PTH
  - Low serum calcium, increased serum phosphate and urine calcium levels
  - Most common cause (~75%) is inadvertent removal or damage to parathyroid glands during thyroid surgery
  - Approximately 80,000 patients in the U.S.
- HP results in diverse physical, cognitive, and emotional symptoms with high burden on the healthcare system despite current standard of care
  - 79% require hospitalizations or emergency department visits
  - 4-fold increased risk of renal disease (calcifications and renal insufficiency)



Sources: 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



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# Diverse Clinical Manifestations of HP

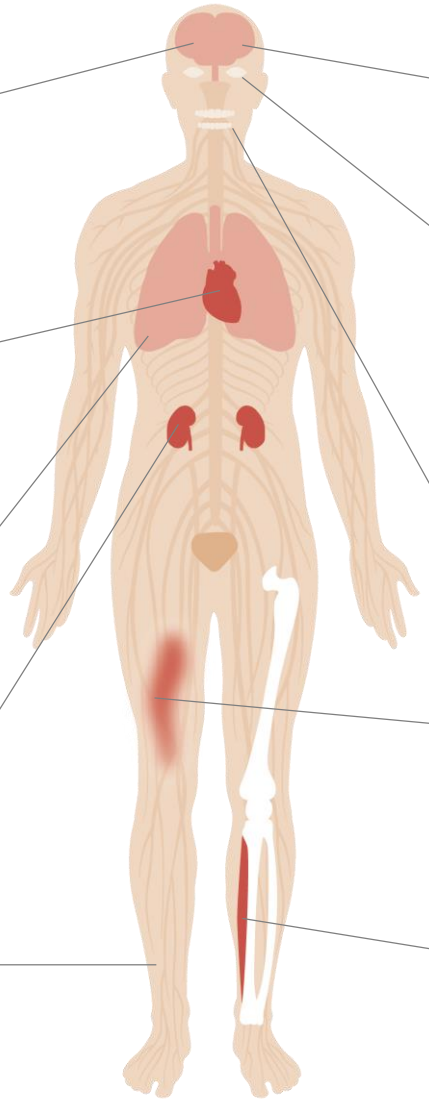
**Central nervous system**
- Seizures
- Calcifications
- Parkinsonism or dystonia

**Cardiovascular system**
- Cardiac arrhythmias
- Hypocalcemia-associated dilated cardiomyopathy

**Respiratory system**
- Laryngospasm

**Renal system**
- Nephrocalcinosis*
- Kidney stones*
- Chronic kidney disease*

**Peripheral nervous system**
- Paresthesia
- Muscle cramps
- Tetany



**Neuropsychiatric system**
- Anxiety and depression

**Ophthalmological system**
- Cataracts
- Papilloedema

**Dental system**
- Altered tooth morphology

**Dermatological system**
- Dry skin
- Onycholysis
- Coarse, thin hair
- Pustular psoriasis

**Musculoskeletal system**
- Myopathy
- Spondyloarthropathy

Adapted from Nature Reviews 2017, 3: 1-20

* These manifestations are mostly the result of treatment with calcium and activated vitamin D rather than of the disorder itself.

# Burden of Illness Despite Treatment: The Patients' View

*I am satisfied with the effectiveness of my medications to treat HP*

**40% strongly disagree**

*Despite taking my medications as prescribed, I still experience symptoms of HP*

**58% strongly agree**

*I am concerned with the long-term complications of my HP medications*

**75% strongly agree**

High burden of illness, despite current standard of care

**72%** experienced >10 symptoms in preceding 12 months; mean of 13 ± 9 hours/day

**85%** report inability to perform household activities

**20%** experienced a disease-related change in employment status



Sources: Endocrine Practice 2014, 20: 671-679; results of Paradox survey of patients (n=374)

# Treatment Contributes to Risk of Renal Disease

**4.8-fold**
*increased risk of renal stones*

**5.0-fold**
*increased risk of renal insufficiency*

**4.3-fold**
*increased risk of renal disease*

Vitamin D & calcium treatment associated with hypercalciuria

**31%** had renal calcifications (renal stones or nephrocalcinosis)

**41%** had chronic kidney disease stage 3 or worse (renal insufficiency)



Sources: J Bone Miner Res 2013, 28: 2277-2285; J Clin Endocrinol Metab 2012, 97(12): 4507-4514

# HP Treatment Strategies Are Evolving

- Conventional treatment by calcium and vitamin D can lead to:[1,2]
  - Hypocalcemia, hypercalcemia and hypercalciuria (short-term)
  - Impaired renal function and extra skeletal calcifications (long-term)
- Once-daily Natpara® /Natpar® has been approved in the U.S. and Europe as an adjunct to calcium and vitamin D
  - Does not fully address all aspects of the disease, including no benefit on clinical episodes of hypocalcemia or hypercalcemia, or effect on 24-hour urine calcium excretion[3]

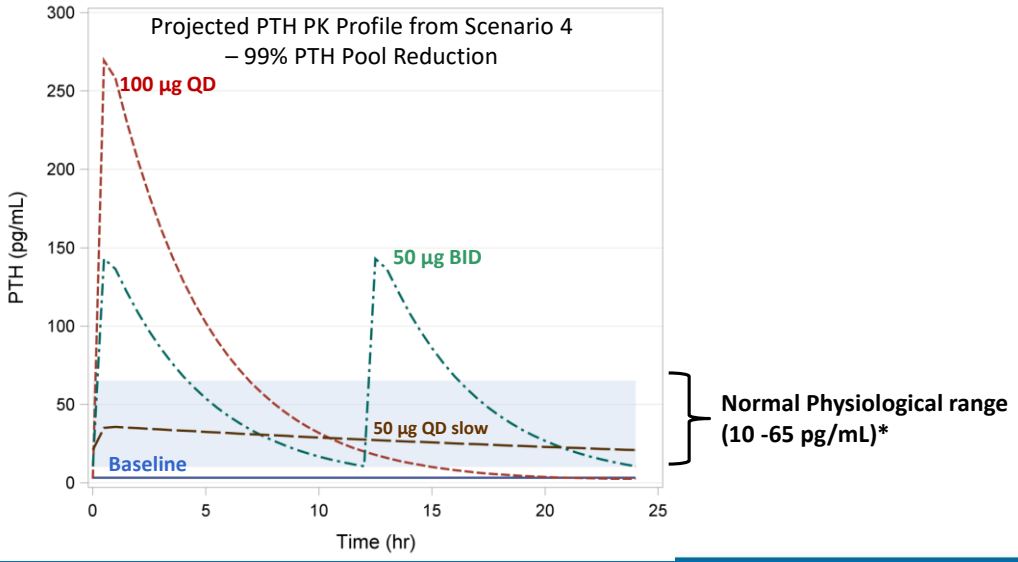
TransCon PTH is designed to address all aspects of the disease by restoring physiological levels of PTH throughout the day

[1] Front. Endocrinol. 2017, 7: 172
[2] Nature Reviews 2017, 3: 1-20
[3] Natpara/Natpar label

# FDA Perspective on Optimal PTH PK Profile[1]

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




20

- Natpara QD provides dose-dependent increases in serum calcium for ~24 hours
- Natpara QD effect on urinary calcium excretion is short-lived (10-12 hours) as kidney reabsorption of calcium follows PK profile



[1] FDA presentation: Natpara Advisory Committee, September 12, 2014



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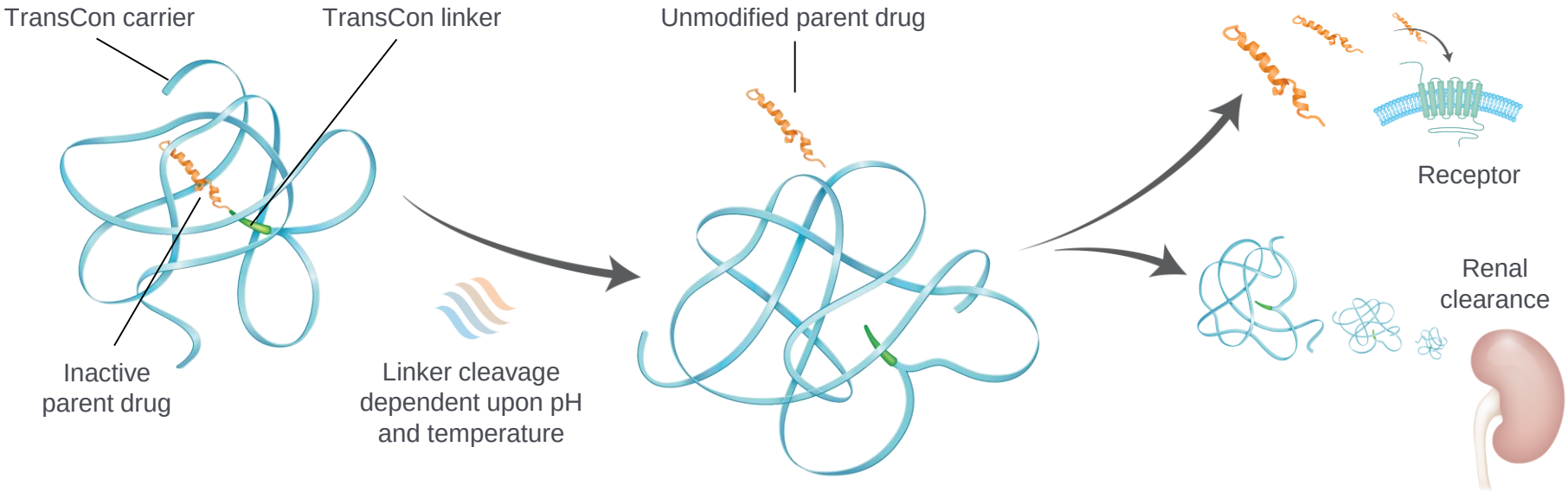
# Continuous PTH Infusion Led to Improved Outcomes

| Desired Treatment Outcomes in HP | Natpara Once-daily[1, 2] | PTH (1-34) Infusion[3-9] |
|---|---|---|
| Increase serum calcium | ✓ | ✓ |
| Reduce pill burden | ✓ | ✓ |
| Normalize urinary calcium excretion | X | ✓ |
| Reduce clinical hypercalcemia | X | ✓ |
| Reduce clinical hypocalcemia | X | ✓ |
| Normalize serum phosphate | ✓ (high-normal range) | ✓ |
| Normalize bone turnover | X (cortical bone loss) | ✓ |

NIH clinical trials demonstrated superiority of continuous infusion > twice-daily injections > once-daily injections

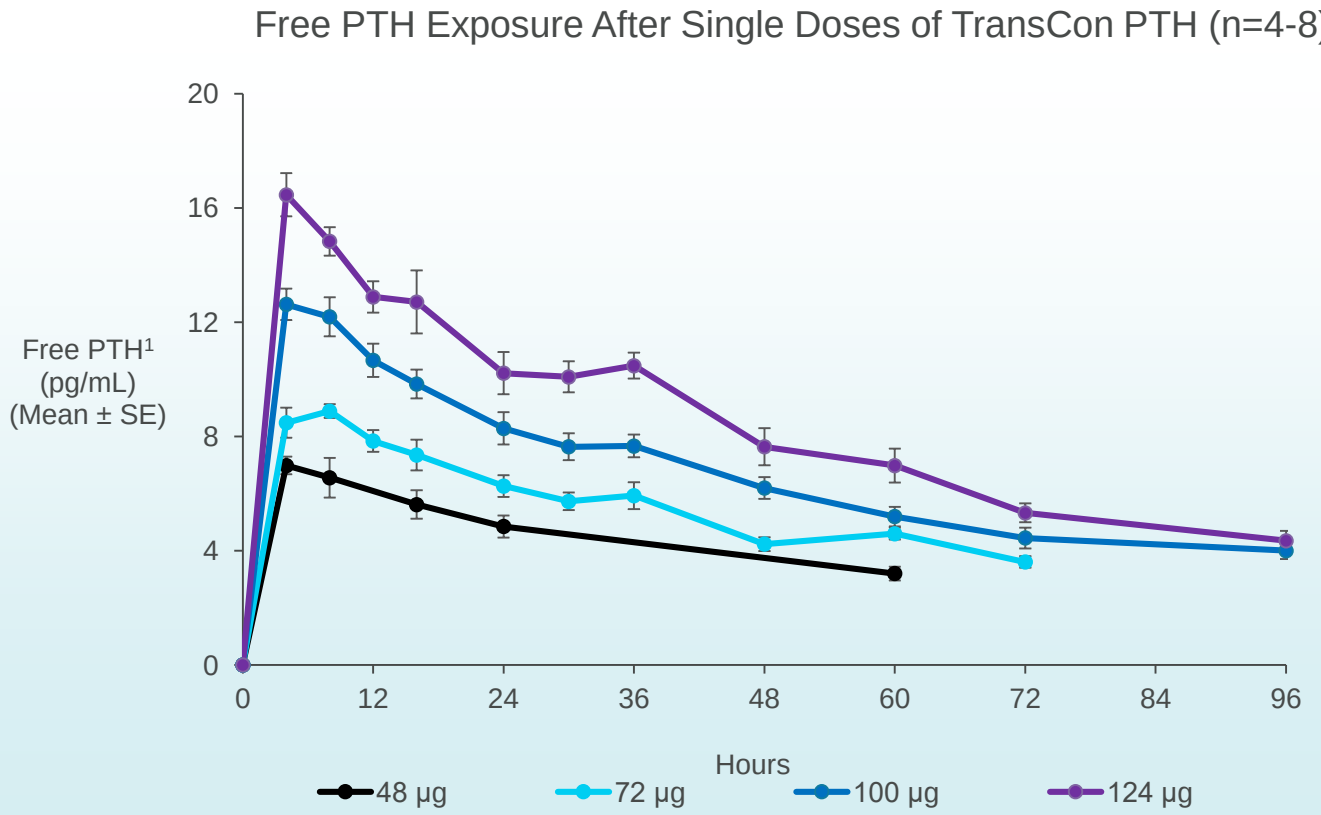

[1] Natpara Product Label
[2] J Clin Endocrinol Metab 2016, 101(7): 2742-2750
[3] JAMA 1996, 276(8): 631-636
[4] J Clin Endocrinol Metab 1998, 83(10): 3480-3486
[5] J Clin Endocrinol Metab 2003, 88(9): 4214-4220
[6] J Clin Endocrinol Metab 2008, 93(9): 3389-3395
[7] J Clin Endocrinol Metab 2011, 96(11): 3308-3312
[8] J Clin Endocrinol Metab 2012, 97(2): 391–399
[9] 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

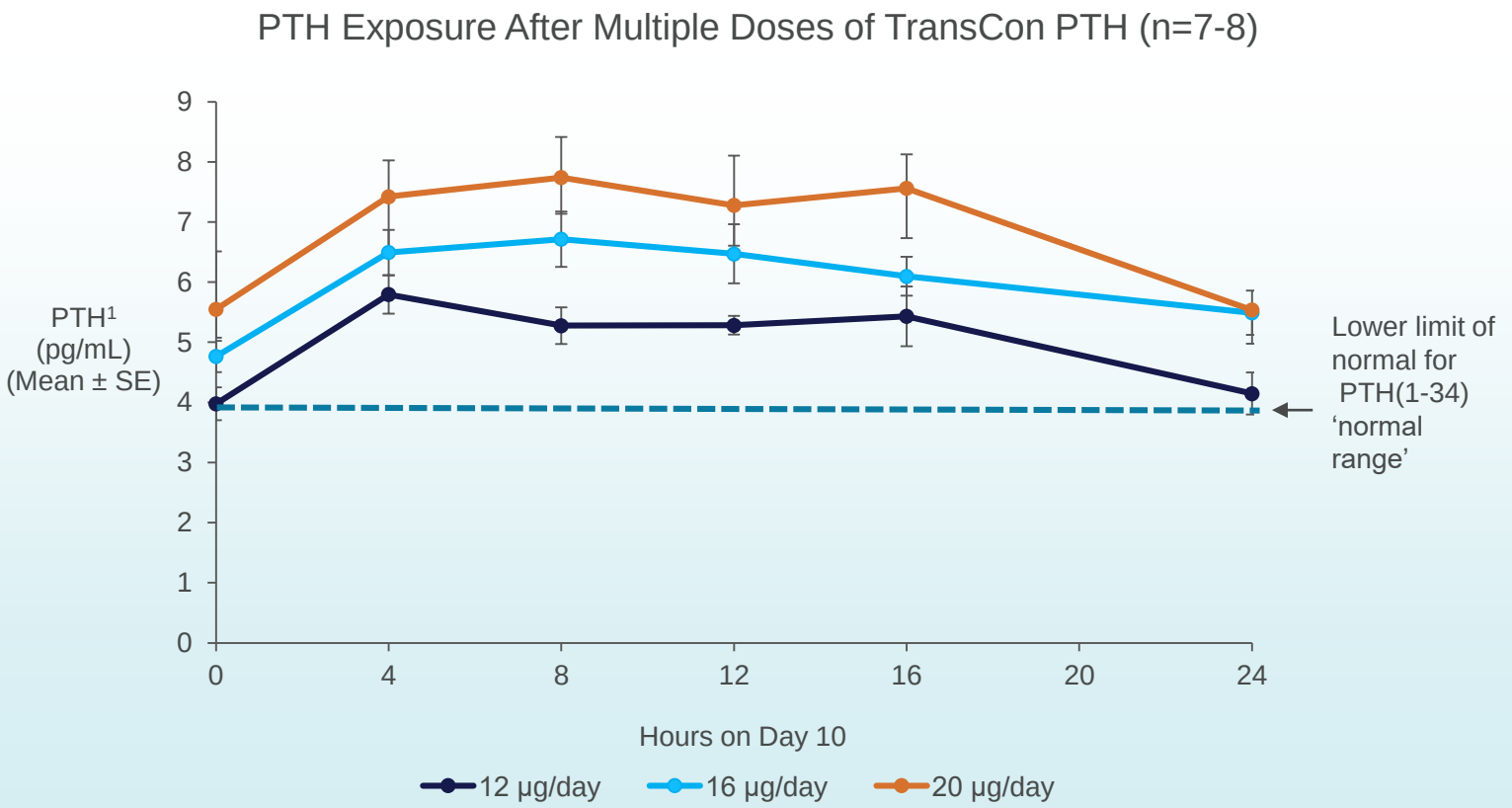
# Single Dose PK Data Support Infusion-Like Profile with Daily Administration




TransCon PTH phase 1 data reproduced PK profile from preclinical studies and showed $t_{1/2}$ of ~60 hours (versus Natpara $t_{1/2}$ ~3 hours)

[1] PTH measured as free PTH(1-34) and PTH(1-33)
Preliminary analyses from phase 1 trial.

# PK Data Support Infusion-like Profile over 24 Hours

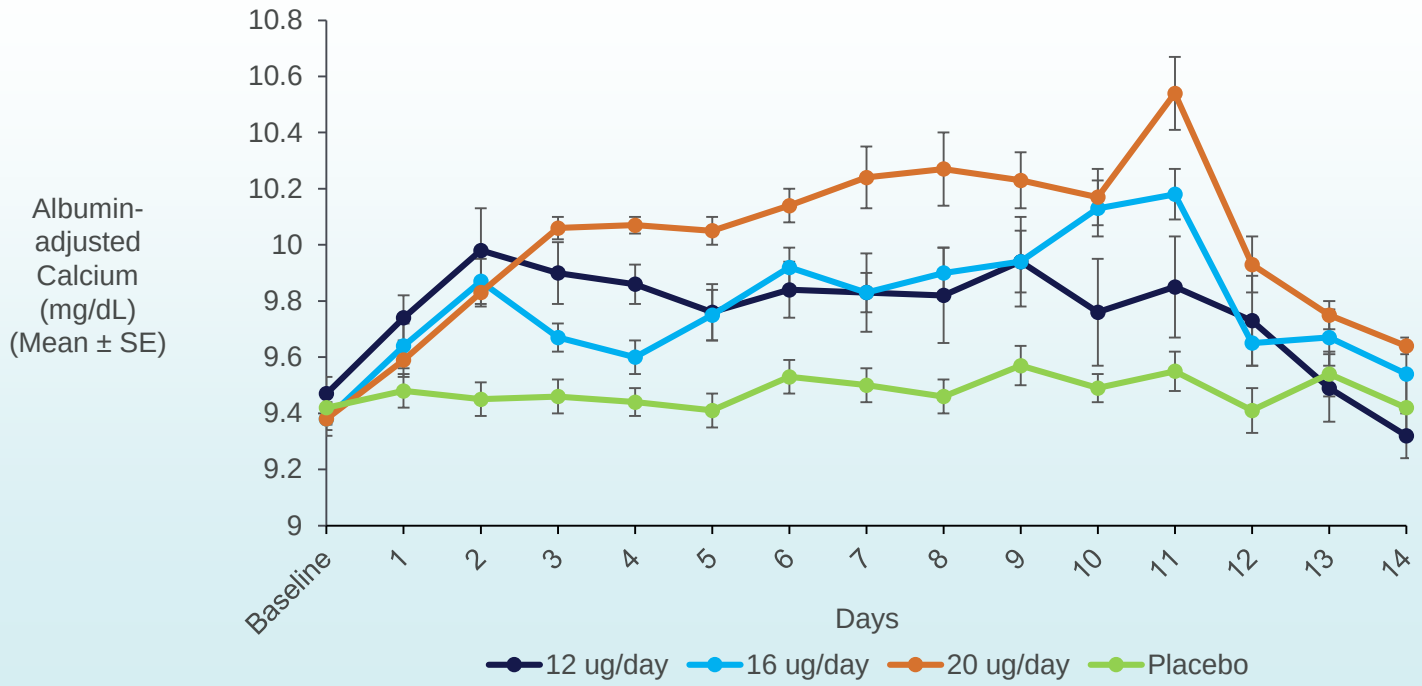



TransCon PTH daily dosing for 10 days provided a flat infusion-like profile with low PTH peak-to-trough ratio at day 10

[1] PTH measured as free PTH(1-34) and PTH(1-33)
Preliminary analyses from phase 1 trial.

# Multiple Doses Provided Dose-Dependent Increase of Serum Calcium

Change in Albumin-adjusted Serum Calcium over 10 Days of TransCon PTH (n=8/group)

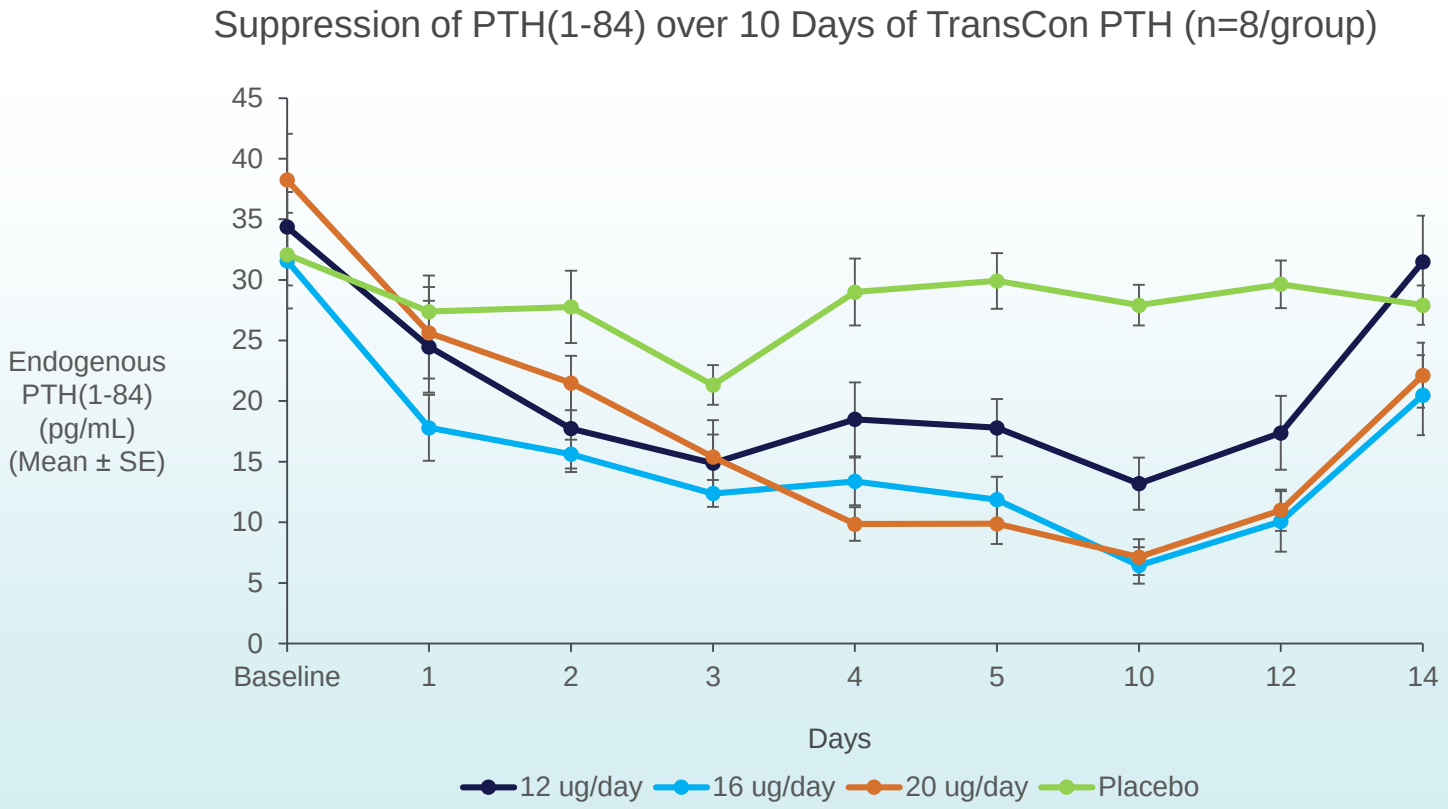



TransCon PTH daily dosing for 10 days provided dose-dependent increase of serum calcium



Preliminary analyses from phase 1 trial.

# Multiple Doses Provided Dose-Dependent Suppression of Endogenous PTH(1-84)



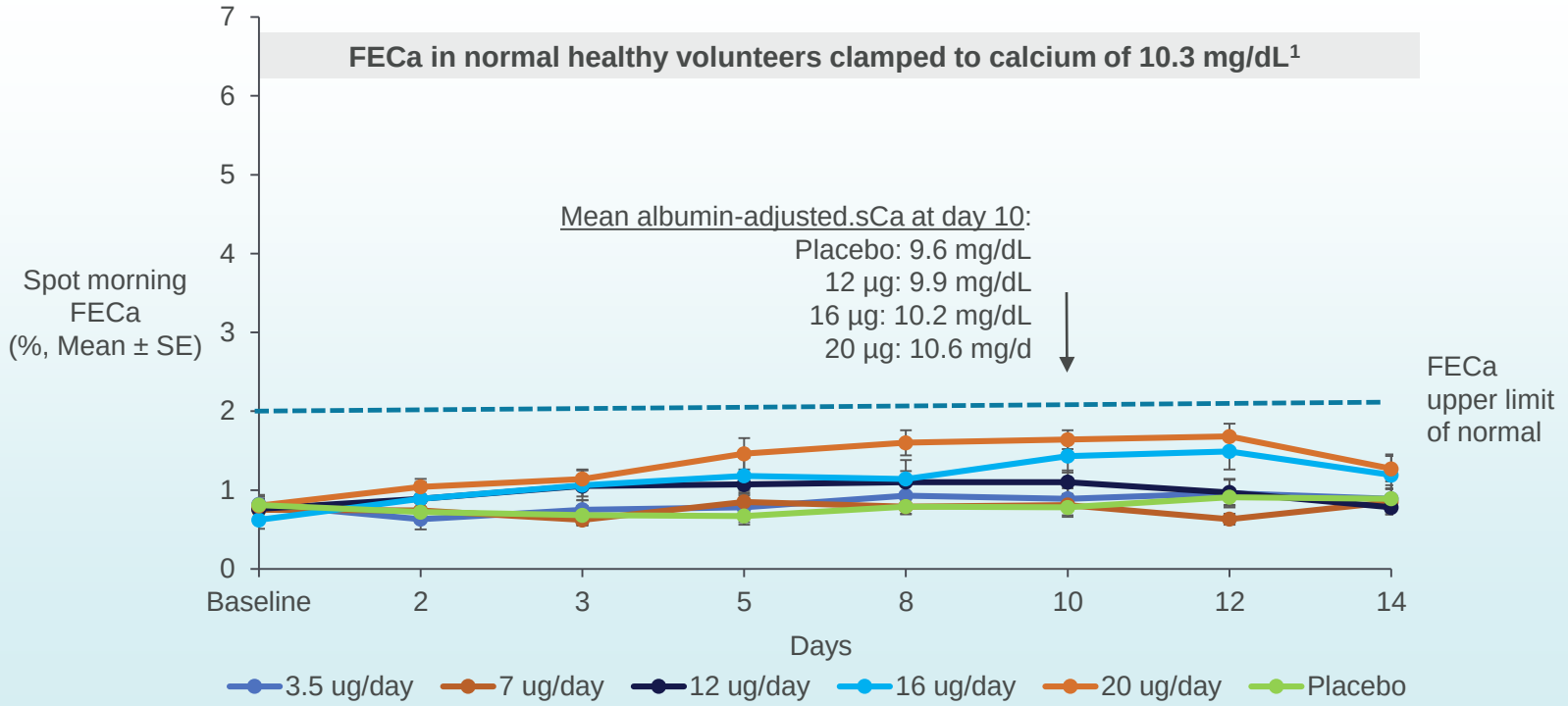

TransCon PTH daily dosing for 10 days provided dose-dependent down regulation of endogenous PTH(1-84)



Preliminary analyses from phase 1 trial.

# Control of Urinary Calcium with Multiple Doses

Spot FECa with daily doses of TransCon PTH (n=8/group) for 10 days



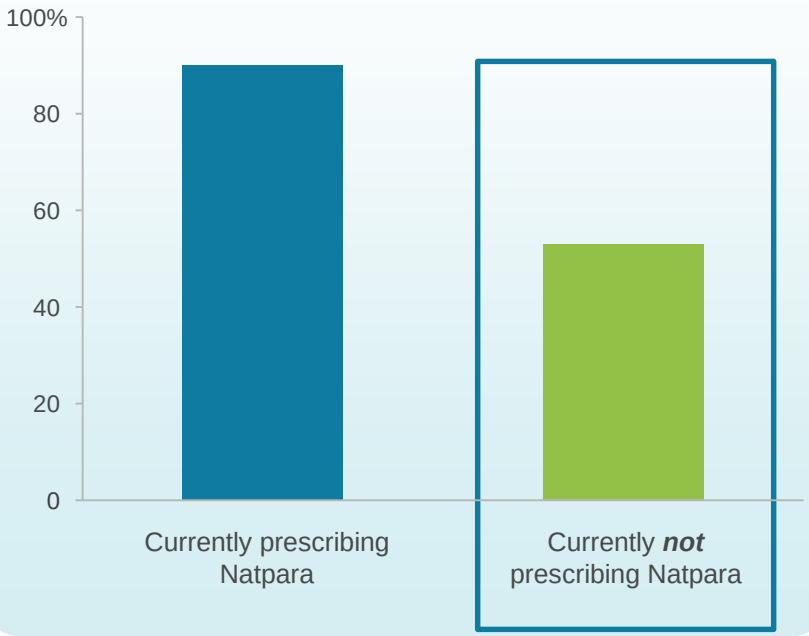

Despite serum Ca at 11 mg/dL, fractional calcium excretion remained normal and below 6.5% range reported for healthy volunteers clamped to serum Ca of 10.3 mg/dL[2], reflecting potent renal Ca reabsorption

[1] J Bone Miner Res 2011, 26(9): 2287–2297
[2] J Clin Endocrinol Metab 2001, 86(4): 1525-1531
Preliminary analyses from phase 1 trial.

# Market Research Validates Unmet Medical Need for TransCon PTH

- Market research with 108 U.S. endocrinologists treating HP[1]
  - Variety of clinical settings, geographies, patient volumes, disease severity, and short-acting PTH use
- Endocrinologists' views on current short-acting PTH:
  - Reduces hypocalcemia, improves quality of life, reduces pill burden
  - Remaining unmet medical needs:
    - Providing true replacement therapy
    - Reducing hypercalciuria

## Physicians Likely to Prescribe TransCon PTH[2] (N=108)




**Confirms TransCon PTH target product profile as a true replacement therapy and reinforces significant unmet need**

[1] Ascendis Pharma 2018 HP Survey; interviews conducted in Q2 2018; data on file
[2] Respondents who selected 5-7 on 1-7 scale considered "likely to prescribe" TransCon PTH

# TransCon PTH: Highlights

- Phase 1 data support TransCon PTH as a true replacement therapy for HP
- Phase 2 trial initiated in adult HP subjects
  - Randomized placebo-controlled study for approximately four weeks with fixed TransCon PTH doses and titration regimen for complete withdrawal of SoC (i.e., active vitamin D and calcium supplements)
  - Validation of disease-specific patient-reported outcomes for use in phase 3 trial
  - Introduction of ready-to-use prefilled pen device in the phase 2 trial
  - Subjects from phase 2 trial expected to enter into a long-term extension trial
- Phase 2 top-line data expected Q4 2019
- Global regulatory discussions to incorporate Asian territories into phase 3 trial
- Multiple patent concepts provide potential protection into 2037

# TransCon CNP:
## **Once-Weekly CNP for Achondroplasia**

# Achondroplasia – Not Only a Skeletal Disease

**Autosomal dominant genetic disorder**

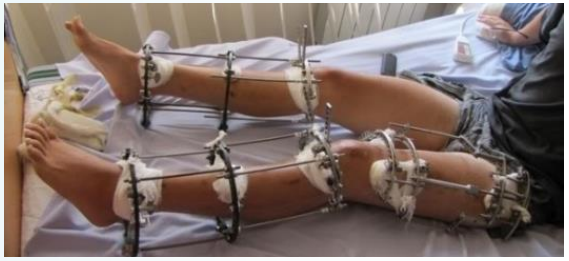
- Most common form of human dwarfism
- Approximately 250,000 patients worldwide[1]
- 80% born to average-sized parents

**Patients suffer numerous comorbidities**

- Back/spine/cord compression
- Cardiovascular complications
- Dental complications
- Ear infections/sleep apnea
- Obesity
- Bowed legs

**No FDA-approved therapy**

- Only option to improve height is surgical limb lengthening





[1] Lancet 2007, 370: 162-172



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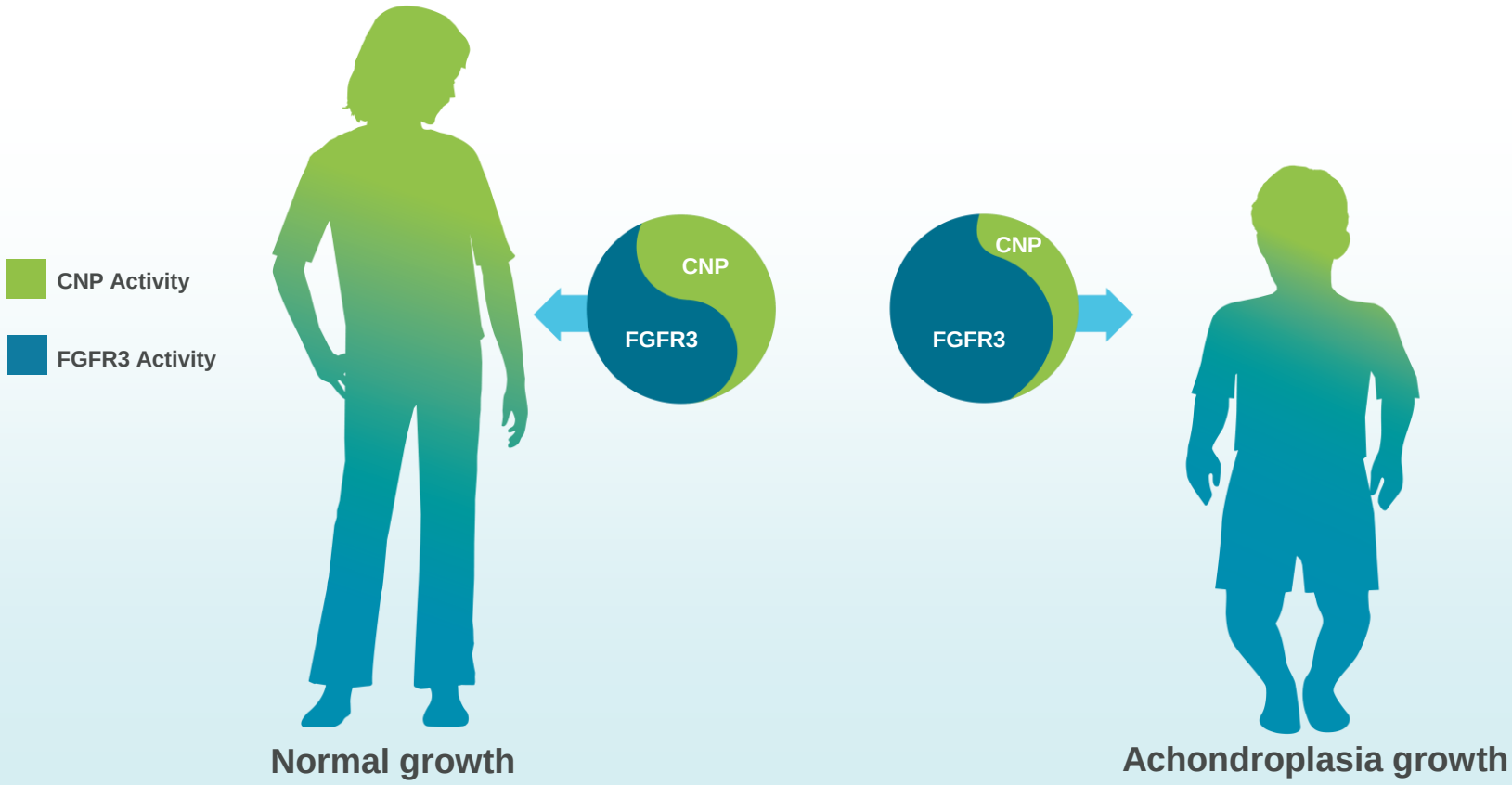
# Balanced Growth Depends on Balanced Pathways

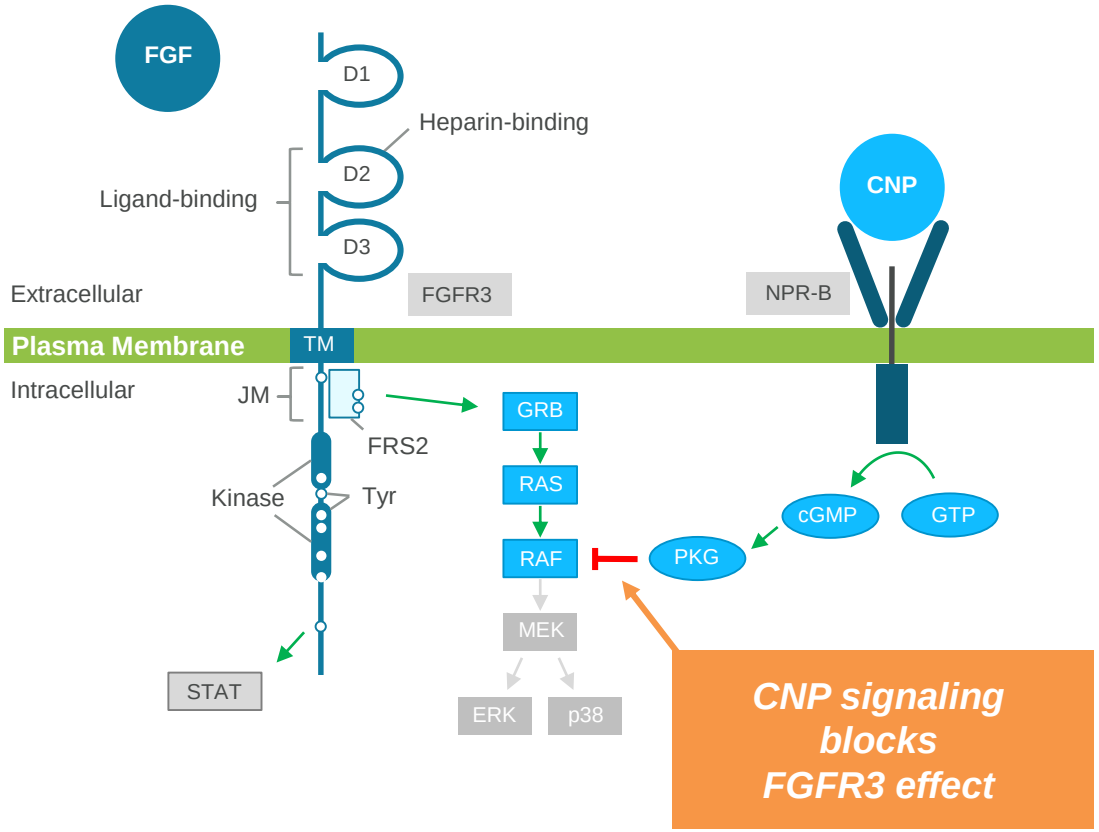



TransCon CNP is designed to provide continuous exposure to CNP to optimize efficacy with a well-tolerated and convenient once-weekly dose

# Achondroplasia Signaling Defect is Well Understood

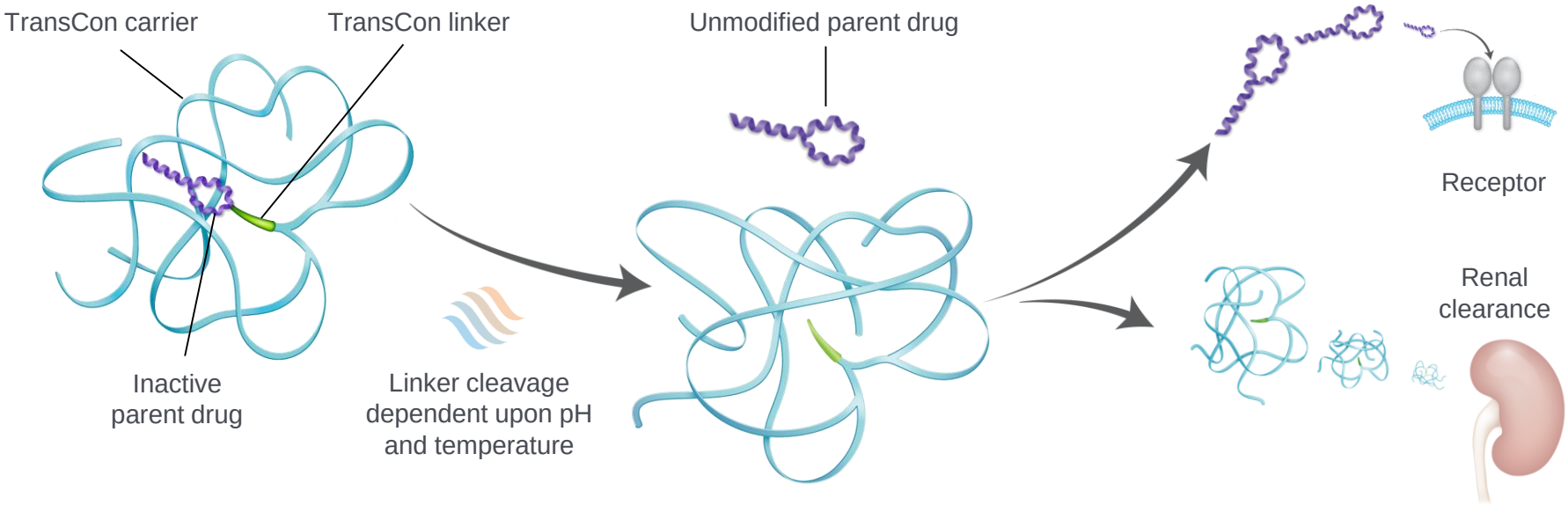
- **FGFR3 negatively regulates chondrocyte proliferation and differentiation and hence bone growth**
- **Achondroplasia results from a mutation in FGFR3 which leaves the receptor constitutively activated**
- **CNP inhibits the FGFR3 pathway and thereby promotes proliferation and differentiation of chondrocytes to restore bone growth**

## FGFR3 Signaling Pathway[1]



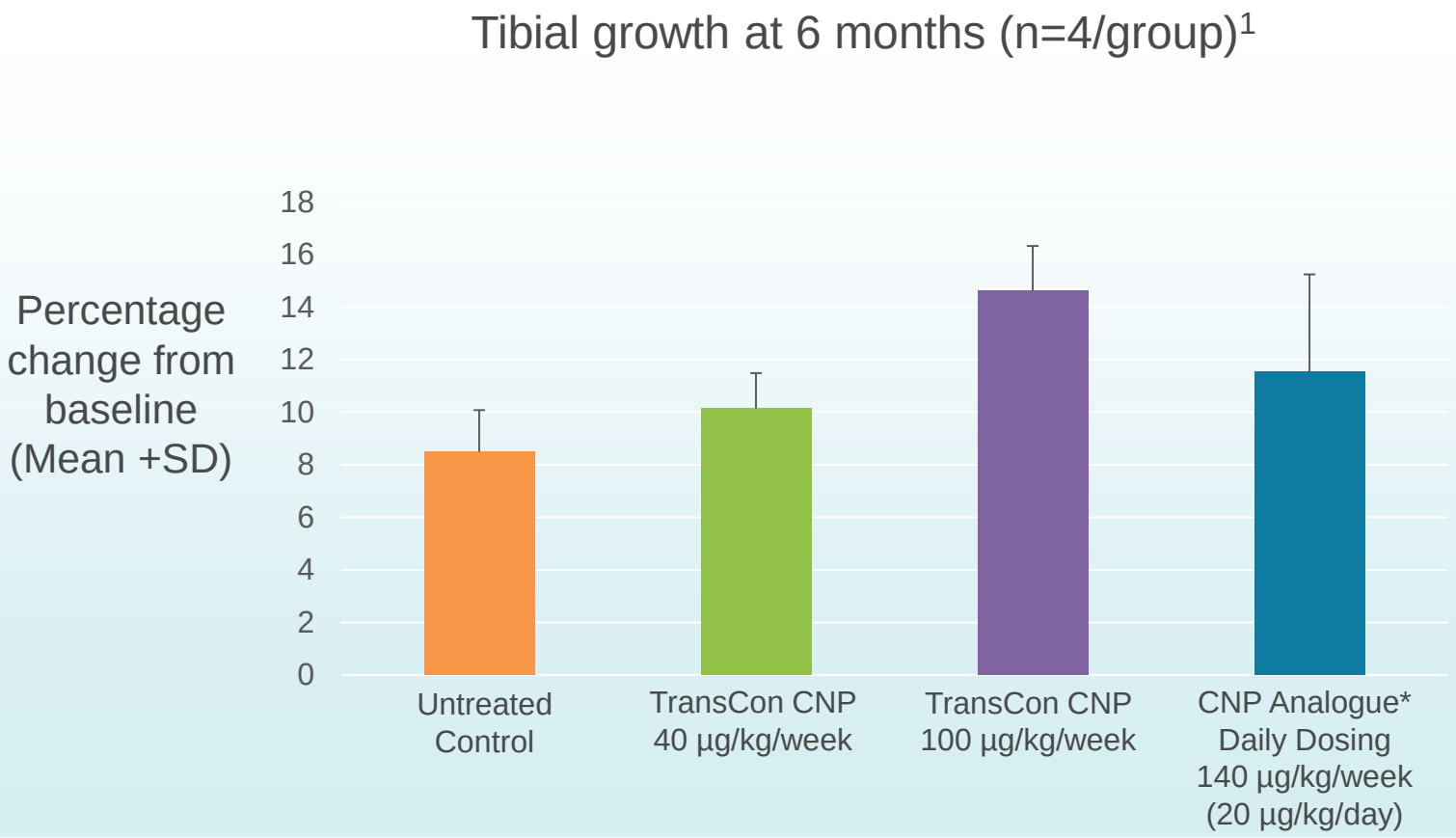

[1]Adapted from Current Opin Pediatrics 2010; 22:516-523

# TransCon CNP Design




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

# Juvenile Healthy Monkey Growth Study



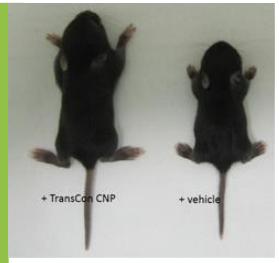

- Demonstrated dose-proportional tibial linear growth; ulnar growth consistent
- Compared to untreated control, growth increased >70% with highest TransCon CNP dose vs. 35% with CNP analogue* at a higher weekly dose

[1] Poster presented at ENDO 2017 and company data
* Refers to a synthesized molecule with a half-life of ~20 mins prepared by Ascendis Pharma

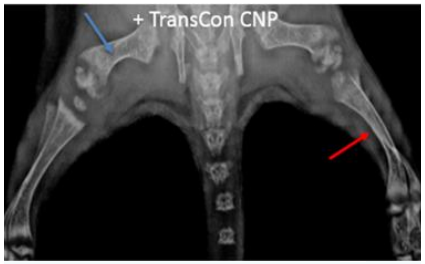
# TransCon CNP in Achondroplasia Disease Model ($Fgfr3^{Y367C/+}$)[1]

## Linear and Skeletal Growth in Achondroplasia Mice

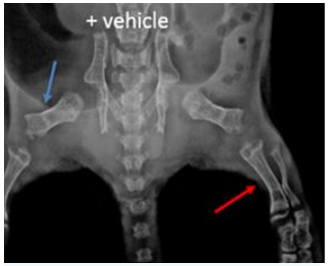
TransCon CNP reversed the phenotype, restoring growth




TransCon CNP/ Vehicle



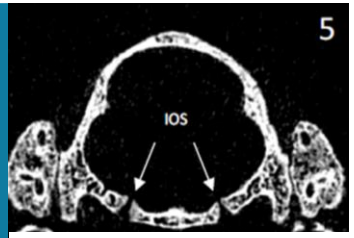

TransCon CNP

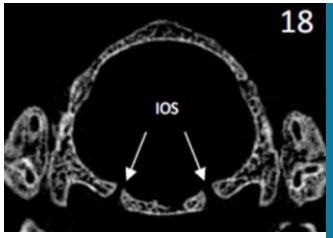


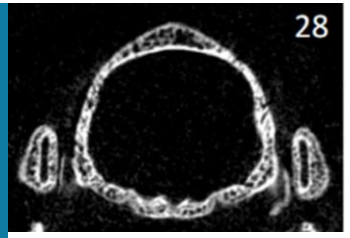

Vehicle

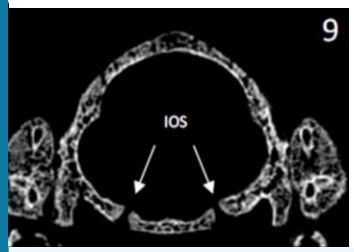
## Preventing Premature Fusion of Synchondroses of Foramen Magnum

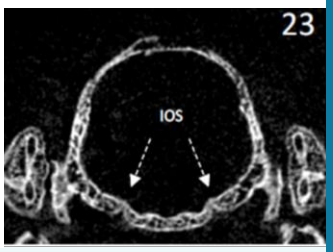
TransCon CNP may ameliorate most disabling achondroplasia traits, including stenosis of the foramen magnum

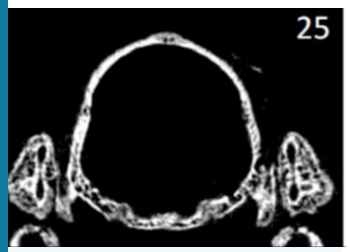



TransCon CNP

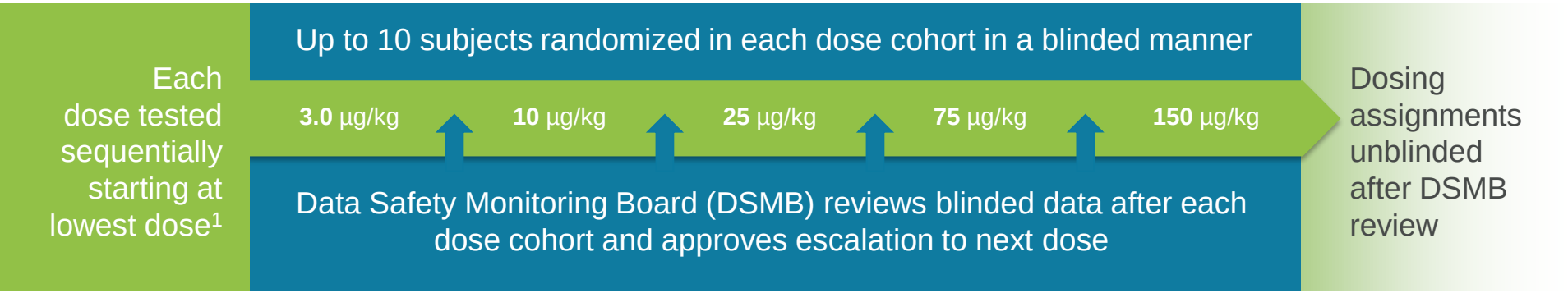
Vehicle

# TransCon CNP: Phase 1 Trial

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Dose Escalation Trial Evaluating Safety, Tolerability and Pharmacokinetics of Subcutaneous Single Doses of TransCon CNP in Healthy Adult Male Subjects

# Phase 1 Trial Design

**45 healthy adult male subjects enrolled at two study centers in Australia**
**TransCon CNP vs. placebo (4:1 randomization)**




## Primary Endpoint

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

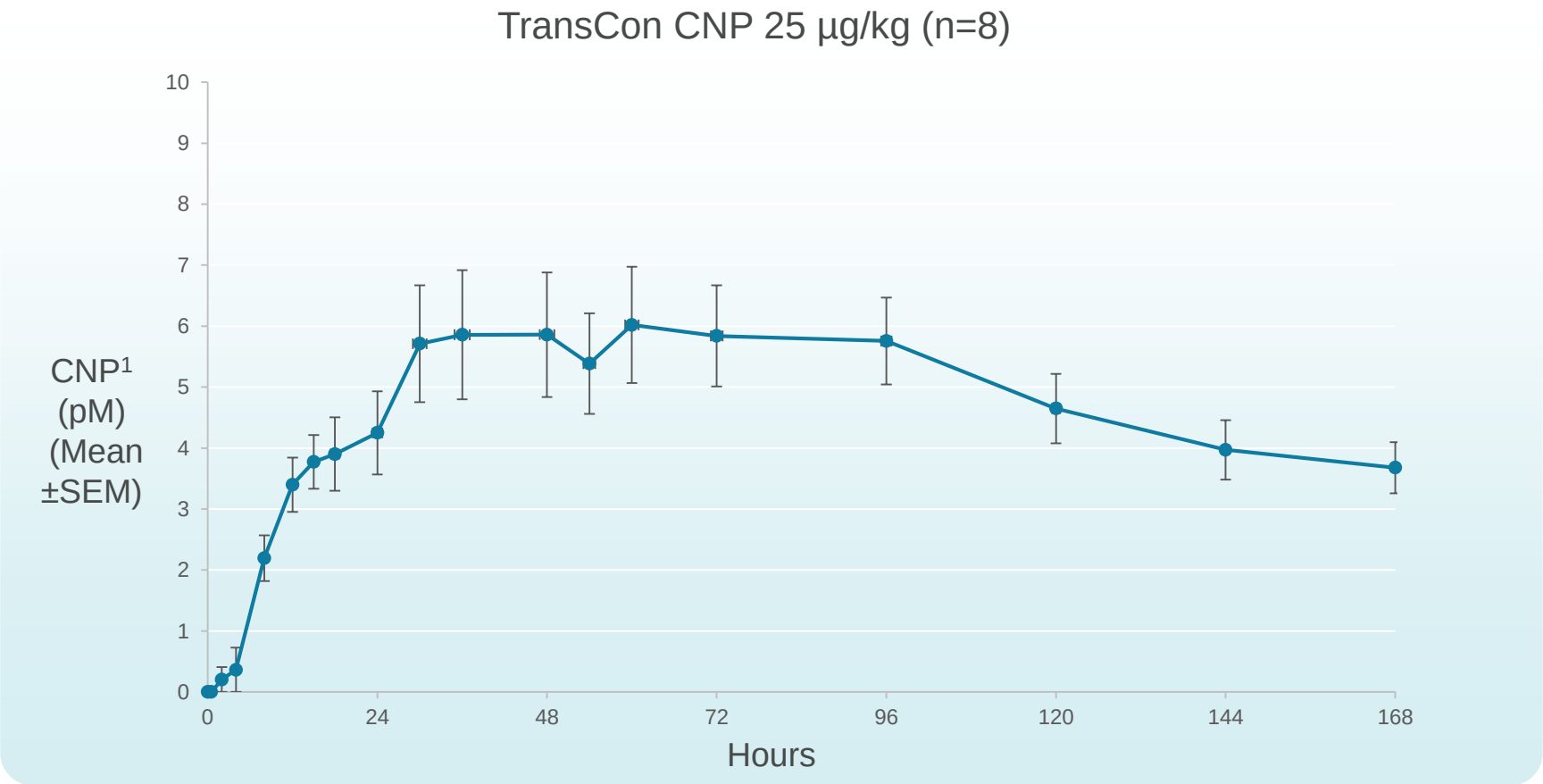
## Secondary/Exploratory Endpoints

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



[1] 300 µg CNP/kg cohort was deemed not clinically relevant based on emerging pharmacokinetic data from previous cohorts and therefore not dosed.

# Sustained CNP Exposure Over One Week



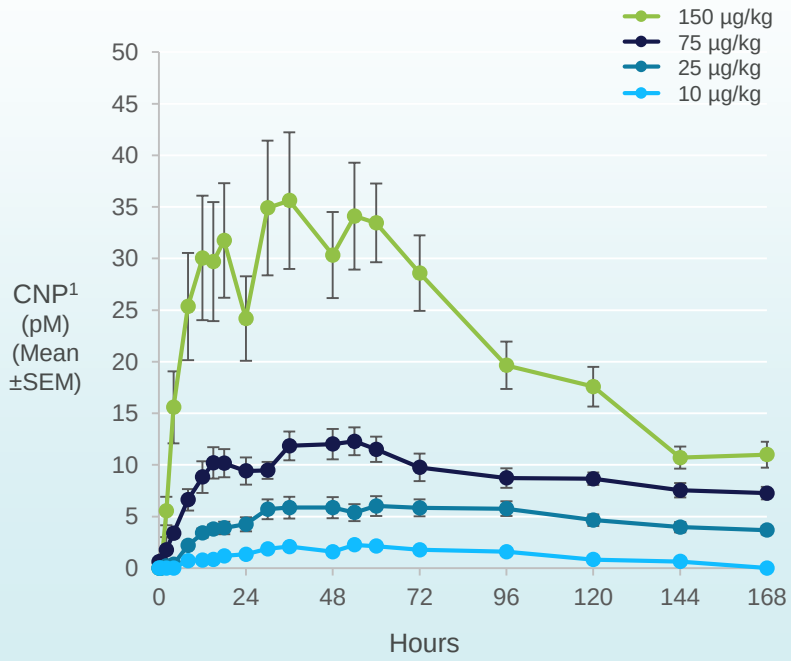

A single dose of TransCon CNP provided continuous CNP exposure over the entire week with low inter-subject variability

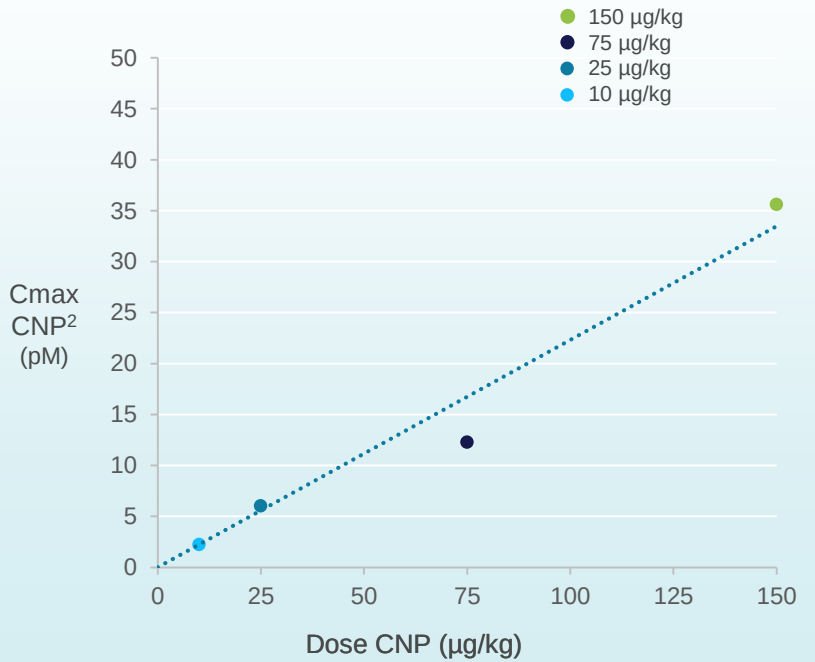
[1] CNP measured as CNP-38

Preliminary analyses from phase 1 trial.

# Dose-related Increase in CNP Exposure

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



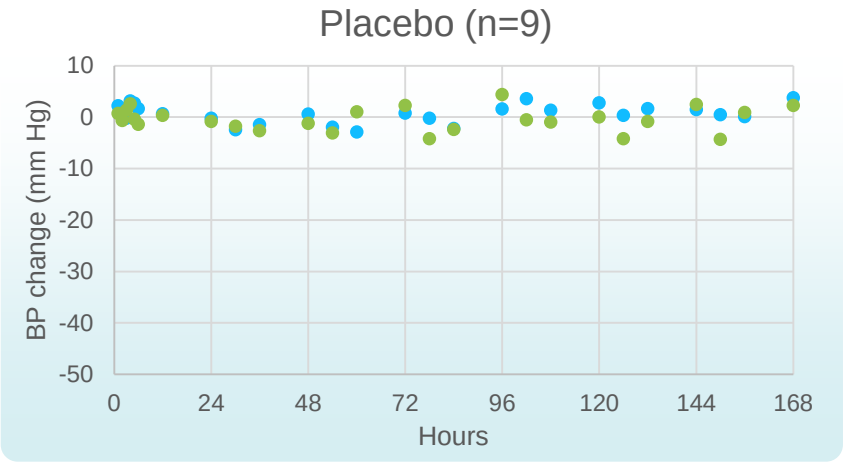



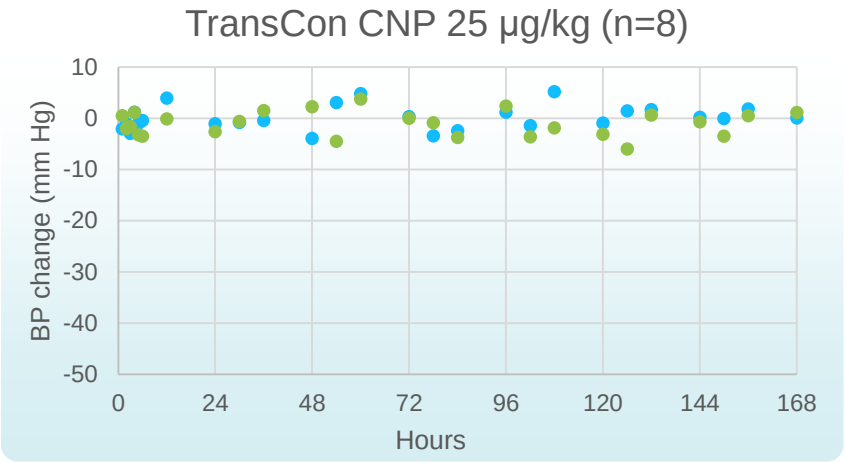

- Dose-related increase in CNP exposure suggests ability to titrate dosing
- Phase 1 showed effective CNP $t_{1/2}$ of ~ 90 hours (native CNP $t_{1/2}$ of 2-3 minutes)

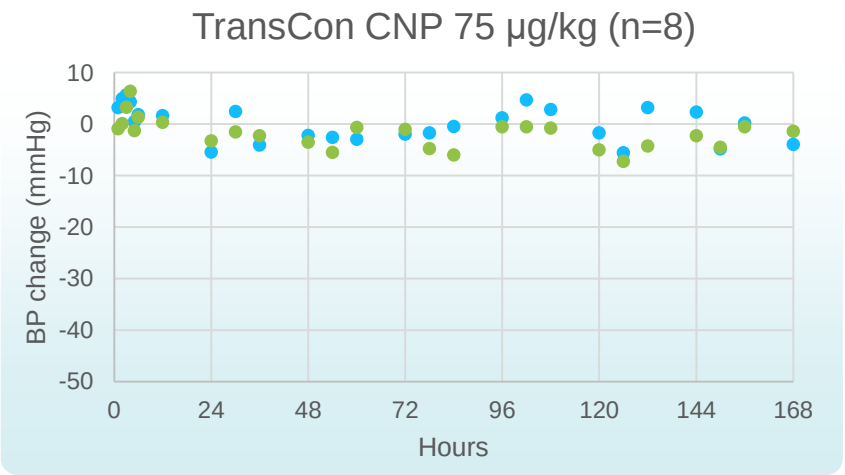
[1] CNP measured as CNP-38

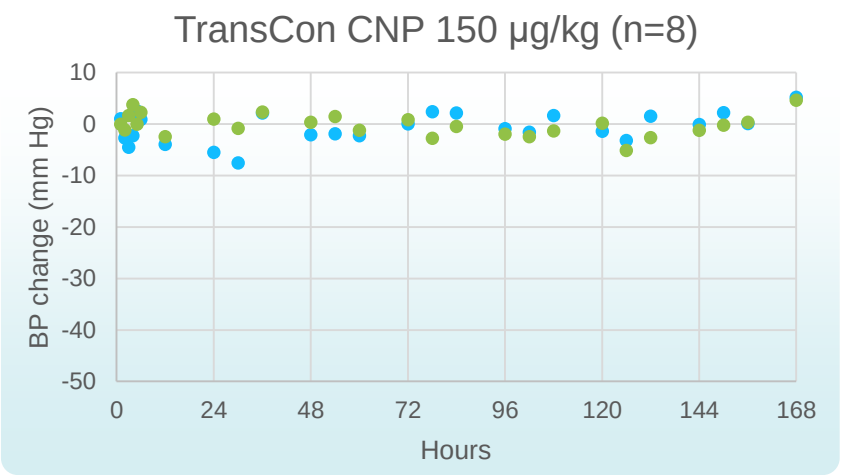
Preliminary analyses from phase 1 trial.

# Mean Resting Blood Pressure Unchanged from Predose[1]



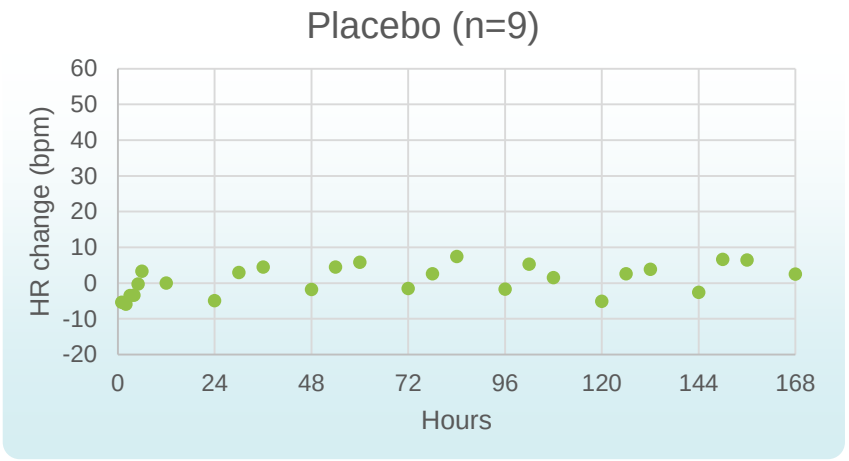



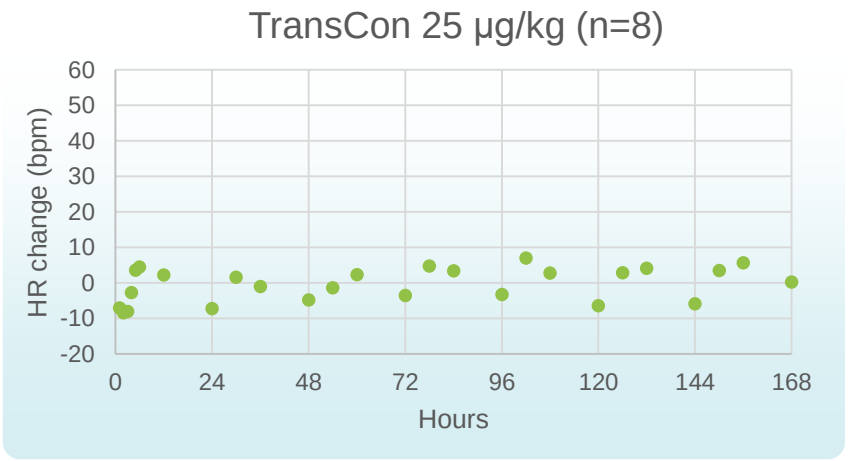


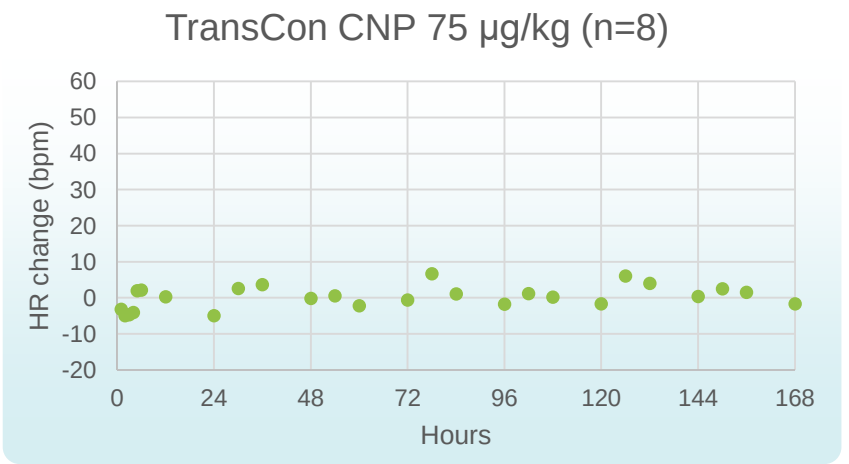


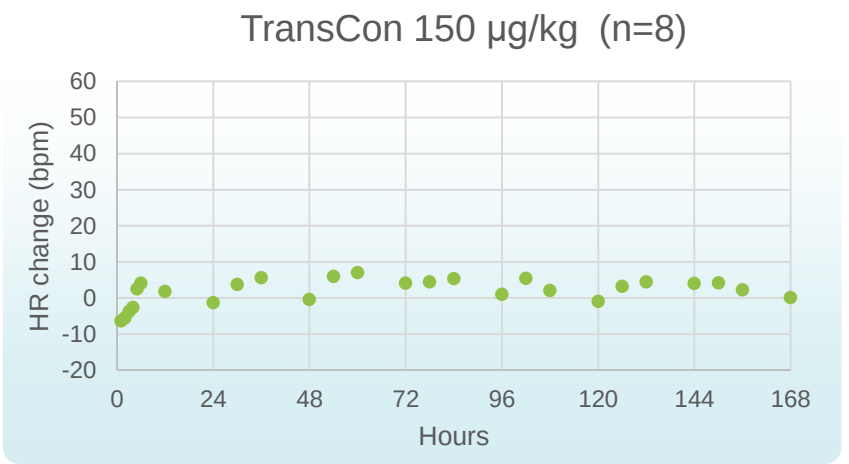
[1] Preliminary data. 3.0 and 10 µg/kg dose levels are not represented. Data from these cohorts are consistent with placebo.

# Mean Resting Heart Rate Unchanged from Predose[1]




Change in heart rate



[1] Preliminary data. 3.0 and 10 µg/kg dose levels are not represented. Data from these cohorts are consistent with placebo.

# Well-tolerated Safety Profile

- No serious AEs were reported in the trial
- TransCon CNP was generally well tolerated at doses up to 150 µg/kg
- Mean resting blood pressure and heart rate were unchanged from predose 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; no reported injection AEs



Preliminary analyses from phase 1 trial.



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# TransCon CNP: Highlights

- TransCon CNP phase 1 data reproduced PK profile and cardiovascular safety from preclinical studies
- Provided continuous CNP exposure over seven days with a single subcutaneous administration, supporting once-weekly dosing
  - Continuous CNP exposure at target levels is important for balancing the CNP/FGFR3 pathways and normalizing growth
- Generally well tolerated across all cohorts
- Potential for a significant impact on patients' lives, not only affecting height but also addressing many comorbidities associated with achondroplasia
- Phase 2 initiation expected Q3 2019
- Multiple patent concepts provide potential protection into 2037

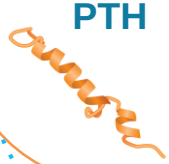
# Vision 3x3:
# **Strategic Roadmap to 2025**

# Vision 20/20: Established the Foundation for a Leading Rare Disease Company

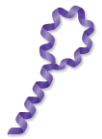
**Clinical validation of 3 product candidates in endocrinology rare disease**

**TransCon hGH**

**TransCon PTH**



**TransCon CNP**



- ✓ Advance our pipeline of three endocrinology rare disease product candidates towards approval
- ✓ Create a leading integrated commercial business primarily focused on the U.S. market with best-in-class products
- ✓ Identify a new rare disease therapeutic area with high-value product opportunities

# Vision 3x3: Strategic Roadmap to 2025

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

- Obtain regulatory approval for 3 Endocrinology Rare Disease products
  - TransCon hGH for pediatric growth hormone deficiency
  - TransCon PTH for adult hypoparathyroidism
  - TransCon CNP for achondroplasia
- Growth of Endocrinology Rare Disease pipeline through:
  - Label expansion programs with the goal of obtaining 9 indications in total
  - Global clinical reach direct or through partnerships
- Build an integrated commercial business for our Endocrinology Rare Disease franchise in North America and select European countries
  - Establish global commercial presence with partners outside our geographic areas
- Create 3 independent therapeutic areas each with a diversified pipeline built on TransCon technologies and our unique algorithm for product innovation
  - Established oncology as next independent therapeutic area

# Extending Global Footprint: VISEN Pharmaceuticals

- Develop and commercialize TransCon hGH, TransCon PTH and TransCon CNP in Greater China
  - Right of negotiation on certain other endocrinology product candidates in Greater China[1]
  - Led by Pony Lu, an experienced Takeda executive in charge of Greater China
- Overview
  - Vivo Capital and Sofinnova Ventures invested $40 million
  - Visen responsible for all development, manufacturing and commercialization costs in Greater China; Ascendis will be reimbursed for clinical trial materials and technical support
  - Strengthens Ascendis global development strategy, increasing potential reach of clinical trials for rare diseases into China
  - Potentially significant upside through 50% equity ownership
  - Governance established through ownership, shareholder protections, board membership, joint development committee and separate licensing and supply agreements

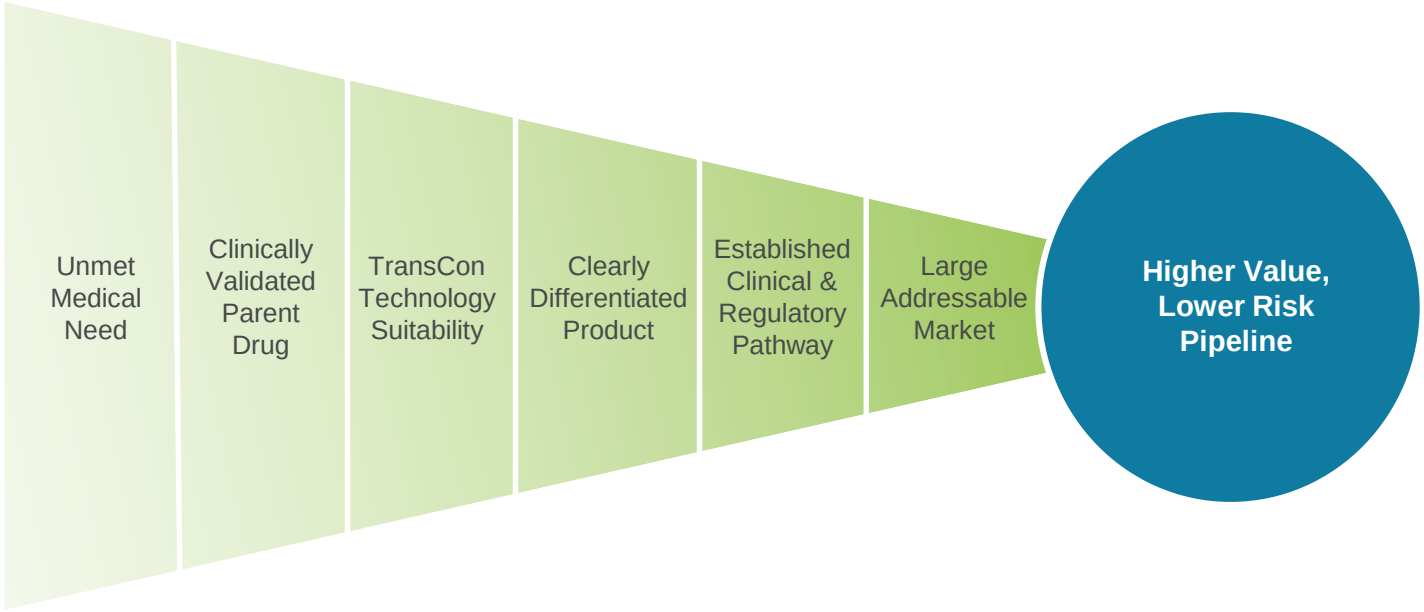
Partnership with experienced investors builds presence in second largest pharmaceutical market in the world and expands rare disease clinical programs



[1] "Greater China" means People's Republic of China, including Hong Kong, Macau and Taiwan.

# Why Oncology?

## Checks all the boxes of the Ascendis product innovation algorithm

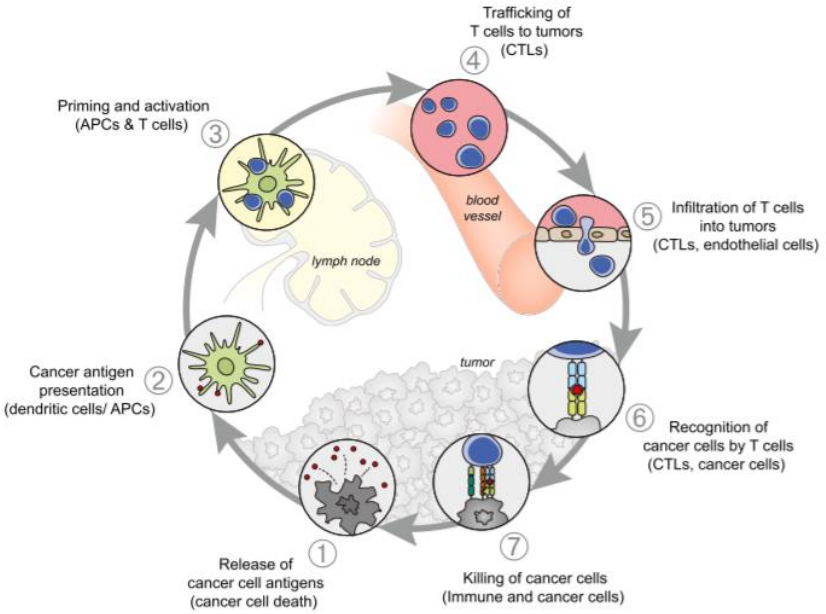



## Both TransCon technologies well suited for Oncology:

- Sustained Systemic Delivery:
  Designed to provide predictable continuous exposure to increase efficacy and reduce toxicity
- Sustained Localized Delivery:
  Designed to maximize intratumoral (IT) exposure while minimizing systemic toxicity

# Oncology Pipeline Strategy

- Impact all aspects of the Cancer Immunity Cycle
  - Stimulators of innate immunity
  - Stimulators of adaptive immunity
  - Modulators of tumor microenvironment

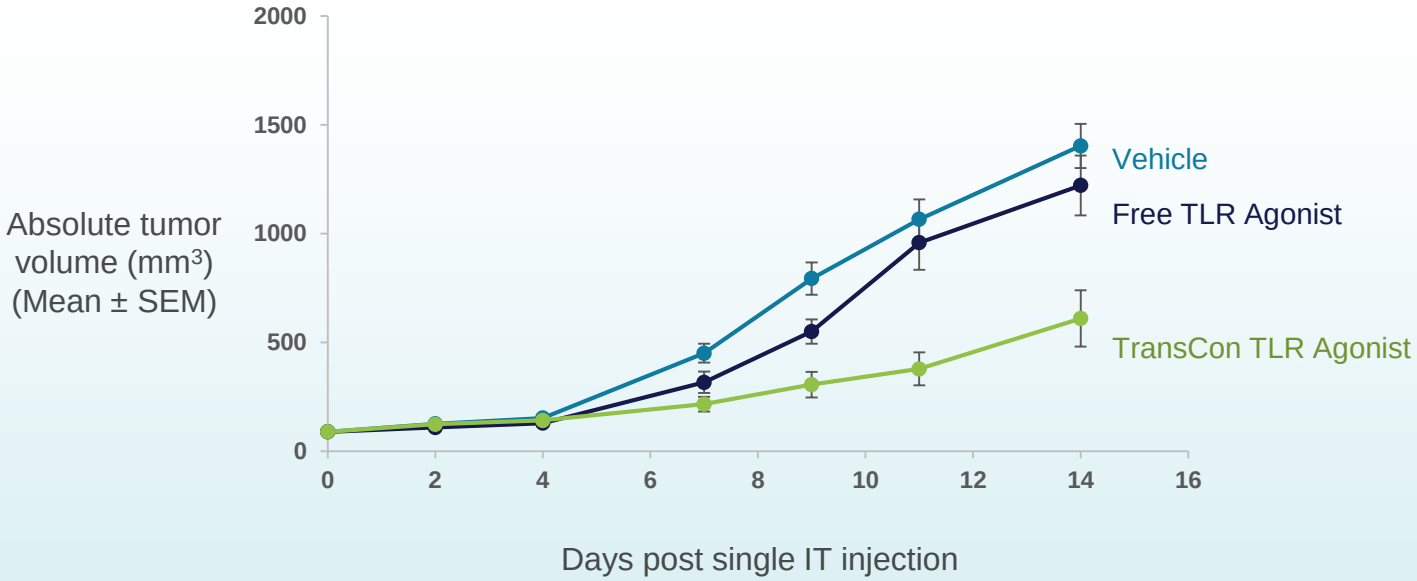



*From Chen & Mellman, Immunity, 2013*

Goal to create at least 3 best-in-class candidates from validated parent drugs – each addressing different aspects of the Cancer Immunity Cycle

# *In Vivo* Sustained Localized Delivery Proof-of-Concept

- Single IT injection of TransCon TLR Agonist demonstrated superiority to equal IT dose of free TLR Agonist in a syngeneic mouse colon-derived tumor model
  - TransCon TLR Agonist was well tolerated and had no effect on body weights




- Sustained localized IT delivery *in vivo* demonstrated potential best-in-class product profile and foundation to expand to other targets

# Selected 2019 Expected Milestones

**Q1 2019**

- ✓ TransCon hGH: heiGHt Trial top-line Phase 3 data
- ✓ TransCon PTH: Phase 2 trial initiation, including pen device

**Q2 2019**

- TransCon hGH: fliGHt Trial top-line Phase 3 data
- TransCon hGH: Introduction of auto-injector into enliGHten Trial
- Research Day: Unveiling oncology pipeline and near-term milestones

**Q3 2019**

- TransCon hGH: Long-term clinical database lock
- TransCon CNP: Phase 2 trial initiation

**Q4 2019**

- TransCon PTH: Phase 2 trial top-line data