Ascendis Pharma A/S

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, licensing or other arrangements, the scope, progress, results and costs of developing our product candidates or any other future product candidates, the potential market size and size of the potential patient populations for our product candidates, timing and likelihood of success, plans and objectives of management for future operations, the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates, 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, 2020 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, changed circumstances or otherwise after the date of this presentation.

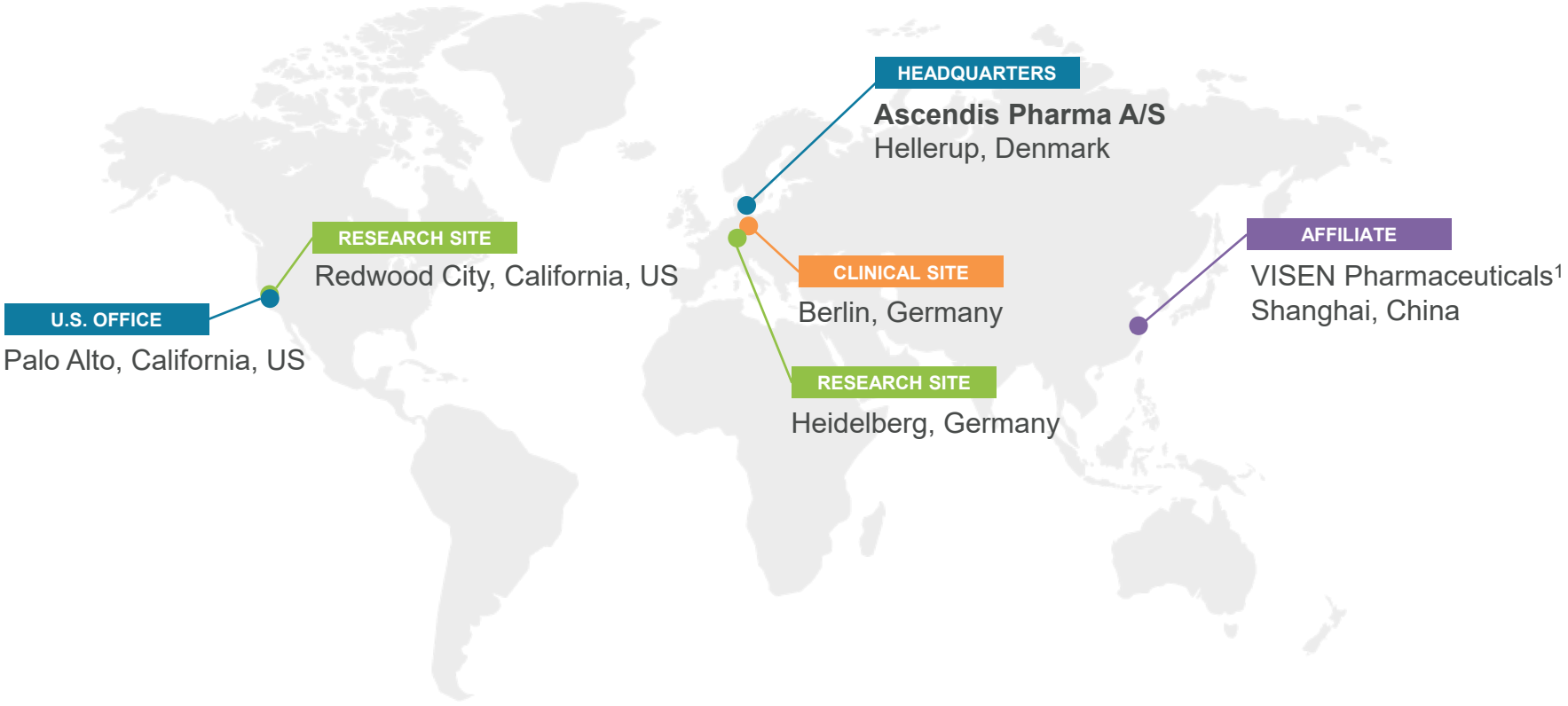
This presentation concerns product candidates that are or have been under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration, European Medicines Agency or other foreign regulatory authorities. These product candidates are currently limited 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
  - TransCon hGH for pediatric GH deficiency: BLA submitted Q2 (PDUFA June 25, 2021) and MAA submitted Q3
  - TransCon PTH for hypoparathyroidism: Long-term data from open-label extension portion of PaTH Forward Q3
  - TransCon CNP for achondroplasia: Phase 2 ACcomplisH dose escalation and initiate second trial in China[1] Q4
  - Build leading market positions for each product with commercial focus on maximizing global reach
  - Strategic investment in VISEN Pharmaceuticals for endocrinology rare disease products in China
- Oncology
  - First IND filing or similar expected for TransCon TLR7/8 Agonist in Q4
  - TransCon IL-2 β/γ IND filing or similar expected in 2021
- As of June 30, 2020, pro forma cash, cash equivalents and marketable securities of €1,052 million[2]

[1]Through VISEN Pharmaceuticals
[2]Includes net proceeds from July 2020 follow-on offering

Ascendis Pharma Global Presence



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

Vision 3x3: Building a Leading BioPharma Company

Our Goal is to Achieve Sustainable Growth through Multiple Approaches

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

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Diverse Pipeline of Independent Product Candidates

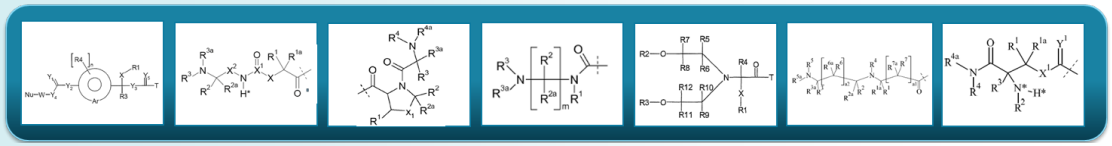
[1] Excludes rights granted to VISEN Pharmaceuticals in Greater China
[2] In phase 3 development for pediatric growth hormone deficiency in Greater China through strategic investment in VISEN Pharmaceuticals.
[3] U.S. PDUFA June 25, 2021.

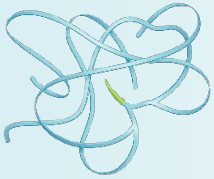
All product candidates are investigational. For investor communication only. Not for use in promotion or product commercialisation.

*Trans*ient *Con*jugation: A Powerful, Flexible Platform

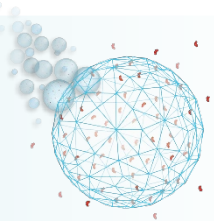
TransCon Prodrug: 3 components

- TransCon Linker
- TransCon Carrier
- Parent Drug





Soluble Carriers



Insoluble Carriers

Antibodies, Antibody Fragments, Proteins, Peptides and Small Molecules

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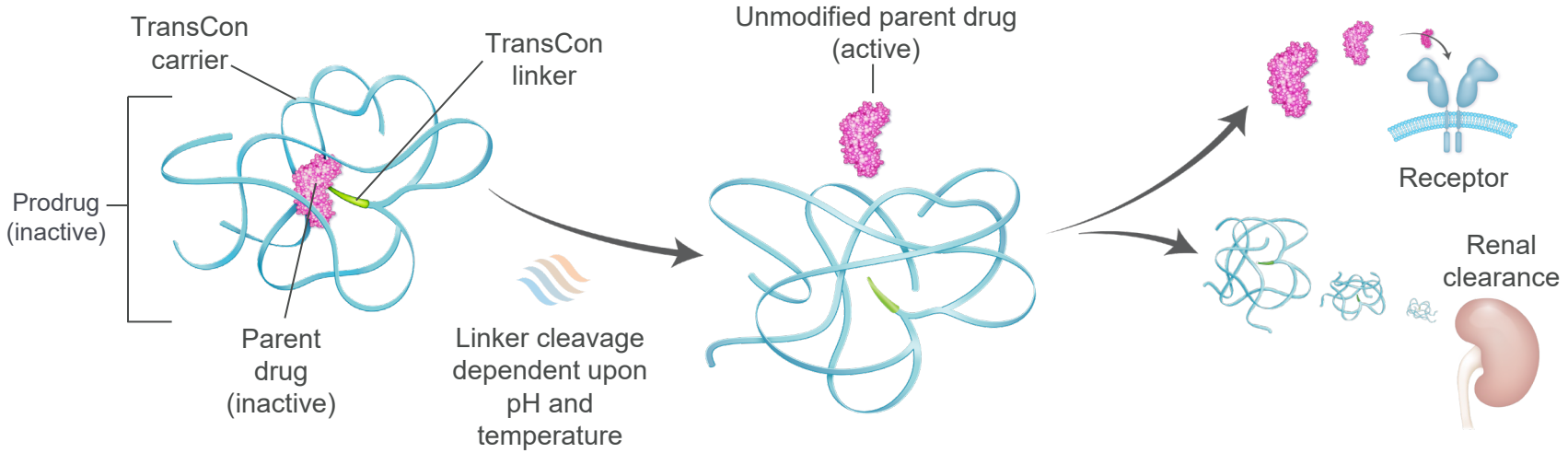
TransCon Technology: Sustained Systemic Release

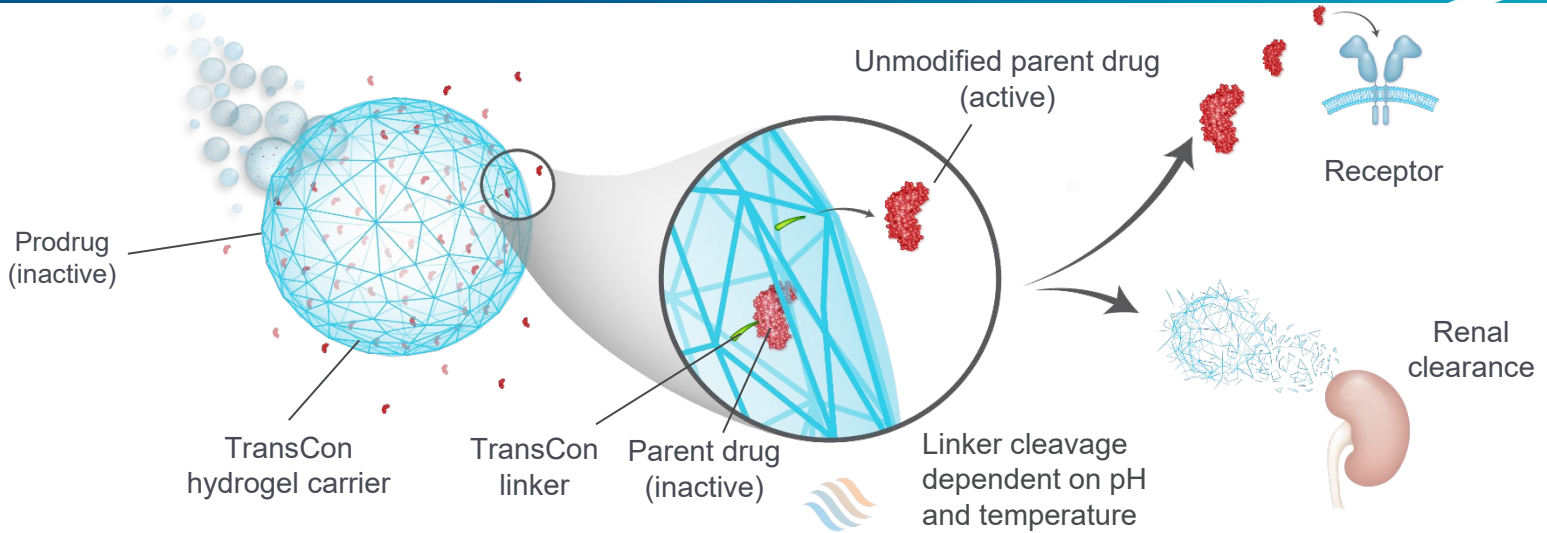


Parent drug is transiently bound to a TransCon linker-soluble carrier moiety, which inactivates and shields parent drug from clearance

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

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

TransCon Technology: Sustained Localized Release

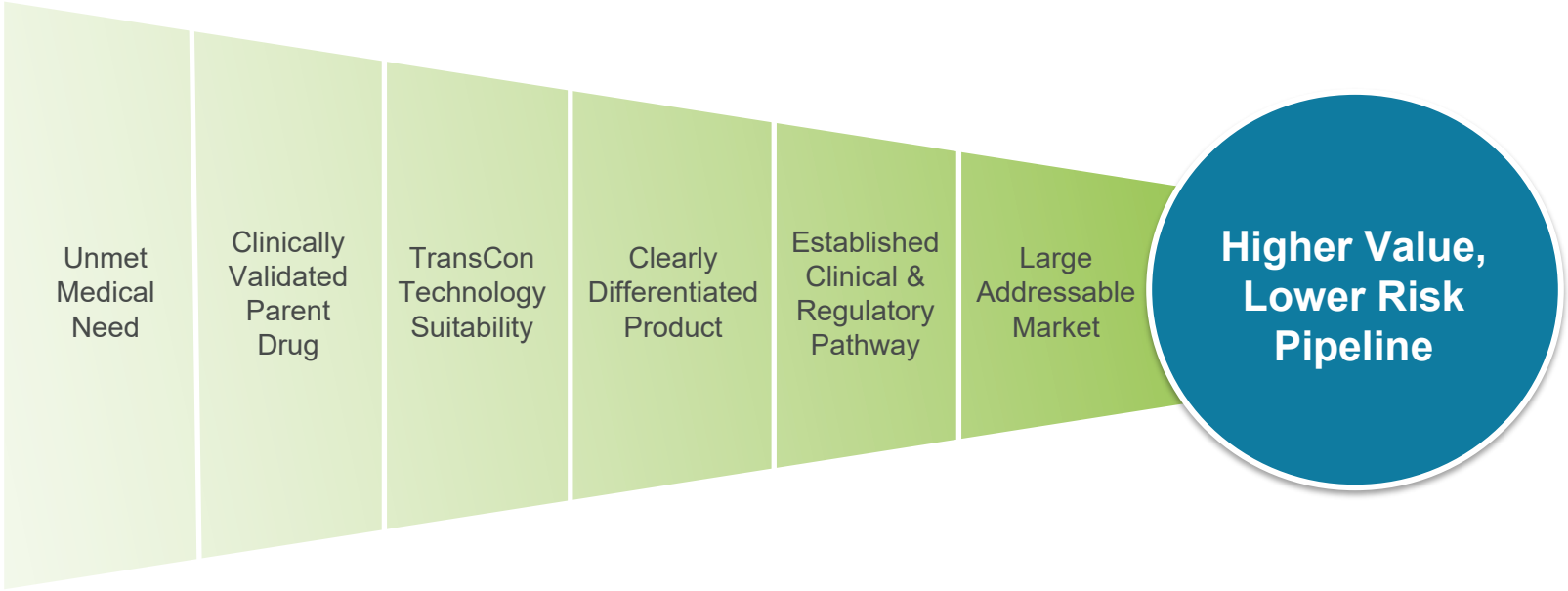


Parent drug is transiently bound to TransCon linker-hydrogel carrier, which inactivates, shields parent drug and prevents clearance

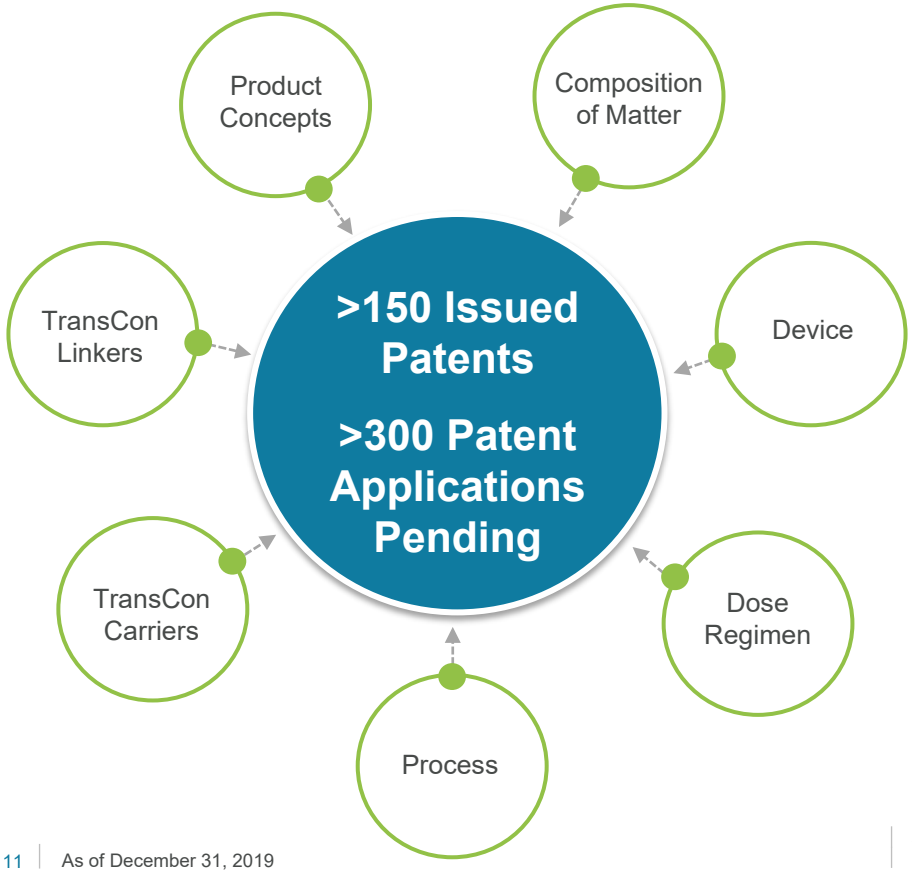
Following injection, the linker is designed to autocleave at a specific rate to predictably release unmodified parent drug

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

Ascendis Algorithm for Product Innovation



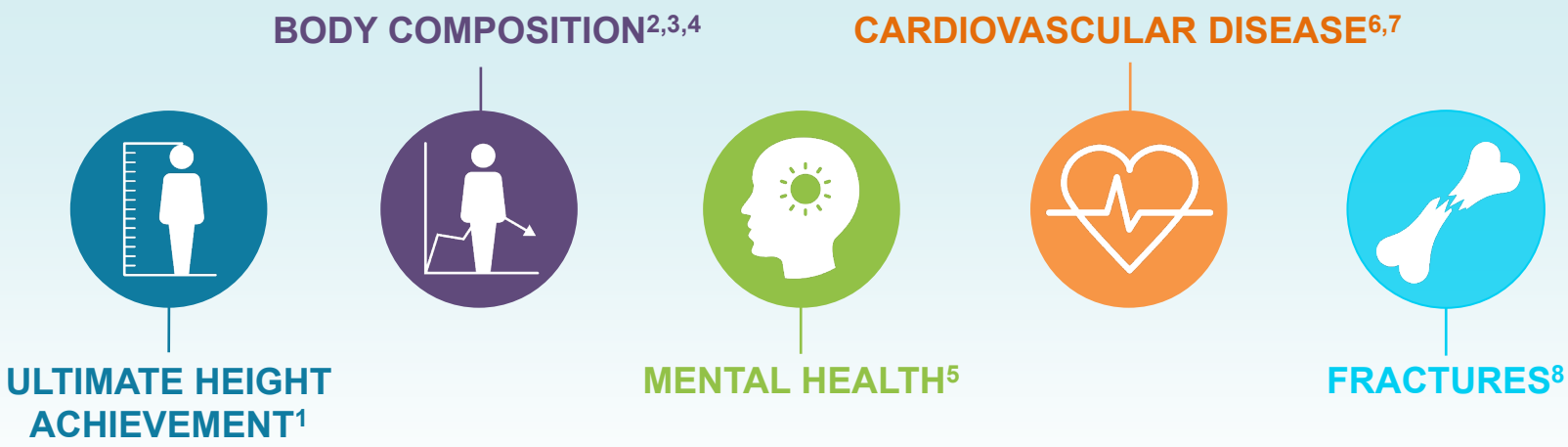
TransCon Enables Multi-level Patent Protection



- TransCon prodrugs eligible for new composition of matter IP
- A multi-layered patent strategy is applied to protect our assets

TransCon Growth Hormone: Once-Weekly Replacement Therapy

Growth Hormone Supports Overall Endocrine Health



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

[1]de Boer, H. et al. *J. Clin. Endocrinol. Metab.* 1997; 82(7): 2032-2036. [2]Rutherford, O. M. et al. *Clin. Endocrinol* 1991; 34(6): 469-475. [3]Colle, M., J. Auzerie. *Horm. Res.* 1993; 39(5-6): 192-196. [4]Johannsson, G., et al. *J. Clin. Endocrinol. Metab.* 1999; 84(12): 4516-4524. [5]Stabler, B. et al. *Horm. Res.* 1996; 45(1-2) 30-33 [6]Leonga, G., Johannsson, G. *Horm. Res.* 2003; 60(suppl1): 78-85 [7]Colao, A. et al. *J. Clin. Endocrinol. Metab.* 2002; 87(8): 3650-3655. [8]Bex, M., Bouillon, R. *Horm. Res.* 2003; 60(suppl3): 80-86.

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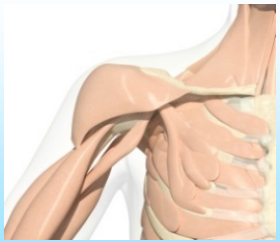
Impact of hGH Distribution

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

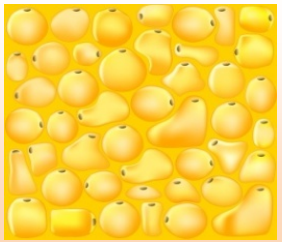
BONE

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



MUSCLE

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

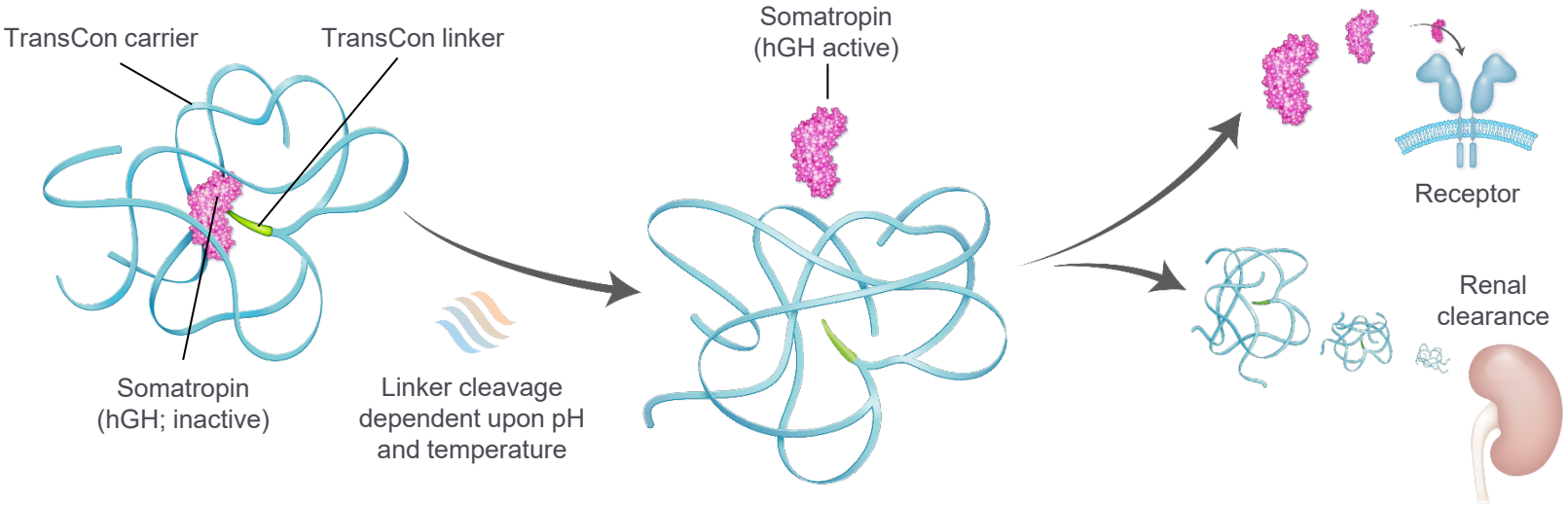


ADIPOSE TISSUE

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

[1]Kaplan SA, Cohen P. *J Clin Endocrinol Metab*. 2007;92(12):4529-4535.

TransCon hGH (lonapegsomatropin) Design

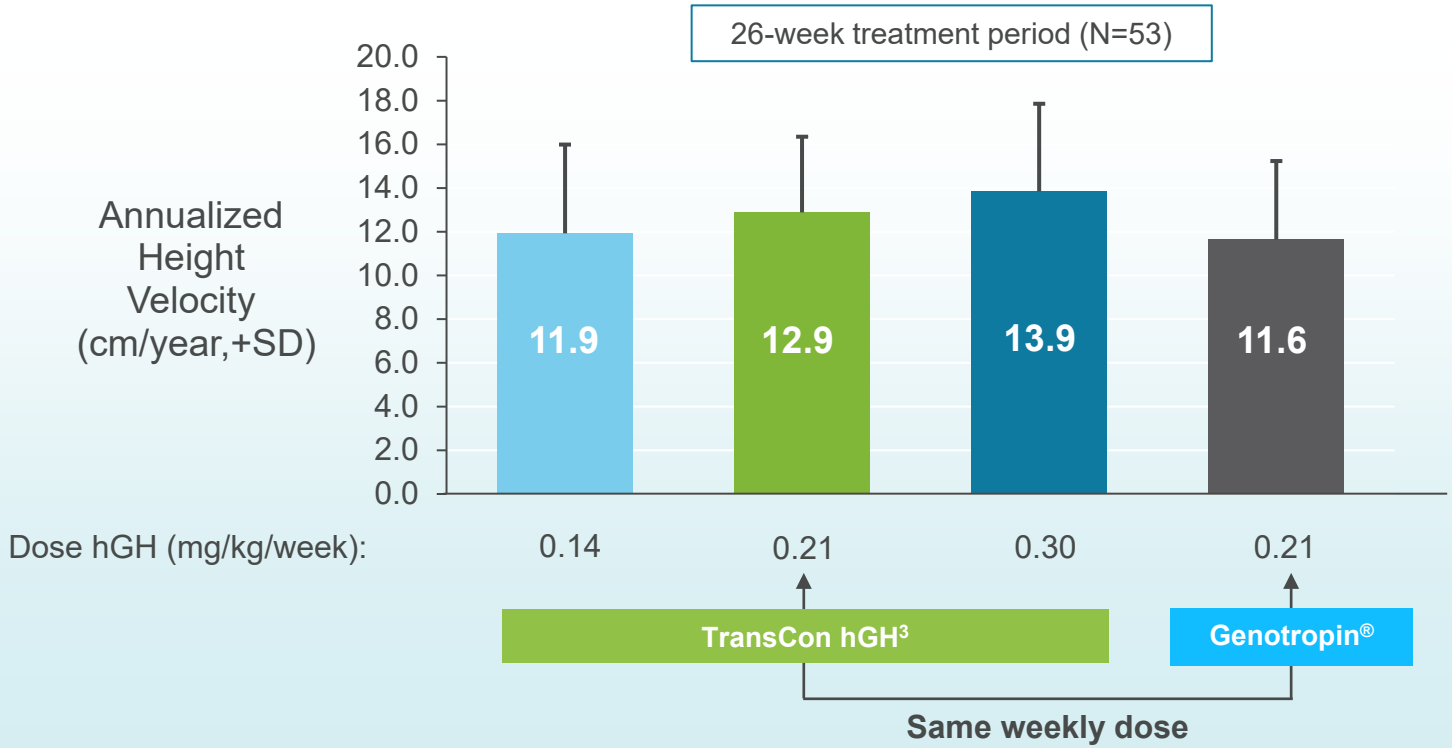


Once-weekly prodrug releases unmodified hGH designed to mimic daily hGH:

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

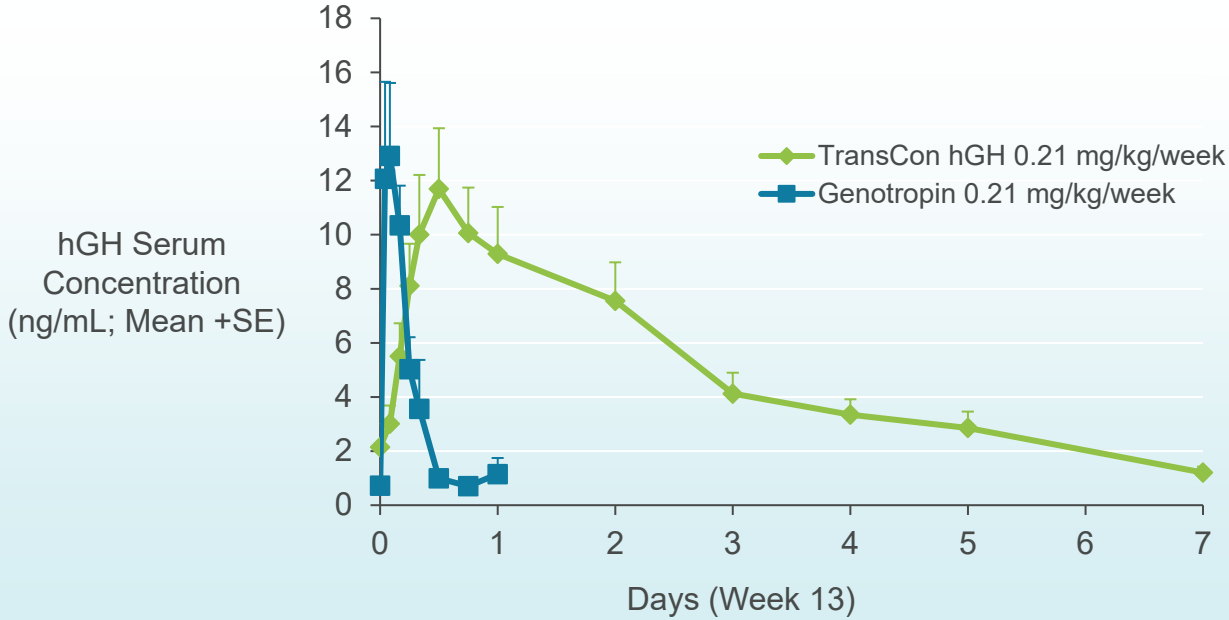
Sprogøe K et al. Endocr Connect. 2017;6(8):R171-R181.

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



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

Sustained hGH Exposure Over One Week in Phase 2



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

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

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=298)

- *BLA/MAA submitted*
- *PDUFA June 25, 2021*

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Adverse Event Profile of TransCon hGH in the Phase 3 Program[1]

	heiGHt Trial		fliGHt Trial	enliGHten Trial[2]
	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)[3]	5 (1.7)[4]
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

[1] All doses expressed in mg/kg/week.
[2] Based on data reported up to September 2019. Data on file.
[3] One subject reported two SAEs; both considered unrelated to study drug.
[4] Two subjects reported two SAEs; all considered unrelated to study drug.

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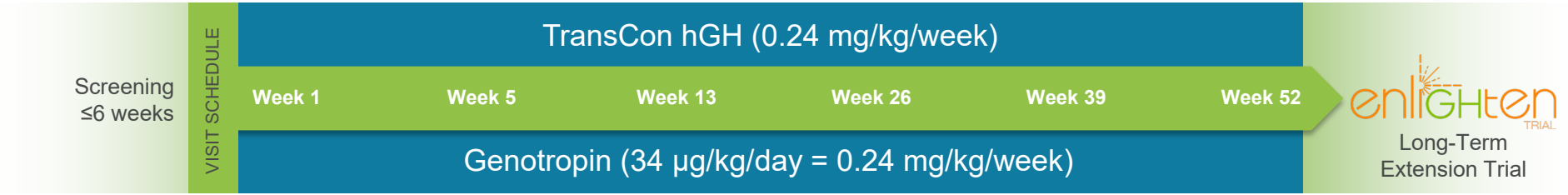
Phase 3 heiGHt Trial

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

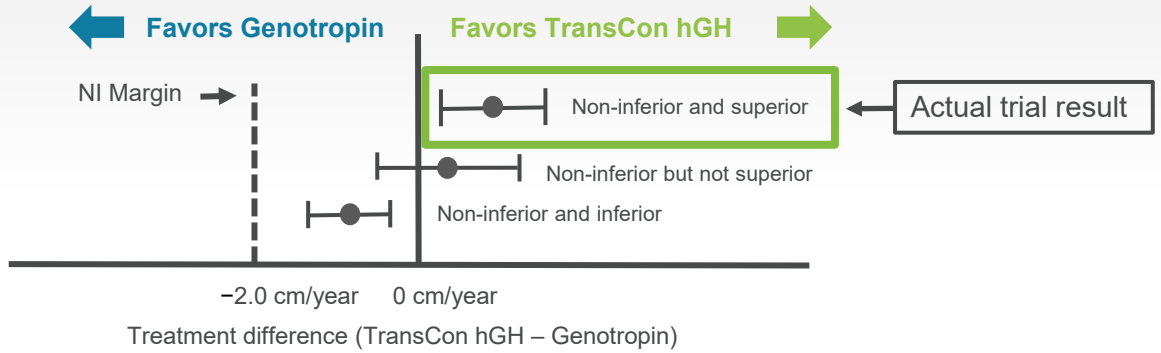
Demographics and Baseline Characteristics Comparable Between Arms

	TransCon hGH (n=105) Mean	Genotropin (n=56) Mean
Age (years)	8.51	8.48
Male (%)	81.9	82.1
Height SDS	−2.89	−3.00
Δ Average Parental Height SDS	−2.32	−2.55
IGF-1 SDS	−2.08	−1.96
Peak Stimulated GH (ng/mL)	5.89	5.48
BMI (kg/m^2)	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

Thornton P, et al. Oral presentation at ENDO 2019.
BMI= body mass index.

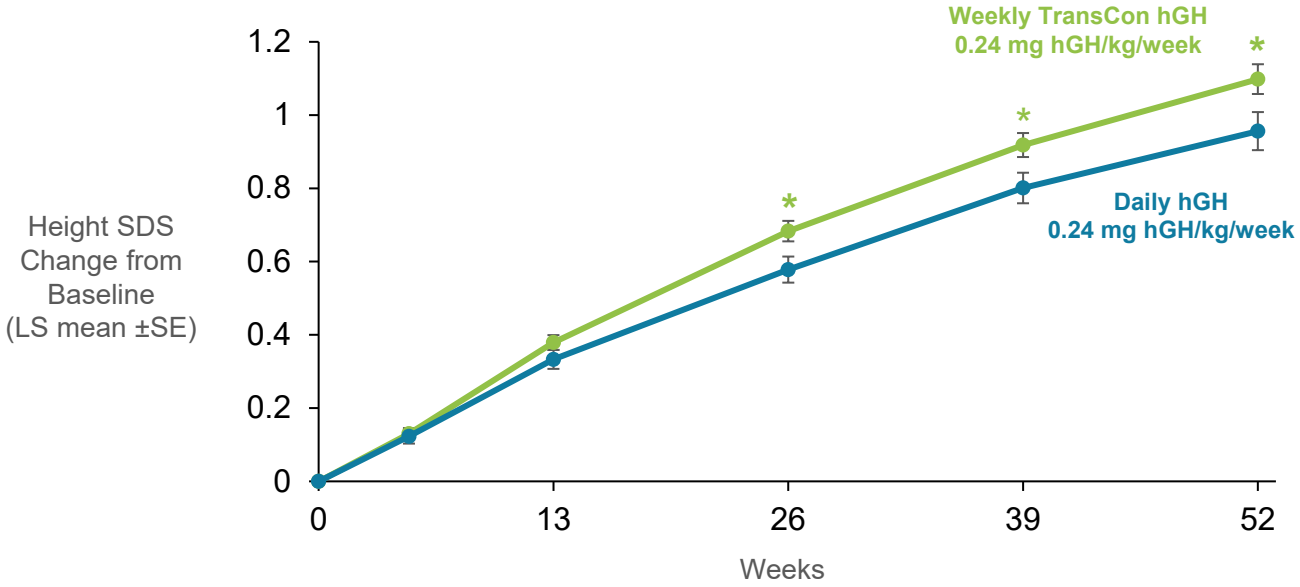
TransCon hGH Demonstrated Non-inferiority and Superiority in Primary Endpoint of AHV at Week 52

	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	



ANCOVA model was applied after missing data were imputed by multiple imputation method.
Thornton P, et al. Oral presentation at ENDO 2019.

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

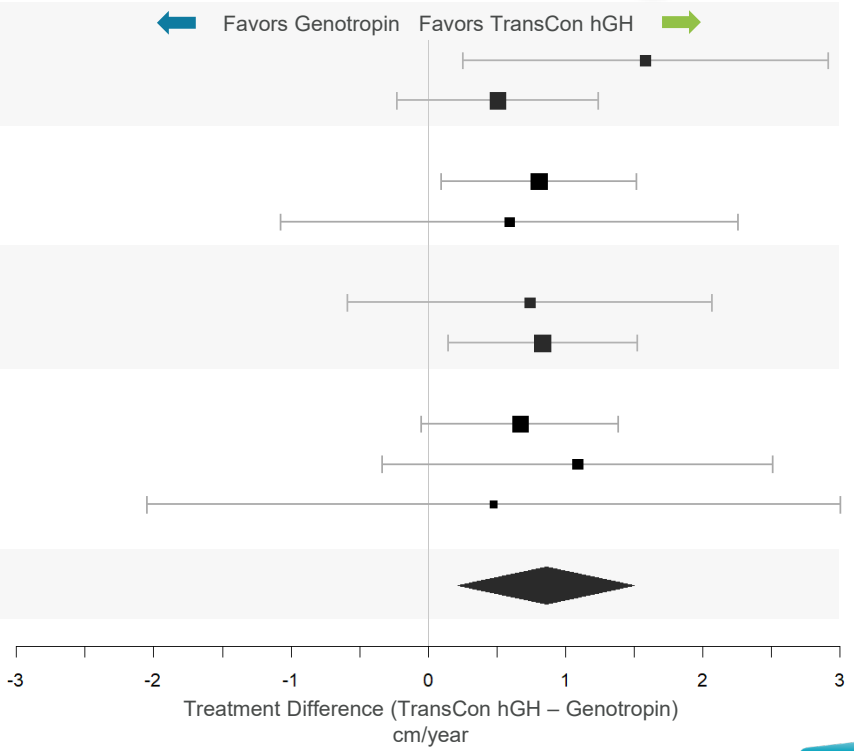


Statistically significant difference between TransCon hGH and Genotropin from week 26

ANCOVA model. *Denotes statistical significance.
Data on file.

Treatment Difference in AHV Favored TransCon hGH Across All Subgroups at Week 52

	TransCon hGH (n=105)	Genotropin (n=56)
Age		
< 6 years	24%	25%
≥ 6 years	76%	75%
Sex		
Male	82%	82%
Female	18%	18%
Baseline GH-Stimulation		
≤ 5ng/mL	35%	38%
> 5 ng/mL	65%	63%
Etiology and Extent of GHD		
Isolated Idiopathic	65%	66%
Isolated Organic	18%	16%
Multiple Pituitary Hormone Deficiency	17%	18%
Overall		



ANCOVA Model.
Vlachopapadopoulou et al. Oral presentation at ESPE 2019.

AHV Poor Responders: Post-hoc Analysis

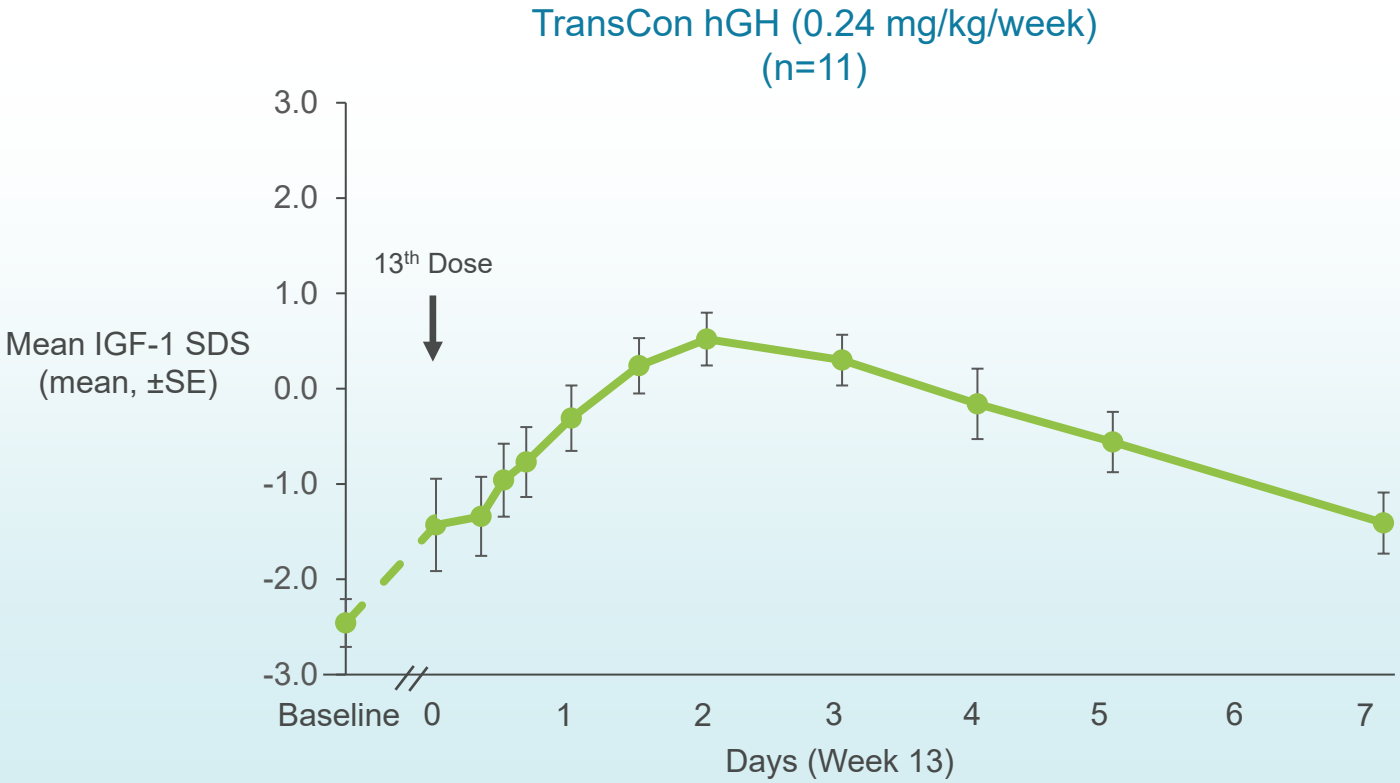
Poor responders defined as AHV <8.0 cm/year[1]

At Week 52[2]	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

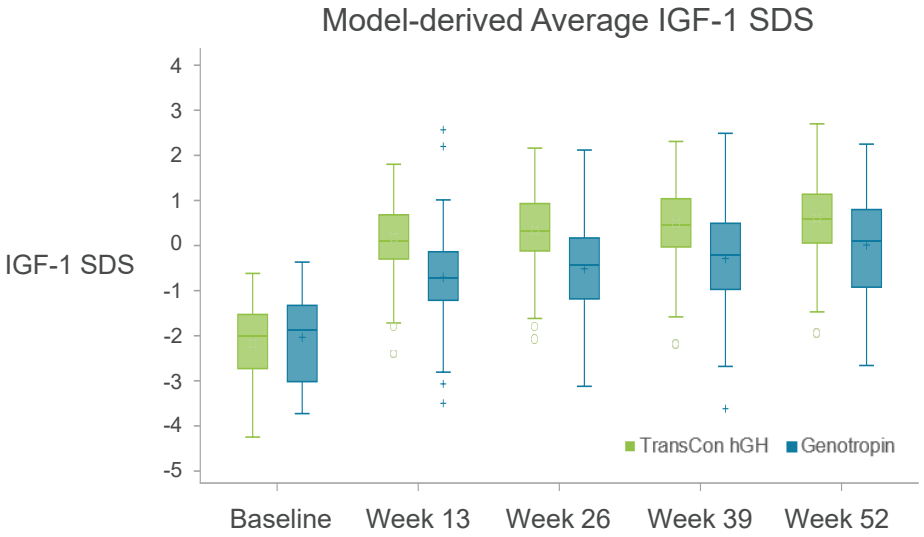
[1] Bakker et. al. *J Clin Endocrinol Metab* 93: 352–357, 2008
[2] Excludes one subject per group with missing Week 52 data (98.8% subjects completed study) Thornton P, et al. Oral presentation at ENDO 2019.

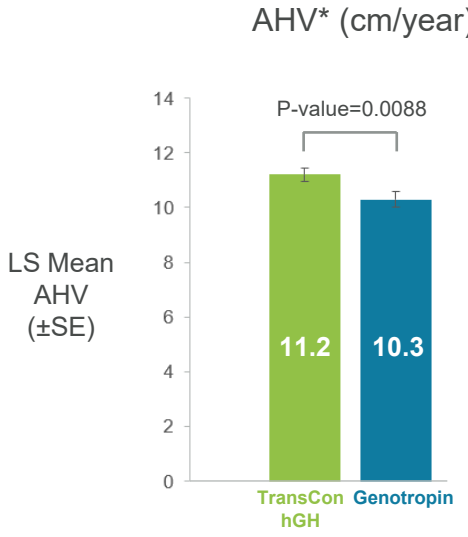
IGF-1 Profile in PK/PD Subset During Week 13



Thornton P, et al. Oral presentation at ENDO 2019.

AHV Paralleled Average IGF-1





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

*ANCOVA model

Vlachopapadopoulou et al. Oral presentation at ESPE 2019.

Stable Glycemic Parameters

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

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

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

Thornton P, et al. Oral presentation at ENDO 2019.

Low Incidence of Anti-hGH Binding Antibodies

Anti-hGH Binding Antibodies	TransCon hGH n=105 n (%)	Genotropin n=56 n (%)
Treatment-emergent positive	**7 (6.7)**	**2 (3.6)**
Transient, non-neutralizing	7 (6.7)	2 (3.6)
Persistent[1]	0	0
Neutralizing	0	0

[1] Persistent is defined as ≥16 weeks between the first and last positive post-baseline sample. Data on file.

Comparable Change in Bone Age Over 52 Weeks

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

TransCon hGH demonstrated superior AHV, while advancing bone age at a rate comparable to Genotropin

Maniatis A et al., PES 2019.

BMI SDS of heiGHt Subjects Over 78 Weeks

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

Mean BMI SDS remained near 0 over 78 weeks

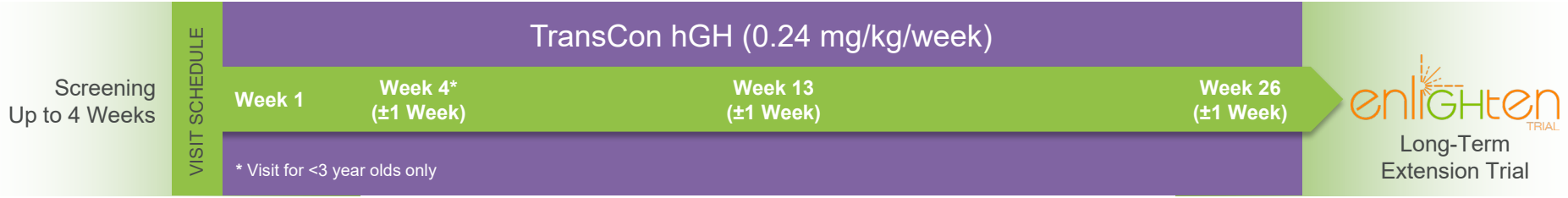
Group A received TransCon hGH in both heiGHt and enliGHten; Group B received Genotropin in heiGHt and TransCon hGH in enliGHten.
Data on file.

heiGHt Trial Summary

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

Phase 3 fliGHt Trial Design

146 children with GHD (143 treatment-experienced)



Primary Objective

- To assess the safety and tolerability of weekly TransCon hGH in children with GHD

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 ≥0.20 mg/kg/week for 13–130 weeks
  - Children <3 years could have been treatment-naïve

Key Endpoints[1]

- 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

[1] Primary outcome measure was safety and tolerability of TransCon hGH over 26 weeks

fliGHt Baseline Demographics[1,2]

	Baseline Mean (N=146)
Male (%)	75.3
Age (years)	10.6
Age Range (years)	1 to 17
Height SDS	−1.42
BMI (kg/m^2)	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

[1]Maniatis A et al. Oral presentation at ENDO 2020. [2]Data on file.

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%)

Maniatis A et al. Oral presentation at ENDO 2020.

Summary of Adverse Events

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

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

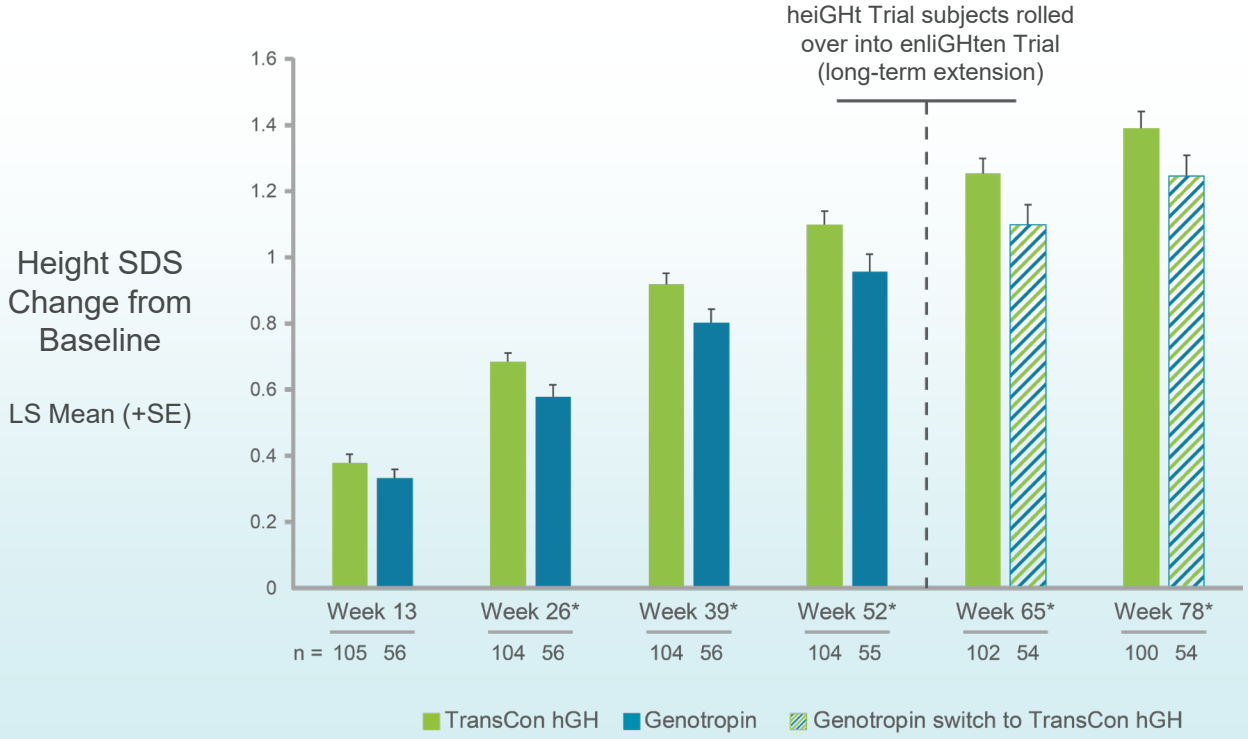
*Specific TEAEs reported by ≥5% of subjects.
Maniatis A et al. Oral presentation at ENDO 2020.

Mean AHV at Week 26 by Subgroups[1,2]

	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

[1]Maniatis A et al. Oral presentation at ENDO 2020. [2]Data on file.

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



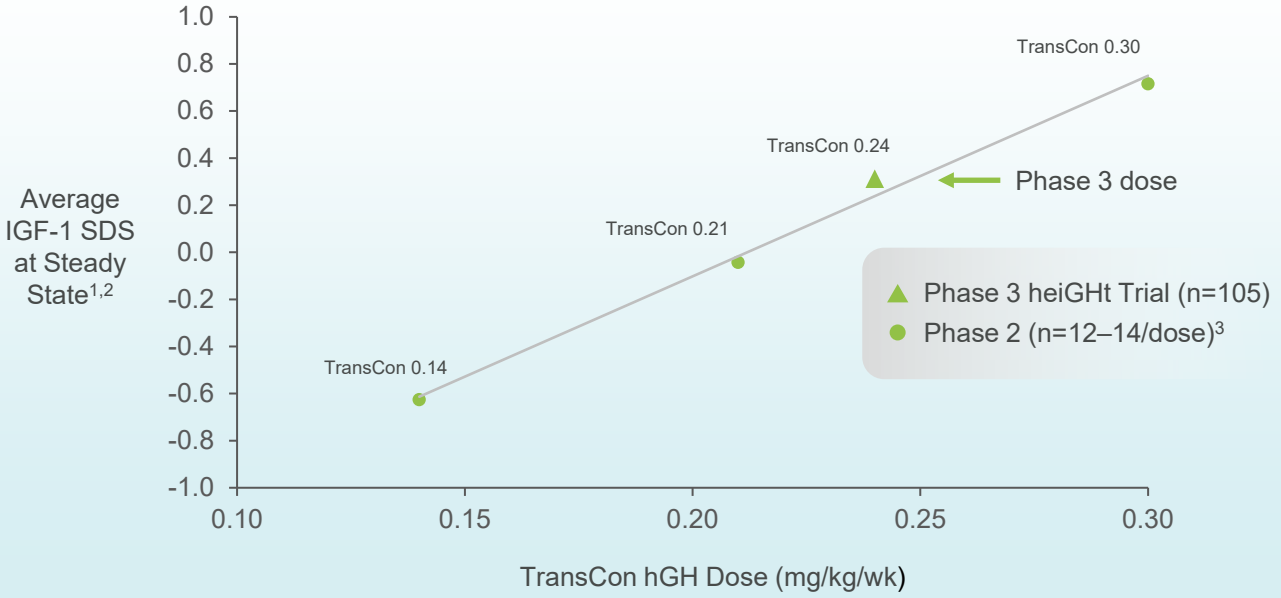
heiGHt subjects treated for 1.5 years with TransCon hGH demonstrated:

- Superior growth after 52 weeks compared to Genotropin[1]
- Superior growth maintained in the enliGHten extension trial

[1] Based on results from phase 3 heiGHt Trial on the primary endpoint of AHV at 52 weeks
*Treatment difference resulted in a nominal p-value <0.05
ANCOVA model
Maniatis A et al. Oral presentation at ENDO 2020.

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

Average IGF-1 SDS vs TransCon hGH Dose

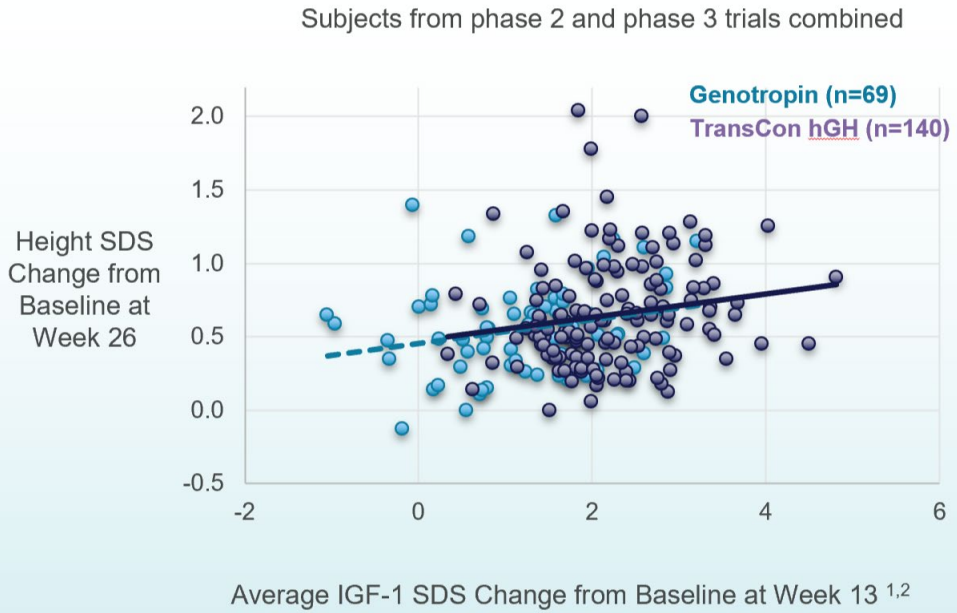


TransCon hGH data support predictable dose titration

[1] Average IGF-1 at Week 13 was used given availability of measured data over one week for the phase 2 trial
[2] Average IGF-1 during Week 13 for phase 3 heiGHt Trial TransCon hGH subjects is model-derived average
[3] Conducted with an earlier bioequivalent version of TransCon hGH
Data on file.

ascendis pharma

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



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

[1] Average IGF-1 at week 13 was used given availability of measured data over one week for the phase 2 trial
[2] Average IGF-1 during week 13 for phase 3 heiGHt Trial TransCon hGH subjects is model-derived average
Data on file.

Key Learnings from TransCon hGH Clinical Trials

- TransCon hGH demonstrated a safety profile comparable to that of a daily hGH
- TransCon hGH demonstrated superior AHV[1] compared to a daily hGH through a PK profile of released hGH that may be more efficiently utilized by target tissues
  - Treatment advantage maintained beyond first year
- TransCon hGH showed predictable linear IGF-1 response to dose titrations
- TransCon hGH data suggests maintenance of the same mode of action as daily hGH and preservation of the biological balance between direct hGH and IGF-1 effects in target tissues
- TransCon hGH demonstrated consistent safety and efficacy profile following switch from daily hGH in both fliGHt and enliGHten trials

[1] Based on results from phase 3 heiGHt Trial on the primary endpoint of AHV at 52 weeks

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
- Enables flexible titration
- Bluetooth® connectivity planned for automatic data capture
- Development of integrated connectivity platform underway

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

TransCon hGH: Raising the Bar

- Phase 3 heiGHt Trial demonstrated superior AHV of TransCon hGH in pediatric GHD, with comparable safety and tolerability to a daily hGH
- Received orphan designation for TransCon hGH in US and Europe for GHD
- In pediatric GHD, submitted BLA in June 2020 and submitted MAA in September 2020
  - PDUFA June 25, 2021
  - PIP approved for children from 6 months to less than 18 years
- User-friendly Auto-Injector part of initial BLA/MAA submissions
- Create further growth:
  - China: Pediatric GHD phase 3 ongoing*
  - Japan: Pediatric phase 3 expected to be initiated Q4 2020
  - Global label expansion: Submitted IND amendment to initiate adult GHD phase 3 in Q1 2020
- Commercial leadership team in place, commercial manufacturing ongoing
- Multiple independent patent filings to provide additional potential protection into 2039

* Conducted by VISEN Pharmaceuticals

TransCon PTH:
PTH Replacement Therapy for Hypoparathyroidism

Hypoparathyroidism

Short-term Symptoms[1]

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

Brain fog

Anxiety due to "fear of crash"

Hypercalcemia
Nocturia, polyuria, constipation, muscle weakness, coma

Patient Burden[2,3]

76%
Either unable to work or report significant interference with work due to HP symptoms

79%
Require hospitalizations or emergency department visits

85%
Report inability to perform household activities

Long-term Complications[4-6]

4-fold
Increased risk of renal disease (nephrocalcinosis, nephrosclerosis, kidney stones & renal insufficiency)

2-fold
Increased risk of depression or bipolar disorder

4-fold
Increased risk of seizures

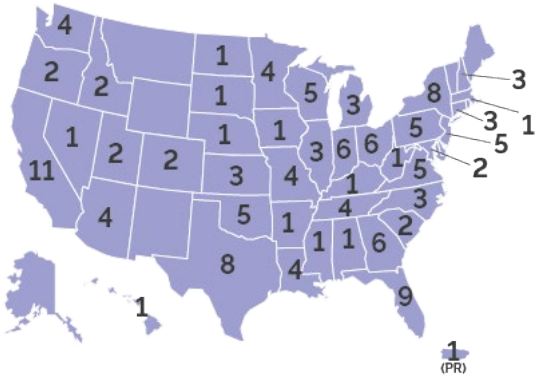
[1] *Nat Rev Dis Primers* 2017 Aug 31;3:17055 [2]Ascendis Pharma HP Patient Experience Research. [3]*Endo Pract.* 2014, 20(7);671-679. [4] *J Bone Miner Res* 2013, 28: 2570-2576; [5]*J Clin Endocrinol Metab* 2012, 97(12): 4507-4514. [6]*J Bone Miner Res* 2013, 28: 2277-2285.

Voices of Hypopara Survey: Managing Calcium Levels Remains a Key Challenge

About the Survey

146	patients with hypopara participated in the survey
89%	were women and the average age was 51 years
60%	have lived with hypopara for 5 years or longer

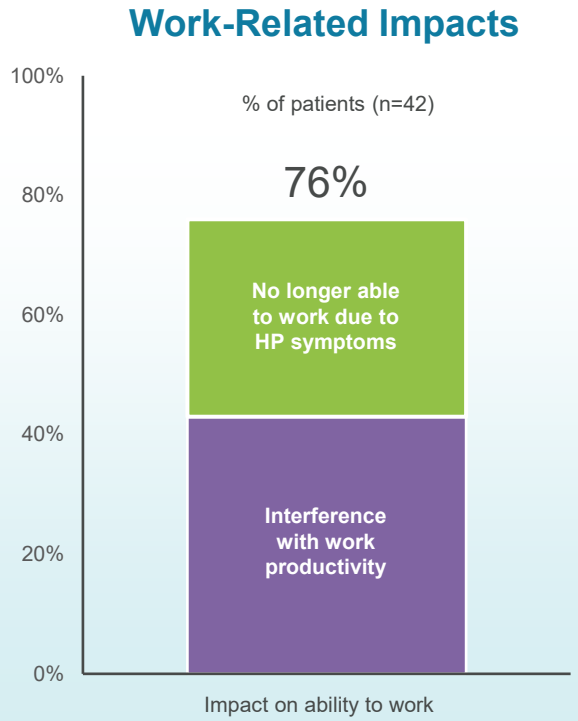
Participants Across the U.S. (N=146)



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

Results reported on World Hypopara Day 2020 by U.S. HypoPARAthyroidism Association, used with permission
Astolfi et al. ASBMR 2020.

Vast Majority of Patients Unable to Work or Less Productive Due to HP Symptoms[1]



- 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

[1] 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

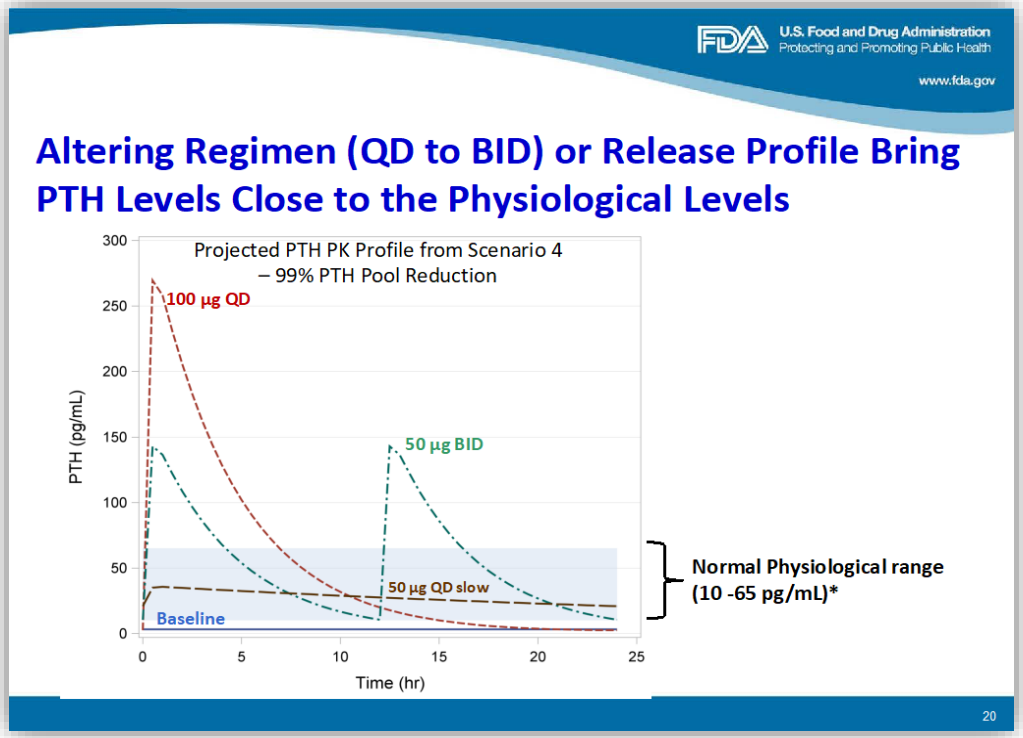
- 2017. Shishiba et. al., Prevalence of postsurgical hypoparathyroidism in Japan: Estimated from the data of multiple institutes
- 1999. Nakamura et. al., Prevalence of Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism in Japan
- Ascendis market research

South Korea

~12k-13k

- S. Korean ICD-10 codes
- Ascendis market research

Constant Normal Level of PTH is Optimal - FDA Perspective[1,2]

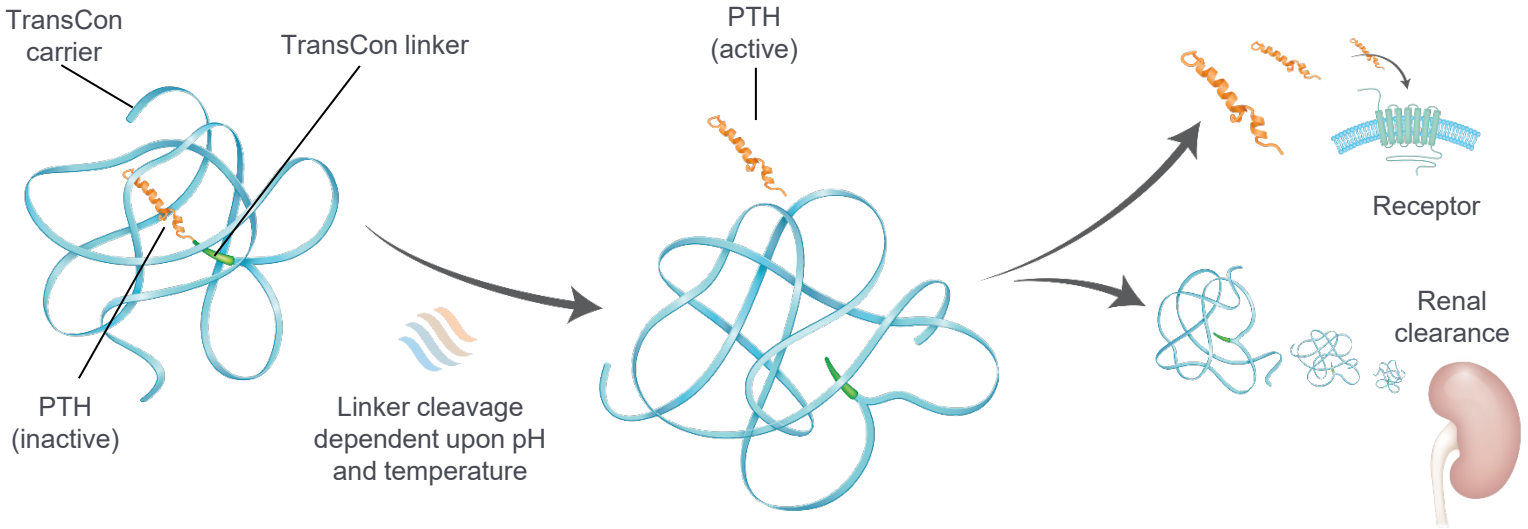


Continuous infusion of PTH demonstrated[3,4]:

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

[1] FDA presentation: Natpara Advisory Committee, September 12, 2014; [2] Khurana M, et al. *Clin Pharmacol Ther*. 2019 105(3):710. [3] Winer K ,et al. *J Clin Endo Metab* 2012 97(2);391–399; [4] Winer K, et al. *J Pediatr* 2014 165(3);556-563.

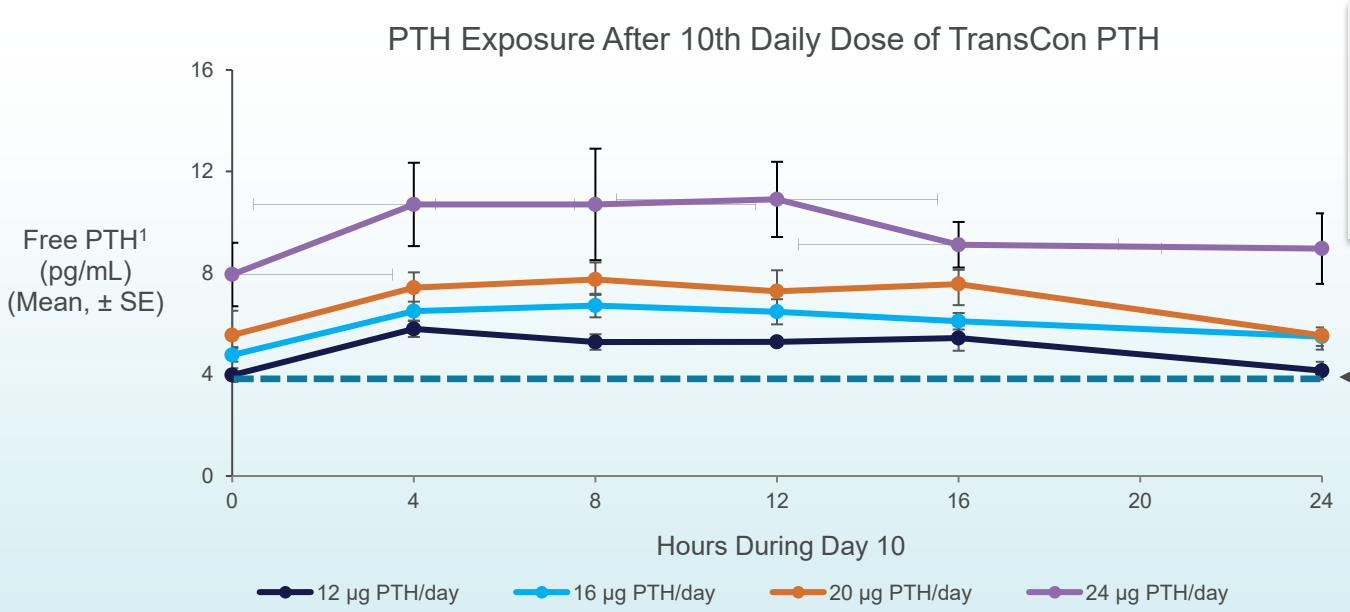
TransCon PTH Design[1]

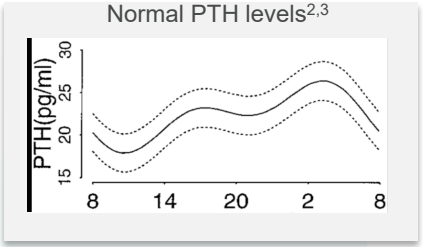


- TransCon PTH is a sustained-release prodrug designed to provide stable PTH levels in the physiological range for 24 hours/day
- TransCon PTH designed to normalize blood and urinary calcium levels, serum phosphate and bone turnover

[1]Karpf DB, et al. *J Bone Miner Res.* 2020; 35(8):1430-1440.

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

[1] PTH measured as Free PTH(1-34) and Free PTH(1-33); [2] FDA presentation: Natpara Advisory Committee, September 12, 2014; [3] Ghada E, et al. *J of Clin Endo.* 1997; 82:281-286. Analyses from TransCon PTH Phase 1 trial; data not shown for doses <12 µg/day, as levels of Free PTH are BLQ; Karpf DB, et al. *J Bone Miner Res.* 2020; 35(8):1430-1440.

TransCon PTH Phase 2 Trial Design

PaTHforward TRIAL

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

Primary Composite Endpoint (4 weeks)

Proportion of subjects with:

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

Key Secondary Endpoints (4 weeks)

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

Additional Endpoints ≥4 weeks

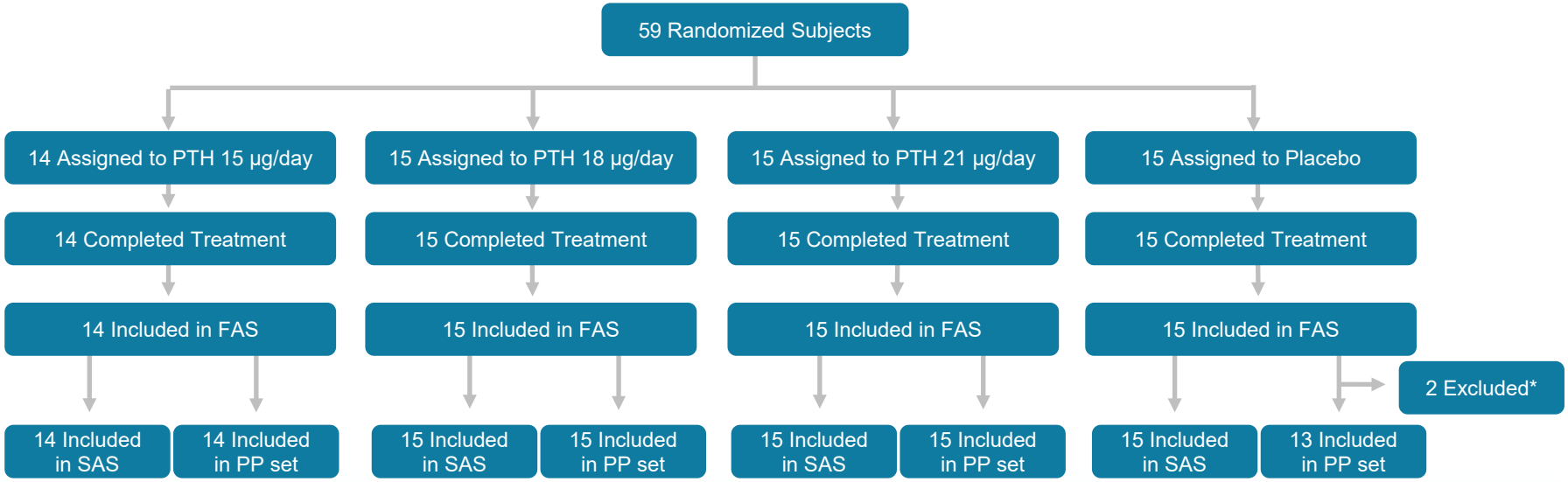
- PRO measures (HPES: a disease-specific PRO for HP)*
- Nephrolithiasis, nephrocalcinosis, vascular calcification, ER/urgent care visits and hospitalizations
- BMD and TBS by DXA, bone turnover markers, 24-hour urine calcium excretion (in extension only)

*PRO = patient-reported outcome. HPES = Hypoparathyroidism Patient Experience Scale.

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

- PaTH Forward top-line data support TransCon PTH as a potential replacement therapy for adult HP
  - TransCon PTH eliminated standard of care (i.e. off active vitamin D and ≤500 mg per day of calcium supplements) in 100% of subjects in the 21 µg/day arm and in 82% of subjects across all dosage arms
  - Both the 21 µg/day arm and the combined TransCon PTH dosage arms showed a statistically significant response for the primary endpoint compared to placebo at 4 weeks
  - TransCon PTH increased mean serum calcium
  - TransCon PTH reduced mean urinary calcium excretion
  - TransCon PTH reduced mean serum phosphate and calcium-phosphate product
  - TransCon PTH demonstrated statistically significant and clinically meaningful treatment effect on SF-36 functional health and well being outcomes
- All doses of TransCon PTH were well tolerated
  - No serious or severe adverse events observed at any point
  - No treatment-emergent adverse events (TEAEs) led to discontinuation of study drug
  - Overall incidence of TEAEs comparable between TransCon PTH and placebo
- No drop-outs in blinded period

PaTH Forward Trial Profile



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

* Two subjects were excluded because they received <0.25 µg BID of calcitriol (active vitamin D)

Demographics and Baseline Characteristics – PP[1,2]

PaTHforward TRIAL

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file

Demographics and Baseline Characteristics – PP[1,2]

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file

HP Disease Characteristics and History – PP[1,2]

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file

Baseline HP Supplements – PP[1,2]

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

2 subjects did not have eDiary information confirmed by prescription information

[1]Khan et al. Oral presentation at ASBMR 2020.

[2]Data on file

Baseline of Spot FECa & Albumin-Adjusted sCa – PP[1,2]

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file

Treatment-Emergent Adverse Event Summary – SAS[1,2]

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

Subjects are counted only in the highest severity category

[1]Khan et al. Oral presentation at ASBMR 2020.

[2]Data on file

Treatment-Emergent Adverse Events of Interest – SAS[1,2]

PaTHforward TRIAL

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

Includes ≥ 2 subjects in the PTH group or hyper- or hypocalcaemia

[1]Khan et al. Oral presentation at ASBMR 2020.

[2]Data on file

PaTH Forward 4-Week Fixed Dose Safety Summary

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

Titration algorithm to eliminate standard of care demonstrated no hypocalcaemic AEs

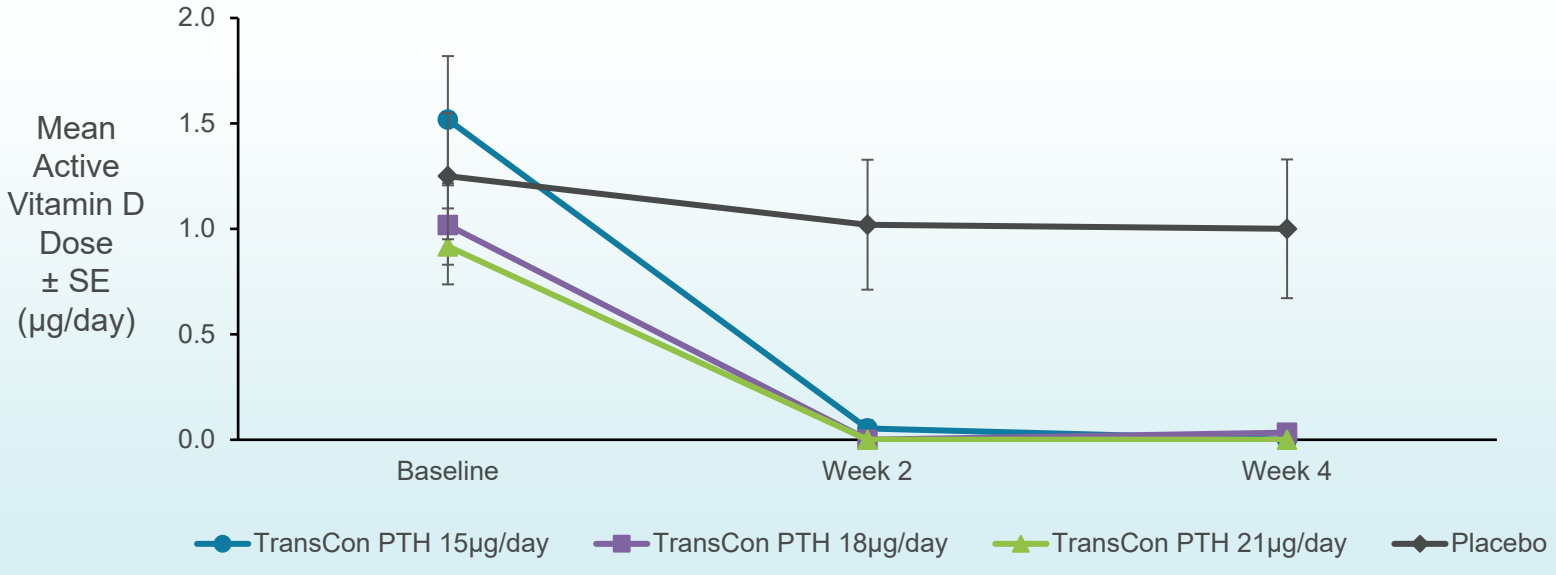
Elimination of Standard of Care – PP

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

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

*Not taking active vitamin D and ≤500 mg/day of calcium supplements
Khan et al. Oral presentation at ASBMR 2020.

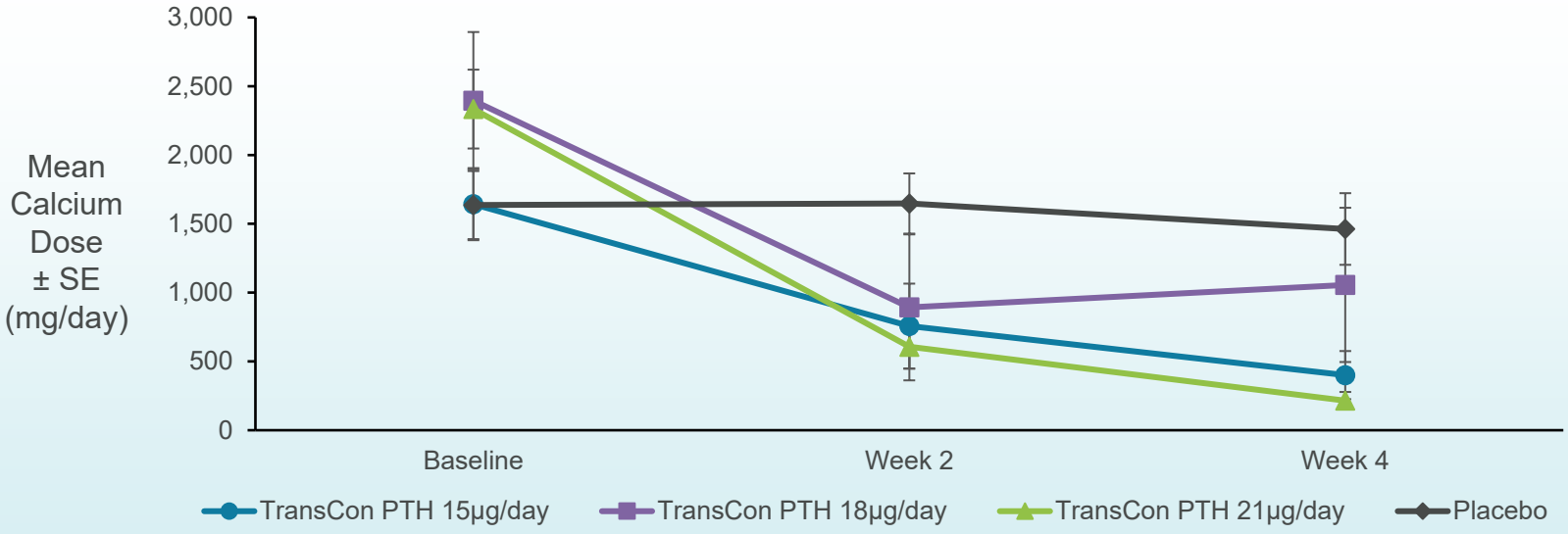
Mean Active Vitamin D Dose by Visit – PP



TransCon PTH enabled discontinuation of active vitamin D at week 2

Khan et al. Oral presentation at ASBMR 2020.

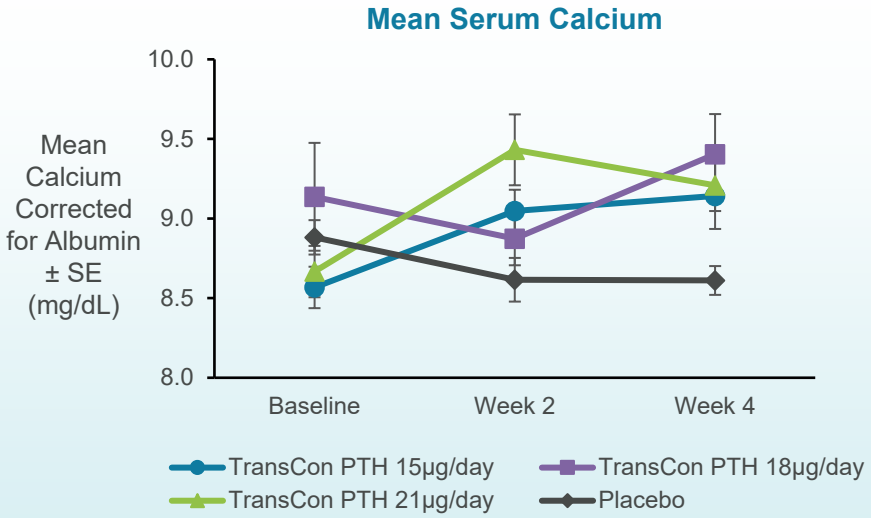
Mean Calcium Supplement Dose by Visit – PP

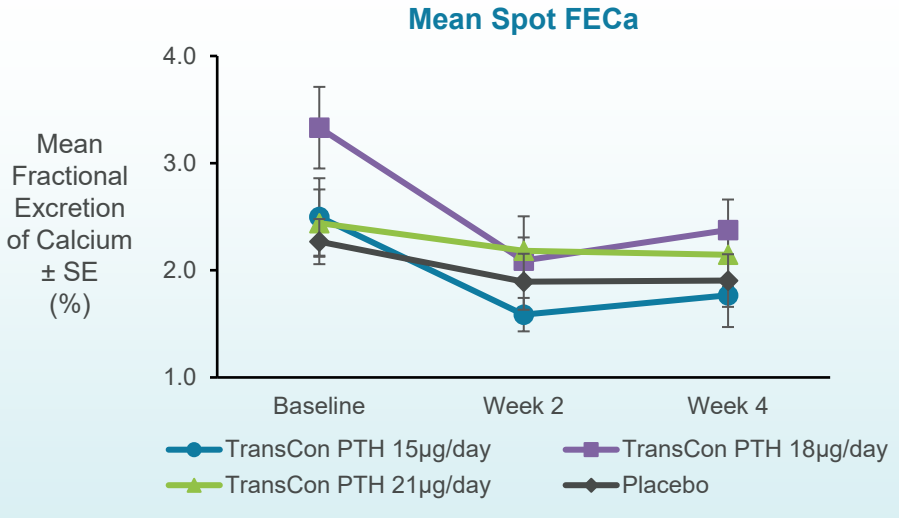


TransCon PTH enabled continuous calcium supplement reduction over 4-week study period

Khan et al. Oral presentation at ASBMR 2020.

Mean Serum Calcium and Spot FECa by Visit – PP

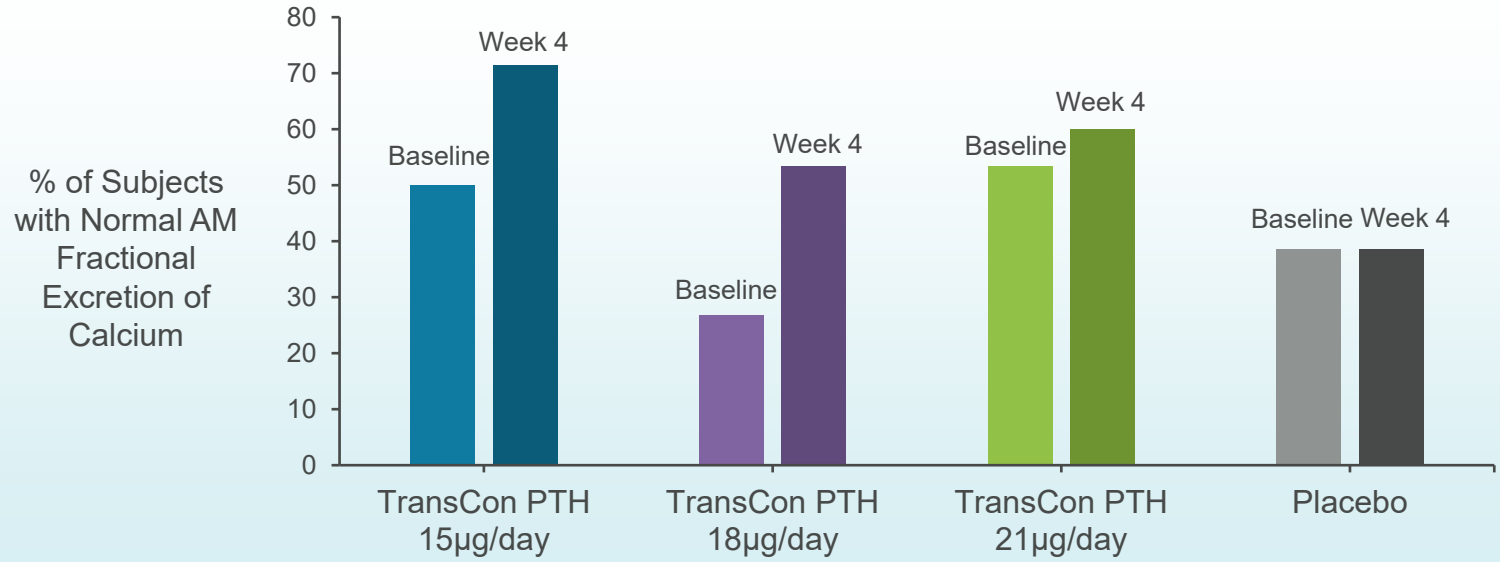




TransCon PTH subjects exhibited reduced FECa, despite increased serum calcium;
For placebo subjects, FECa followed serum calcium levels

Khan et al. Oral presentation at ASBMR 2020.

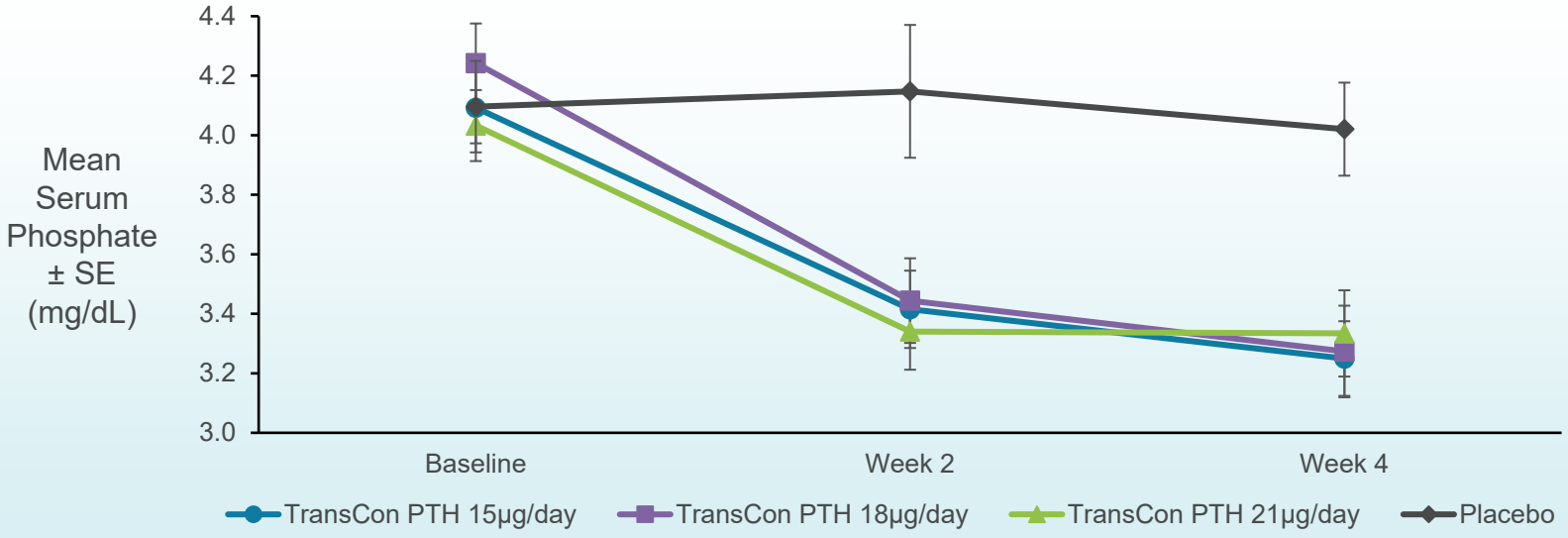
TransCon PTH Increased Number of FECa Responders – PP



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

Khan et al. Oral presentation at ASBMR 2020.

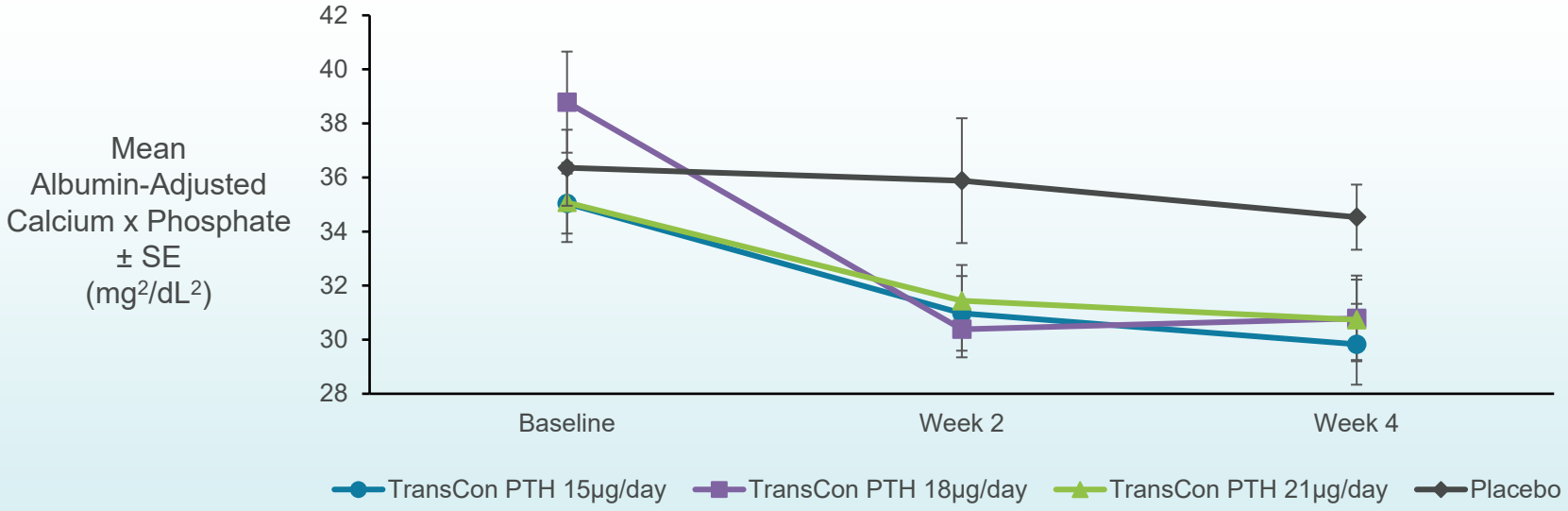
Mean Serum Phosphate by Visit – PP



TransCon PTH subjects demonstrated consistent, sustained reductions in serum phosphate

Khan et al. Oral presentation at ASBMR 2020.

Mean Calcium-Phosphate Product by Visit – PP



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

Khan et al. Oral presentation at ASBMR 2020.

Primary Composite Endpoint at Week 4 – PP[1,2]

PaTHforward TRIAL

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

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file.

Key Secondary Composite Endpoint at Week 4 – PP[1,2]

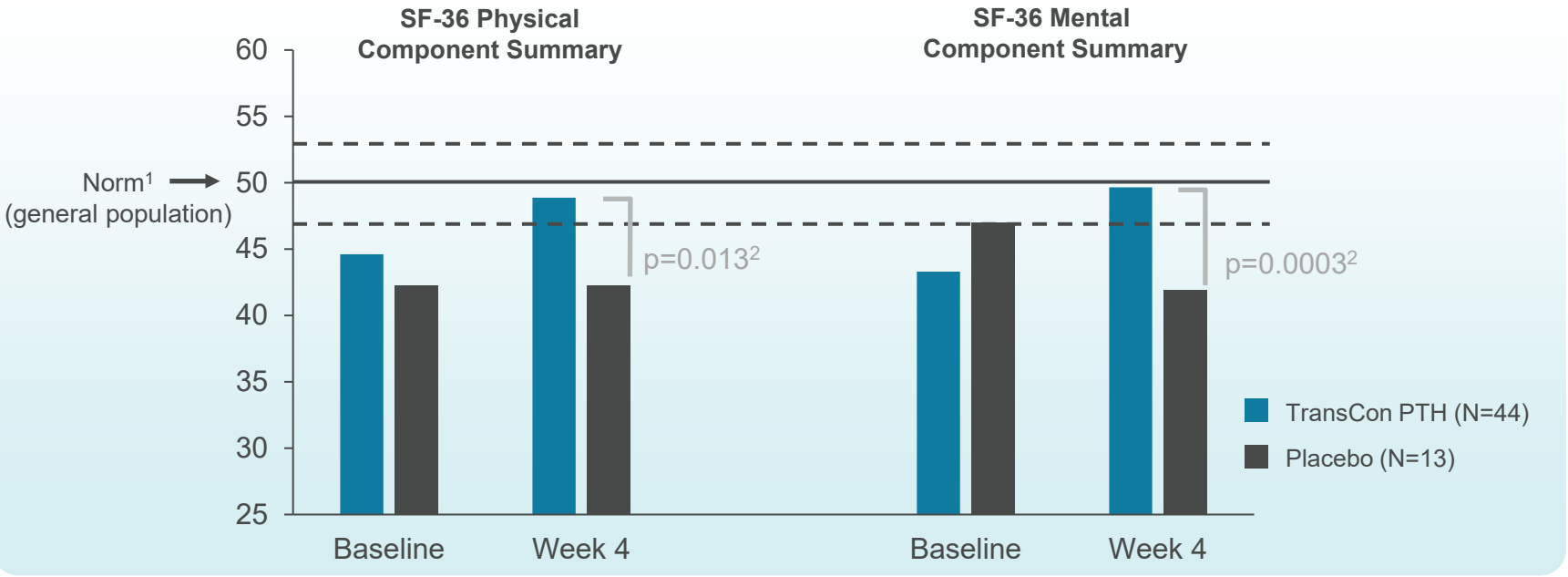
	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	Total PTH Subjects (N=44)	Placebo (N=13)
Number of Subjects Meeting Key Secondary Composite Endpoint at Week 4 with Fixed Dosing	7	4	9	20	2
Proportion (95% CI)	50 (23, 77)	27 (7.8, 55)	60 (32, 84)	45 (30, 61)	15 (1.9, 45)
P-value	0.10	0.65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

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

[1]Khan et al. Oral presentation at ASBMR 2020.
[2]Data on file.

TransCon PTH Demonstrated Statistically Significant and Clinically Meaningful Treatment Effect on SF-36[1] Functional Health and Well Being Outcomes

PaTH Forward Trial Double-Blinded Results at Week 4

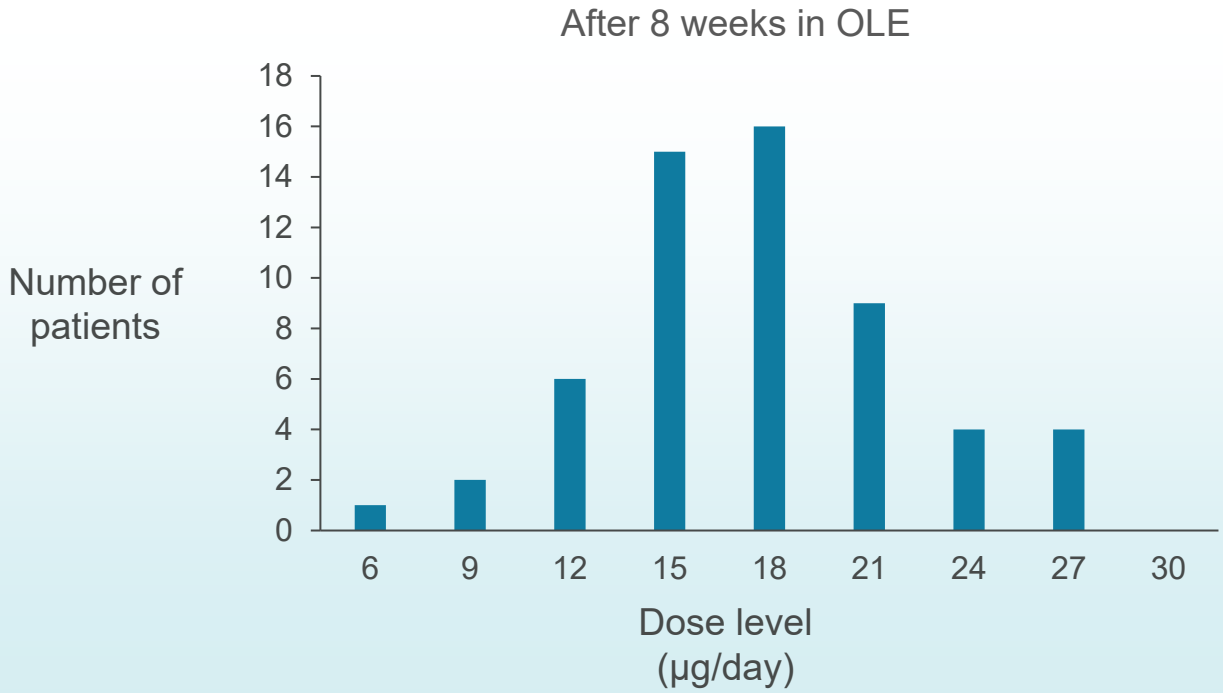


[1]Note. The dashed lines (----) indicate the upper (53) and lower (47) bounds of T scores considered to be in the range of average functioning for the U.S. general population of group level data. Group mean scores lower than 47 indicate impairment. Source: Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated. [2]TransCon PTH vs. placebo at week 4 (ANCOVA model including baseline as a covariate and treatment as a fixed factor).
Khan et al. Oral presentation at ASBMR 2020.

Open-label Extension (OLE) Trial

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

Distribution of Doses* in Phase 2 Open-label Extension



*At Visit 7 (week 12 of PaTH Forward, 8 weeks in OLE, N=57)

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 (≤0.1 mL)
- Small (31G), short (5 mm) safety pen needle

Pen injector planned for commercial launch being used in phase 2

PaTHforward TRIAL

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TransCon PTH: A Potential 24-hour PTH Replacement Therapy

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

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TransCon CNP: The New Frontier of Growth Biology

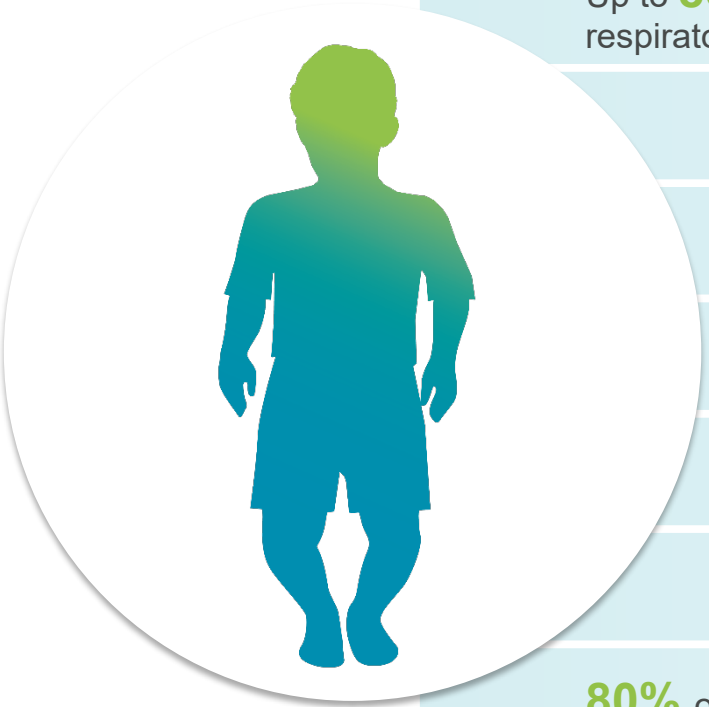
TransCon CNP: The New Frontier of Growth Biology

- C-type natriuretic peptide (CNP) is a potential 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

Wendt DJ, et al. *J Pharmacol Exp Ther.*. 2015 Apr;353(1):132-49.

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 cevicomedullary 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

The Application of Clinical Genetics, 2014:7117-125

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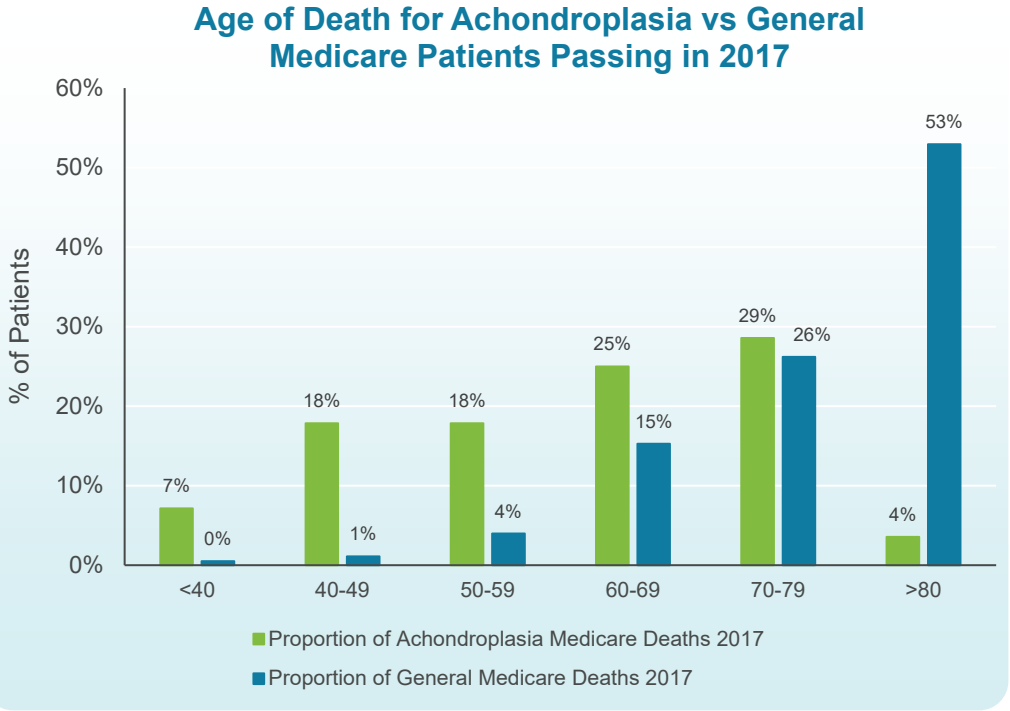
Achondroplasia: Higher Mortality

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

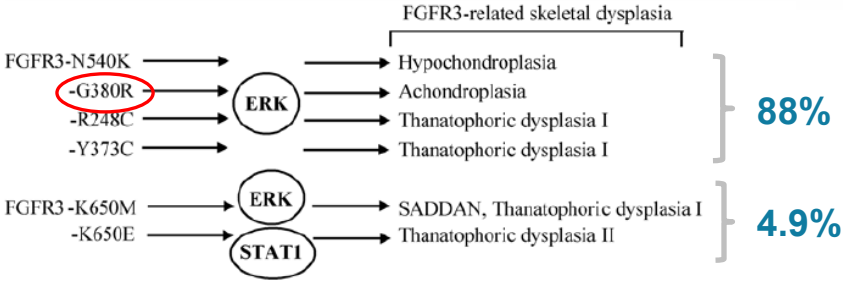
Markedly higher rates of death in these patients compared to the overall Medicare population, especially among patients <70 years



Data on file.

Achondroplasia: Autosomal Dominant Mutation in *FGFR3*

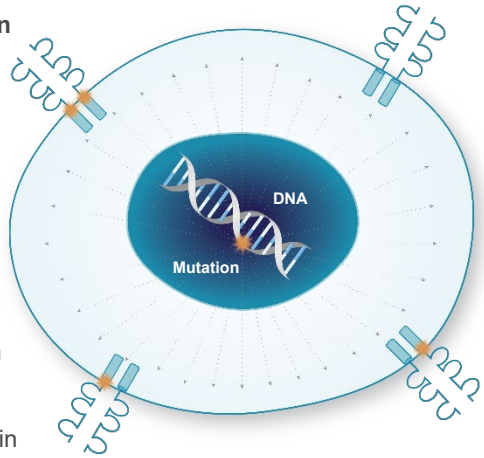
Mutations leading to different Skeletal Dysplasias[1]



Different Conformations of the FGFR3 G380R mutated dimer[2]

Double mutation
2.5 increase in activation in absence of ligand

Wildtype
Ligand-dependent activation



Single mutation
Activation in absence of ligand uncertain

Single mutation
Activation in absence of ligand uncertain

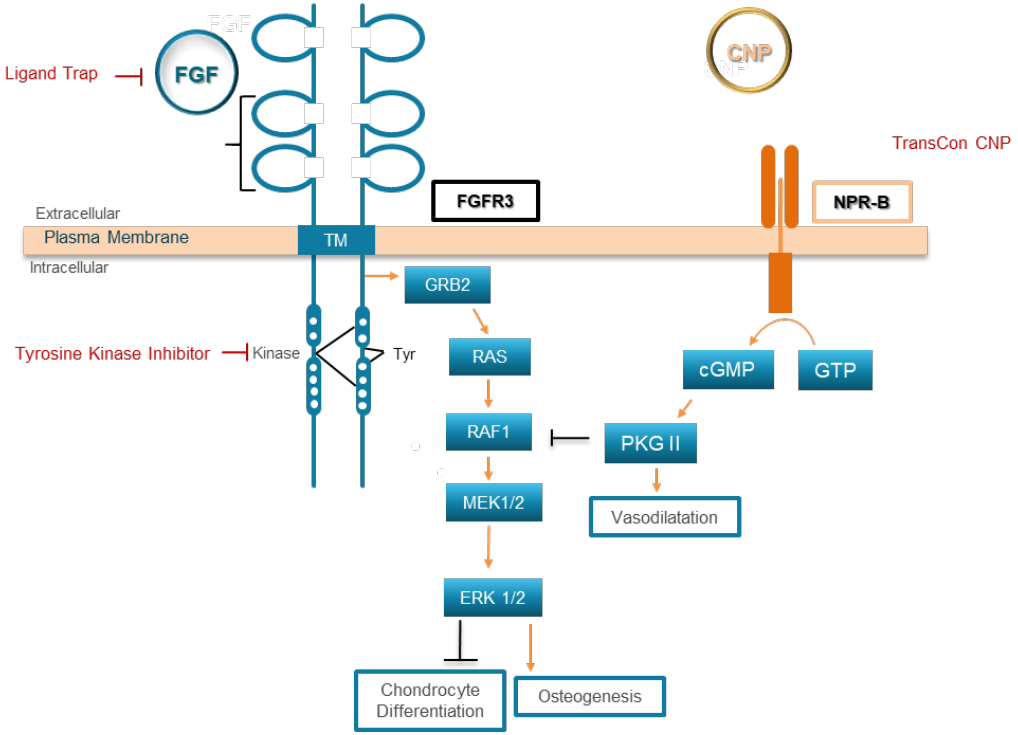
Downstream inhibition required to inhibit ligand-independent signaling

[1]Adapted from: Krejci P, et al. *PLoS ONE*, 2008, 3(12), e3961.
[2]He L, et al. *J Biological Chemistry*, 2010 Sep 24;285(39):30103-14.

Achondroplasia Signaling Defect is Well Understood

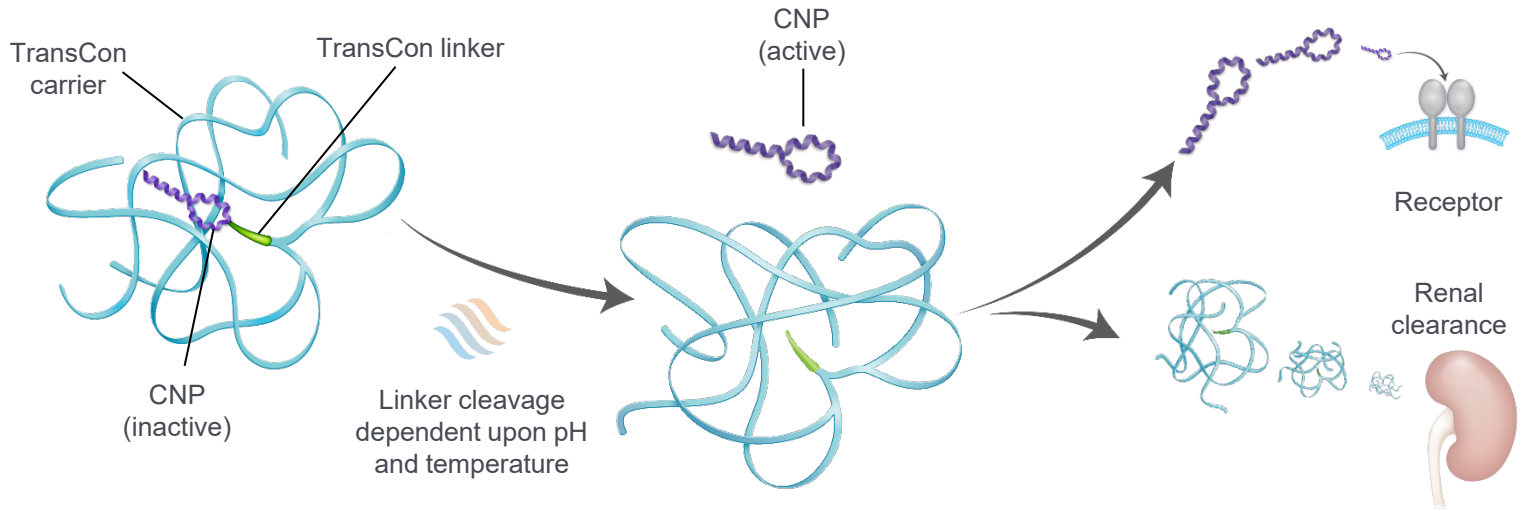
TransCon CNP continuously inhibits abnormal FGFR3 signaling, restoring proliferation and differentiation of chondrocytes to rebalance bone growth

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



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

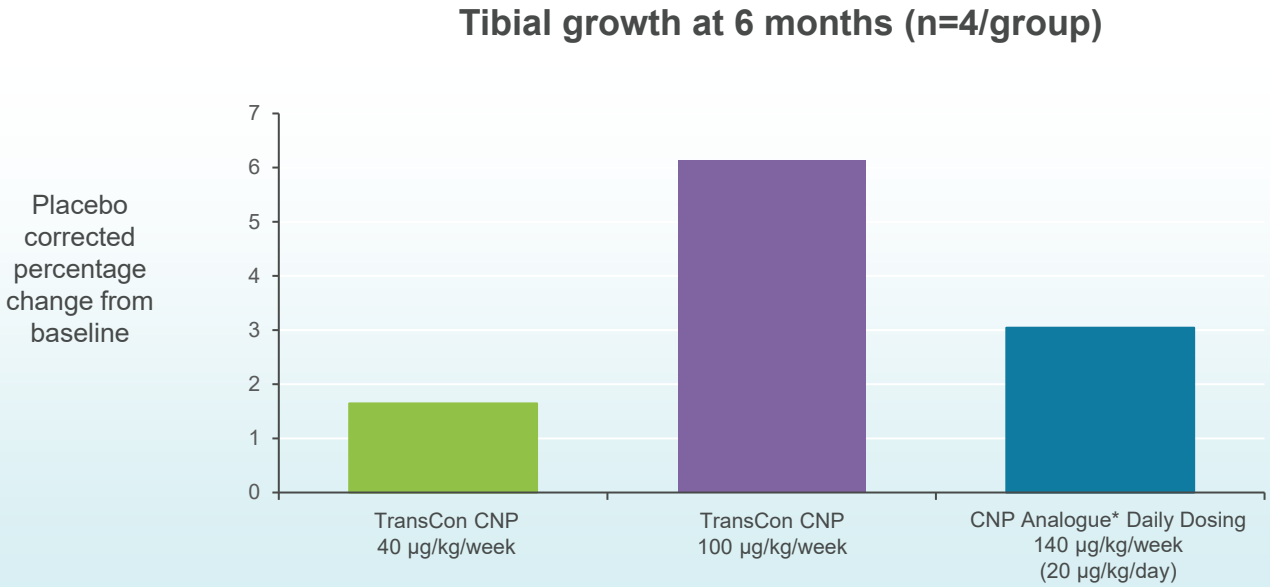
TransCon CNP Design



- 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

Breinholt VM et al. J Pharmacol Exp Ther. 2019;370(3):459-471.

Juvenile Healthy Monkey Growth Study



- 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

*Refers to a synthesized CNP analogue with a half-life of ~20 mins prepared by Ascendis Pharma

Breinholt VM et al. J Pharmacol Exp Ther. 2019;370(3):459-471.

Phase 1 Trial Design

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

Each dose tested sequentially starting at lowest dose[1]

Up to 10 subjects randomized in each dose cohort in a blinded manner

3 µg/kg → **10** µg/kg → **25** µg/kg → **75** µg/kg → **150** µg/kg

Data Safety Monitoring Board (DSMB) reviews blinded data after each dose cohort and approves escalation to next dose

Dosing assignments unblinded after DSMB review

Primary Endpoint

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

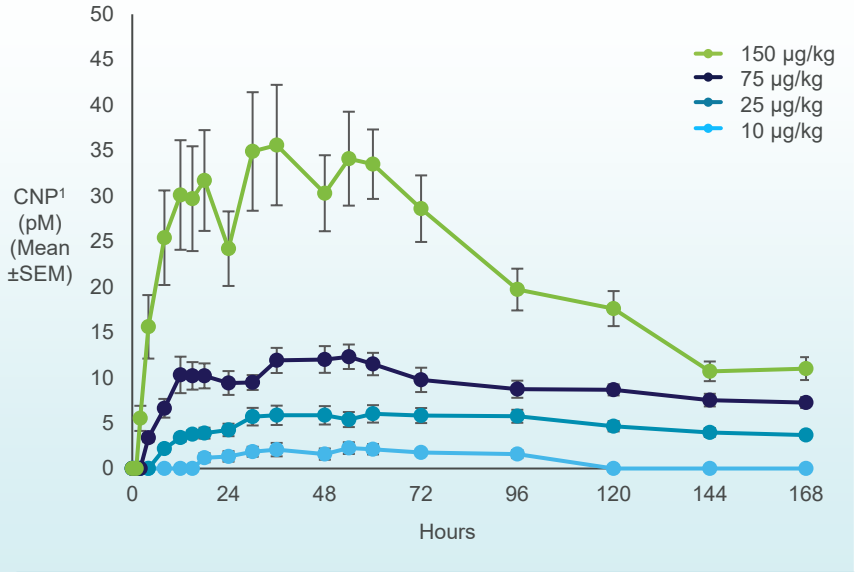
Secondary/Exploratory Endpoints

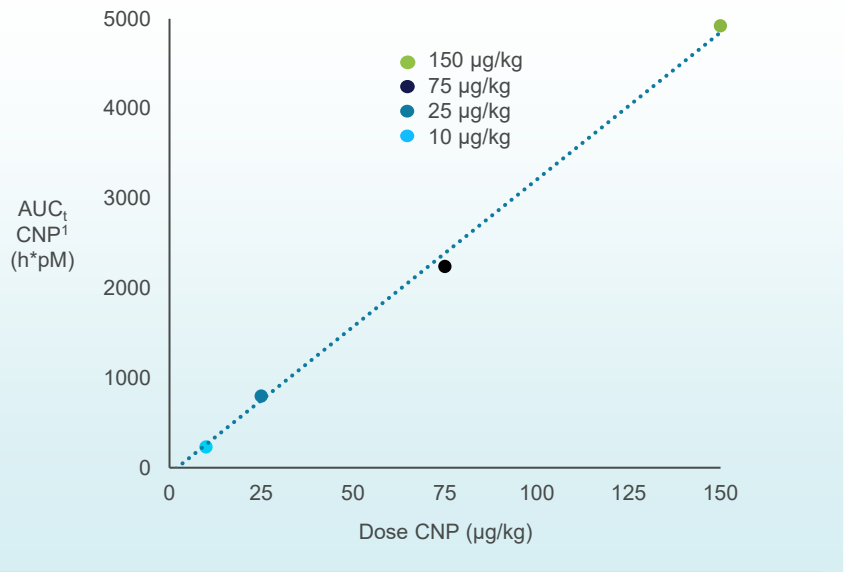
- Safety parameters and local tolerability assessment
- Pharmacokinetic parameters
- Other exploratory endpoints

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

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)

[1]CNP measured as CNP-38
Ota et al. Oral presentation at ISDS 2019.

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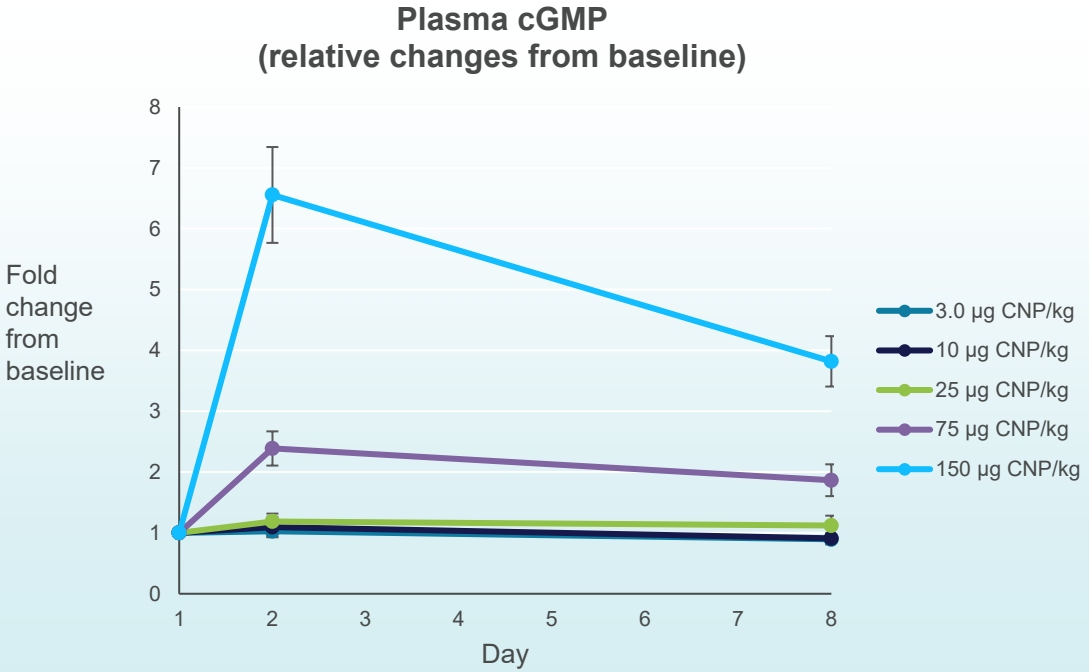
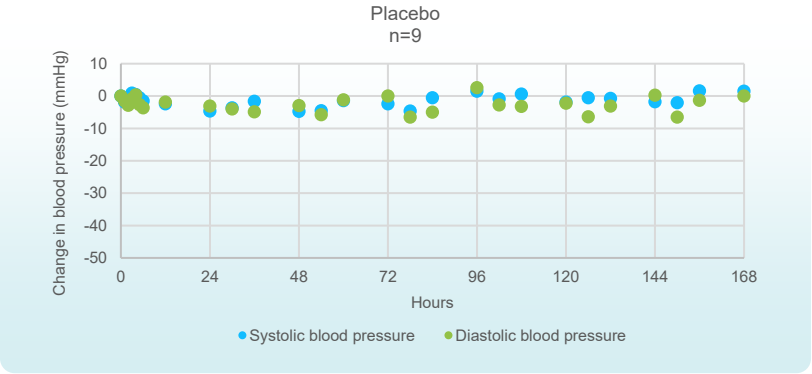
Dose Dependent cGMP[1] Response Demonstrated Receptor Engagement For 7 Days

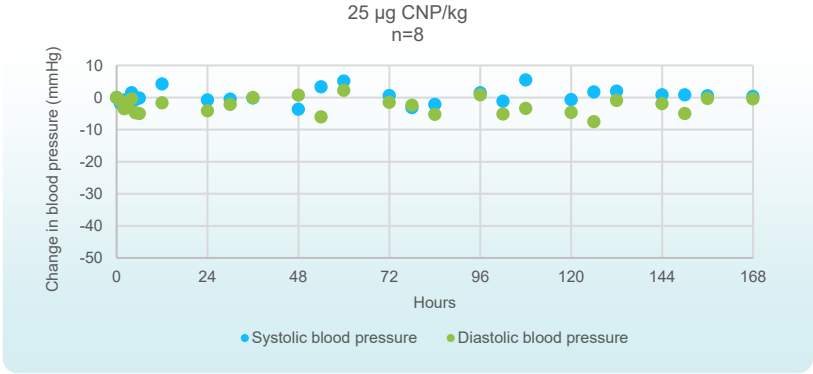
- cGMP is a secondary messenger of NPR-B activation by CNP
- cGMP levels correlated with TransCon CNP PK

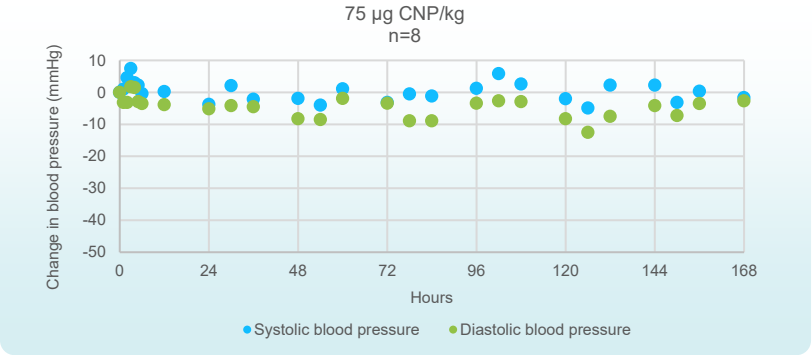


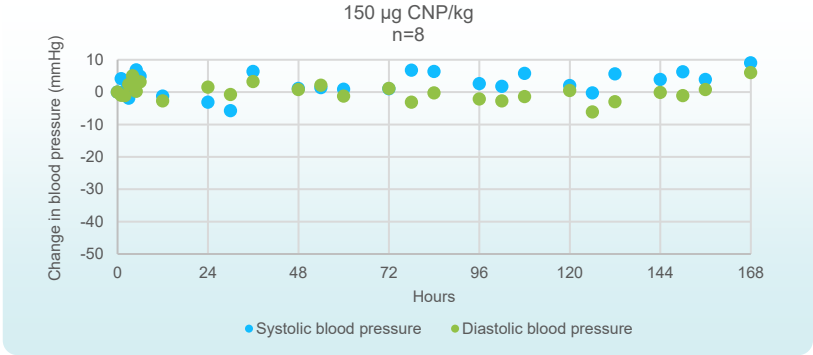
[1]cGMP=cyclic guanosine monophosphate.
Data on file.

Mean Resting Blood Pressure Unchanged from Predose[1]









Change in systolic blood pressure Change in diastolic blood pressure

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

TransCon CNP: Safety Profile in Phase 1

- No serious AEs were reported in the trial
- TransCon CNP was generally well tolerated at doses up to 150 µg/kg
- No anti-CNP antibodies detected in any subjects
- Mean resting blood pressure and heart rate were unchanged from pre-dose at all time points, in all cohorts
- Mean orthostatic changes in vital signs appear unrelated to TransCon CNP exposure; consistent between placebo and TransCon CNP cohorts
- Injections were well tolerated in all dose cohorts

ACHieve Ongoing and Enrolling

ACHieve STUDY

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

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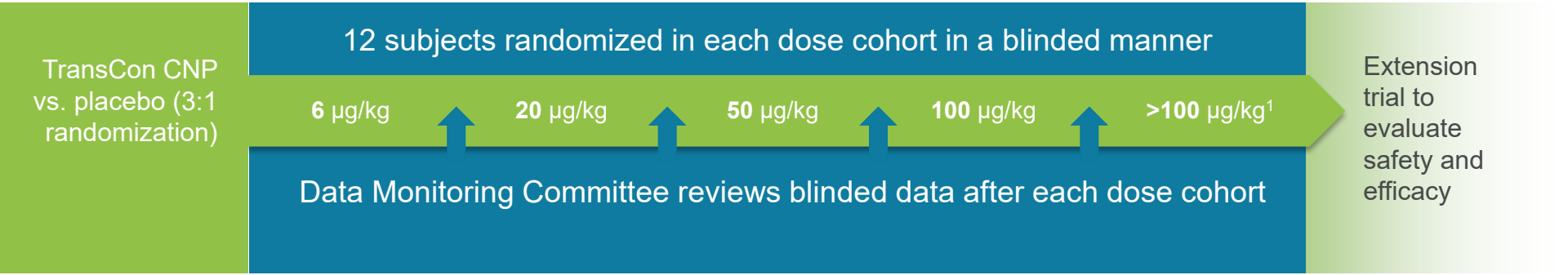
TransCon CNP: Phase 2 Trial Design

ACcomplisH TRIAL

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



Primary Endpoint

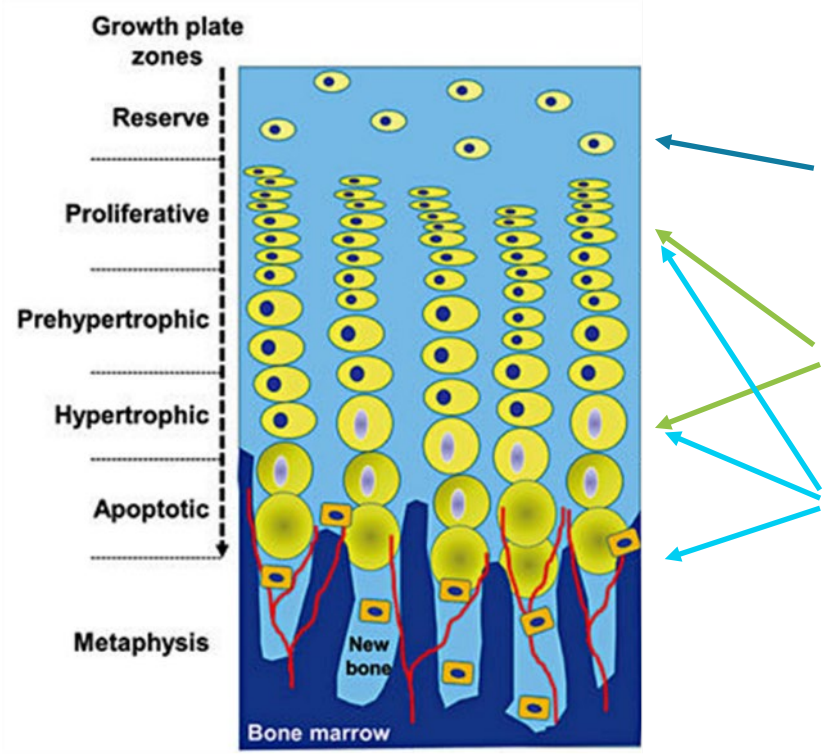
- Annualized height velocity, as measured after 12 months of weekly TransCon CNP treatment

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

[1]Dose to be determined. If needed, based on emerging data.

Growth Biology: Rationale for Combination Effects of Different Pathways



Williams GR, Eur Thyroid J 2013;2:3

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

IGF-1 stimulates chondrocyte proliferation, hypertrophy and survival

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

Sources: Endocrine Reviews 1987 8 426–438. Endocrine Connections (2018) 7, R212–R222. J Mol Endocrinol. 2014; 53(1): T1–T9.

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 designed to provide 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 ACcomplisH phase 2 trial (ages 2–10 years) initiated, with escalation of sequential dose cohorts in ACcomplisH throughout 2020
- Expansion of clinical program in China through VISEN Pharmaceuticals
  - ACHieve initiated; ACcomplisH China expected to be initiated Q4 2020
- Received orphan designation for TransCon CNP in US and Europe for achondroplasia
- Potential for significant impact on patients' lives, including height and comorbidities

Oncology

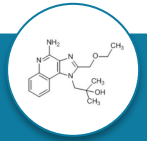
Vision in Oncology

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

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

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

Advancing a diversified high-value pipeline



TransCon TLR7/8 Agonist

TransCon IL-2 β/γ

TransCon VEGF-TKI

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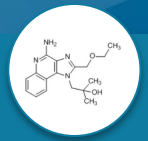
TransCon TLR7/8 Agonist

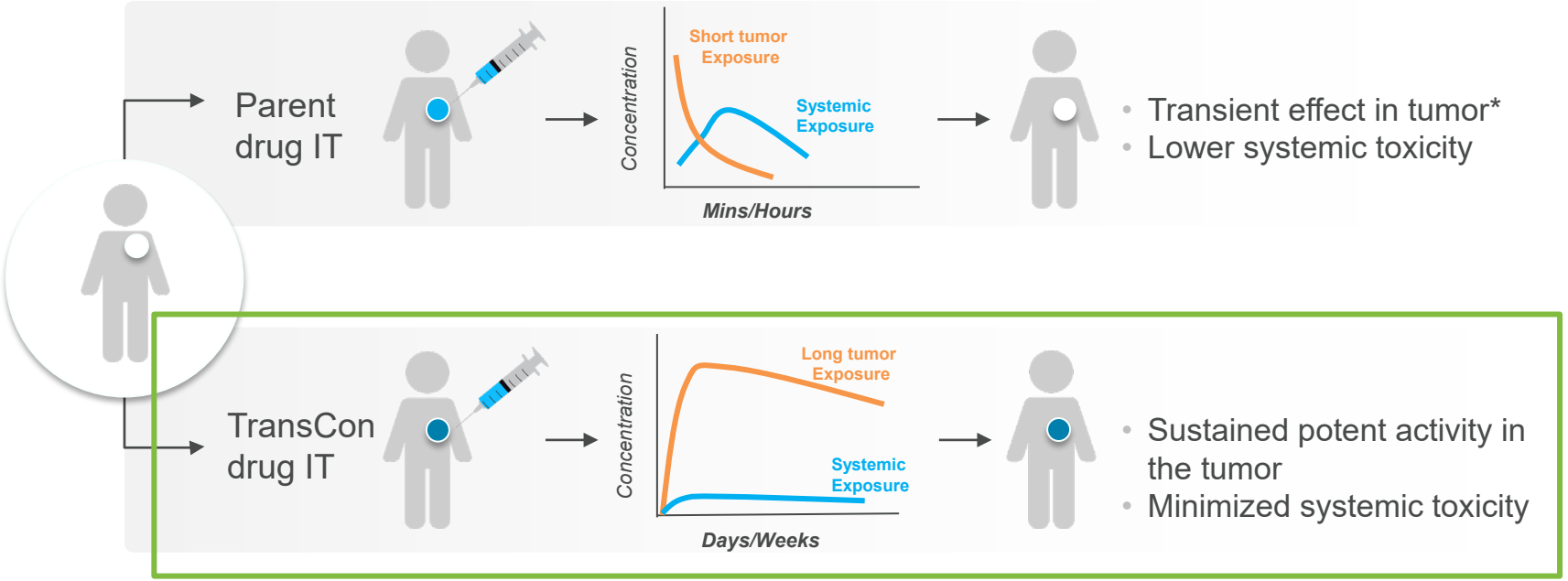
Oncology Product Candidate



TransCon TLR7/8 Agonist

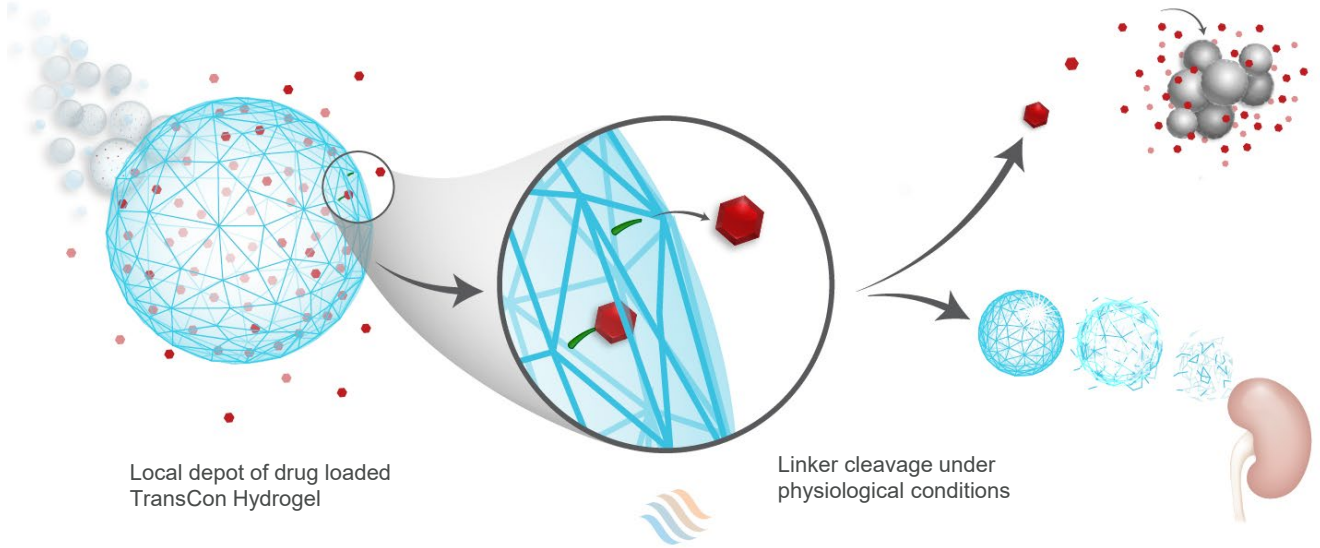
Potential to Transform Efficacy, Safety and Practicality of Intratumoral Treatments

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



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

Resiquimod Loaded onto TransCon Hydrogel for Intratumoral Sustained Delivery

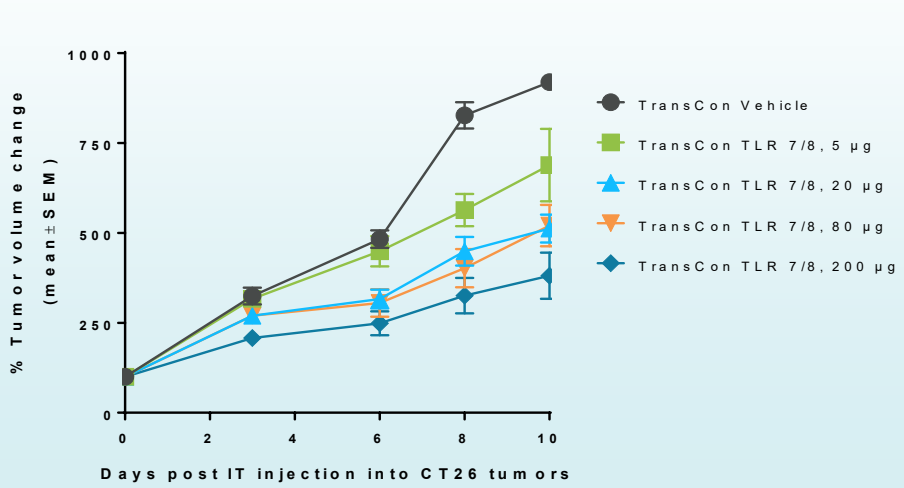


- Resiquimod transiently conjugated to TransCon Hydrogel carrier, designed to provide sustained local release of unmodified parent drug
- Designed to provide sustained activation of tumoral myeloid lineages driving tumor antigen release/presentation and induction of immune stimulatory cytokines

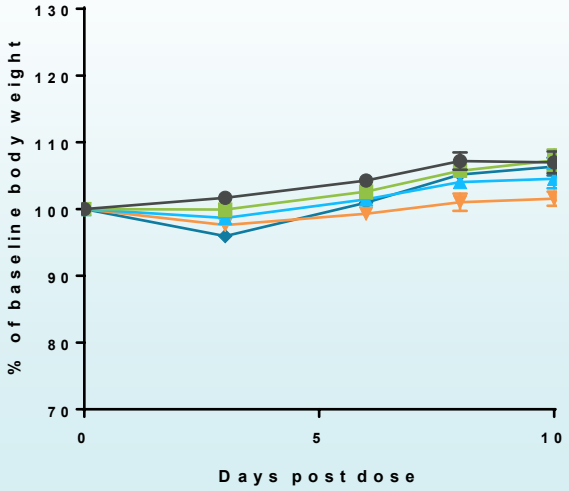
Dose-dependent Tumor Growth Inhibition Following a Single IT Injection of TransCon TLR7/8 Agonist

Single IT Dosing

Tumor Growth:
Dose-dependent Inhibition



Body Weights:
All Doses Well Tolerated



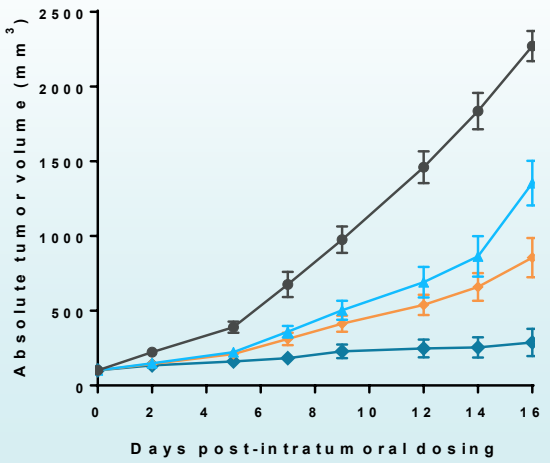
Consistent with MOA, local inflammation and some tumor ulcerations observed

Zuniga et al. SITC 2019.

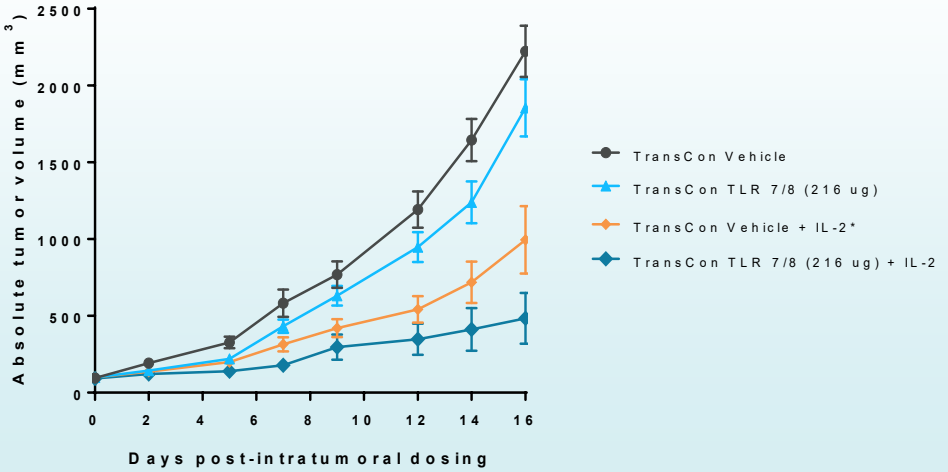
Single-dose of TransCon TLR7/8 Agonist Triggered Abscopal Anti-Tumor Inhibition and Enhanced Anti-tumor Effects of IL-2

Single IT Dosing

Injected Tumor



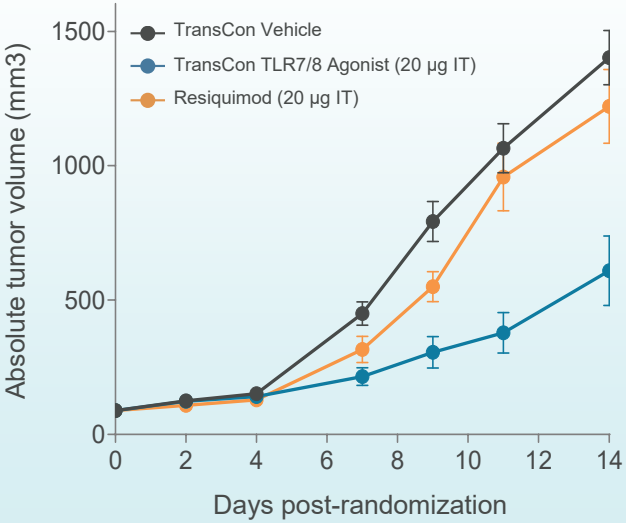
Non-injected Tumor

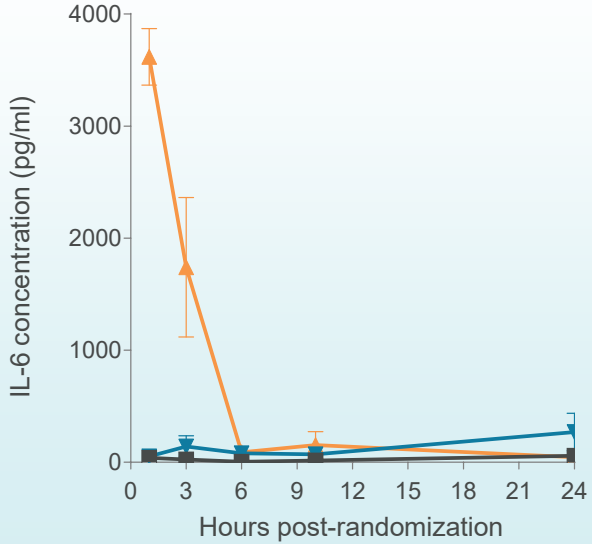


*IL-2 dosed at 20 ug twice daily on days 0-4, once daily on days 8-12
Zuniga et al. SITC 2019.

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

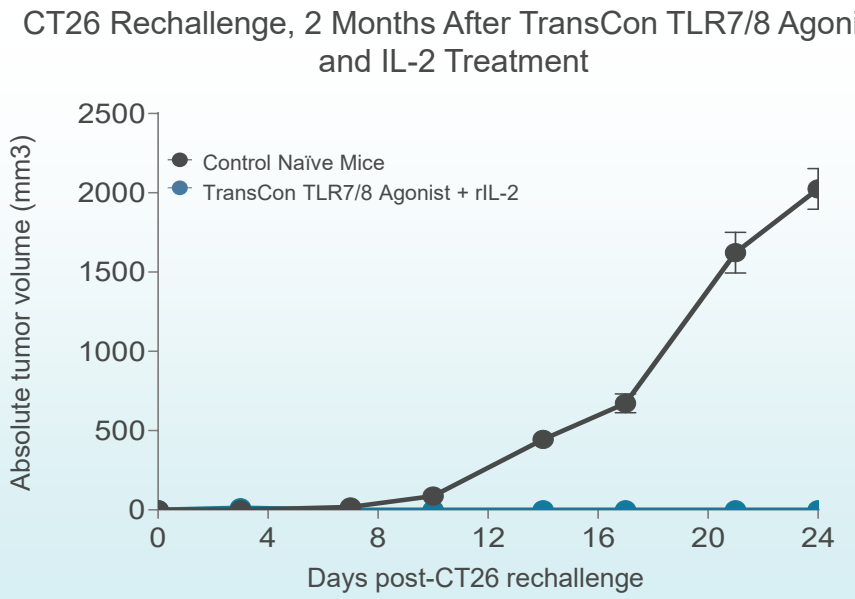
Tumor Growth Inhibition (CT26) with Low Systemic Cytokine Induction





Zuniga et al. SITC 2019.

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



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 ± SEM.

Zuniga et al. SITC 2019.

TransCon TLR7/8 Agonist - Summary

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

TransCon IL-2 β/γ

Oncology Product Candidate

TransCon
IL-2 β/γ

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

Suboptimal receptor binding

- Two receptors: IL-2Rα/β/γ and IL-2Rβ/γ
- α/β/γ receptor activates Tregs and endothelial cells, reducing efficacy and increasing risk of capillary leak syndrome

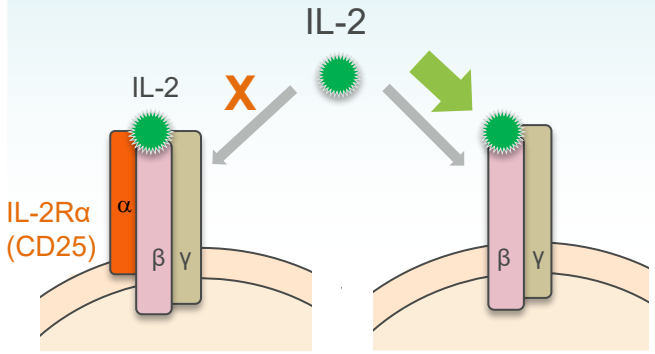
Suboptimal PK

- Short half life of IL-2 (~1.5 h)
- High Cmax 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-2Rα binding to selectively activate IL-2Rβ/γ



Promotes Treg
Limit anti-tumor responses

Promotes CD8⁺
Promote anti-tumor responses

2) Generate a product with long-lasting exposure avoiding high Cmax

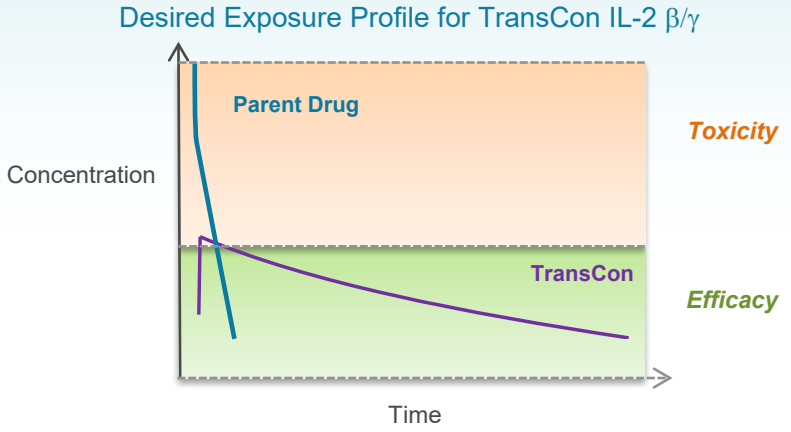


Figure adapted from Onur et al., Biomed Intell, 2019

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Design of TransCon IL-2 β/γ: 1) Designed for Desired Receptor Binding

Generation of IL-2 Variant

Introduction of cysteine at α–binding site of IL-2 (aldesleukin)

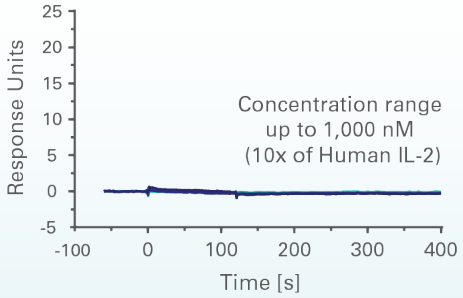
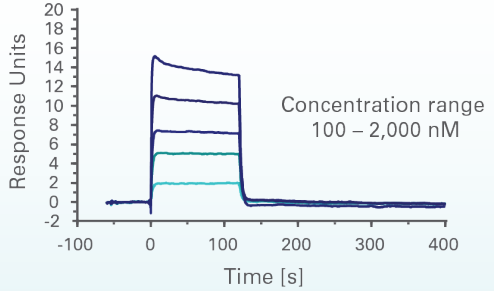
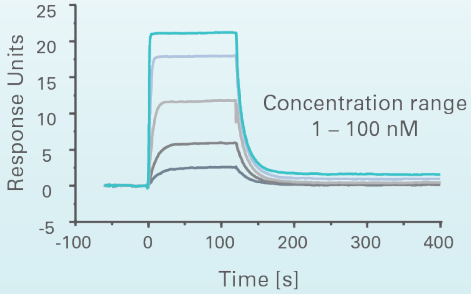
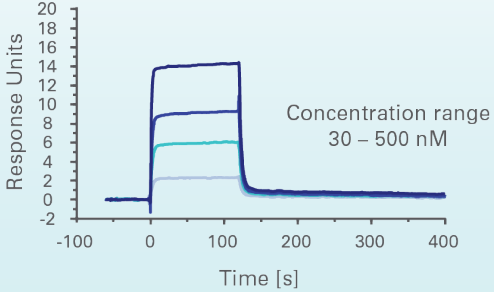
Blocking IL-2Rα–binding

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

Optimized IL-2 β/γ receptor selectivity and potency by permanent site-selective PEG conjugation at IL-2Rα–binding site

Rosen et al. AACR 2020.

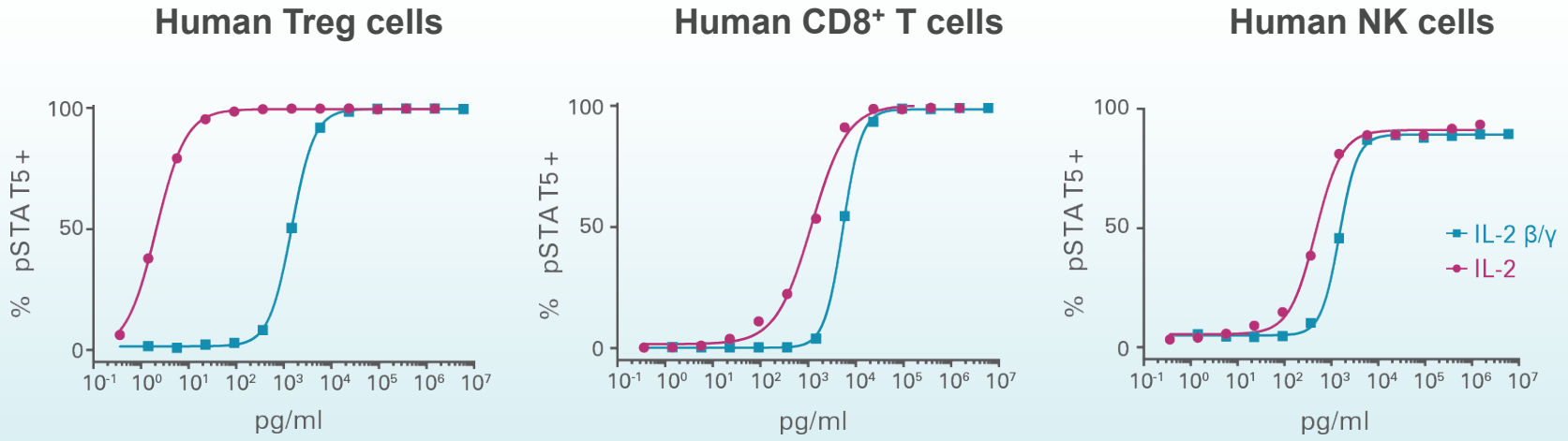
Receptor Selectivity Demonstrated in Binding Assays

	Binding to IL-2R α-chain	Binding to IL-2R β-chain
IL-2 β/γ		
Human IL-2		

IL-2 β/γ demonstrated strong receptor bias with reduced IL-2Rα binding and well-retained IL-2Rβ binding

Rosen et al. AACR 2020.

Receptor Selectivity Confirmed in Primary Human Cells



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

Rosen et al. AACR 2020.

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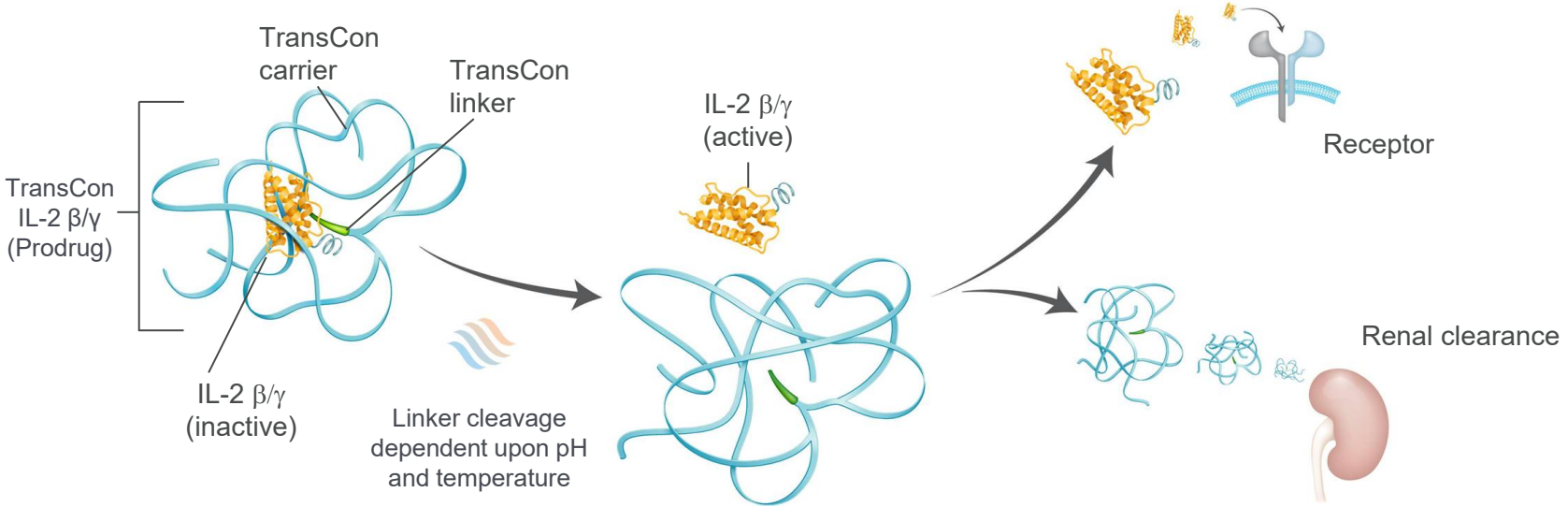
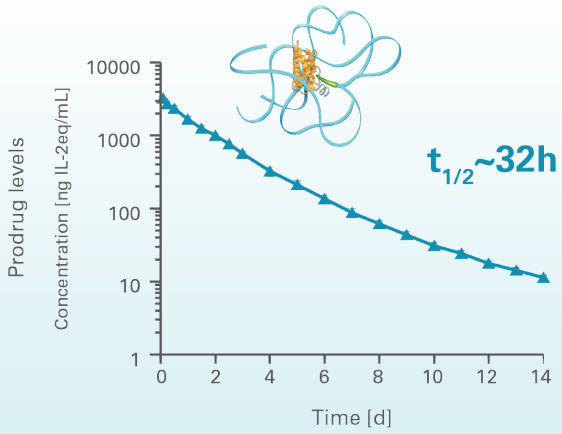
Design of TransCon IL-2 β/γ:
2) TransCon Technology to Optimize Exposure



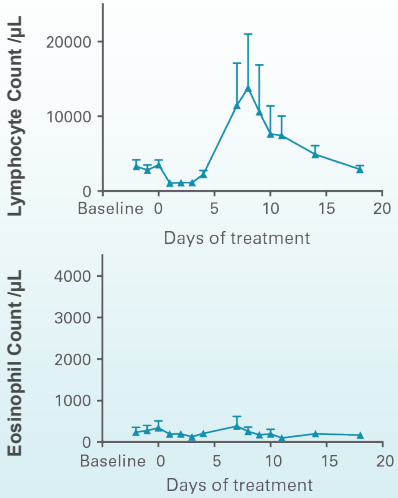
Sustained, long-lasting exposure utilizing the TransCon hGH linker and carrier, which could support every 3 week dosing

Single Dose TransCon IL-2 β/γ Induced Robust Lymphocyte but Lower Eosinophil Expansion in NHP* When Compared to Aldesleukin

TransCon IL-2 β/γ prodrug plasma PK

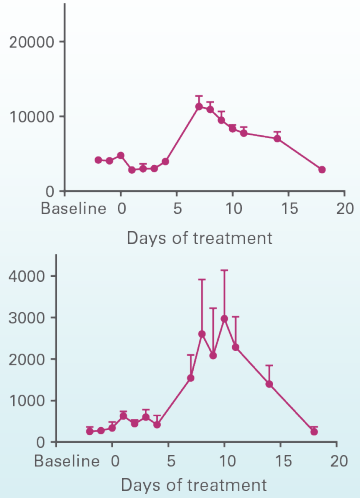


TransCon IL-2 β/γ (single 1mg dose)



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

Aldesleukin (0.4 mg/day x 5 days)



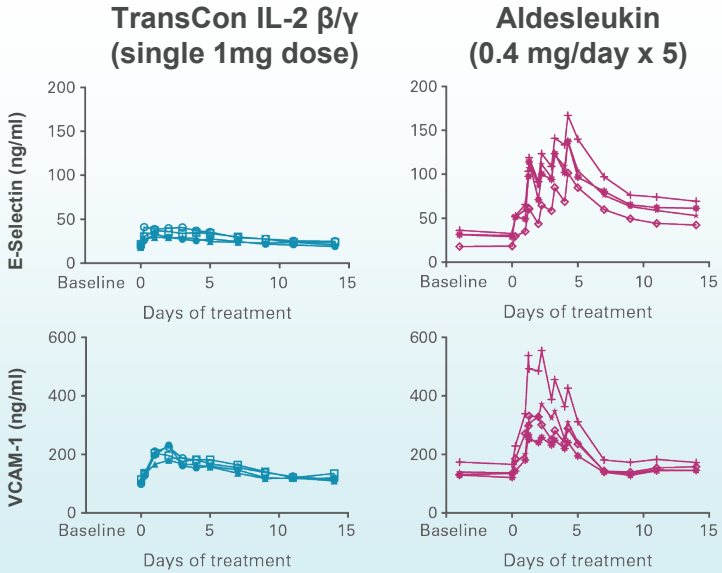
0.4 mg daily dose /animal;
average animal weight 9.2 kg (7.7–10.6 kg)

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

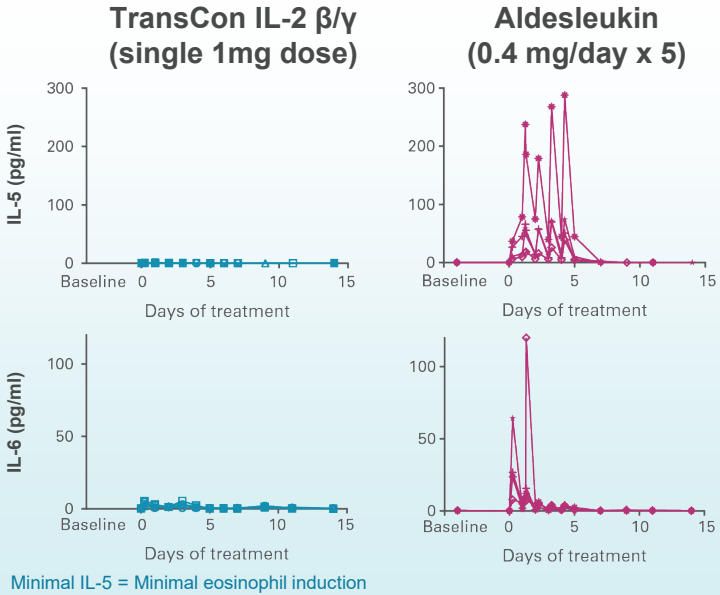
NHP = non-human primates
Rosen et al. AACR 2020.

Single Dose TransCon IL-2 β/γ Induced Lower Endothelial Cell Injury and Systemic Inflammation Markers in NHP When Compared to Aldesleukin

Endothelial cell injury markers



Systemic inflammation markers



Minimal IL-5 = Minimal eosinophil induction

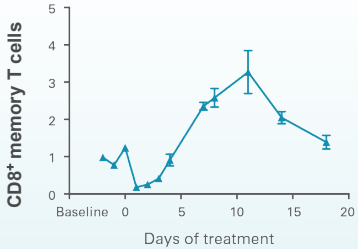
Well tolerated in vivo with lower induction of markers of endothelial cell injury or systemic inflammation, suggesting potential low risk of vascular leak syndrome (VLS)

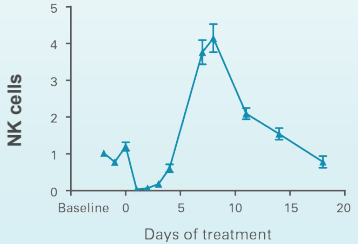
Rosen et al. AACR 2020.

Single Dose TransCon IL-2 β/γ Induced Sustained CD8+ T Cell and NK Cell Expansion and Activation in NHP

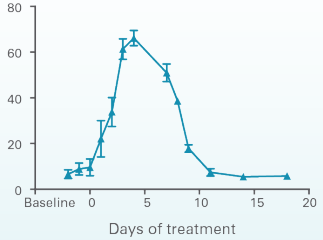
CD8+ T cell and NK cell expansion

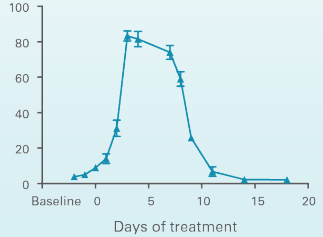
Fold Change





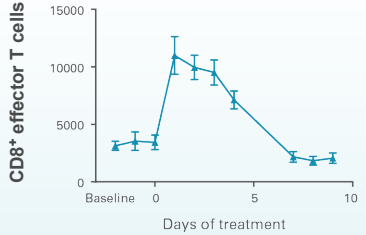
% Ki67+

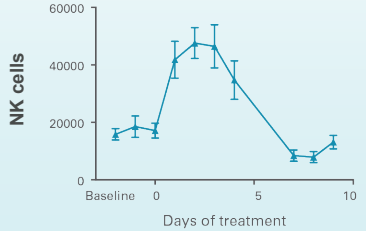




CD8+ T cell and NK cell activation

Granzyme B MFI





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

Rosen et al. AACR 2020.

TransCon IL-2 β/γ – Potential Best-in-Class IL-2 Molecule

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

TransCon VEGF-TKI

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

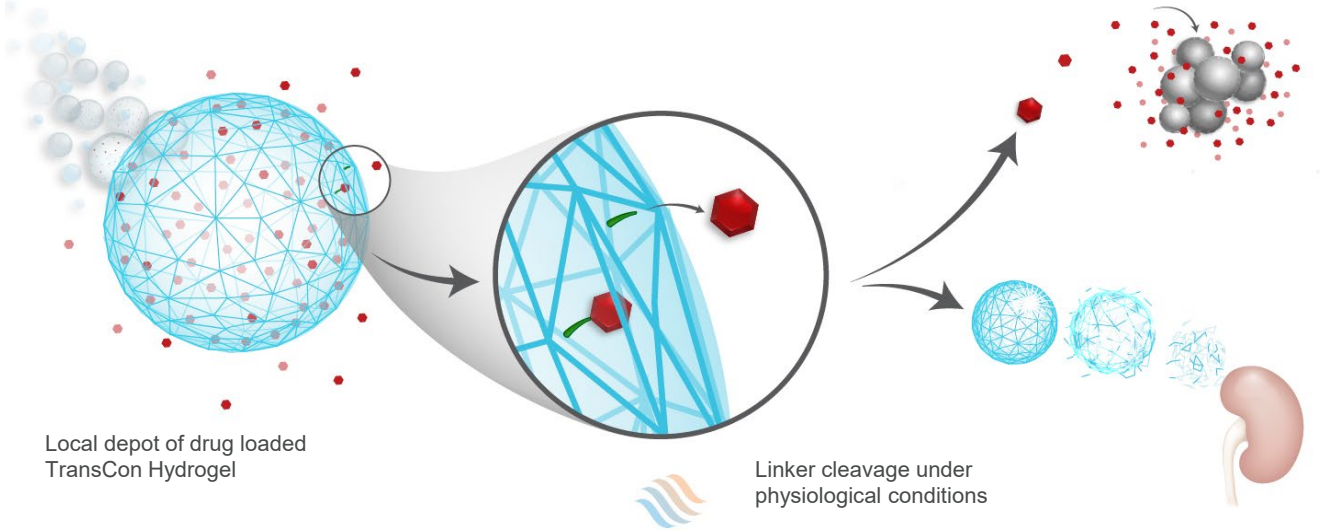
Safety
- Lower systemic exposure expected to enable aggressive multiagent therapies

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

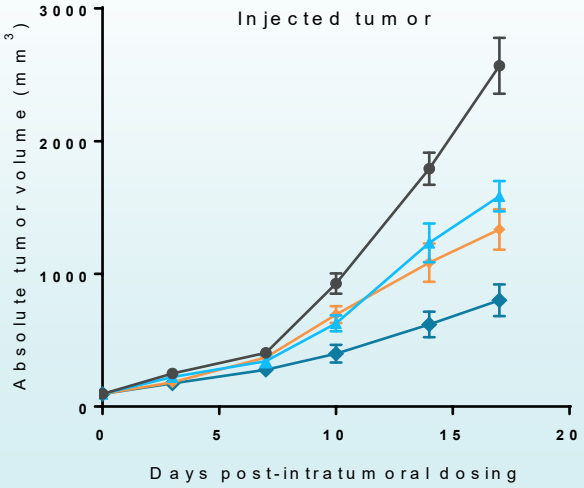
TransCon VEGF-TKI: Axitinib Loaded onto TransCon Hydrogel for Intratumoral Sustained Delivery

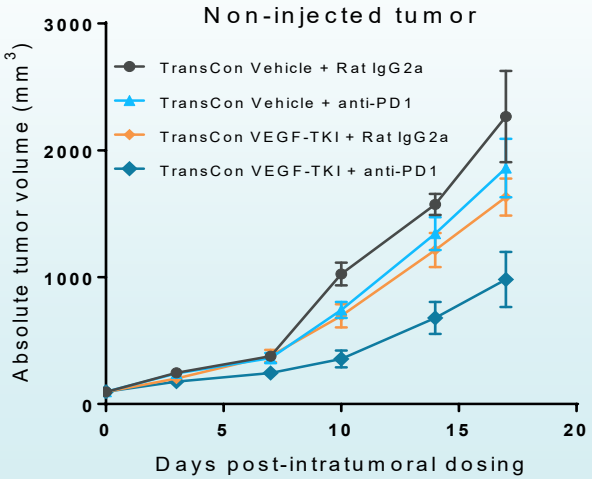


- Axitinib transiently conjugated to TransCon hydrogel carrier, designed to provide sustained release of unmodified axitinib
- Designed to provide sustained modulation of the tumor microenvironment with potential for direct anti-tumor effects

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)





Data on file.

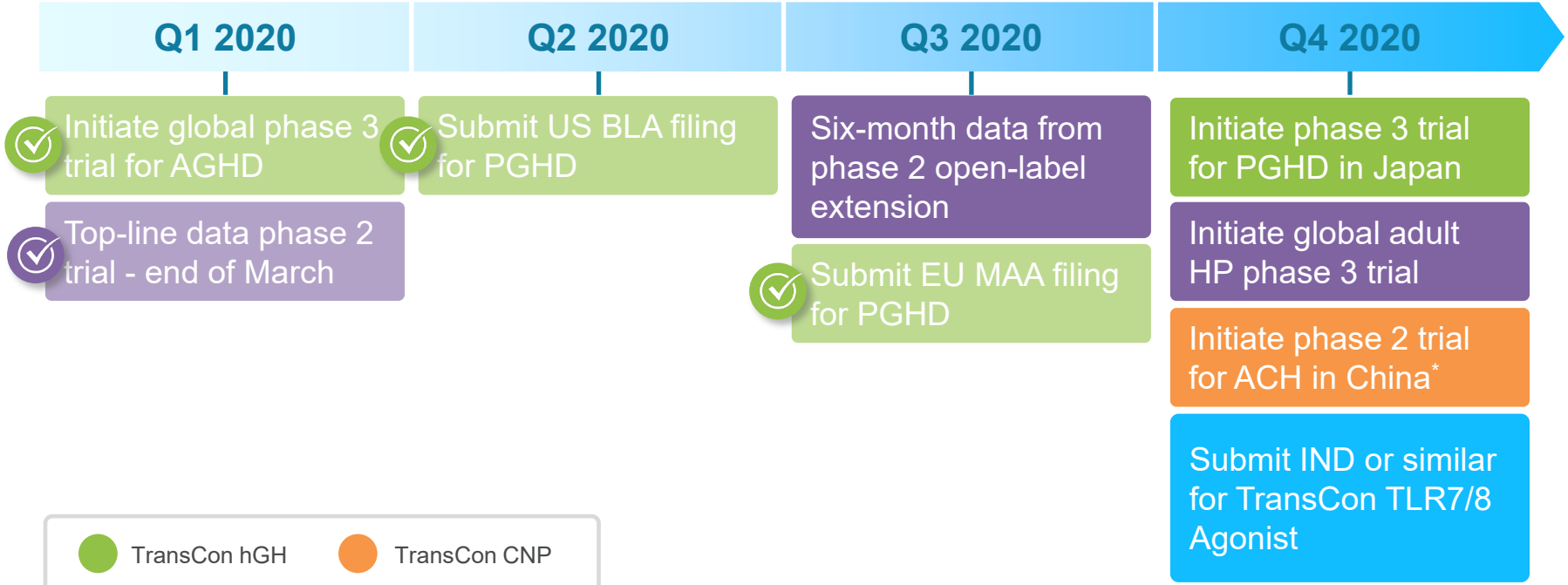
TransCon VEGF-TKI – Summary

- New approach to modulation of tumor microenvironments, with the potential for direct anti-tumor effects
  - 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 observed with small molecules, cytokines and antibodies
  - TransCon intratumoral technologies acceptance into the FDA´s Emerging Technology Program
- Potentially differentiated product candidates in multiple indications
  - TransCon TLR7/8 Agonist
  - TransCon IL-2 β/γ
  - TransCon VEGF-TKI
- Potent anti-tumor activity of TransCon oncology candidates observed in preclinical studies
- First IND or similar expected to be filed for TransCon TLR7/8 in Q4 2020, followed by TransCon IL-2 β/γ in 2021
- Over 20 patents and applications covering TransCon oncology candidates

Selected 2020 Expected Milestones



*Conducted through strategic investment in VISEN Pharmaceuticals