UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO SECTION 13a-16 OR 15d-16
UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the month of December, 2021

Commission File Number: 001-36815

Ascendis Pharma A/S

(Exact Name of Registrant as Specified in Its Charter)

Tuborg Boulevard 12
DK-2900 Hellerup
Denmark
(Address of principal executive offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F.

Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

The presentation slides attached hereto as Exhibit 99.1 were presented in a webcast on December 14, 2021 at the Company's virtual R&D Program Update.

The furnishing of the attached presentation is not an admission as to the materiality of any information therein. The information contained in the presentation is summary information that is intended to be considered in the context of more complete information included in the Company's filings with the Securities and Exchange Commission (the "SEC") and other public announcements that the Company has made and may make from time to time. The Company undertakes no duty or obligation to update or revise the information contained in this report, although it may do so from time to time as its management believes is appropriate. Any such updating may be made through the filing or furnishing of other reports or documents with the SEC or through other public disclosures.

Exhibits

99.1 Virtual R&D Program Update Presentation.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Ascendis Pharma A/S

Date: December 15, 2021

By: /s/ Michael Wolff Jensen
Michael Wolff Jensen
Senior Vice President, Chief Legal Officer

Exhibit 99.1

ASCENDIS PHARMA A/S

Virtual R&D Program Update

December 14, 2021

Welcome
& Agenda Overview

Scott T. Smith
Senior Vice President, Chief Financial Officer

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, expectations regarding prospective products, availability of funding, clinical trial results, product approvals and regulatory pathways, collaborations, licensing or other arrangements, the scope, support 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 SKYTROFA and 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, future results of current and anticipated products, and the future operations of VISEN Pharmaceuticals, 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 preliminary prospectus supplement related to the proposed public offering and our most recent Annual Report on Form 20-F filed with the SEC on March 10, 2021 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.

SKYTROFA has been approved by the U.S. Food and Drug Administration for the treatment of pediatric growth hormone deficiency. SKYTROFA is and has been under clinical investigation and has not yet been approved for marketing by the European Medicines Agency or other foreign regulatory authorities. In addition, this presentation concerns other product candidates that are 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.

Virtual R&D Program Update Agenda

9:00-9:05 a.m. E.T.

Welcome & Agenda Overview
Scott T. Smith *SVP, CFO*

9:05–9:10 a.m. E.T.

Opening Comments
Jan Møller Mikkelsen, *President & CEO*

9:10–9:55 a.m. E.T.

TransCon™ PTH
Aimee D. Shu, M.D.
VP, Clinical Development, Endocrine Medical Sciences

Guest Speaker
Aliya Khan, M.D., *Clinical Professor of Medicine and Director of the Calcium Disorders Clinic at St. Joseph's Healthcare, McMaster University*

9:55–10:35 a.m. E.T.

TransCon CNP
Kennett Sprogøe, Ph.D.
SVP, Head of Innovation and Research

Marie-Louise C. Hartoft-Nielsen, M.D., Ph.D.
Senior Medical Director, Clinical Development

10:35–11:15 a.m. E.T.

TransCon TLR7/8 Agonist
Kennett Sprogøe, Ph.D.
SVP, Head of Innovation and Research

Stina Singel, M.D., Ph.D.
Head of Clinical Development, Oncology

11:15–11:30 a.m. E.T.

Questions & Answers

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Opening Comments

Jan Møller Mikkelsen
President & Chief Executive Officer

Introduction to Ascendis Pharma

- **Founded** in 2007 in Copenhagen, Denmark
- **Publicly listed** on NASDAQ since 2015 (ASND)
- **TransCon™**: Innovative technology platform utilized in all product candidates
- **Diverse** clinical stage Endocrinology Rare Disease and Oncology pipeline
- **Our mission**: Develop best-in-class therapeutics addressing unmet medical needs
- **Our values**: Patients, Science and Passion

An expanding global footprint

Committed to Making a Meaningful Difference in Patients' Lives

*VISEN Pharmaceuticals (known as Visen) was established in 2018 to develop and commercialize endocrinology rare disease therapies in Greater China.

Vision 3x3: Building a Leading Global BioPharma Company

Our Goal Is to Achieve Sustainable Growth through Multiple Approaches

- Obtain regulatory approval for three independent Endocrinology Rare Disease products:
  - TransCon hGH 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]Received positive CHMP opinion on November 12, 2021. Final EC decision expected within 67 days, or by end of January 2022.
[2]In development in Greater China through strategic investment in VISEN Pharmaceuticals.
[3]Japanese riGHt Trial.
[4]Global foresiGHt Trial.
[5]North American and European PaTHway Trial, Japanese PaTHway Japan Trial.
[6]North America, Europe, and Oceania ACcomplisH Trial.
[7]transcendIT-101 Trial.
[8]IL-2elieve Trial.

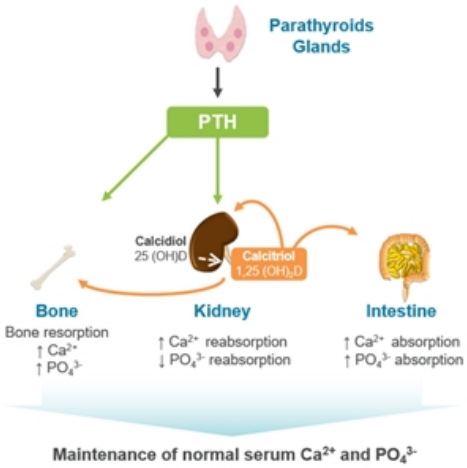
All product candidates are investigational.
For investor communication only. Not for use in product promotion.
Not for further distribution.

TransCon PTH Clinical Update

Aimee D. Shu, M.D.
VP, Clinical Development,
Endocrine Medical Sciences

Hypoparathyroidism: Insufficient Parathyroid Hormone

- An **intact PTH axis** maintains normal serum calcium and phosphate
  - By acting on bone, kidney, and intestine
  - Promoting normal nerve and muscle function
- **Hypoparathyroidism** is a two-hormone deficiency
  - Resulting in broad systemic dysfunction



Hypoparathyroidism is the last classical hormone deficiency for which complete hormone replacement has been elusive

DeLuca HF. *N Engl J Med.* 1973 Aug 16;289(7):359-365. Haussler MR et. al. *N Engl J Med.* 1977 Nov 3;297(18):974-983. Reichel H et. al. *N Eng J Med.* 1989 Apr 13; 320(15):980-991. Bilezikian JP, et. al. *J Bone Miner Res.* 2011 Oct;26(10):2317-37.

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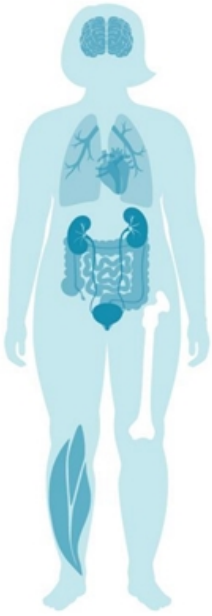
Hypoparathyroidism: Multiple Complications

- Brain fog
- Laryngospasm & bronchospasm
- Infections
- Renal failure
- Numbness & tingling
- Muscle spasms
- Fatigue



- Seizures
- Anxiety & depression
- Heart failure
- Arrhythmias
- Abnormal skeletal dynamics
- Abnormal tissue calcifications
- Pain

Shobak DM et. al. *J Clin Endocrinol Metab.* 2016 June 01;101(6):2300-2312

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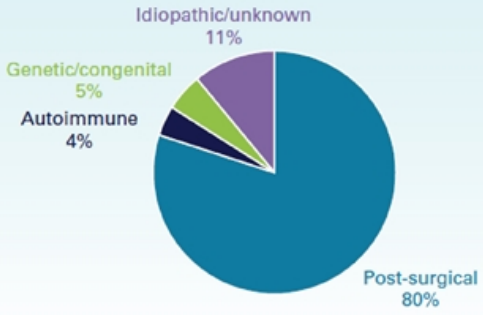
Hypoparathyroidism: Acquired and Inherited Etiologies

Cause of Hypoparathyroidism



Time to Hypoparathyroidism Diagnosis

	Post-surgical (n=117)	Non-surgical (n=29)
~6 months	51%	21%
6 months-1 year	29%	24%
1-2 years	9%	14%
3-4 years	6%	10%
5-10 years	1%	3%
11-15 years	3%	10%
16-20 years	0%	7%
>20 years	1%	10%

Etiologies as reported by 146 respondents to the *Voices of Hypoparathyroidism* survey

Murphy *et. al.*, Voices of Hypopara survey, poster presented at The Endocrine Society meeting, 2021.
Clarke et. al. *J Clin Endocrinol Metab.* 2016;101(6):2284-2299.

Chronic Hypoparathyroidism: Significant Patient Population

Estimated Prevalence: ~400k in these 5 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

China

~180k–220k

- 2020, Sui et. al, Time trend analysis of thyroid cancer surgery in China: single institutional database analysis of 15,000 patients
- 2019, Zhao et. al., Features and trends of thyroid cancer in patients with thyroidectomies in Beijing, China between 1994 and 2015: a retrospective study
- World Bank, 2018
- Ascendis market research

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Conventional Therapy Targets Symptoms, Not Underlying Disease

Calcitriol (active vitamin D)
or its analogue alfacalcidol

Endogenous production diminished due to insufficient PTH

Calcium

Often requires high pill burden

Fails to restore normal PTH physiology and introduces secondary complications

- Attempts to increase serum calcium to prevent symptoms
- Fails to normalize skeletal dynamics
- Fails to improve diminished quality of life
- Increases filtered load of calcium—increasing the risk for developing kidney stones, nephrocalcinosis, and chronic kidney disease

Bilezikian JP et. al. *J Clin Endocrinol Metab.* 2016;101(6):2313-2324

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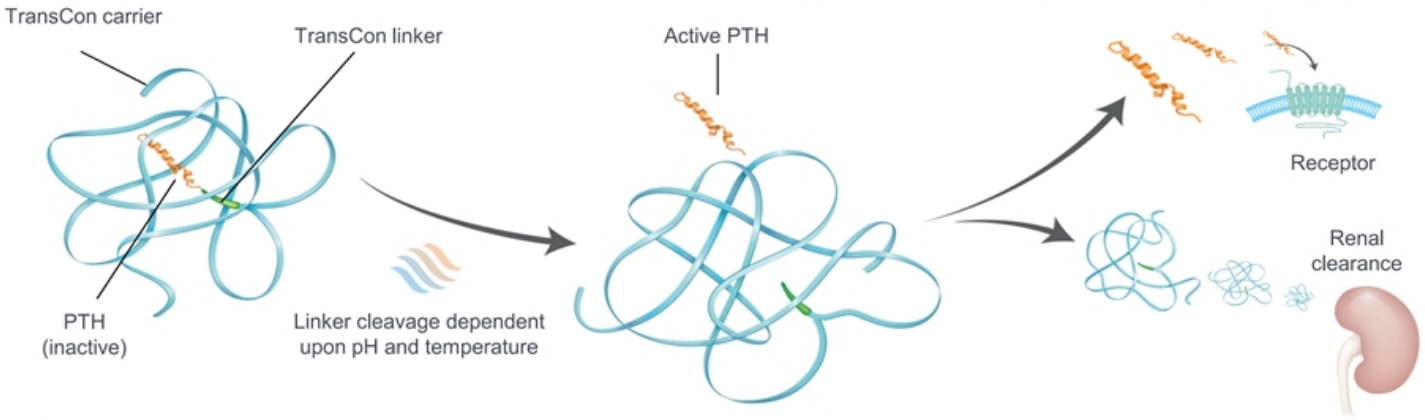
Hypoparathyroidism: Goals of an Ideal Therapy

	Untreated hypoparathyroidism	Ideal therapy
Serum calcium	↓	normalize
Serum phosphate	↑	normalize
Urine calcium	↑	normalize
Independence from conventional therapy	n/a	yes
Skeletal health	↓	normalize
Quality of life	↓	normalize

TransCon PTH Designed to Be a Hormone Replacement Therapy



- TransCon PTH is a sustained-release prodrug designed to provide stable PTH levels in the physiological range for 24 hours/day

Holten-Andersen L, et. al. *J Bone Miner Res.* 2019 Nov;34(11):2075-2086.
Karpf DB, et. al. *J Bone Miner Res.* 2020 Aug;35(8):1430-1440

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TransCon PTH PaTH Forward (Phase 2) Trial Design

PaTHforward TRIAL

Adults with hypoparathyroidism who required conventional therapy (active vitamin D + calcium) at baseline

Primary Composite Endpoint (4 weeks)

Proportion of subjects with:

- Normal serum calcium; ***and***
- Independence from active vitamin D; ***and***
- Requiring ≤ 1,000 mg/day calcium supplements; ***and***
- Normal FECa (or at least 50% decrease from baseline)

Week 58 and 84 Endpoints

- Intake of active vitamin D and calcium supplements
- Serum calcium and phosphate
- 24-hour urine calcium
- Adverse events
- Bone mineral density (Week 58 only)
- Patient-reported outcomes (Week 58 only)

FECa, fractional excretion of calcium

Khan AA, et al. *J Clin Endocrinol Metab*. 2021 Aug 4. Epub ahead of print

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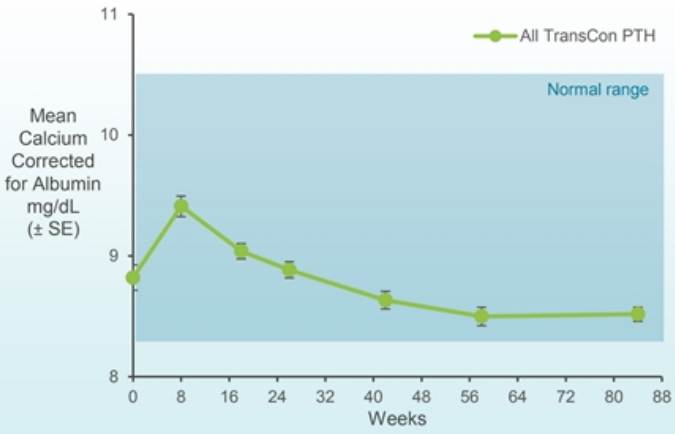
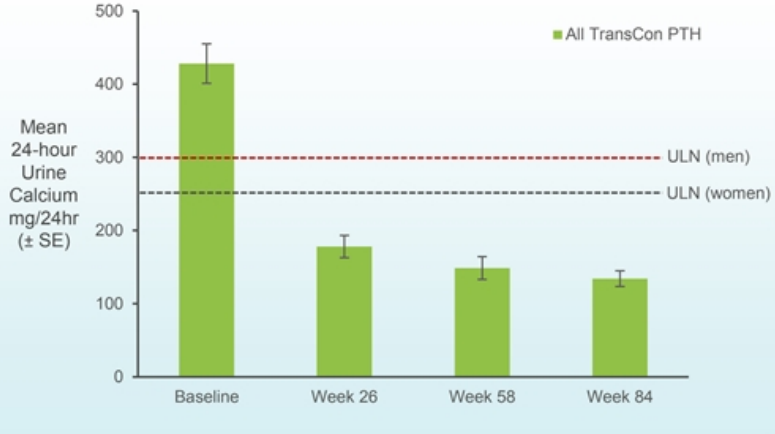
PaTH Forward: Mean Serum Calcium and 24-Hour Urine Calcium Through Week 84

Mean Serum Calcium



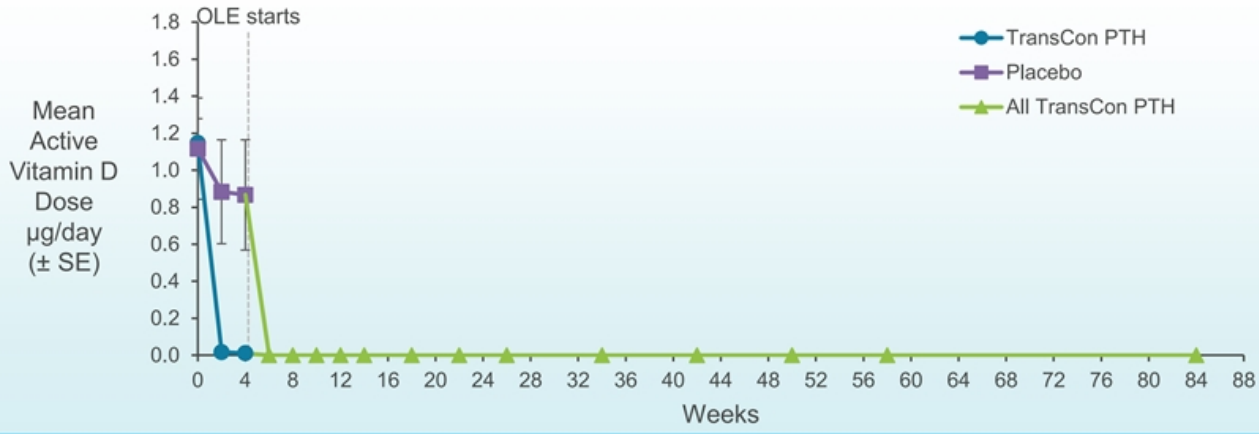
Mean 24-hour Urine Calcium



Mean 24-hour urine calcium normalized while maintaining normal mean serum calcium

Data on file, Ascendis Pharma 2021.
ULN = Upper Limit of Normal

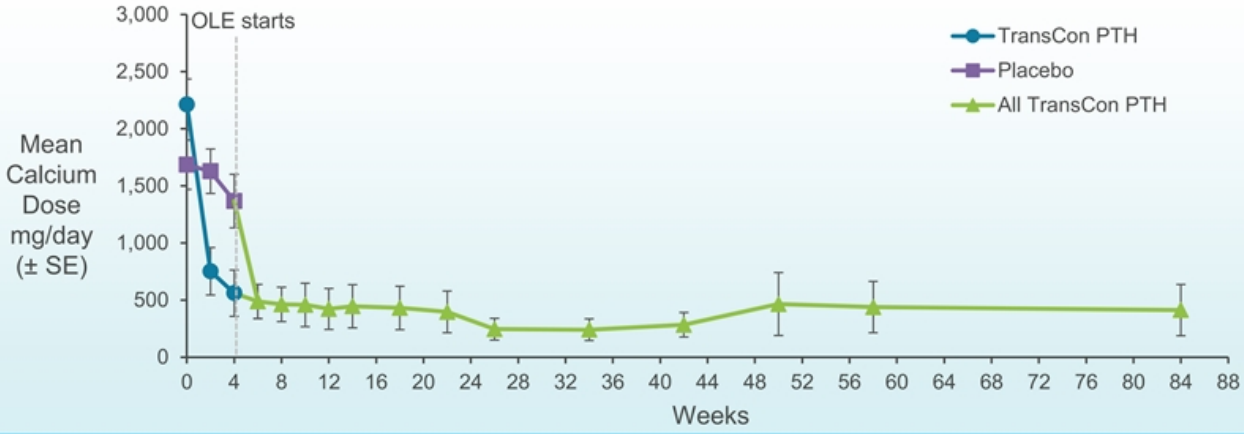
PaTH Forward:
Mean Active Vitamin D Dose Through Week 84



TransCon PTH enabled discontinuation of active vitamin D within two weeks of treatment initiation

Data on file, Ascendis Pharma 2021.

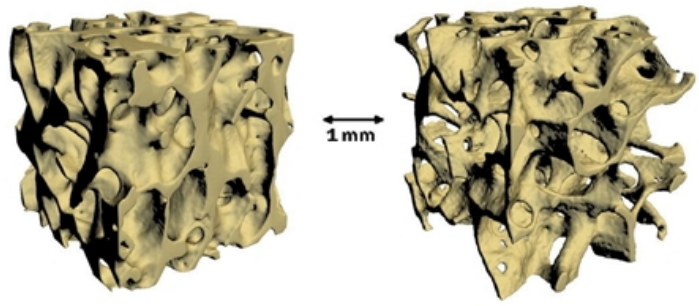
PaTH Forward:
Mean Calcium Supplement Dose Through Week 84



TransCon PTH enabled rapid and continuous calcium supplement reduction;
43 of 58 subjects were taking 0 mg, and 54 of 58 subjects were taking 0 to 600 mg at week 84

Data on file, Ascendis Pharma 2021.

Abnormal Skeletal Dynamics in Hypoparathyroidism



Representative images above show bone biopsies of the iliac crest as scanned by microcomputed tomography (microCT) [1]

Lack of PTH-driven skeletal remodeling results in abnormal bone structure and may be associated with poor bone quality and increased risk of fractures[2]

1. Rubin MR, et. al., *Bone* 2010 Jan;46(1):190-195
2. FDA presentation: Natpara Advisory Committee, September 12, 2014;

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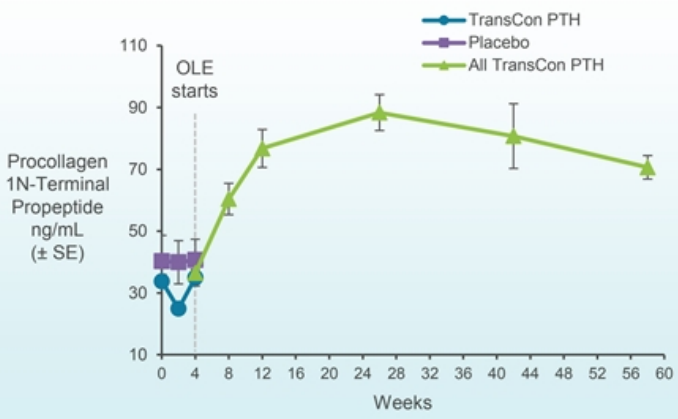
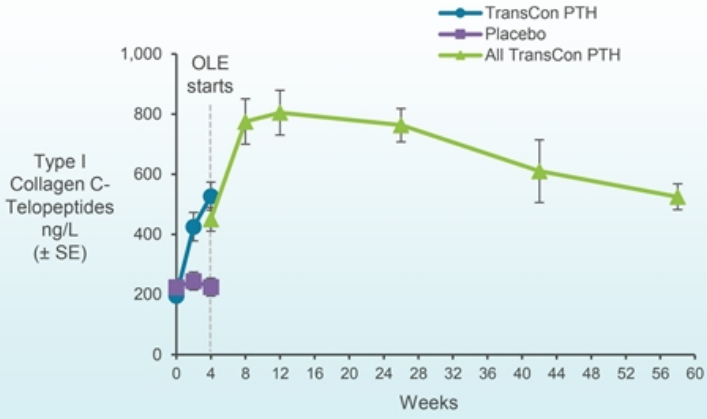
PaTH Forward: Serum Markers of Skeletal Dynamics

PaTHforward TRIAL

Mean P1NP



Mean CTx



With TransCon PTH treatment, markers of anabolic and catabolic bone turnover increased above baseline, peaking in the initial weeks and trending to the mid-normal range by Week 58

Data on file, Ascendis Pharma 2021.

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PaTH Forward: Bone Mineral Density by DXA

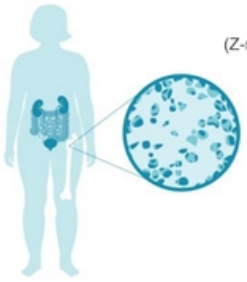
Mean Z-scores (n = 43[1])

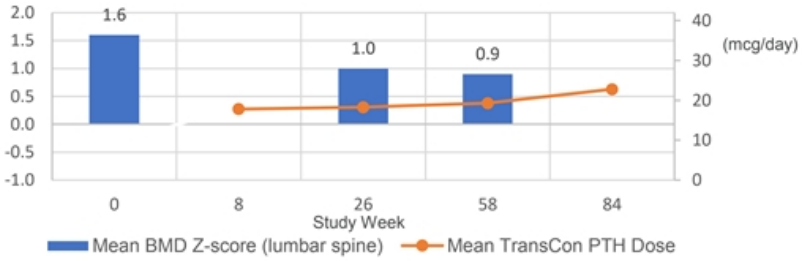
Region	Baseline	Week 26	Week 58	Week 58 change from baseline
Lumbar spine L1-L4	1.6	1.0	0.9	–0.7
Femoral neck	1.0	0.5	0.4	–0.6
Total hip	1.0	0.6	0.5	–0.5
1/3 radius	0.4	0.3	0.3	–0.1

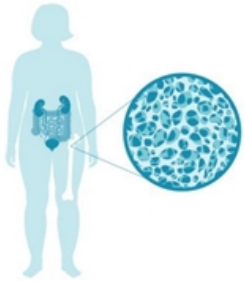
With TransCon PTH treatment, Week 58 mean Z-scores trended toward normalization and stabilization

DXA, dual energy x-ray absorptiometry
[1]includes subjects with DXA scans at both baseline and post-baseline. Two subjects missed their Week 26 scan; 2 different subjects missed their Week 58 scan. One subject had evaluable DXA scans at baseline, Week 26, and Week 58 at the hip region only.
Data on file, Ascendis Pharma 2021.

PTH Requirements Change as Skeletal Dynamics Normalize







- In hypoparathyroidism, rates of bone turnover are lower than normal, resulting in above-average BMD

- With physiologic PTH exposure, the skeleton mobilizes excess calcium as bone turnover increases

- Over time, rates of bone turnover normalize
- Higher PTH exposure may now be required to enhance calcium-promoting activities from intestine, kidney, and bone

BMD, bone mineral density

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PaTH Forward:
Treatment-Emergent Adverse Events Through Week 84

	Week 84
	All TransCon PTH (N =59)
Subjects With – n (%)	
Treatment-Emergent Adverse Events (TEAE)	51 (86)
Serious TEAE	5 (8)
Severity	
Severe TEAE	3 (5)
Moderate TEAE	17 (29)
Mild TEAE	31 (53)
Related TEAE*	22 (37)
Related Serious TEAE	0
TEAE Related to Hyper- or Hypocalcemia Leading to ER/Urgent Care Visit and/or Hospitalization	0
TEAE Leading to Discontinuation of Study Drug	0
TEAE Leading to Discontinuation of Trial	0
TEAE Leading to Death	0

PaTH Forward week 84 top-line data. Percentages are calculated based on the number of subjects in the Safety Population. In the severity categories, subjects are displayed for the highest severity only. An AE is considered a TEAE if it occurred after the first dose of TransCon PTH. *Headache, hypocalcemia, nausea, dizziness, paresthesia, hypercalcemia and asthenia occurred in two or more subjects.
Data on file, Ascendis Pharma 2021.

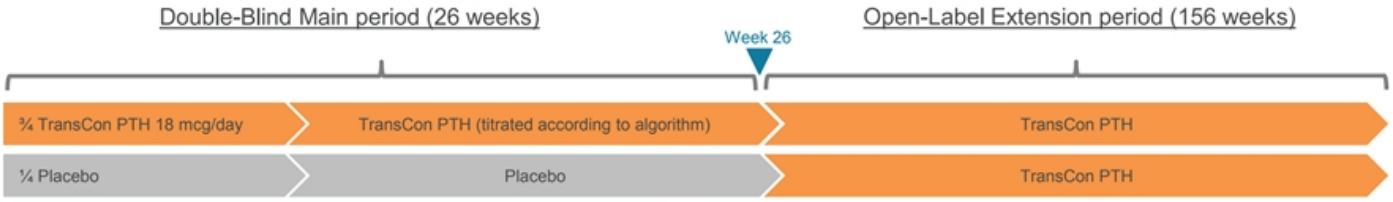
Summary: PaTH Forward Trial Results Through Week 84

- 58/59 subjects remain in the trial beyond Week 84[1]
- At Week 84, 93% of subjects were independent from active vitamin D and therapeutic doses of calcium
- Mean serum and urine biochemistries continued to be in the normal range
- Through Week 58, markers of skeletal health (bone density and markers of bone turnover) continued to trend toward normalization
- Symptoms, impact, and health-related quality of life continued to be improved from baseline
- The majority of adverse events have been mild and unrelated
- No urgent/emergent visits or hospitalizations related to hypo- or hypercalcemia

1. And as of December 13, 2021.

TransCon PTH PaTHway (Phase 3) Trial Design

Double-blind, placebo-controlled trial with an open-label extension period
82[1] adults with chronic hypoparathyroidism randomized 3:1 (TransCon PTH:placebo)



Primary Objective
Confirm treatment effect of TransCon PTH in adults with hypoparathyroidism

Key Eligibility Criteria

- Adults with chronic hypoparathyroidism (*i.e.* for at least 26 weeks)
- Age ≥18 years
- Reliant on calcitriol ≥0.50 mcg per day or alfacalcidol ≥1.0 mcg per day, **and** therapeutic elemental calcium ≥800 mg/day
- Serum calcium in normal (or just below normal) range: 7.8 – 10.6 mg/dL (1.96 – 2.64 mmol/L)
- No PTH or PTHrP therapy within 4 weeks prior to Screening

Countries

- Europe (Germany, Denmark, Norway, Italy, Hungary)
- North America (United States, Canada)

Primary Composite Endpoint at Week 26

Proportion of subjects with:

- Serum calcium in the normal range (8.3 – 10.6 mg/dL) ***and***
- Independence from active vitamin D ***and***
- Independence from calcium supplements[2]

Selected Other Endpoints at Week 26

- 24-hour urine calcium
- Serum phosphate levels
- Domains from Hypoparathyroidism Patient Experience Scale measures
- Domains from 36-Item Short Form Survey (SF-36) measure

[1] Sample size selected to ensure evaluable data for 68.
[2] If needed to meet recommended dietary intake of calcium, it is permitted to take calcium supplements ≤600 mg/day as a nutritional supplement.

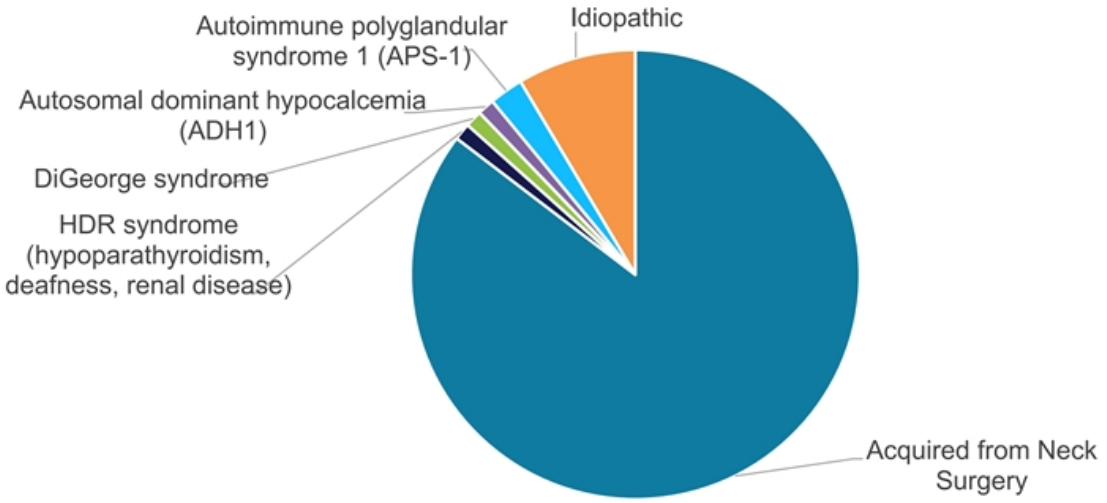
PaTHway Phase 3 Trial: Baseline Characteristics

Characteristics	Total Randomized (N=82)
Age, mean years	49 years
Female sex, %	78%
Geographic region, %	
North America	62%
Europe	38%
Postmenopausal, %	28%
Duration of hypoparathyroidism, mean years	12 years
Post-surgical etiology of hypoparathyroidism, %	85%

Baseline characteristics of phase 3 trial are similarto those of the phase 2 trial

Preliminary data from an ongoing trial; data snapshot 10 AUG 2021. Subject to revisions

PaTHway Trial Includes Diverse Etiologies



Preliminary data from an ongoing trial; subject to revisions

Potential New Treatment Paradigm for Hypoparathyroidism

TransCon PTH has the potential to be the first hormone replacement therapy for hypoparathyroidism addressing major unmet medical need for a large rare disease patient population

Anticipated near-term milestones for global reach and indication expansion

- Phase 3 PaTHway Trial (North America + EU) top-line results expected Q1 2022
- Planned NDA submission Q3 2022
- PaTHway Japan Trial top-line results expected Q3 2022
- Planned MAA submission Q4 2022
- Initiation of pediatric hypoparathyroidism program planned Q4 2022

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Three Patient Journeys from the PaTH Forward Trial

Aliya Khan MD, FRCPC, FACP, FACE, FASBMR
Clinical Professor of Medicine
Director, Calcium Disorders Clinic
Director, Fellowship in Metabolic Bone Disease
McMaster University

Aliya Khan MD, FRCPC, FACP, FACE, FASBMR

- Professor of Clinical Medicine at McMaster University
- Director of the Calcium Disorders Clinic
- Director of Fellowship in Metabolic Bone Disease at McMaster University
- Graduated from the University of Ottawa Medical School with honors
- Completed postgraduate training at the University of Toronto
- Published over 200 scientific papers and numerous chapters and books on osteoporosis and parathyroid disease
- Received numerous national and international awards
- Including Queen's Diamond Jubilee Medal for excellence
- International Hypoparathyroidism Award
- International Osteoporosis Foundation award for publishing excellence
- Recognized by Osteoporosis Canada for outstanding contributions to research and education
- Recognized as being in the top 0.1% of the world experts in hyperparathyroidism by Expertscape.

Disclosure

- For profit
  - Research grants from Amgen, Ascendis, Alexion, Radius, Takeda, Ultragenyx
- Not for profit
  - Chair, Rapid Response Committee, Osteoporosis Canada
  - Co-Chair, Knowledge Translation Committee, Osteoporosis Canada
  - Chair, International Osteonecrosis of the Jaw (ONJ) Taskforce
  - Scientific Advisor to International Osteoporosis Foundation
  - Canadian Ambassador for American Society of Bone and Mineral Research

Calcium Disorders Clinic at McMaster University Medical Centre

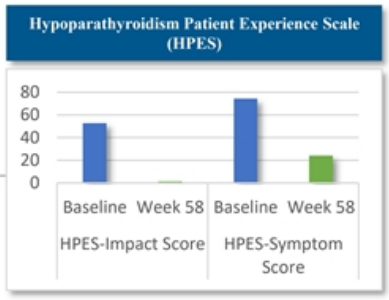
- Specialized Calcium Disorders Clinic (CDC) was established at St Joseph's Healthcare in Hamilton in 2005.
  - CDC has serves as a Center of Excellence for the diagnosis and management of complex calcium disorders.
  - **Tertiary referral center** for patients with complex calcium disorders from across Canada
  - Serves as a focal point for **clinical research** in parathyroid disease
- AK is the principal investigator for the Canadian National Hypoparathyroidism Registry – evaluating presentation, complications, and treatment approaches
  - AK led the development of Canadian and International Guidelines for primary hyperparathyroidism as well as hypoparathyroidism
  - Leader in clinical research and medical management trials of primary hyperparathyroidism (alendronate and cinacalcet)
  - Leader for parathyroid replacement in hypoparathyroidism (PTH(1-84), oral PTH, TransCon PTH, and calcilytics)
- **Medical education** for medical students, residents and fellows.
  - AK is Director of Fellowship in Metabolic Bone Disease – the only program in Canada providing both 1-year and 2-year Fellowship programs in Metabolic Bone Disease
  - Previous fellows have been recipients of international awards most recently ASBMR Young Investigator Award 2021 by the ASBMR for case series on Barakat Syndrome - rare genetic disorder associated with hypoPT

Patient 1: History

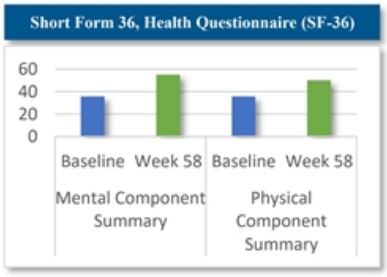
- 57-year-old male
- Past medical history of:
  - Hypertension
  - Parathyroid adenoma with subsequent total parathyroidectomy
  - Thyroid nodule and thyroidectomy—April 17,2015
- Hypoparathyroidism Etiology: postsurgical
- Complicated by recurrent hospital admissions for hypocalcemia and hypercalcemia
- Employment history
  - Automobile painter, but took early retirement due to complications of hypoparathyroidism
  - Contractor: was able to return to the work force after starting TransCon PTH

Patient 1: Clinical Course

- Prior to trial
  - Very symptomatic with significant muscle cramps and paresthesias daily as well as tetany
  - Laryngospasm in June 2017 requiring hospitalization
  - Several admissions hypocalcemia and hypercalcemia
- Post TransCon PTH
  - Symptoms have all resolved
  - Returned to work – able to complete 10-12 hours physically demanding construction projects
  - Able to participate in sports again – recently qualified for golf tournament finals

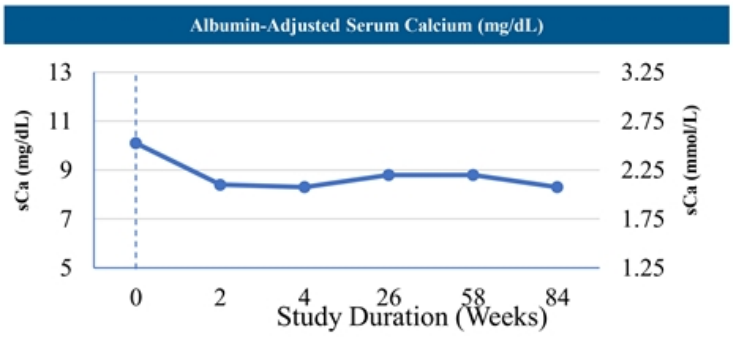


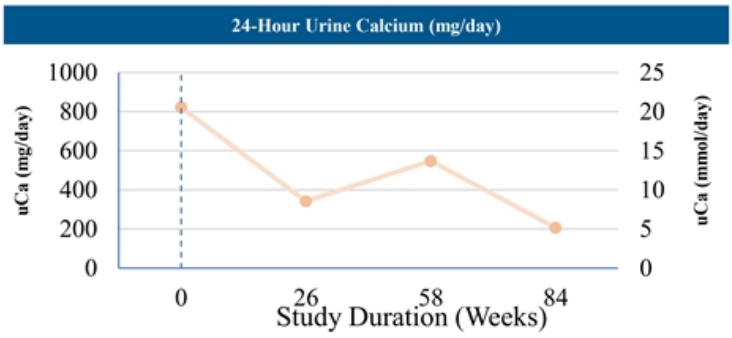
Note: lower is better

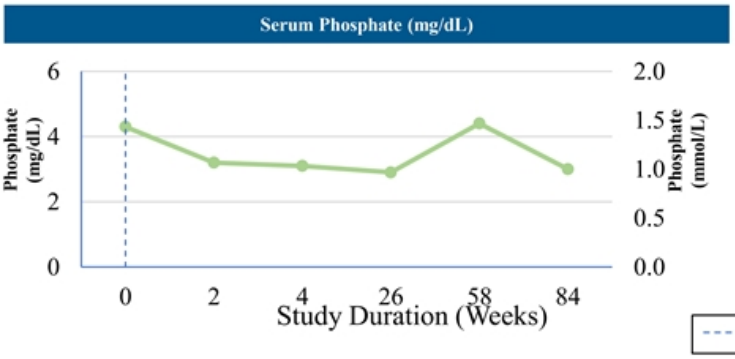


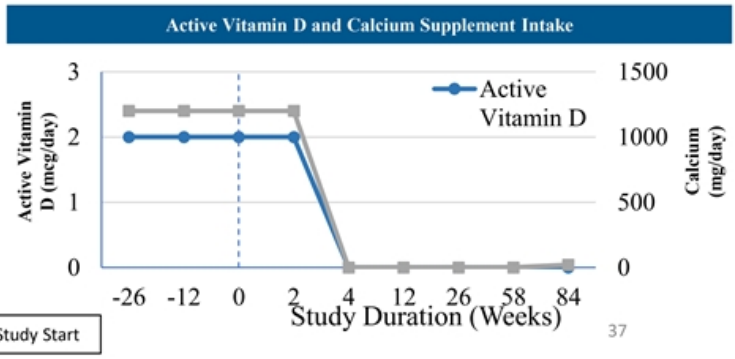
Note: higher is better

Patient 1: Laboratory Data









Patient 2: History

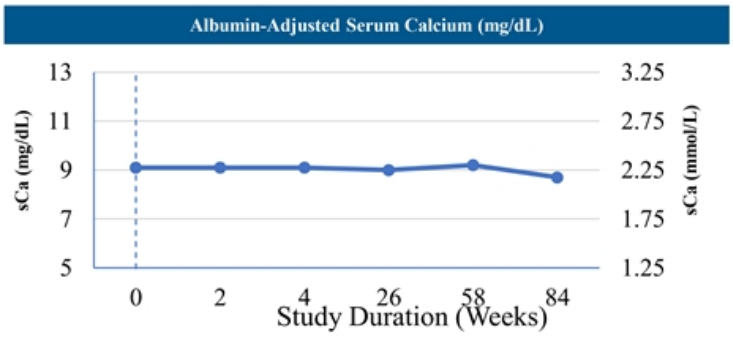
- 62-year-old female
- Past medical history of:
  - Hypertension
  - Goiter, total thyroidectomy- Nov 2012
  - Asthma
- Hypoparathyroidism
  Etiology: postsurgical
- Church organist and pianist

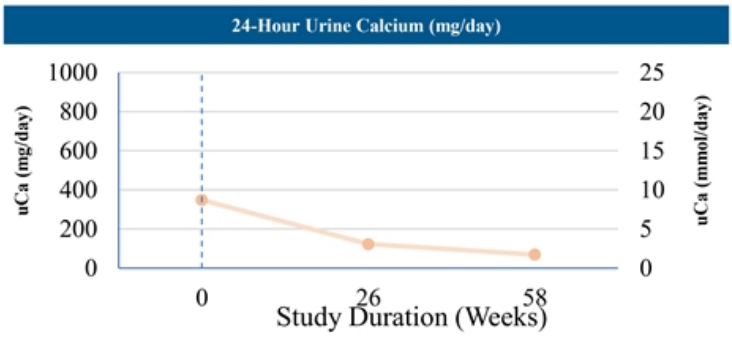
Patient 2: Clinical Course

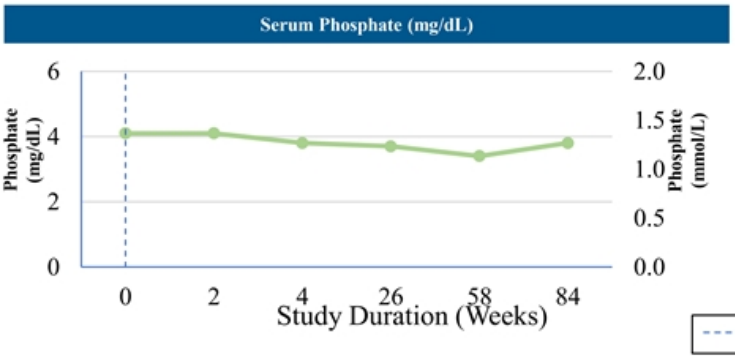
- Prior to trial
  - Daily feet cramps and peri-oral numbness and tingling 3-4x/week
  - Afraid to hold her grandchild due to muscle cramping

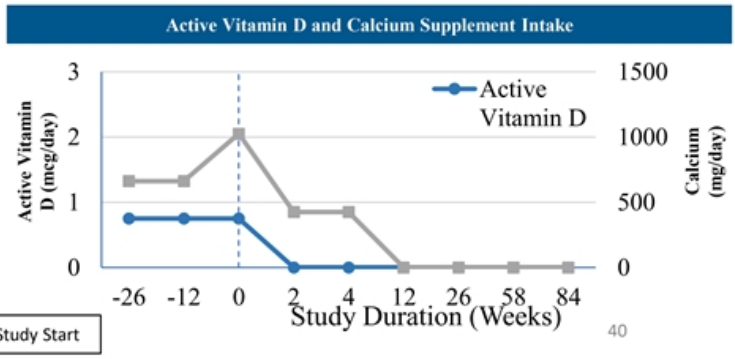
- Post TransCon PTH
  - Improved energy and sleep
  - Able to play the organ again as the finger cramping resolved
  - Able to enjoy her time with her grandchildren

Patient 2: Laboratory Data







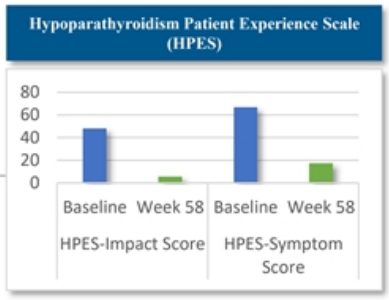


Patient 3: History

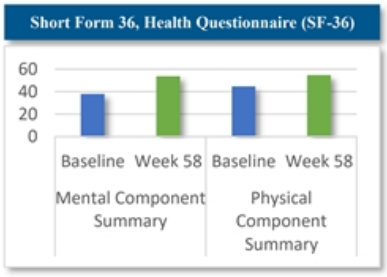
- 44-year-old female
- Past medical history of:
  - Colorectal cancer
  - Goiter
  - Papillary thyroid cancer
  - Thyroidectomy- Jan 2016
  - Myalgia
- Hypoparathyroidism Etiology: postsurgical
- Occupation: Operating Room Nurse

Patient 3: Clinical Course

- Prior to trial
  - Very symptomatic with overwhelming fatigue and headaches , brain fog , irritability and depression
  - Had to resign from position as OR nurse
- Post TransCon PTH
  - Clarity of thought , energy and sleep all dramatically improved and feeling “fantastic” and experiencing major increase in energy
  - States the medication has given her “new life”
  - Was able to return to her position as an OR nurse



Note: lower is better



Note: higher is better

Discussion: Impacts on Overall Health

- Through my lenses
  - Psychosocial aspects
  - Impacts on family
  - Pill burden and adherence to conventional therapy

Science and Biology of C-type Natriuretic Peptide (CNP) as a Treatment for Achondroplasia

Kennett Sprogøe, Ph.D.
SVP, Head of Innovation and Research

Growth Hormone Deficiency and Achondroplasia Differ at the Level of the Growth Plate

	Growth Hormone Deficiency	Achondroplasia (ACH)
Cause	Pituitary gland malfunction Insufficient endogenous GH	Constitutive hyperactive FGFR3 signaling caused by receptor mutation
Untreated growth plate condition	Normal organization	Dysfunctional growth plate
Treatment approach	Replacement of insufficient GH	Inhibit hyperactive FGFR3 signaling with continuous CNP exposure
Initial Treatment effect	Catch-up growth response	Reorganization of growth plate leading to promoted growth

Conditions heterogeneous in phenotypic manifestations

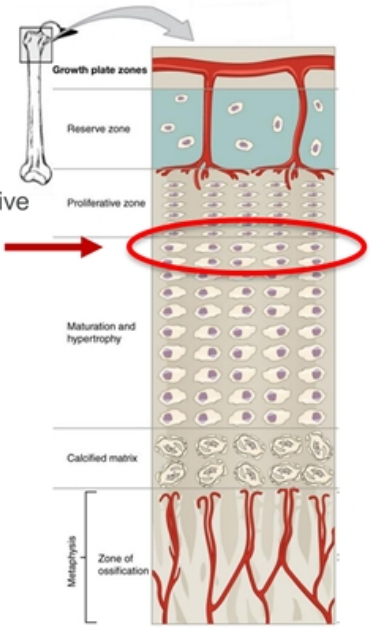
Grimberg A, et al. Horm Res Paediatr. 2016;86(6):361-397.
Laederich MB, et al. Curr Opin Pediatr. 2010;22(4):516-523

Target Cells (Chondrocytes) Are in The Growth Plate

Achondroplasia caused by heterozygous mutation
Different conformations of the FGFR3 G380R mutated dimer

Constitutive hyperactive FGFR3 signaling occurs in the presence and absence of ligand

Constitutive hyperactive FGFR3 signaling in the growth plate blocks growth



He et al. *J Biological Chemistry*, 2010 Sep 24;285(39):30103-14. He et al. (2011) *J Biol Chem* **286**:13272-13281. Zhou et al. *Hum Mol Genet* **24**:1764-1773.
Figure with permission, http://cnx.org/content/col11496/1.6/

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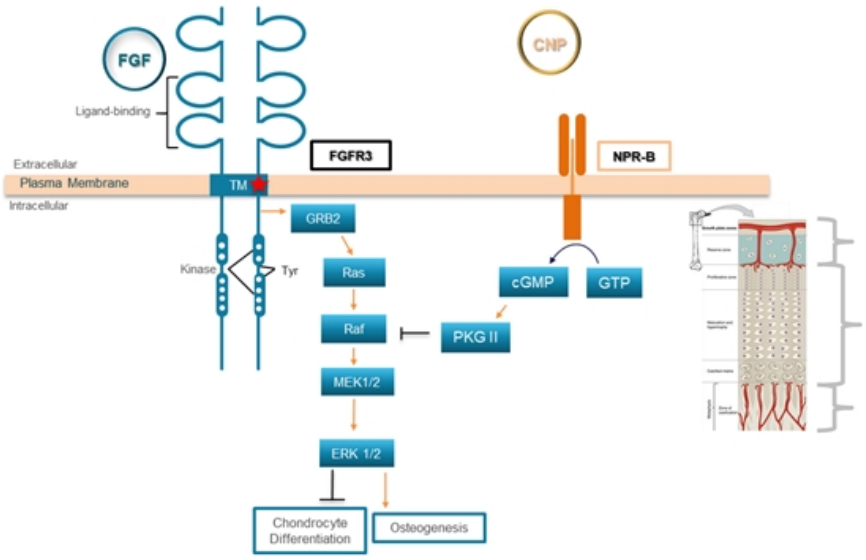
Hyperactive FGFR3 Signaling and the Effect of CNP on Achondroplasia Are Well-Described



CNP inhibits hyperactive FGFR3 signaling to counteract the block of growth plate function

Copyrighted Image

Wild-type (Normal) | ACH | ACH +CNP

Adapted from Laederich MB, et al. Curr Opin Pediatr. 2010;22(4):516-523. Yasoda et al. (2009) *Endocrinology* **150**:3138-3144. http://cnx.org/content/col11496/1.6/ Figures with permission

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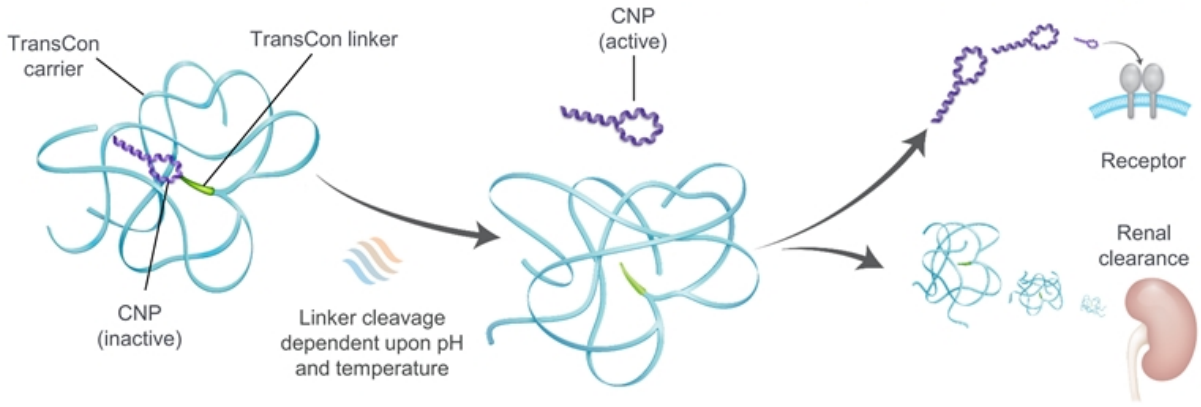
TransCon CNP Design

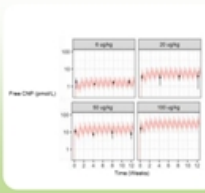


- TransCon technology is designed to provide effective shielding of CNP:
  - From neutral endopeptidase degradation in subcutaneous tissue and blood compartment
  - Minimize binding of TransCon CNP to the NPR-B and NPR-C receptors to avoid hypotension and minimize clearance
- TransCon CNP is designed to provide continuous exposure of free CNP enabling exposure to the growth plate

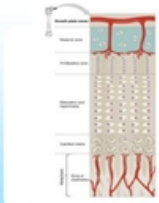
Breinholt VM et al. J Pharmacol Exp Ther. 2019;370(3):459-471.

Stages for TransCon CNP to Promote Growth in Achondroplasia

TransCon CNP designed to promote growth in three sequential stages



TransCon CNP provides continuous plasma exposure of free CNP



Continuous free CNP plasma exposure enables CNP exposure to the growth plate

Continuous CNP exposure in growth plate inhibits hyperactive FGFR3 signaling

Yasoda et al. (2009) *Endocrinology* **150**:3138-3144.
http://cnx.org/content/col11496/1.6/ Figures with permission

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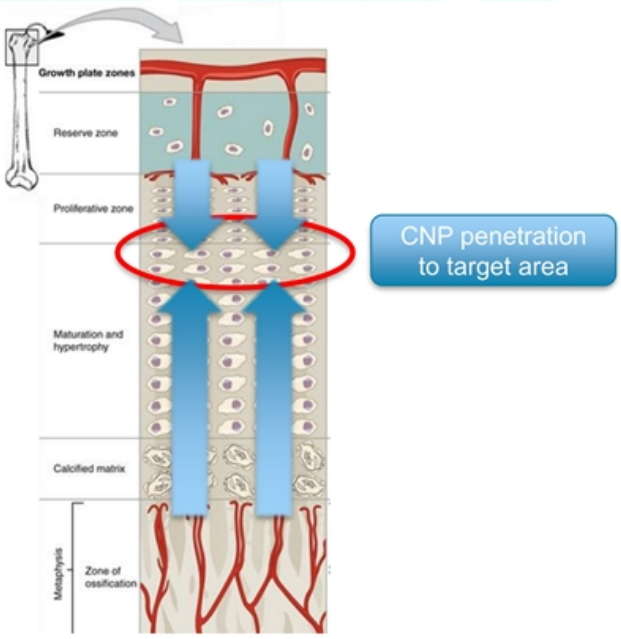
TransCon CNP Designed to Provide Continuous Free CNP Exposure

- Continuous exposure
  - Steady-state exposure is achieved within weeks
- Dose-proportionality
  - Predictable continuous plasma exposure of free CNP
- Low C_{max}
  - C_{max} targeted well below levels reported to induce hypotension in humans[1,2]
- Once-weekly dosing

1. Igaki et al. (1998) *Hypertension Research* **21**:7-13.
2. Hunt et al. (1994) *J Clin Endocrinol Metab* **78**:1428-1435.

Continuous Free CNP Plasma Exposure Enables CNP Exposure to the Growth Plate

- Growth Plate Characteristics
  - Avascular
  - Hydrophilic and negatively charged matrix
- Molecular penetration to target area restricted by size[1] and charge
- CNP-38 properties facilitate growth plate penetration
  - Small size < 4 kDa
  - Hydrophilic
  - Positively charged



1.Farnum et al. (2006) *Anat Rec A Discov Mol Cell Evol Biol* **288**:91-103. http://cnx.org/content/col11496/1.6/ Figure with permission

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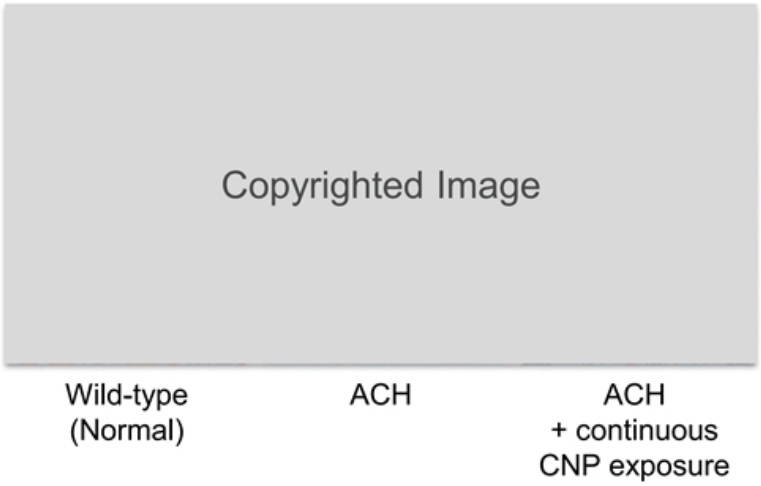
Continuous Free CNP Exposure Inhibits Constitutive Hyperactive FGFR3 Signaling

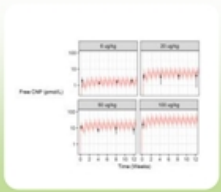
- FGFR3 hyperactive signaling in ACH is constitutive
- CNP mode-of-action in ACH was revealed with sustained CNP exposure[1-2]
- CNP over-expression in humans results in increased linear growth[3-4]



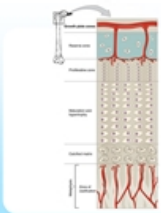
1. Yasoda et al. (2004) *Nat Med* **10**:80-86. 2. Yasoda et al. (2009) *Endocrinology* **150**:3138-3144. 3. Bocciardi et al.(2007) *Hum Mutat* **28**:724-731. 4. Ko et al. (2015) *Am J Med Genet A* **167A**:1033-1038. Figure used with permission

TransCon CNP Designed to Address Key Manifestations of Achondroplasia

Continuous Exposure



Growth Plate Penetration



Growth Promotion

TransCon CNP

- Dose-Proportionality
- C_{max} targeted well below levels reported to induce hypotension
- Once-weekly dosing

CNP properties and exposure

- Continuous exposure
- Molecular properties facilitate growth plate penetration

CNP effect

- Inhibits constitutive hyperactive FGFR3 signaling
- Promotes growth

Yasoda et al. (2009) *Endocrinology* **150**:3138-3144.
http://cnx.org/content/col11496/1.6/ Figures with permission

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TransCon CNP for Achondroplasia

Marie-Louise C. Hartoft-Nielsen, M.D., Ph.D.
Senior Medical Director, Clinical Development

Achondroplasia – Most Frequent Skeletal Dysplasia

- Achondroplasia is the most common cause of short-limbed short stature[1]
- Autosomal dominant gain-of-function mutation of the FGFR3 gene[2,3,4]
- Estimated prevalence of ~ 4 per 100,000 births[5,6]
- 80% spontaneous mutations, 20% inherited
- Approximately 250,000 people living with ACH worldwide[1]
- Usually diagnosed at birth or within the first year[7]

1. Horton WA, et al. *Lancet* 2007, 370(9582): 162-172, **2**. Rousseau F et al. *Nature* 1994;371(6494):252-4 **3** Shiang R et al. Cell. 1994 ;78(2):335-42, **4** Webster MK, Donoghue DJ. *EMBO J.* 1996 Feb 1;15(3):520-7 **5**. Coi A, *AM J Med Genet* Part A, 2019, 1:179: 1-8 **6**. Foreman PK, *Am J Med Genet*. 2020: 182A, 2297-2316. **7**. Horton WA et al. *Lancet* 2007; 370: 162–72 2007

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Primary Skeletal Manifestations and Key Related Complications Lifelong Disease Burden[1-10]

Manifestations

- Short stature
- Short limbs & rhizomelia
- Narrowing of foramen magnum
- Midfacial hypoplasia
- Frontal bossing
- Trident hand

Complications

- Foramen magnum stenosis
- Spine deformities
- Spinal stenosis
- Sleep apnea
- Recurrent otitis media
- Pain
- Obesity

Interventions

- Cervicomedullary decompression
- Grommets
- Tonsillectomy/ Adenoidectomy
- Continuous positive airway pressure
- Bone lengthening surgery

Life expectancy impacted by risk of infant death and increased mortality in adults

1. Pauli, R.M. *Orphanet J Rare Dis* 14. 2019; 14(1):1-49 **2** Langer Lo et al. Am J Roentgenol 1967 100: 12-26, **3.** Hunter AG et al. *J Med Genetic*. 1998; 35(9):705-12 **4.** Afsharpaiman S, et al., *Paediatr Respir Rev*. 2013;14(4):250-255. **5.** Reid CS, et al. *J Pediatr*. 1987;110(4):522-530. **6.** Schkrohowsky JG, et al. *J Pediatr Orthop*. 2007;27(2):119-122. **7.** Saleh M et al. Orthop Clin North Am . 1991; 22:589-99 **8.** Hecht JT et al. Am J Hum Genet. 1987; 41(3): 454–464. **9.** Wynn et al J, *Am J Med Genet*. 2007; 143A:2502-11, **10.** Hecht JT et al. *Am J Med Genet* 1988; 31:597-602

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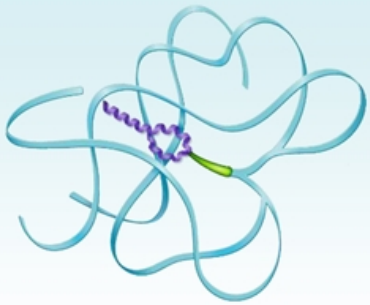
TransCon CNP Investigational Drug Characteristics

- Dose proportionality with continuous exposure over one week and low C_{max}
- Utilizes wild-type CNP peptide sequence
- Designed to provide meaningful impact on clinical manifestations and burden of achondroplasia



Designed to continuously inhibit hyperactive signaling of FGFR3 with low risk of cardiovascular side effects and low immunogenicity

Data on file, Ascendis Pharma; 2019.

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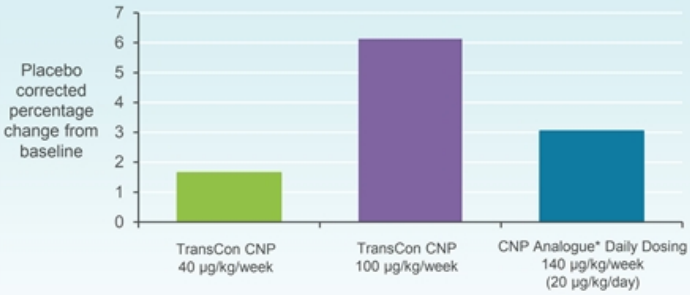
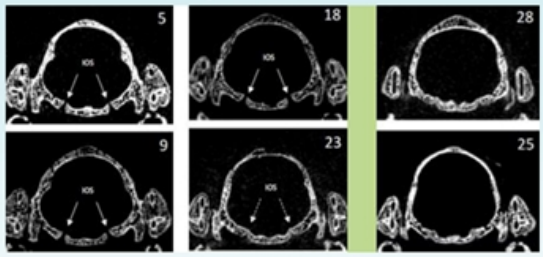
Non-Clinical Data Support Safety and Efficacy

Tibial growth in young cynomolgus monkeys at 6 months (n=4/group)[1]



Synchondroses of Foramen Magnum in ACH Model[2]

$Fgfr3^{y367C/+}$ mice



- Dose-dependent linear growth and potential to prevent premature fusion of synchondroses of foramen magnum in an ACH model
- Well-tolerated in non-clinical models

1. Breinholt VM, et al. *J Pharmacol Exp Ther.* 2019;370(3):459-471. **2.** Poster presented at ENDO 2017

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

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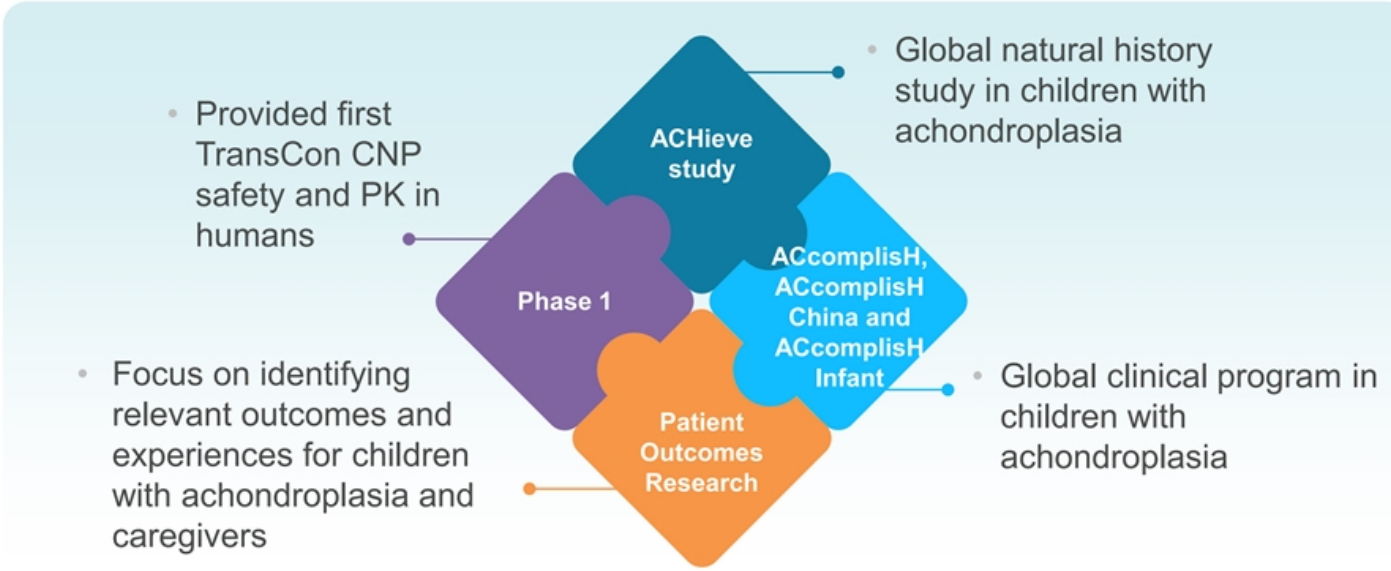
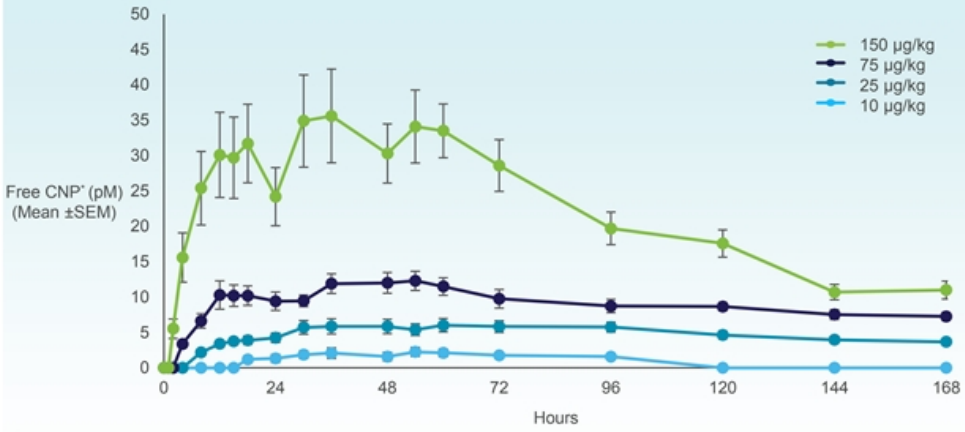
Integrated & Patient-Focused Clinical Development Program



- Global natural history study in children with achondroplasia
- Provided first TransCon CNP safety and PK in humans
- Focus on identifying relevant outcomes and experiences for children with achondroplasia and caregivers
- Global clinical program in children with achondroplasia

Data on File, Ascendis Pharma 2021.

Phase 1 Pharmacokinetics



- Dose proportional increase in Free CNP exposure
- Continuous exposure and apparent $T_{1/2}$ of ~ 120 hours in adults

Continuous and dose-dependent exposure, $T_{½}$ supports weekly dosing

*CNP measured as CNP 38
Ota et al. Oral presentation at ISDS 2019.

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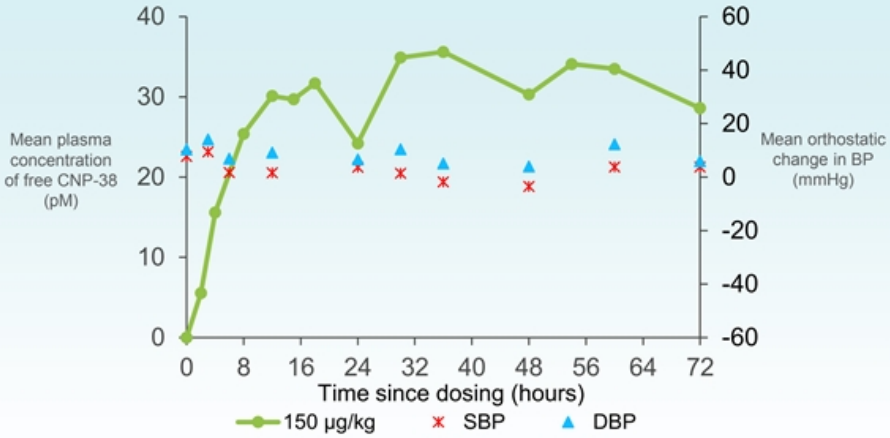
TransCon CNP Was Well-Tolerated Up to 150 µg/kg in Phase 1

- Mean resting blood pressure and heart rate were unchanged from pre-dose
- Mean orthostatic changes in vital signs appear unrelated to CNP exposure; consistent with placebo
- No serious AEs were reported
- Injections were well tolerated
- No anti-CNP antibodies detected



Well-tolerated with mean orthostatic vital signs unchanged

Data on file.

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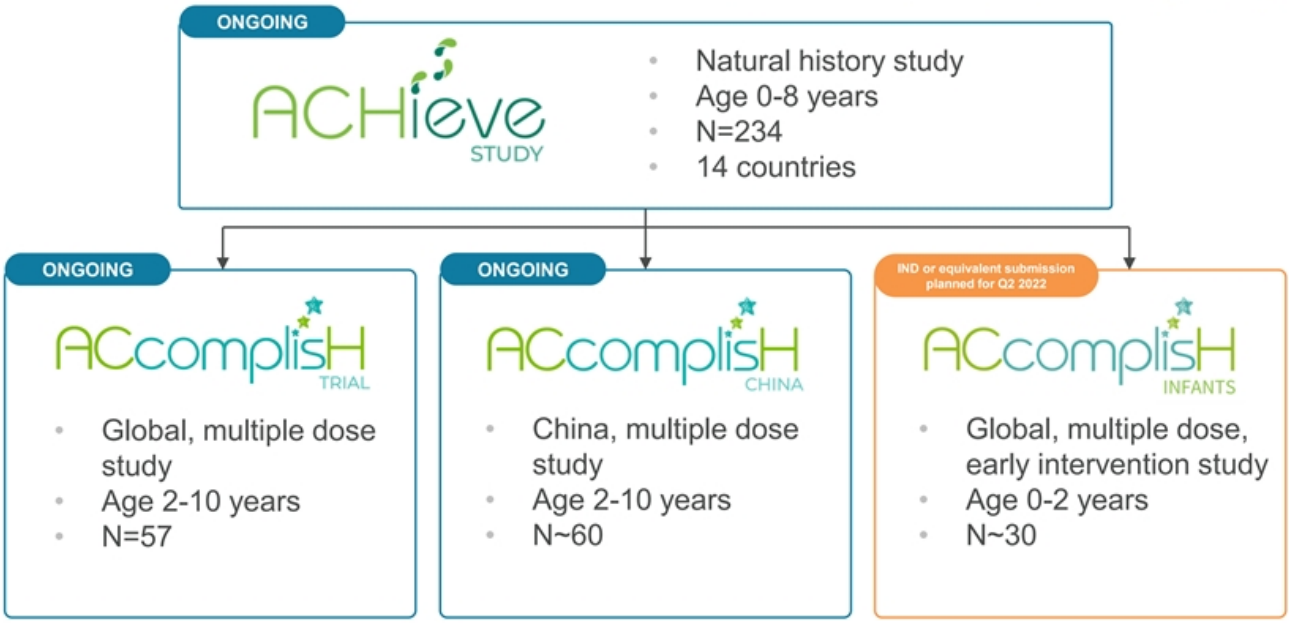
Clinical Development Program



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TransCon CNP: Phase 2 Trial Design

ACcomplisH TRIAL

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

TransCon CNP vs. placebo (3:1 randomization)

12 subjects randomized in each dose cohort in a blinded manner

6 µg/kg → **20** µg/kg → **50** µg/kg → **100** µg/kg → **>100** µg/kg

Data Monitoring Committee reviews blinded data after each dose cohort

Open Label Extension Period to evaluate long-term safety and efficacy

Primary Endpoint

- Annualized height velocity

Key Secondary/Additional Endpoints

- Change in body proportionality
- Patient reported outcome (PRO) measures
- Exploratory biomarkers evaluated

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04085523?term=ACcomplisH&draw=2&rank=5. Accessed 05/23/2021.

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Baseline Characterics ACcomplisH - Enrollment Complete

Demographics	Cohort 1 (N = 13)	Cohort 2 (N = 15)	Cohort 3 (N = 14)	Cohort 4 (N = 15)
Age (years)				
Mean (SD)	6.4 (2.82)	6.2 (3.13)	5.6 (2.91)	5.5 (2.51)
Age Group (years), n (%)				
2–5 years	5 (38.5)	7 (46.7)	6 (42.9)	6 (40.0)
5–8 years	4 (30.8)	5 (33.3)	4 (28.6)	6 (40.0)
> 8 years	4 (30.8)	3 (20.0)	4 (28.6)	3 (20.0)
Sex, n (%)				
Female	7 (53.8)	5 (33.3)	5 (35.7)	7 (46.7)
Male	6 (46.2)	10 (66.7)	9 (64.3)	8 (53.3)
Age at ACH Diagnosis, n (%)				
Pre-Birth	0	1 (6.7)	4 (28.6)	0
At Birth	4 (30.8)	3 (20.0)	2 (14.3)	2 (13.3)
0–6 months	9 (69.2)	9 (60.0)	7 (50.0)	8 (53.3)
6–12 months	0	2 (13.3)	1 (7.1)	1 (6.7)
> 12 months	0	0	0	1 (6.7)
Height SDS				
Mean (SD)	–5.4 (1.10)	–5.0 (0.66)	–4.7 (0.82)	–4.8 (0.79)

Data on file, Ascendis Pharma; Q4 2021

Baseline Characterics ACcomplisH - Enrollment Complete

Demographics	Cohort 1 (N = 13)	Cohort 2 (N = 15)	Cohort 3 (N = 14)	Cohort 4 (N = 15)
Age (years)				
Mean (SD)	6.4 (2.82)	6.2 (3.13)	5.6 (2.91)	5.5 (2.51)
Age Group (years), n (%)				
2–5 years	5 (38.5)	7 (46.7)	6 (42.9)	6 (40.0)
5–8 years	4 (30.8)	5 (33.3)	4 (28.6)	6 (40.0)
> 8 years	4 (30.8)	3 (20.0)	4 (28.6)	3 (20.0)
Sex, n (%)				
Female	7 (53.8)	5 (33.3)	5 (35.7)	7 (46.7)
Male	6 (46.2)	10 (66.7)	9 (64.3)	8 (53.3)
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Pre-Birth	0	1 (6.7)	4 (28.6)	0
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Data on file, Ascendis Pharma; Q4 2021

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5–8 years	4 (30.8)	5 (33.3)	4 (28.6)	6 (40.0)
> 8 years	4 (30.8)	3 (20.0)	4 (28.6)	3 (20.0)
Sex, n (%)				
Female	7 (53.8)	5 (33.3)	5 (35.7)	7 (46.7)
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Age at ACH Diagnosis, n (%)				
Pre-Birth	0	1 (6.7)	4 (28.6)	0
At Birth	4 (30.8)	3 (20.0)	2 (14.3)	2 (13.3)
0–6 months	9 (69.2)	9 (60.0)	7 (50.0)	8 (53.3)
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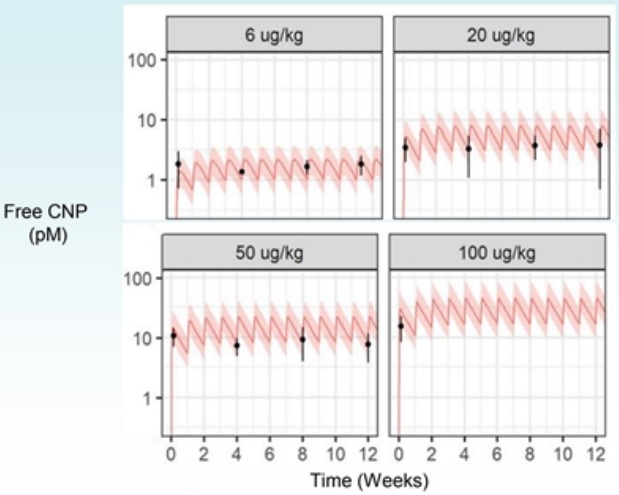
> 12 months	0	0	0	1 (6.7)
Height SDS				
Mean (SD)	–5.4 (1.10)	–5.0 (0.66)	–4.7 (0.82)	–4.8 (0.79)

Data on file, Ascendis Pharma; Q4 2021

ACcomplisH – Continuous Exposure with Low C_{max}

Pharmacokinetics



Red represents modeling data built on Phase 1 PK
Black represents actual data from ACcomplisH Trial

- Continuous exposure over the weekly dosing interval (Free CNP $T_{½}$ ~ 110 hours)
- Dose proportionality
- Steady-state plasma concentration of free CNP reached after four doses
- C_{max} well below levels reported to induce hypotension in humans[1,2]

1. Igaki et al. (1998) Hypertension Research 21:7-13.
2. Hunt et al. (1994) J Clin Endocrinol Metab 78:1428-1435.

ACcomplisH - Preliminary Safety Profile (N=57)*

- No withdrawals or discontinuations for any reason
- No serious adverse events related to trial drug
- 13 AEs related to trial drug or procedures
  - Of these, eight mild and transient injection site reactions (in over 1900 injections)
- Injections generally well tolerated in all dose cohorts
- No AEs related to orthostatic blood pressure changes
- No treatment-emergent anti-CNP antibodies detected

Well-tolerated in children with achondroplasia up to 65 weeks follow-up

*As per December 8 2021

Upcoming Trials

ACcomplisH* CHINA

- **Objectives:** Efficacy (AHV at week 52), safety, PK
- **Design:** Randomized, double-blind, placebo-controlled trial
- **Age:** 2-10 years
- **Doses:** 50 and 100 µg/kg/week selected from blinded data from ACcomplisH Trial
- **Region:** Greater China
- **Number of subjects:** 60
- **Status:** Enrolling

ACcomplisH INFANTS

- **Objective:** Early intervention to prevent growth disorder progression; safety, PK
- **Design:** Pending interactions with regulatory agencies
- **Age:** 0-2 years
- **Doses:** TBD
- **Region:** Global (US, Europe and Oceania)
- **Number of subjects:** 30 (planned)
- **Status:** IND or equivalent planned for Q2 2022

*In collaboration with VISEN Pharmaceuticals

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The Patient & Caregiver Experience of Achondroplasia [1-6]

- Physical signs and symptoms
- Functioning and daily life
- School participation
- Emotional well-being
- Social well-being

We are committed to understanding achondroplasia beyond growth

1. Bloemeke, J, et al. Qual Life Res 28, 2553–2563 (2019). 2. Bloemeke J,. et al. Disabil Rehabil. 2019 Jul;41(15):1815-1825. 3. Dogba MJ, et al. Health Qual Life Outcomes. 2014 Oct 25;12:151. 4. Gollust SE, et al. Am J Med Genet A. 2003 Aug 1;120A(4):447-58. 5. Sommer R, et al. J. Disabil Rehabil. 2017 Dec;39(24):2499-2503. 6. Pfeiffer KM, et al. Am J Med Genet. 2020;185(1):33-45.

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TransCon CNP Clinical Program Is Progressing

- ACcomplisH enrollment complete (N=57)
- Interim blinded data informed dose selection of 50 and 100 μg/kg/week for ACcomplisH China
- Preliminary PK and safety data on TransCon CNP suggest continuous CNP is well-tolerated across all doses administered
- ACcomplisH Infant in children 0–2 years of age; evaluate early intervention in ACH to prevent growth disorder progression; safety, PK

- Upcoming milestones:
  - ACcomplisH Infants Trial IND equivalent submission planned for Q2 2022
  - ACcomplisH Trial top-line data anticipated in Q4 2022

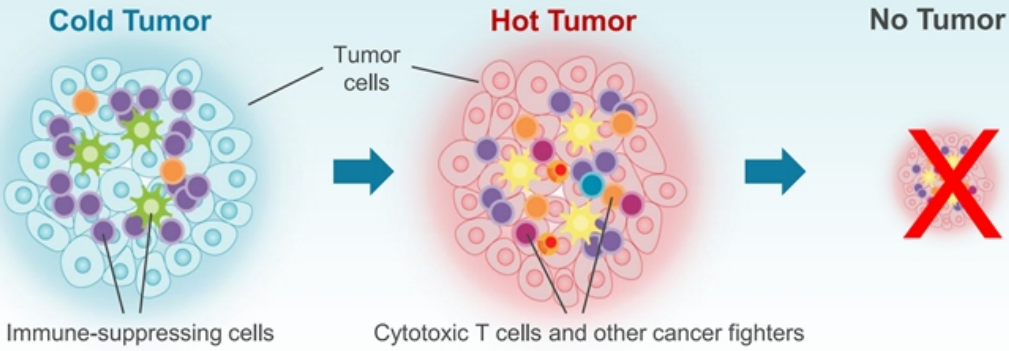
TransCon™ Technology for Intratumoral Administration

Kennett Sprogøe, Ph.D.
SVP, Head of Innovation and Research

TransCon Positioned to Potentially Transform Cancer Therapy

TransCon systemic and intratumoral technologies designed to enhance anti-tumor effects by

- Providing sustained modulation of tumor microenvironments
- Activating cytotoxic immune cells



Applicable to diverse drug classes and mechanisms of action; opportunity for combination approaches

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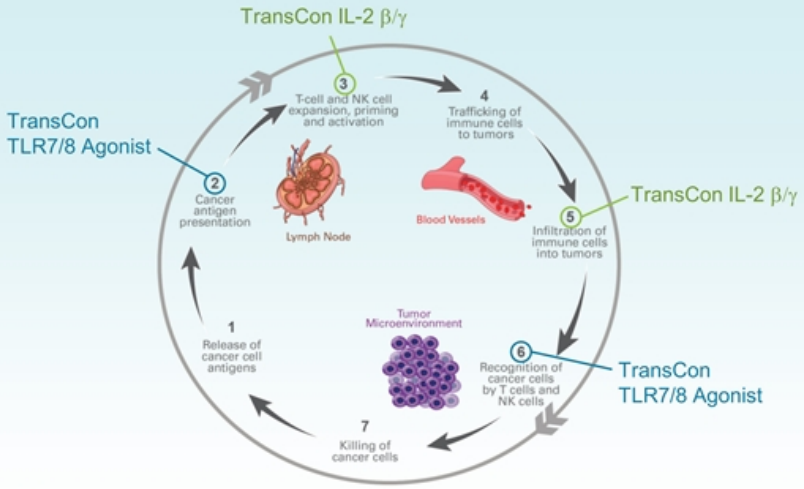
Two Clinical Candidates – Potential to Address Multiple Steps of the Immunity Cycle



TransCon TLR7/8 Agonist for IT delivery and enhanced tumor-antigen presentation

Designed to enhance antigen presentation and, thereby, promote activation of cytotoxic immune cells and drive systemic immune activation

TransCon IL-2 β/γ for systemic activation of tumor-antigen specific cytotoxic cells

Designed to aid T cell and NK cell expansion and infiltration of immune cells into tumors

Additional TransCon Candidates

New TransCon candidates with the potential to affect all steps in the immunity cycle

Combination approaches to enable impact on all critical steps of anti-tumor response

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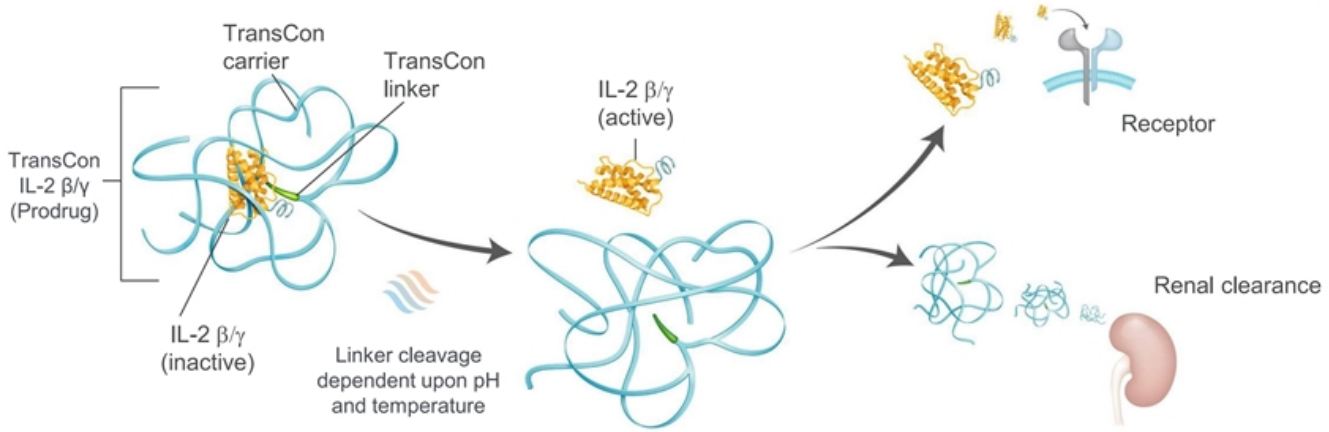
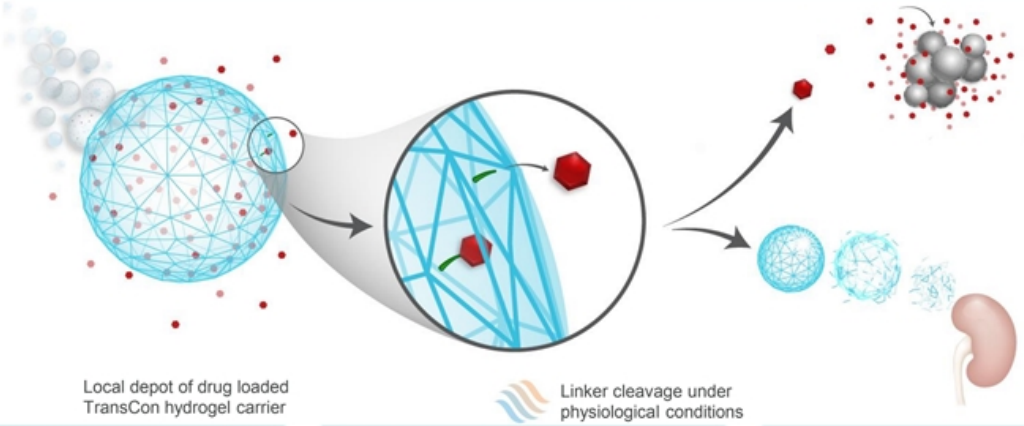
TransCon IL-2 β/γ: Soluble Carrier, as in Endocrine Pipeline



TransCon IL-2 β/γ is designed to provide sustained, long-lasting exposure of a highly-potent, proprietary IL-2 variant using the linker and carrier from TransCon hGH

TransCon TLR7/8 Agonist: Sustained Intratumoral (IT) Release of Resiquimod



Local depot of drug loaded TransCon hydrogel carrier

Linker cleavage under physiological conditions

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

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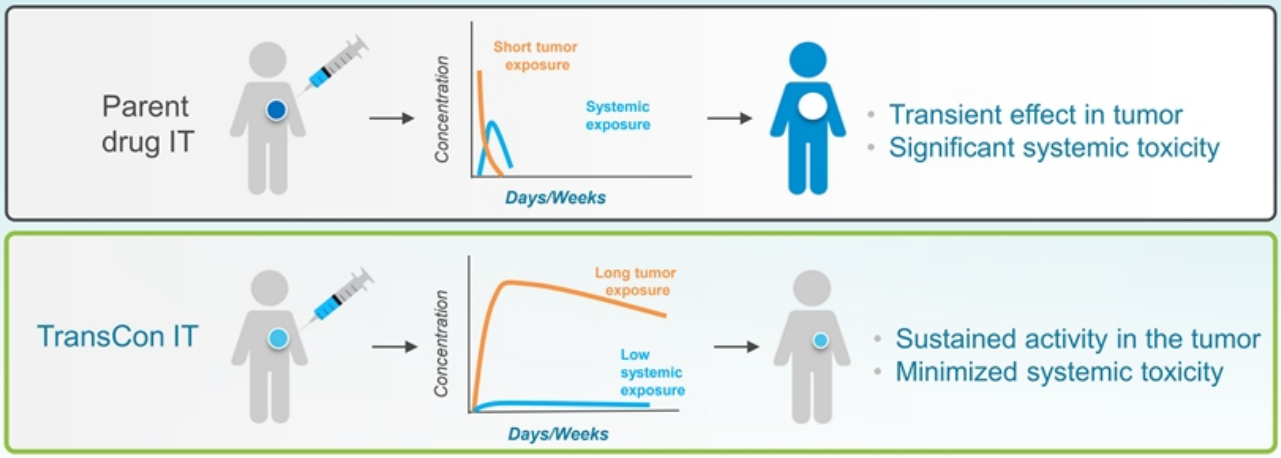
TransCon IT Represents a Potential Paradigm Shift in Cancer Therapy



TransCon technology provides potential for sustained modulation of tumor microenvironments with infrequent dosing and minimized systemic toxicity

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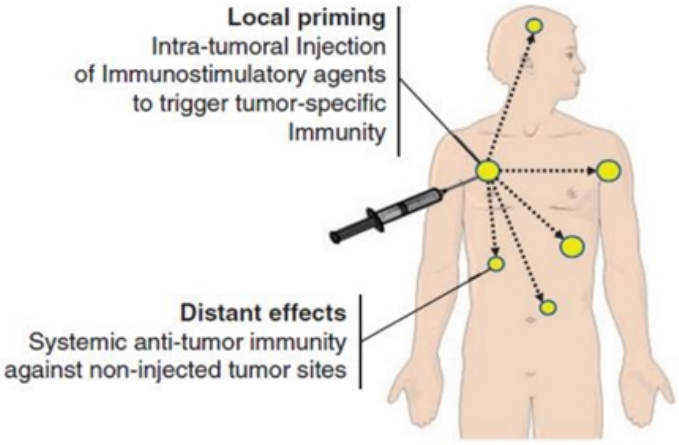
TransCon IT Designed for Local and Abscopal Anti-Tumor Effects



Designed to Enable Immune Activation in the Draining Lymph Nodes
Cytotoxic T effector Cells Primed in Lymph Nodes Capable of Targeting Abscopal Tumors

Adapted from Yeo et al, Front. Immunol., 2017; and Marabelle et al., Ann Onc, 2017

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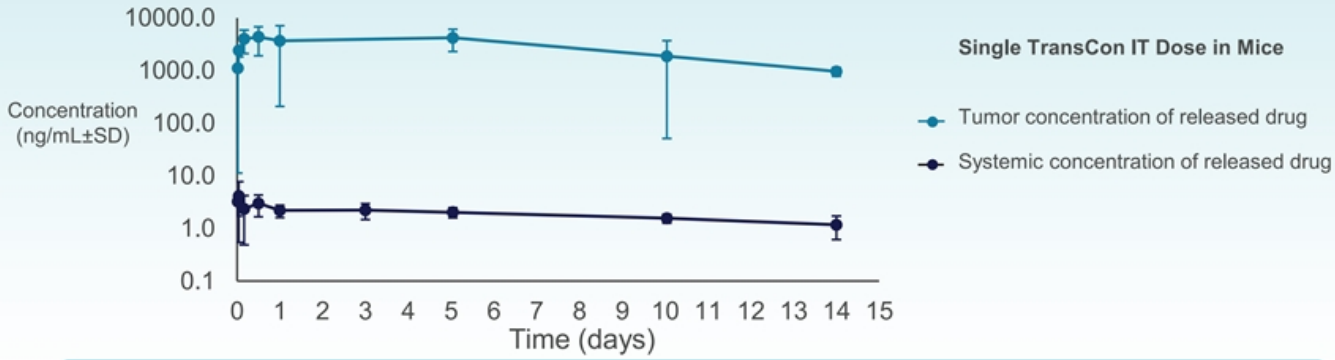
TransCon IT: Potential Paradigm Shift in Intratumoral Delivery

TransCon Intratumoral (IT) addresses the problems of conventional IT administration including rapid clearance from the tumor, high systemic exposure and toxicity



TransCon IT is designed to stay in the tumor and slowly release the drug, ensuring high tumor drug concentration and low systemic exposure

Data on file.

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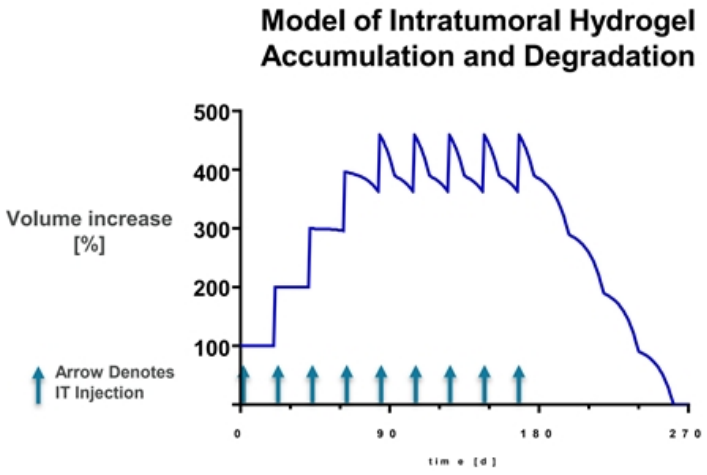
Modeled Volume of Hydrogel in Injected Tumor



Q3W dosing leads to accumulation of 4-5 depots within the tumor at steady state

Upon cessation of dosing, the hydrogel degrades and is cleared from the tumor site

* In vitro data; Data on file
Following injection, the hydrogel carrier disintegrates into small polymer fragments after approximately 3 months*

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Algorithm for Product Innovation: Building an Oncology Pipeline

We are continuing to apply our successful algorithm applied in endocrinology to build a pipeline in oncology and we are committed to entering a 3rd therapeutic area

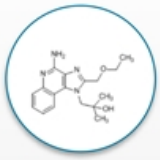
Opportunity for TransCon TLR7/8 Agonist in Solid Tumors

Efficacy
- Each injection designed to provide sustained exposure in the tumor to enhance immune activation
- Systemic immune activation may lead to abscopal tumor effects

Safety
- Low systemic toxicity expected to reduce dose-limiting adverse events
- Infrequent dosing designed to improve practicality and reduce injection-related complications

Broad application
- Essentially all solid tumor lesions that can be biopsied may be considered for injection

TransCon TLR7/8 Agonist



Designed for ***superior efficacy*** with ***minimal systemic toxicity***

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Potential Paradigm Shift in How Cancer Is Treated

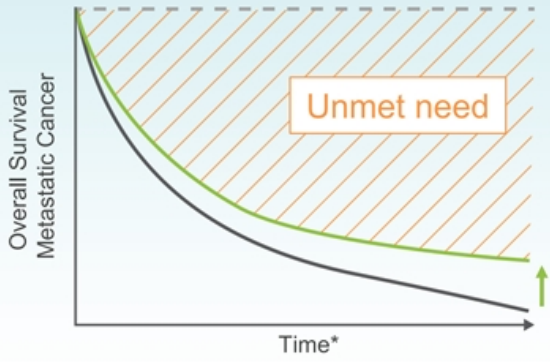
- Oncology pipeline using TransCon technologies that may enable a new treatment paradigm, based on well-known biology
- Two clinical-stage product candidates with potentially best-in-class properties using systemic and localized TransCon technology
  - TransCon TLR7/8 Agonist designed for IT, long-term sustained release for superior efficacy with minimal systemic adverse events
  - TransCon IL-2 β/γ designed for optimized IL-2Rβ/γ bias and potency, combined with low C_{max} and long exposure
- TransCon technology offers a new treatment paradigm for oncology, providing both systemic and IT sustained delivery options with potential for superior efficacy and safety

TransCon TLR7/8 Agonist Clinical Update

Stina Singel, M.D., Ph.D.
Head of Clinical Development, Oncology

Unmet Medical Need Remains High Despite Advancements

- Immunotherapy has given hope for dramatic improvement in cancer treatment…
- But most cancer patients today are not benefiting from immunotherapy



- U.S. cancer patients eligible for checkpoint inhibitors (CPI) increased from 1.5% in 2011 to 43.6% in 2018
- Percentage of patients estimated to respond to CPI was 0.1% in 2011 and increased to 12.5% in 2018

Immunotherapy has "raised the tail" for multiple tumor types

More effective therapies are urgently needed

* Graph is illustrative and does not represent specific observed data.
Haslam A and Prasad V. *JAMA Netw Open*. 2019;2(5):e192535.

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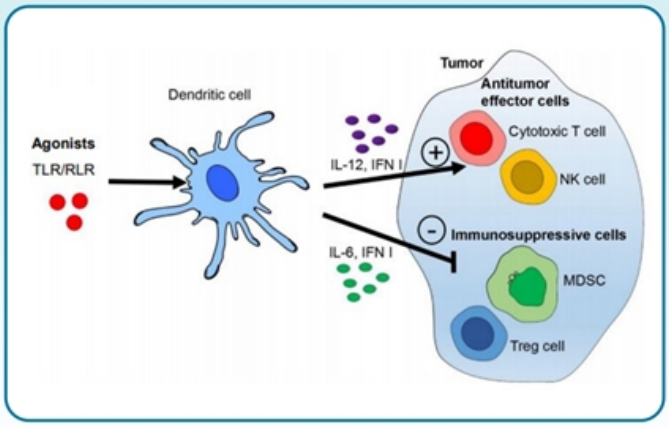
Toll-Like Receptors (TLRs): Well-Validated Targets for Activation of Innate and Adaptive Immunity[1]

- Activate innate immunity in particular antigen presenting cells (APCs)
- Prime and expand cytolytic and helper T cells
- Inhibit suppressive mechanisms limiting anti-tumor responses
- Resiquimod has been clinically evaluated as a potent TLR7/8 Agonist[2,3]



TLRs activate several key pathways critical in host defense against tumors

1. Bourquin C, et al. *Pharmacol Res*, 2020; 154:104192
2. Vasilakos J and Tomai M. Exp Rev Vaccines, 2013; 12:809-819.
3. Rook A, et al. Blood. 2015;126(25):2765.

Limitations of TLR Agonists in Clinical Setting

- Systemic administration[1] leads to high toxicity such as cytokine release syndrome
- Previous IT approaches cannot deliver prolonged exposure of active drug levels needed for anti-tumor activity
  - Consistent with short exposure, pharmacodynamic effects of previous IT TLR agonists in the tumor have only been reported at ~24 hours post dose[2,3]

Sustained IT exposure of resiquimod is likely needed for therapeutic benefit while minimizing systemic toxicity

[1]Pockros et al. 2007 *J of Hepatology* 47: 174-182; [2] Babiker et al. ESMO 2020, abs 1031P; [3] Diab et al. SITC 2020, abs 368

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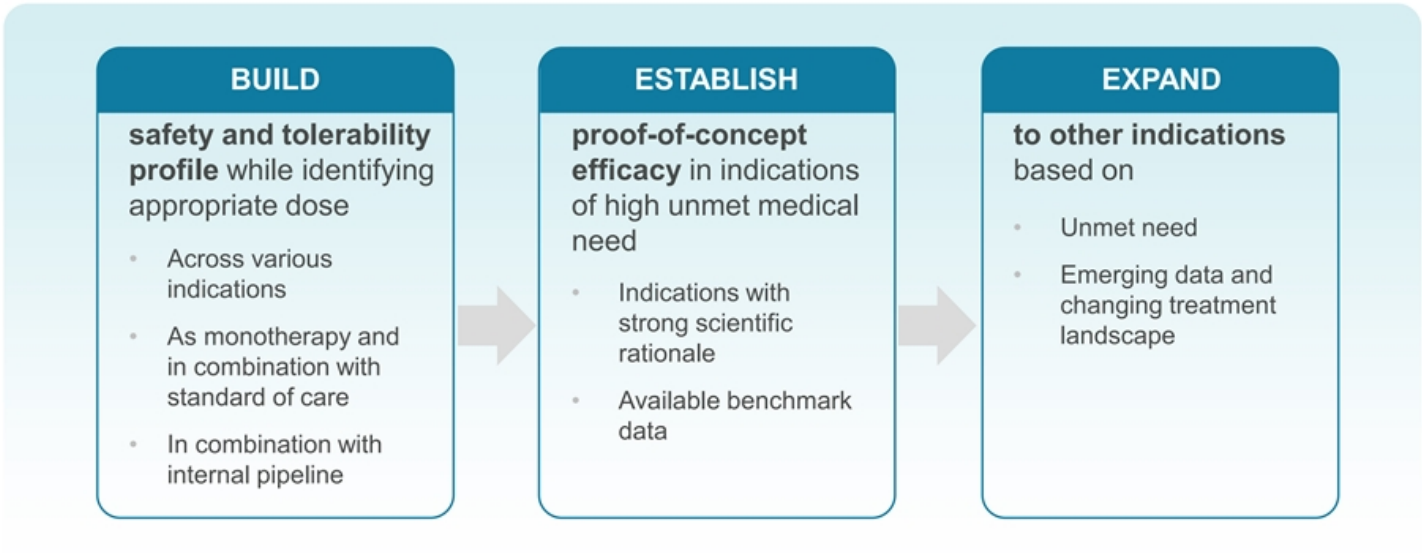
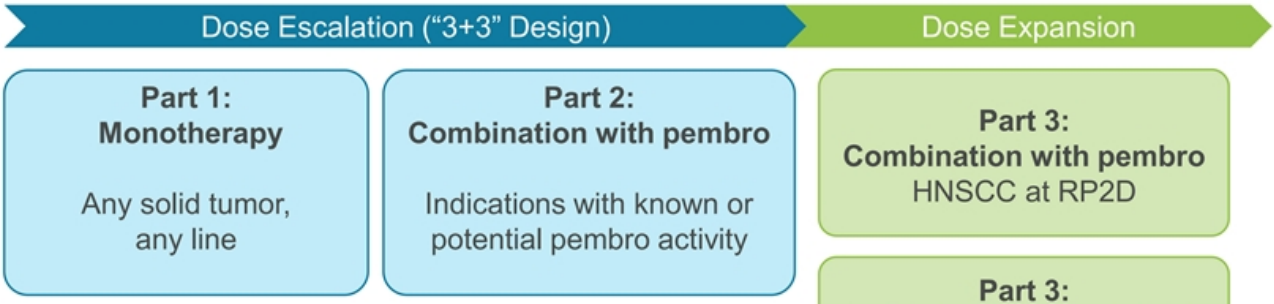
Clinical Development Strategy in Oncology to Take Advantage of the Clinically Validated TransCon Platform



Status Update on transcendIT-101: TransCon TLR7/8 Agonist First-in-Human Trial



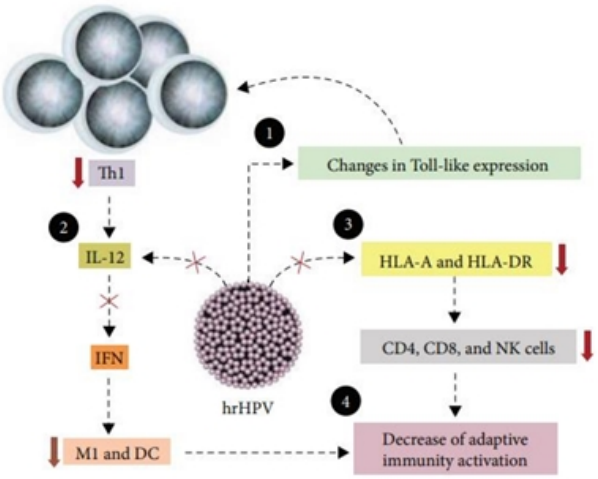
Objectives:

- Safety and tolerability; define MTD and RP2D
- Pharmacokinetics/pharmacodynamics (PK/PD)
- Preliminary anti-tumor efficacy (ORR, duration of and time to response)

Abbreviations: recommended phase 2 dose (RP2D), maximum tolerated dose (MTD), overall response rate using RECIST 1.1 (ORR)

Initial Indications of HPV-associated Cancers Selected Based on Strong Scientific Rationale

TLRs and HPV-associated cancers[1]



Dose Expansion

Combination with CPI

HPV-associated tumors:

- HNSCC
- Others (anal, cervical, vulvar, penile, vaginal)

Other indications will be added based on

- Unmet need
- Emerging data and changing treatment landscape

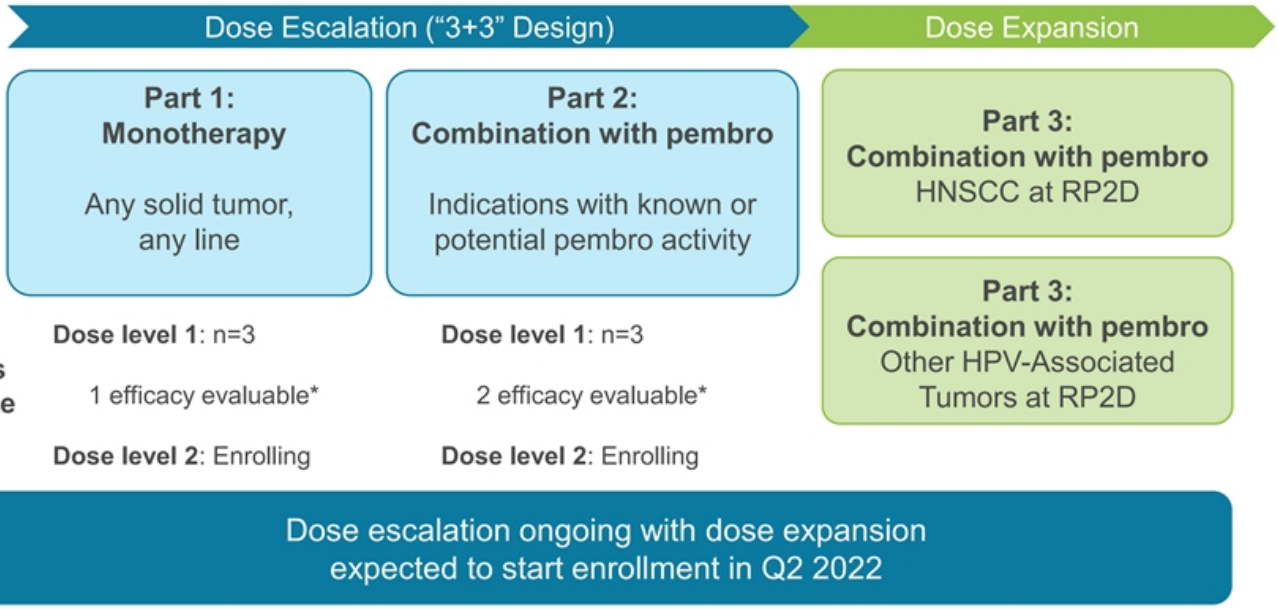
HNSCC: HPV+ prevalence rising -- for every 2 new cases of HPV-oropharyngeal carcinoma diagnosed, 5 new cases HPV+[2]

Anal, cervical, vulvar, penile, vaginal: vast majority (>70-90%) are HPV+

HNSCC: head and neck squamous cell carcinoma;
HPV: human papillomavirus

[1]Barros M, et al. *J Immunology Res*. 2018; 2912671:1-17.
[2]Mahal B, et al. *Cancer Epidemiol Biomarkers Prev*. 2019; 10:1660-1667.

Interim Status Update on transcendIT-101: TransCon TLR7/8 Agonist First-in-Human Trial

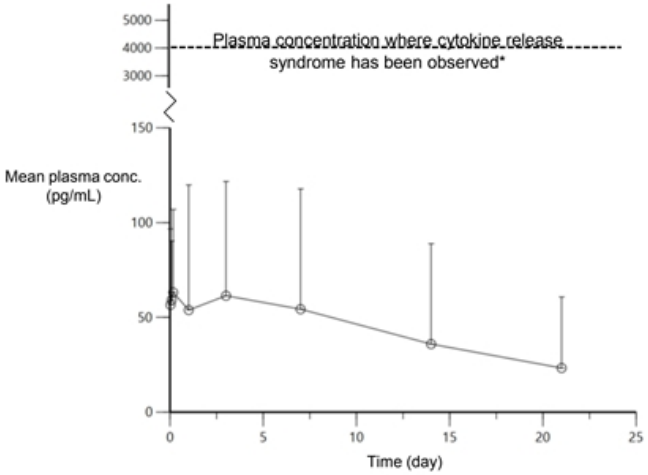


Dose escalation ongoing with dose expansion expected to start enrollment in Q2 2022

* Efficacy evaluable: at least 1 post-baseline tumor assessment

transcendIT-101: Low Systemic Exposure with Half-life of ~7 Days

Resiquimod mean (+SD) plasma concentrations following one intratumoral injection



- Plasma concentrations 15-fold below levels where cytokine release syndrome has been observed (~4000 pg/mL*)
- Mean systemic half-life of resiquimod is ~7 days

Peripheral PK indicates sustained release of resiquimod with a half-life of ~7 days and systemic exposure with wide safety margin

Mean of n=7 (6 at dose level 1 and 1 at dose level 2)

* Pockros PJ et al. *J Hepatol.* 2007;47(2):174-182.

Demographic and Safety Data*

Select Demographics	Monotherapy (n=5)		Combination (n=3)	
Tumor types	Melanoma (n=3) TNBC (n=1) Pancreatic (n=1)		Melanoma (n=1) Basal Cell Carcinoma (n=1) Pancreatic (n=1)	
Median prior anti-cancer treatment regimens	3		2	
Prior anti-PD(L)1	4 (80%)		2 (67%)	
Overview of Safety				
Subjects with at least 1 AE	4 (80%)		2 (67%)	
Subjects with at least one SAE	3 (60%)	**Related: 0**	1 (33%)	**Related: 0**
Subjects with at least one ≥3 AE	3 (60%)	**Related: 0**	1 (33%)	**Related: 0**
Subjects with an AE leading to study drug withdrawn or study discontinuation	**0**		**0**	
Subjects with Death related to AE	**0**		**0**	

TransCon TLR7/8 Agonist is well-tolerated as monotherapy or in combination with pembrolizumab, consistent with low systemic exposure

*Datacut date: 16 Nov 2021

Initial Interim Data Indicate TransCon TLR7/8 Agonist Is Well-Tolerated as Monotherapy or in Combination with Pembrolizumab

- No dose-limiting toxicities observed
- Limited safety-evaluable population (n=8) so far indicates no systemic side effects related to TransCon TLR7/8 Agonist
  - Consistent with low systemic exposure of resiquimod
- Transient, mild injection site-related reactions (Grade 1/2) are the only related AEs
  - 2 out of 5 patients treated with monotherapy
  - No injection site reactions have been reported so far for 3 patients treated with combination treatment

transcendIT-101: Study Status

N=8 treated with study treatment as of 16 Nov 2021*

- **3 efficacy evaluable patients with at least 1 post-baseline tumor assessment**
- 2 discontinued due to progressive disease (before first tumor assessment at week 9)
- 1 discontinued due to physician decision (patient left study for hospice care before week 9)
- 2 patients ongoing but have not yet reached first efficacy assessment at week 9

TransCon TLR7/8 Agonist Dose Level 1	Tumor type (# prior anti-cancer treatment regimens)	Prior PD(L)1
Monotherapy	Melanoma (2)	yes
Combination with pembro	Pancreatic Cancer (2)	no
Combination with pembro	Basal Cell Carcinoma (2)	yes

Datacut date:16 Nov 2021 with tumor response data only updated on 3 Dec 2021 due to new pathology data;
* Median follow up (time from study treatment start to the date of death or the date patient is last known to be alive): 59 d (range 15-190)

Early Signs of Clinical Activity from Efficacy-Evaluable Patients (#1)

Patient Profile #1	Best Overall Response per RECIST v1.1 (latest investigator assessment)	Available On-Treatment Pathology
Tumor Type: Melanoma Prior Treatment Regimens: 2 Prior PD(L)1: yes—pembro Treated with: TransCon TLR7/8 Monotherapy Dose Level 1	**uPR (week 27)** Target lesions Baseline wk9 wk18 wk27 Injected (mm) 25 → 24 → 24 → 30 Non-injected (mm) 11 → 10 → 9 → 0	**Injected lesion:** 3 core biopsies at week 27 after 9 doses showed **tumor cells found in up to 50% of total tissue**; focal foreign material (hydrogel carrier) surrounded by granulomatous inflammation **Non-injected lesion:** Punch biopsy at week 27 (lesion site previously marked) showed mild chronic inflammation, reactive changes, **no evidence of malignancy**

Pathological confirmation of complete response in non-injected lesion indicates abscopal effect of monotherapy TransCon TLR7/8 Agonist in a patient previously treated with pembro

uPR = unconfirmed partial response; Datacut date: 3 Dec 2021

Early Signs of Clinical Activity from Efficacy-Evaluable Patients (#2)

Patient Profile #2	Best Overall Response per RECIST v1.1 (latest investigator assessment)	Available On-Treatment Pathology
Tumor Type: Pancreatic Cancer Prior Treatment Regimens: 2 Prior PD(L)1: no Treated with: TransCon TLR7/8 Dose Level 1 Combination with Pembro	**SD (week 9)** Target lesions — Baseline — wk9 Injected once in Cycle 1 (mm) 22 → 30 Non-injected (mm) 90 ↘ Injected since Cycle 2 (mm) 90	**Injected lesion:** 3 core biopsies **at week 7 after 1 dose showed no tumor present**; minimal lymphohistiocytic reaction

Pathological evaluation after a single dose suggests early and potentially deep response in injected tumor

SD = stable disease; Datacut date: 3 Dec 2021

Early Signs of Clinical Activity from Efficacy-Evaluable Patients (#3)

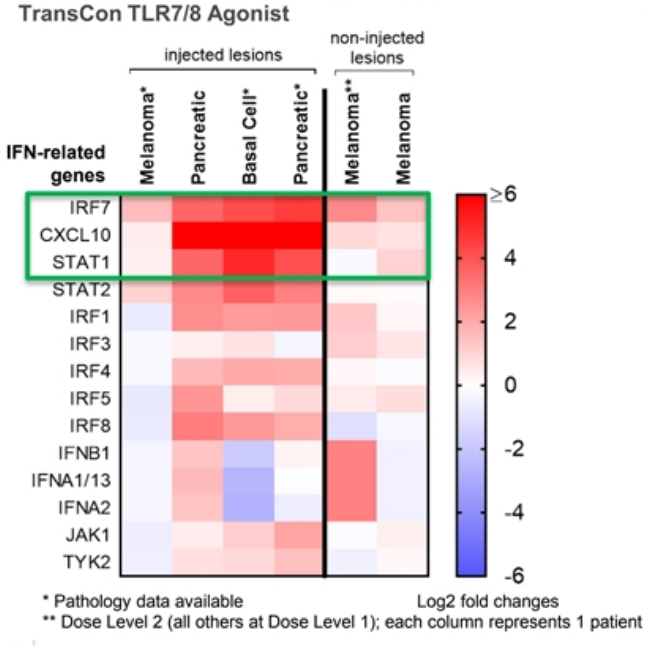
Patient Profile #3	Best Overall Response per RECIST v1.1 (latest investigator assessment)	Available On-Treatment Pathology
Tumor Type: Basal Cell Carcinoma Prior Treatment Regimens: 2 Prior PD(L)1: yes—cemiplimab progression immediately prior to enrollment Treated with: TransCon TLR7/8 Dose Level 1 Combination with Pembro	**SD (week 9)** Target lesions — Baseline → wk9 Injected (mm): 42 → 47.5 Non-injected (mm): 17 → 18.4	**Injected lesion:** Punch biopsy at week 9 after 3 doses showed atypical basaloid proliferation at base of biopsy. **No evidence of malignancy**.

Pathological evaluation at time of first tumor assessment suggests early and potentially deep response in injected tumor in a patient who progressed on anti-PD1

SD = stable disease; Datacut date: 3 Dec 2021

Target Activation of Key Immunological Pathways Maintained Through at Least 7 Days Post-Dose in Injected and Non-Injected Lesions

Gene Expression at 7 Days After 1 Dose of TransCon TLR7/8 Agonist



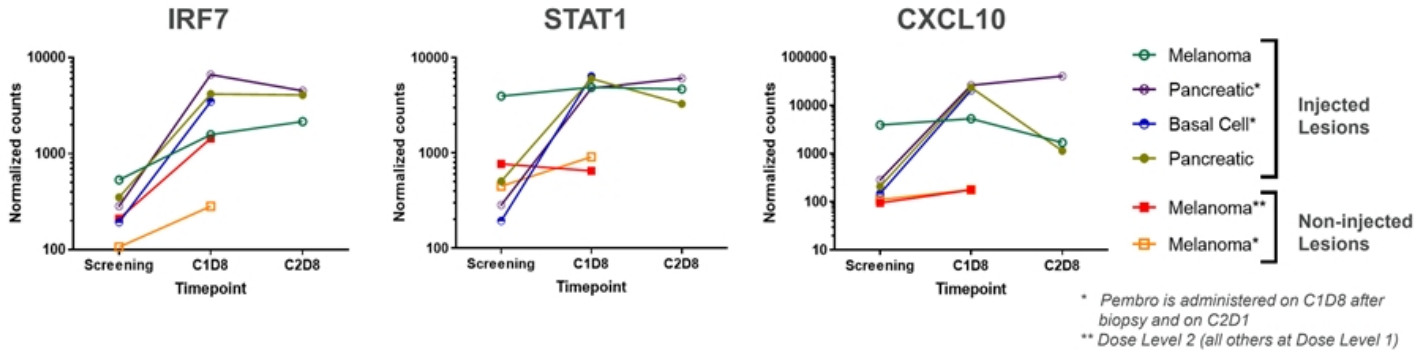
* Pathology data available

** Dose Level 2 (all others at Dose Level 1); each column represents 1 patient

- **Target engagement of TLR7/8 Agonist**
  - Consistent increase of IRF-7
- **Innate immune activation**
  - Strong increase in CXCL10 expression
- **Interferon (IFN) pathway activation**
  - Consistent increase of STAT1 expression
- **Data consistent across different tumor types**
  - Melanoma, Basal Cell Carcinoma, Pancreatic Cancer
- **Similar effects observed in non-injected lesions**

Consistent and robust immune activation in tumor tissue is observed for at least 7 days post dose

Sustained Upregulation of IFN-Related Genes in Tumor Tissue with Repeat Dosing



* *Pembro is administered on C1D8 after biopsy and on C2D1*
** *Dose Level 2 (all others at Dose Level 1)*

- Downstream of TLR7 and TLR8
- Upregulation indicates target engagement of TLR7/8 agonist

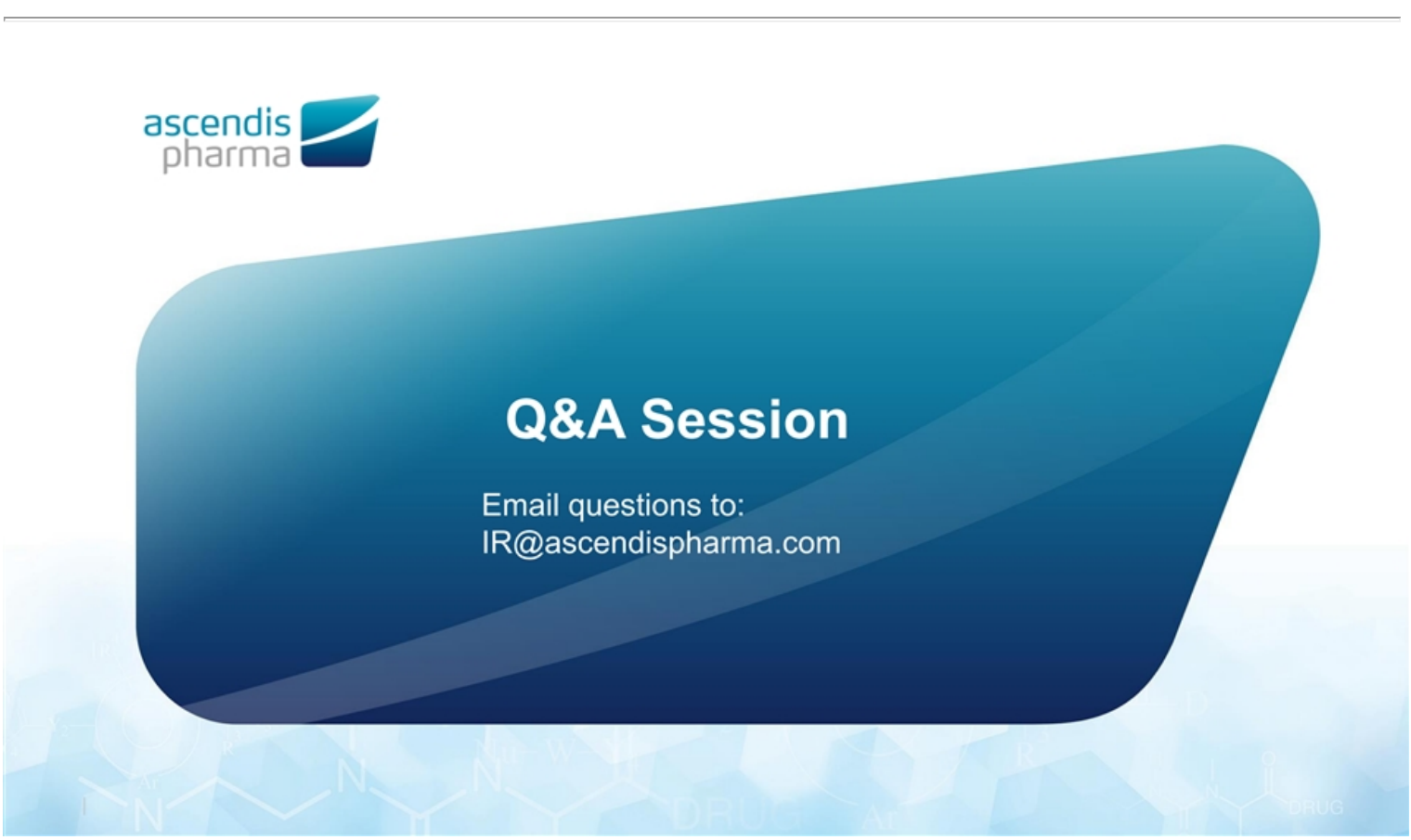
- Central signaling molecule in the IFN-I pathway
- Upregulation indicates IFN pathway activation

- Induced by IFN-γ
- Upregulation indicates engagement of the innate immune system

Sustained immune activation of key immunologic pathways is maintained with repeat dosing

TransCon Represents a Potential Paradigm Shift in Cancer Treatment

- Early data from ongoing TransCon TLR7/8 Agonist first-in-human trial (transcendIT-101) indicated:
  - Early signs of activity in three out of three evaluable patients including those previously treated with checkpoint inhibitors
  - Monotherapy activity
  - Consistent and robust target engagement
  - Well-tolerated safety profile
  - Expected low systemic exposure based on early PK data
- TransCon TLR7/8 Agonist has the potential for:
  - Sustained immune activation
  - Systemic anti-tumor response with infrequent dosing
- Create a pipeline using TransCon technologies that may enable a new treatment paradigm building upon well-known biology
  - TransCon IL-2β/γ first-in-human trial (IL βelieγe; NCT05081609) is now open for enrollment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pharma
Q&A Session
Email questions to:
IR@ascendispharma.com