TransCon PTH, a Long-acting PTH, in Patients with Hypoparathyroidism: Results of the Phase 2 PaTH Forward Trial

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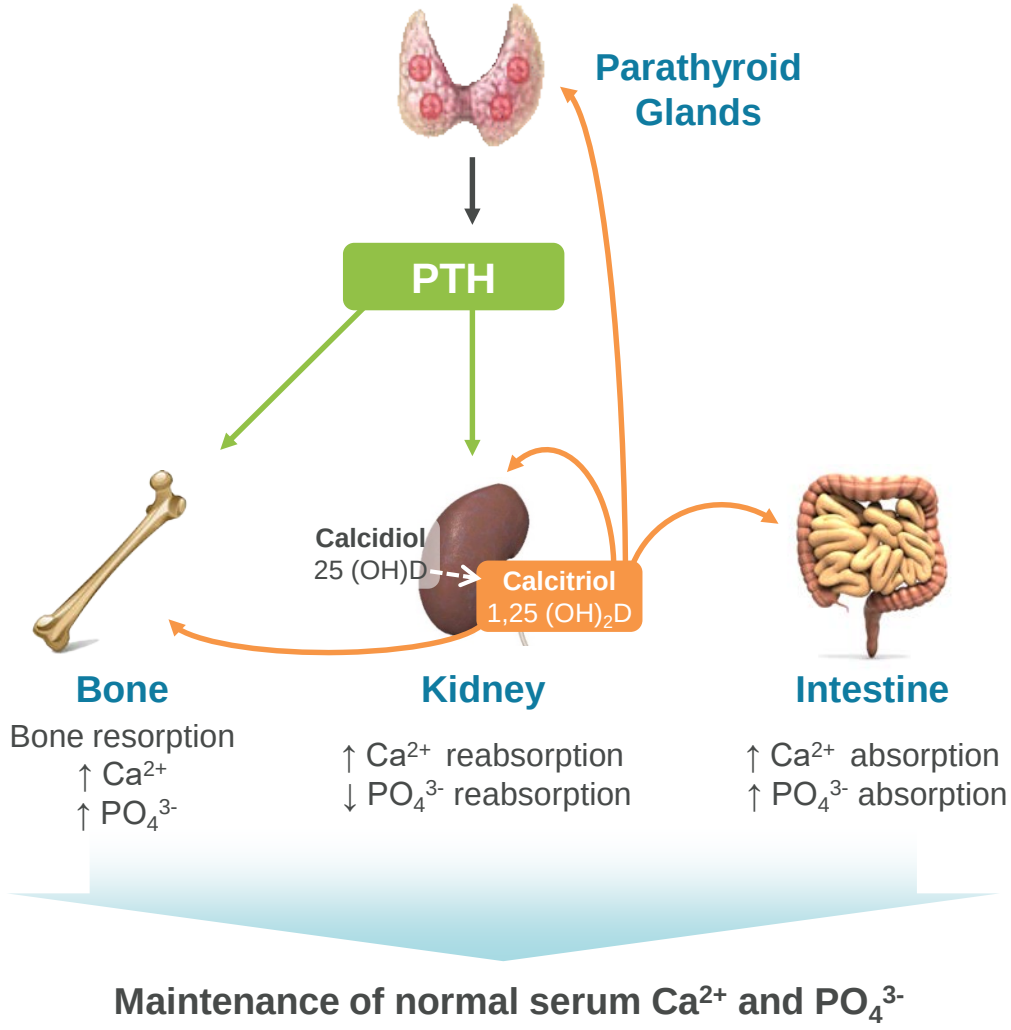
Disclosures

- Dr. Tanja Sikjaer is an investigator for Ascendis Pharma Inc. and a speaker for Takeda Pharmaceutical Company Limited

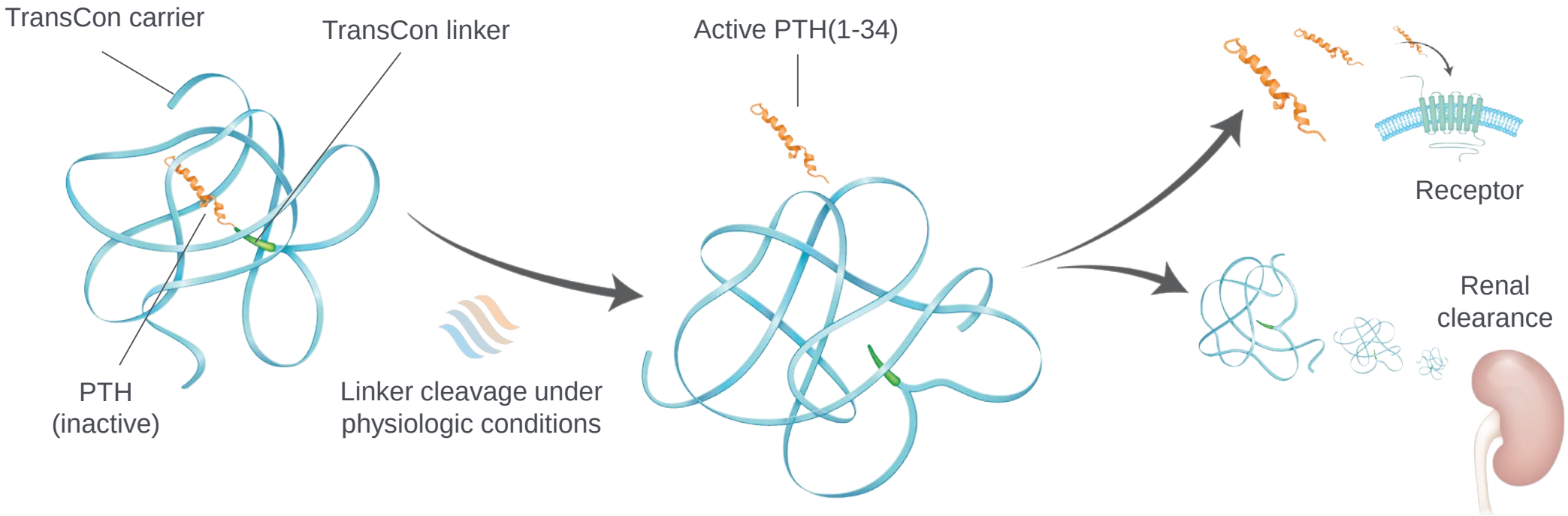
PTH Replacement for Hypoparathyroidism

- PTH is important for the regulation of serum calcium, phosphate, urinary calcium and bone turnover
- Conventional therapy for hypoparathyroidism includes calcium and active vitamin D (e.g. calcitriol, alfacalcidol) supplementation
- The ideal PTH replacement therapy would restore physiologic levels of PTH
  - And thus also restore downstream physiologic levels of calcitriol promoting independence from calcium and active vitamin D supplementation



PTH, parathyroid hormone.

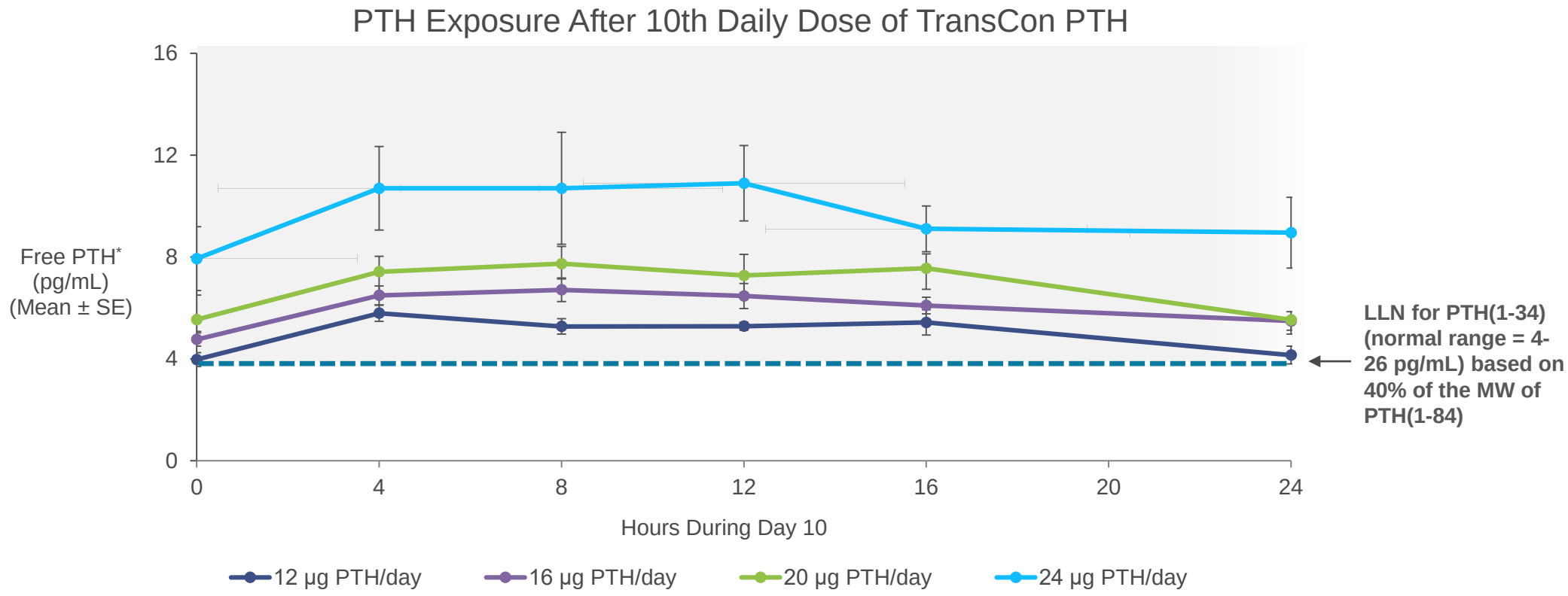
TransCon PTH Design



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

Karpf DB, et al. J Bone Miner Res. 2020 Mar 25.

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



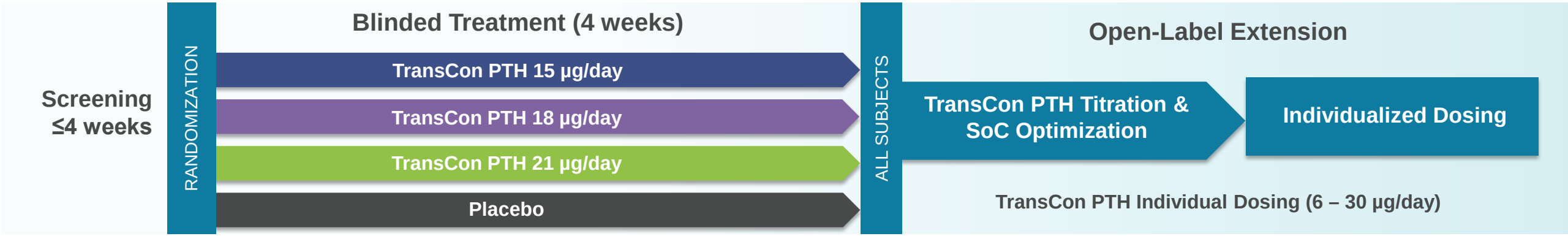
TransCon PTH daily dosing provided a flat infusion-like profile of released PTH

*PTH measured as Free PTH(1-34) and Free PTH(1-33)
Analyses from TransCon PTH Phase 1 trial; data not shown for doses <12 µg/day, as levels of Free PTH are BLQ.
Karpf DB, et al. J Bone Miner Res. 2020 Mar 25.

TransCon PTH Phase 2 Trial Design

PaTHforward TRIAL

~40 adult subjects with HP currently receiving standard of care (active vitamin D + calcium)



Primary Composite Endpoint (4 weeks)

Proportion of subjects with:

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

Key Secondary Composite Endpoint (4 weeks)

- Primary composite ***and*** requiring ≤ 500 mg/day calcium supplements

FECa, fractional excretion of calcium; HP, hypoparathyroidism; SoC, standard of care.

Demographics and Baseline Characteristics

	PTH 15 µg/day (n=14)	PTH 18 µg/day (n=15)	PTH 21 µg/day (n=15)	All PTH Subjects (n=44)	Placebo (n=13)
Age (years), mean (SD)	47 (13)	47 (11)	54 (11)	49 (12)	50 (13)
Age group (years), %					
< 30	7	7	0	5	8
≥ 30 - < 65	79	93	87	86	85
≥ 65	14	0	13	9	8
Sex, %					
Female	86	80	80	82	77
Race, %					
White	100	80	87	89	100
Geographical Region, %					
North America	50	80	67	66	54
Europe	50	20	33	34	46

This trial enrolled 59 subjects; 57 subjects met criteria for Per Protocol Analysis.

Disease Characteristics and Baseline Supplementation

	PTH 15 µg/day (n=14)	PTH 18 µg/day (n=15)	PTH 21 µg/day (n=15)	All PTH Subjects (n=44)	Placebo (n=13)
Cause of HP, %					
Acquired from neck surgery	71	80	80	77	85
Autoimmune disease	7	0	0	2	0
Idiopathic disease	21	20	20	20	15
Duration of HP (years), mean (range)	12 (1-39)	9 (2-29)	12 (3-25)	11 (1-39)	13 (3-30)
Calcium					
Mean TDD (mg)	**1643**	**2395**	**2334**	**2129**	**1636**
Calcium ≤ 1000 mg TDD, %	36	13	7	18	23
Calcium ≤ 2000 mg TDD, %	79	60	40	59	69
Calcitriol (Active Vitamin D), %	71	79	87	79	67
Mean TDD (µg)	**1.03**	**0.75**	**0.75**	**0.83**	**0.72**
Alfacalcidol (Active Vitamin D), %	29	21	13	21	33
Mean TDD (µg)	**2.75**	**2.00**	**2.00**	**2.33**	**2.50**

TDD, total daily dose.
Per Protocol Analysis.
No subjects had known baseline brain or vascular calcification or cataract. 1 subject (2.3%) in Total PTH had history of ectopic calcification.
1 subject each in Total PTH (2.3%) and placebo group (7.7%) has history of seizure.
HP Supplements at Baseline collected by eDiary/TDD; 2 subjects did not have eDiary information confirmed by prescription information.

Primary Composite Endpoint at Week 4 (Fixed-Dosing)

	PTH 15 µg/day (n=14)	PTH 18 µg/day (n=15)	PTH 21 µg/day (n=15)	All PTH Subjects (n=44)	Placebo (n=13)
Subjects Meeting Primary Composite Endpoint, n	7	6	9	22	2
Proportion, %	50	40	**60**	**50**	**15**
P-value	0.10	0.22	**0.02**	**0.03**	
Subjects Meeting Each Component, %					
sCalcium within the normal range	86	80	93	86	92
Active vitamin D = 0 µg/day	100	93	100	98	31
Calcium ≤1000 mg/day	93	87	100	93	46
Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline	71	53	60	61	38

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

Per Protocol Analysis.

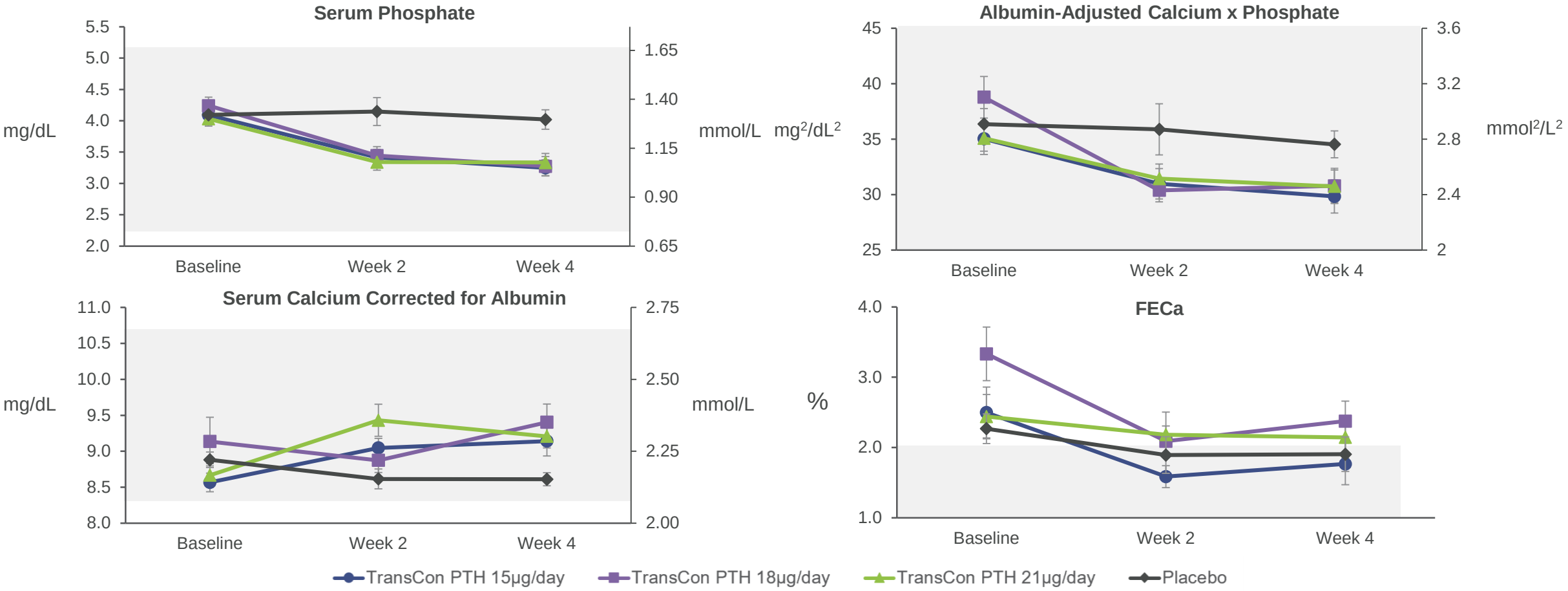
Elimination/Reduction of Conventional Therapy

Proportion of subjects meeting each component, %	PTH 15 µg/day (n=14)	PTH 18 µg/day (n=15)	PTH 21 µg/day (n=15)	All PTH Subjects (n=44)	Placebo (n=13)
Active vitamin D = 0 µg/day	100	93	100	98	31
Calcium ≤1000 mg/day	93	87	100	93	46
Calcium ≤500 mg/day	86	60	100	82	15
Calcium = 0 mg/day	50	47	53	50	0
Active vitamin D = 0 µg/day ***and*** Calcium ≤500 mg/day	86	60	100	82	15
Active vitamin D = 0 µg/day ***and*** Calcium = 0 mg/day	50	47	53	50	0

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

*Not taking active vitamin D and ≤500 mg/day of calcium supplements.
Per Protocol Analysis.

Mean Serum Phosphate, Calcium x Phosphate, Serum Calcium, and FECa by Visit



Subjects treated with TransCon PTH had greater decreases in serum phosphate and calcium x phosphate and exhibited reduced FECa despite increased serum calcium

Per Protocol Analysis.
Values shown are mean ± SE.
Grey boxes indicate normal reference range.

Treatment-Emergent Adverse Event Summary

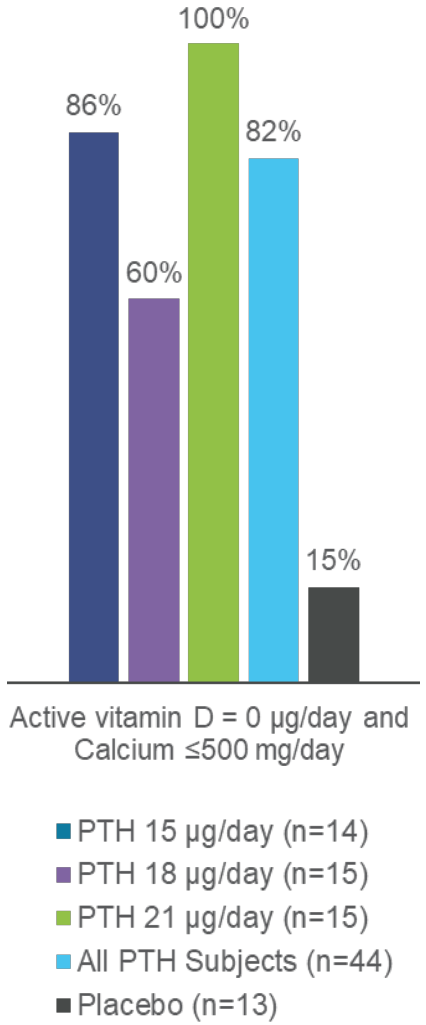
TEAE, n (%)	PTH 15 µg/day (n=14)	PTH 18 µg/day (n=15)	PTH 21 µg/day (n=15)	Total PTH Subjects (n=44)	Placebo (n=15)
Any TEAE*	6 (43)	3 (20)	8 (53)	17 (39)	5 (33)
Headache	3 (21)	1 (7)	2 (13)	6 (14)	0
Nausea	2 (14)	1 (7)	1 (7)	4 (9)	1 (7)
Hypocalcemia	0	0	0	0	1 (7)
Serious TEAE	0	0	0	0	0
Severity**					
Severe TEAE	0	0	0	0	0
Moderate TEAE	1 (7)	1 (7)	1 (7)	3 (7)	3 (20)
Mild TEAE	5 (36)	2 (13)	7 (47)	14 (32)	2 (13)
Related TEAE	3 (21)	1 (7)	5 (33)	9 (20)	1 (7)
TEAE Related to Hyper- or Hypocalcemia Leading to ER/Urgent Care Visit and/or Hospitalization	0	0	0	0	0

*Specific TEAEs reported by ≥5% of subjects in total PTH or placebo groups.
**Subjects are counted only in the highest severity category.
TEAE, treatment-emergent adverse event.
Safety analysis set.
None of the TEAE led to discontinuation of the study drug or trial or death.
There were no serious related TEAE and none of the TEAE related to hypo- or hypercalcemia led to ER/Urgent Care visit or hospitalization.

Conclusions from 4-Week Blinded, Placebo-Controlled, Fixed-Dose Period

PaTHforward TRIAL

- Population recruited reflective of known epidemiology and characteristics of patients with chronic hypoparathyroidism[1,2]
  - Typical doses of conventional therapy at baseline
- Data from the end of the 4-week blinded period support the potential for TransCon PTH as a replacement therapy
  - The majority of subjects randomized to fixed doses of TransCon PTH demonstrated independence from conventional supplements while
    - Maintaining serum calcium in the normal range
    - Reducing serum phosphate
    - Reducing urinary calcium excretion
  - All 3 fixed TransCon PTH doses were well-tolerated
    - No adverse events of hypocalcemia or hypercalcemia requiring visit to hospital, emergency room, or urgent care



[1]Clarke BL et. al. JCEM 2016: 2284-2299.
[2]Mitchell DM et. al. JCEM 2012: 4507-4514.

Future Directions: PaTH Forward Trial Continues

- Continued excellent subject retention
- 4-years of follow-up planned
  - Serum calcium, phosphate
  - Independence from conventional therapy
  - Urine calcium (24-hour urine excretion)
  - Serum markers of bone turnover
  - Bone mass (BMD and TBS by DXA)
  - Quality of life assessments (including SF-36 and a disease-specific questionnaire for HP)
- TransCon PTH will be evaluated in a global phase 3 study