# Durable Benefit of TransCon PTH, a Potential Hormone Replacement Therapy for Patients with Hypoparathyroidism, Over 58 Weeks in the PaTH Forward Trial

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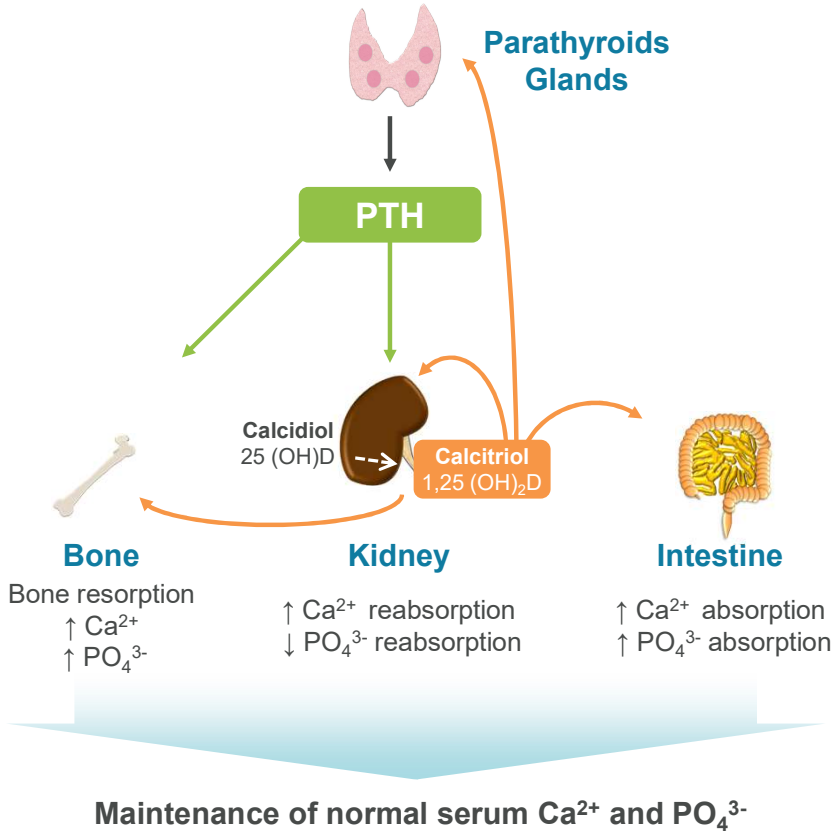
# Disclosures

- (Dr Khan to add)

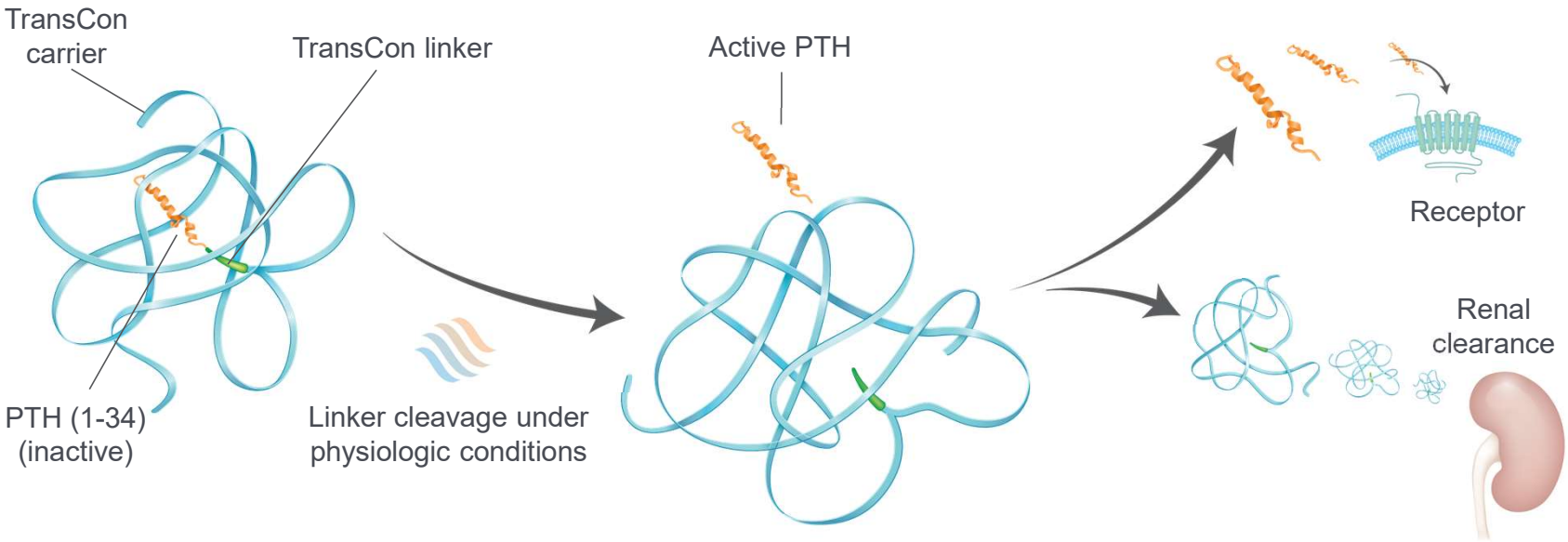
# Parathyroid Hormone (PTH) Replacement for Hypoparathyroidism

- PTH is important for the regulation of serum and urine calcium and phosphate, and bone turnover[1,2]
- Conventional therapy for hypoparathyroidism includes calcium and active vitamin D (e.g. calcitriol, alfacalcidol) supplementation[1]
- Replacement of PTH at physiological levels may lead to optimal therapeutic outcomes
  - And thus also restore downstream physiologic levels of calcitriol promoting independence from calcium and active vitamin D supplementation and normalization of quality of life[1,3]




1. Rubin MR. F1000Res. 2020;9:*F1000 Faculty* Rev-766. 2. Peacock M. *Calcif Tissue Int*. 2020. doi: 10.1007/s00223-020-00686-3.
3. Rejnmark L, et al. *Endocrinol Metab* (Seoul). 2015;30(4):436-442.

# TransCon PTH Design

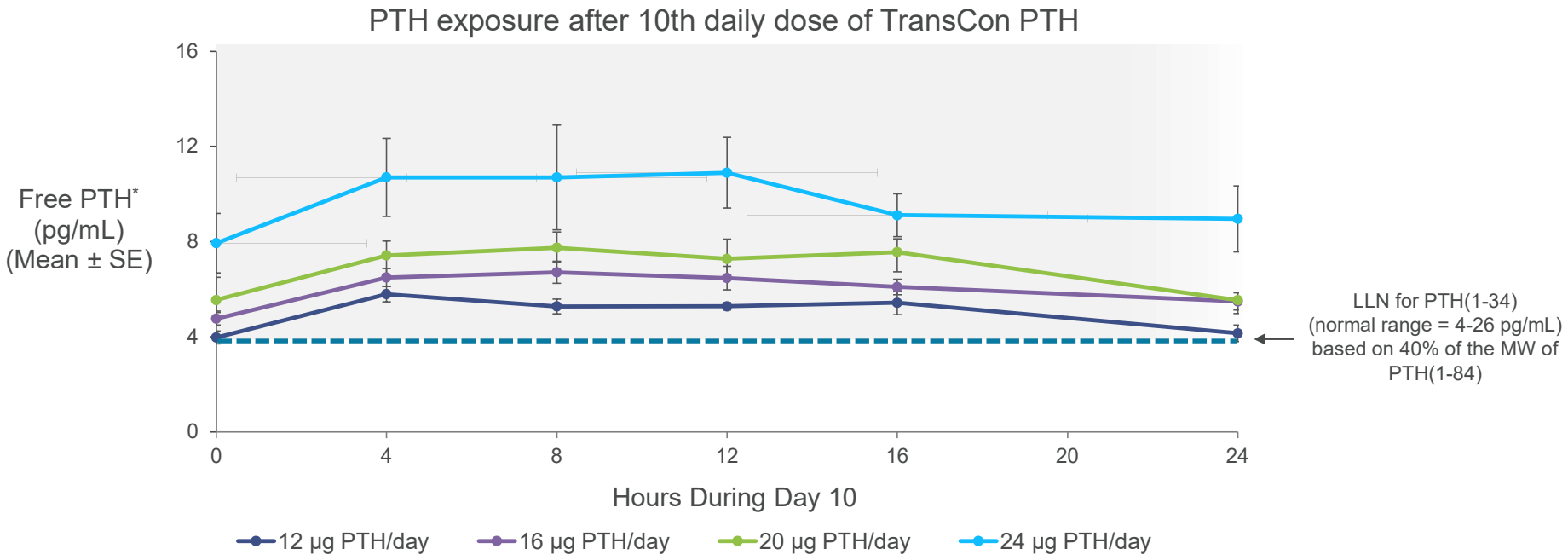



- TransCon PTH is a sustained-release prodrug designed to provide stable PTH levels in the physiological range for 24 hours/day
- TransCon PTH is designed to normalize blood and urinary calcium levels, serum phosphate and bone turnover



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

# PK Data Support Infusion-like Profile Over 24 Hours



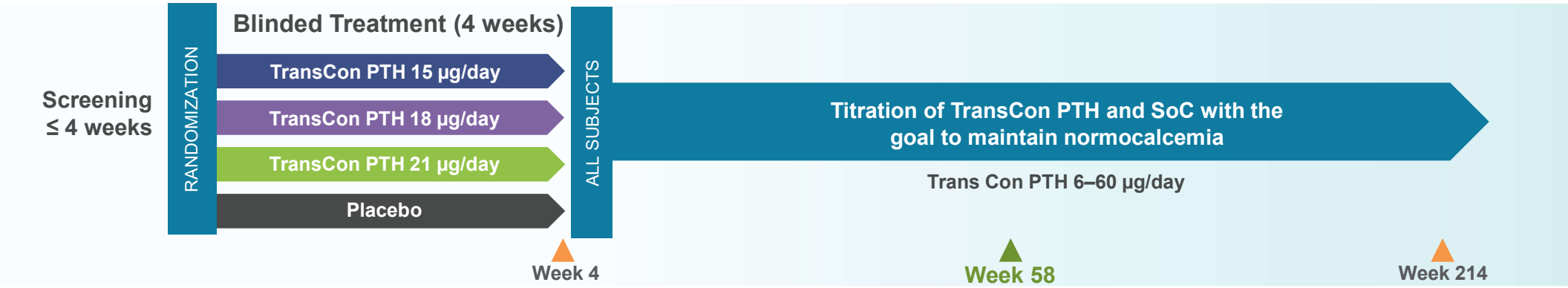

**TransCon PTH daily dosing provided an infusion-like profile of released PTH**

*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.
LLN: Lower limit of normal
Karpf DB, et al. *J Bone Miner Res*. 2020 Mar 25

# TransCon PTH Phase 2 Trial Design

PaTHforward TRIAL

**Adults with hypoparathyroidism who required SoC (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 Endpoints

- Intake of active vitamin D and calcium supplements
- 24-hour urine calcium, serum calcium, serum phosphate, and calcium phosphate product
- Quality of life assessments (including the SF-36 and HPES)
- Safety: adverse events, hypo- and hypercalcemia, injection site tolerability, vital signs and physical exam



FECa, fractional excretion of calcium; HPES, Hypoparathyroidism Patient Experience Scales; SF-36, Short Form-36; SoC, standard of care

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

# Baseline Demographics, Disease Characteristics, and Supplementation

| | All Subjects (N = 59) |
|---|---|
| **Age (years), mean (SD)** | 50 (12) |
| **Age group (years), %** | |
| < 30 | 5 |
| ≥ 30 –< 65 | 86 |
| ≥ 65 | 9 |
| **Sex, %** | |
| Female | 81 |
| **Race, %** | |
| White | 92 |
| **Geographical Region, %** | |
| North America | 64 |
| Europe | 36 |

| | All Subjects (N = 59) |
|---|---|
| **Cause of HP, %** | |
| Acquired from neck surgery | 80 |
| Autoimmune disease | 2 |
| Idiopathic disease | 19 |
| **Duration of HP (years), mean (range)** | 12 (1–39) |
| **Calcium** | |
| Mean TDD (mg) | 2079 |
| Calcium ≤ 1000 mg TDD, % | 19 |
| Calcium ≤ 2000 mg TDD, % | 63 |
| **Calcitriol (Active Vitamin D), %** | 76 |
| Mean TDD (µg) | 0.79 |
| **Alfacalcidol (Active Vitamin D), %** | 22 |
| Mean TDD (µg) | 2.38 |

TDD, total daily dose
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

# Subject Disposition – Extension Period

| | Total TransCon PTH (N = 59) n (%)* |
|---|---|
| Full Analysis Population | 59 (100) |
| Safety Population | 59 (100) |
| PK Population | 59 (100) |
| | |
| Completed Visit 15 (Week 58) | 58 (98.3) |
| Discontinued Treatment During Extension Period+ | 1 (1.7) |
| Discontinued Trial During Extension Period+ | 1 (1.7) |

*Percentages are calculated based on the Full Analysis Population
+Protocol Violation

# Elimination of Conventional Therapy

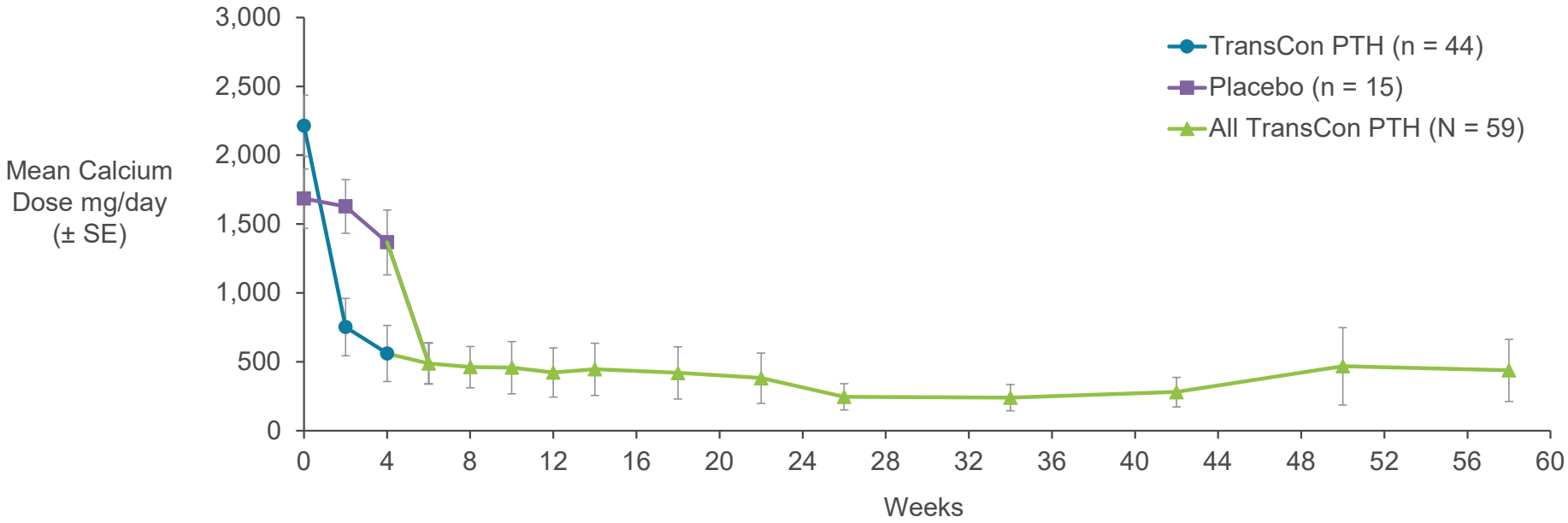
| | All TransCon PTH | |
|---|---|---|
| | Week 26<br>N = 59 | Week 58<br>N = 59 |
| Number of subjects reaching key timepoint, n | 58 | 58 |
| active vitamin D = 0 mcg QD | 58 (100%) | 58 (100%) |
| calcium supplement ≤ 500 mg QD | 53 (91%) | 52 (90%) |
| calcium supplement = 0 mg QD | 44 (76%) | 40 (69%) |
| active vitamin D = 0 mcg *and* calcium supplement ≤ 500 mg | 53 (91%) | 52 (90%) |
| active vitamin D = 0 mcg *and* calcium supplement = 0 mcg | 44 (76%) | 40 (69%) |

90% of subjects continue to be independent from conventional therapy [a]
and almost 70% of subjects were able to eliminate all supplements at Week 58



Percentages calculated based on number of subjects with Week 58 visit
[a]Not taking active vitamin D and taking ≤ 500 mg/day of calcium supplements

# Mean Calcium Supplement Dose



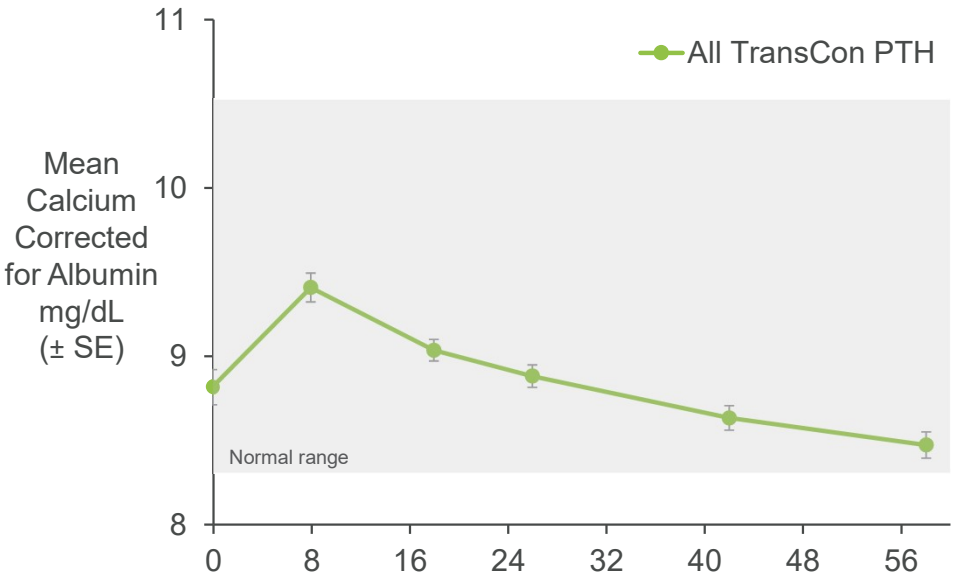

TransCon PTH enabled rapid and continuous calcium supplement reduction;
40 of 58 subjects were taking 0 mg, and 53 of 58 subjects were taking 0 to 600 mg through Week 58



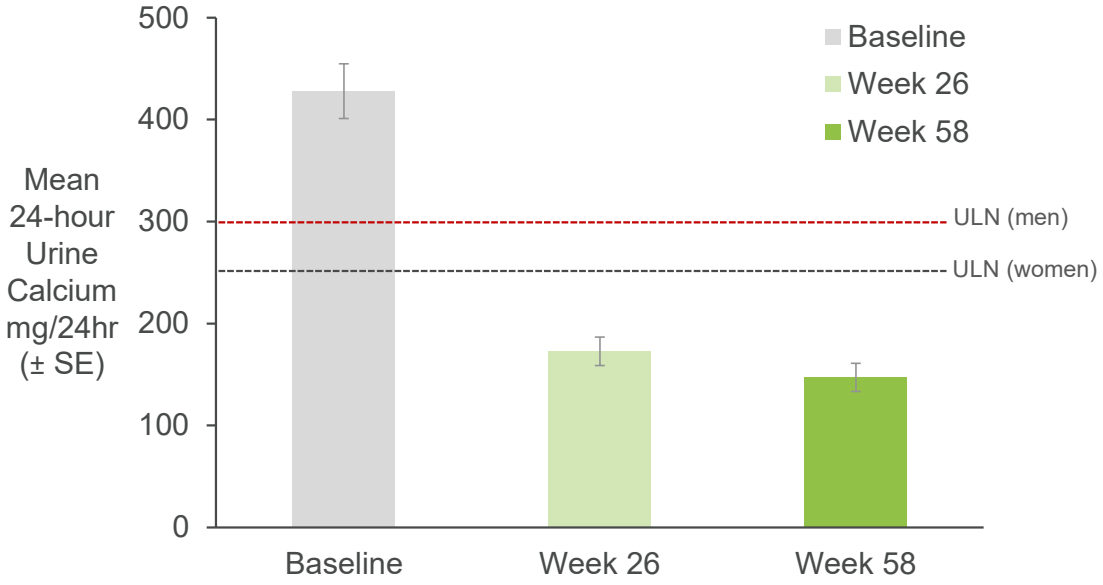
Preliminary PaTH Forward OLE week 58 data from live database snapshot. Data on file.

# Mean Serum Calcium and Mean 24-Hour Urine Calcium

## Mean Serum Calcium




## Mean 24-hour Urine Calcium



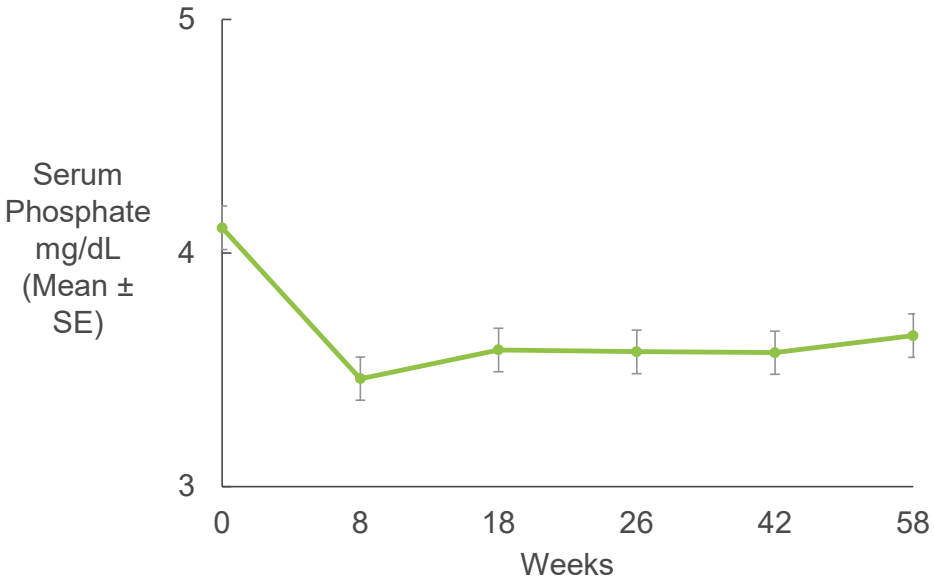

**Mean 24-hour urine calcium normalized while maintaining normal mean serum calcium through Week 58**



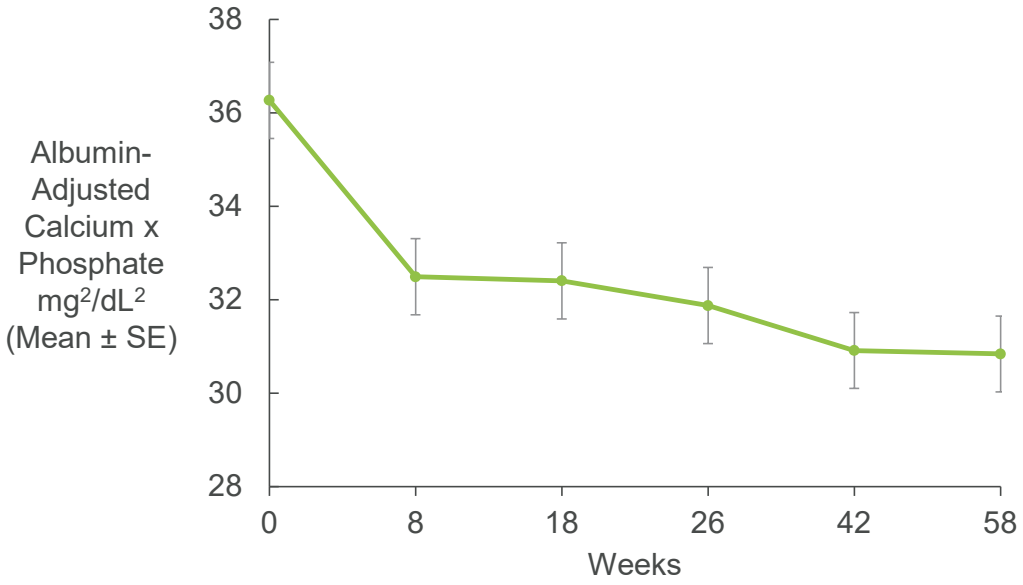
Preliminary PaTH Forward OLE week 58 data from live database snapshot. Data on file
ULN = Upper limit of normal

# Serum Phosphate and Calcium x Phosphate Product

## Serum Phosphate



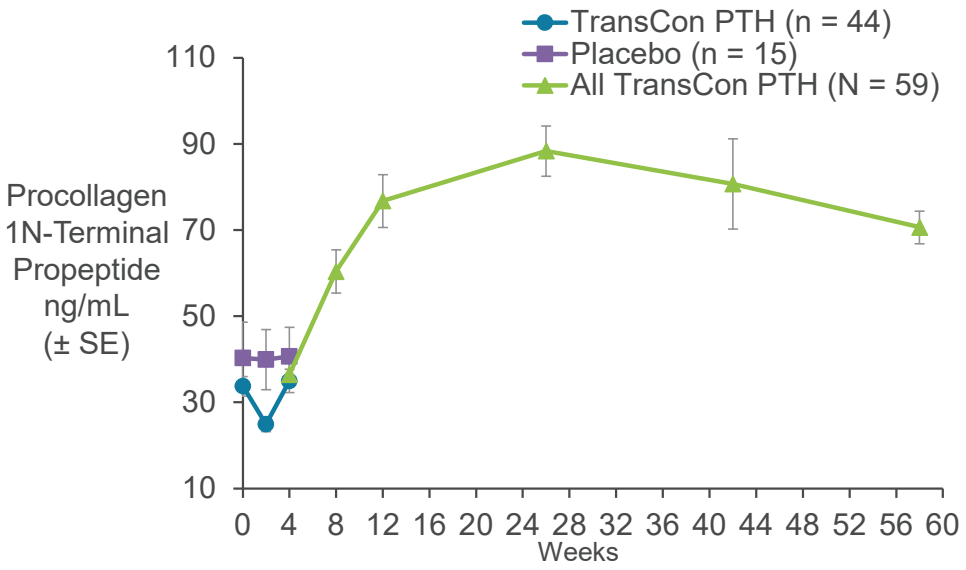

## Calcium x Phosphate Product



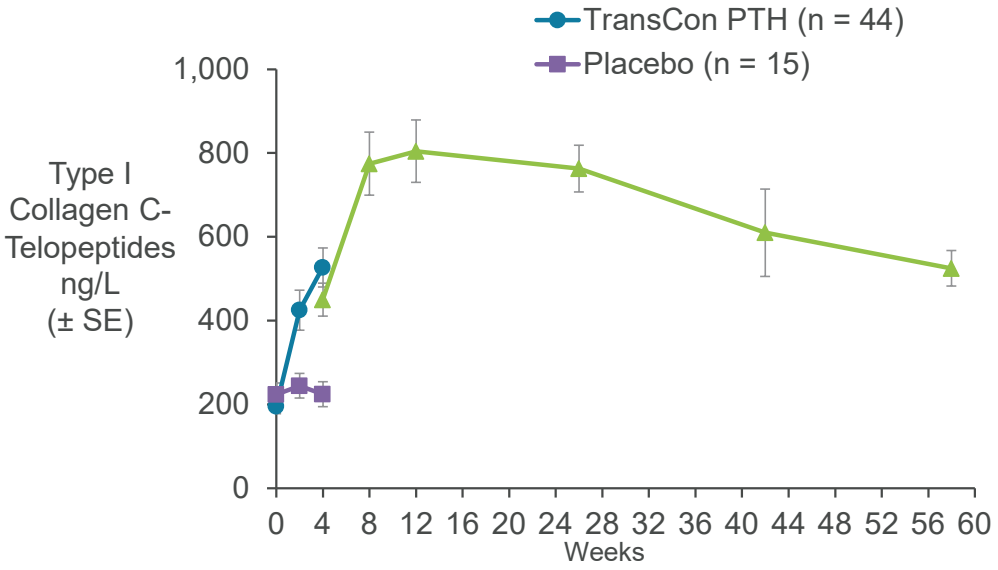

TransCon PTH continues to demonstrate consistent, sustained reductions in serum phosphate and calcium x phosphate product through Week 58

# P1NP and CTx Bone Markers

## Mean P1NP




## Mean CTx




TransCon PTH treatment initially increased the levels of anabolic and catabolic bone markers and trended to mid-normal levels at Week 58

# Bone Mineral Density by DXA

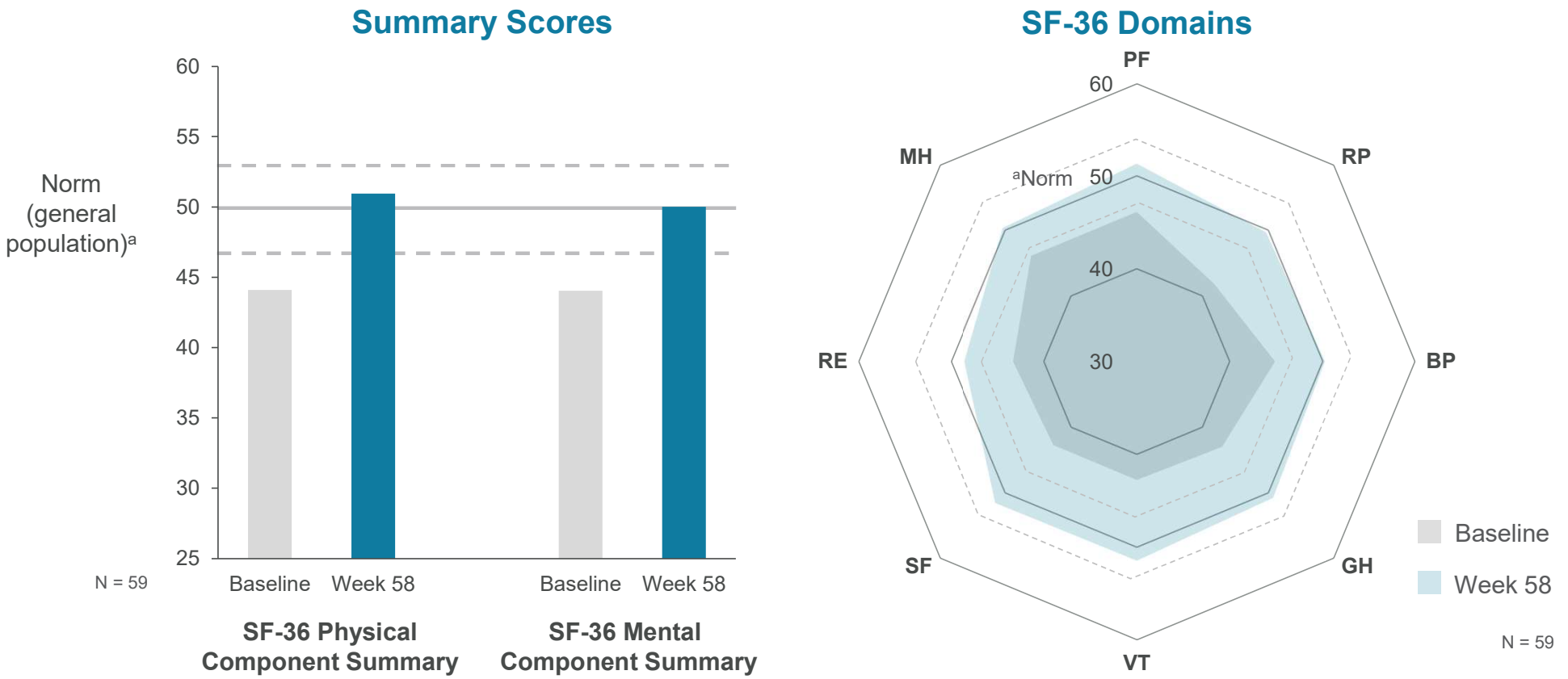
| Anatomic region | | Group A[1] – Week 26 | | | Group B[1] – Week 58 | | |
|---|---|---|---|---|---|---|---|
| | | Z-score, mean | | | Z-score, mean | | |
| | | Baseline | Week 26 | Change from baseline | Baseline | Week 58 | Change from baseline |
| Lumbar spine L1-L4[2] | n = 42 | 1.6 | 1.0 | –0.6 | 1.6 | 0.9 | –0.7 |
| Femoral neck[2] | n = 43 | 1.0 | 0.5 | –0.5 | 1.0 | 0.5 | –0.6 |
| Total hip[2] | n = 43 | 1.0 | 0.6 | –0.4 | 1.0 | 0.5 | –0.5 |
| 1/3 radius[3] | n = 41 | 0.3 | 0.3 | 0.1 | 0.3 | 0.3 | 0.0 |

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

[1] Groups A and B included all subjects who had both Week 26 and matching baseline, and Week 58 and matching baseline scans, respectively, read by the central lab.
[2]One subject in Group A was not in Group B, and one subject in Group B was not in Group A.
[3]Two subjects in Group A were not in Group B, and two subjects in Group B were not in Group A.

BMD, bone mineral density. Numbers rounded to the nearest tenth.
Data on file, Ascendis Pharma; 2021.

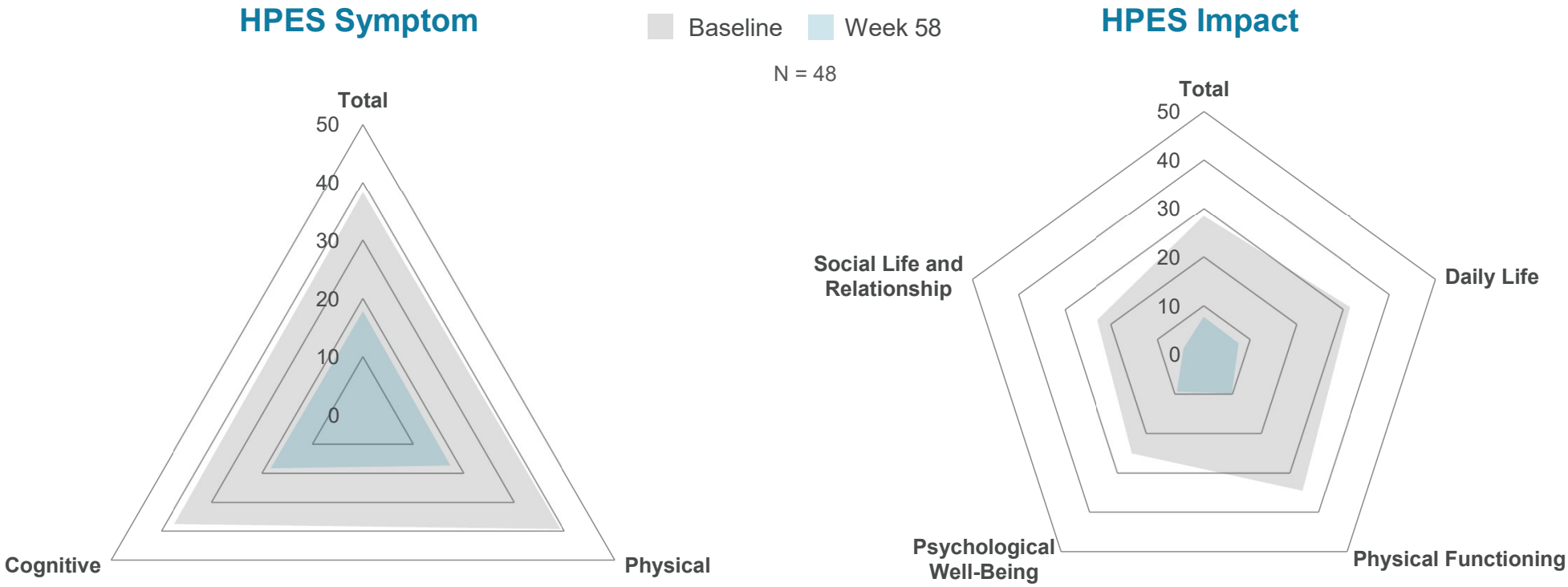
# Treatment Effect of TransCon PTH on SF-36 Functional Health and Well-Being




BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

[a]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

# Treatment Effect of TransCon PTH on Hypoparathyroidism Patient Experience Scales (HPES)




Disease-specific HPES scores all decreased from baseline to Week 58

# PaTH Forward Overall TEAE Summary

| | Up to Week 26 | Up to Week 58 |
|---|---|---|
| | All TransCon PTH (N = 59) | All TransCon PTH (N = 59) |
| Subjects With – n (%) | | |
| Treatment-Emergent Adverse Events (TEAE) | 37 (63) | 44 (75) |
| Serious TEAE | 2 (3) | 3 (5) |
| Severity | | |
| Severe TEAE | 1 (2) | 2 (3) |
| Moderate TEAE | 9 (15) | 10 (17) |
| Mild TEAE | 27 (46) | 32 (54) |
| Related TEAE* | 15 (25) | 16 (27) |
| Serious Related TEAE | 0 | 0 |
| TEAE Related to Hyper- or Hypocalcemia Leading to ER/Urgent Care Visit and/or Hospitalization | 0 | 0 |
| TEAE Leading to Discontinuation of Study Drug | 0 | 0 |
| TEAE Leading to Discontinuation of Trial | 0 | 0 |
| TEAE Leading to Death | 0 | 0 |

Preliminary PaTH Forward OLE week 58 data from live database snapshot. Data on file.
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

# Conclusions from PaTH Forward

- Data from Week 58 of the PaTH Forward trial support the potential for TransCon PTH as a replacement therapy for patients with hypoparathyroidism
  - At least 90% of subjects demonstrated independence from conventional supplements while
    - Maintaining serum calcium in the normal range
    - Reducing serum phosphate, calcium phosphate product, and urine calcium excretion
    - Demonstrating enhanced quality of life (as evident by SF-36 and HPES)
  - After initial expected increase in bone turnover, trend is returning to normal physiologic levels of skeletal remodeling
- TransCon PTH continues to be well-tolerated
    - No adverse events of hypocalcemia or hypercalcemia requiring visit to hospital, emergency room, or urgent care
- As of 17 SEP 2021, 58 subjects remain in the trial