



UniSR
Università Vita-Salute
San Raffaele



I.R.C.C.S. Ospedale
San Raffaele
Gruppo San Donato

CORSO DI AGGIORNAMENTO

**NUOVE TRAIETTORIE
NELLA CURA
DELL' IPOPARATIROIDISMO**

**IRCCS OSPEDALE SAN RAFFAELE
UNIVERSITÀ VITA E SALUTE
SAN RAFFAELE MILANO
Aula Pinta**

3 luglio 2025

Come sostituire il PTH nell'Ipoparatiroidismo

Il Palopegteriparatide

Giuseppe Vezzoli

Terapia dell'ipoparatiroidismo

Standard of care for HP patients

oral calcium and active vitamin D supplementation,

serum calcium just below or within the lower normal range (8.0 to 9.5 mg/dL or 2.0 to 2.38 mmol/L).

increases the risk of nephrocalcinosis, nephrolithiasis, and chronic kidney disease

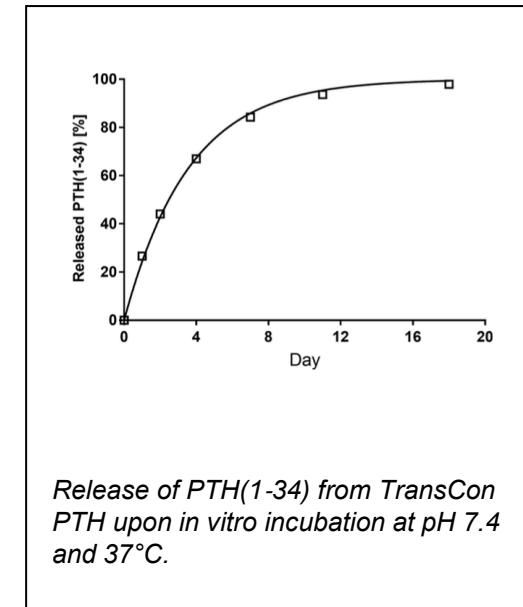
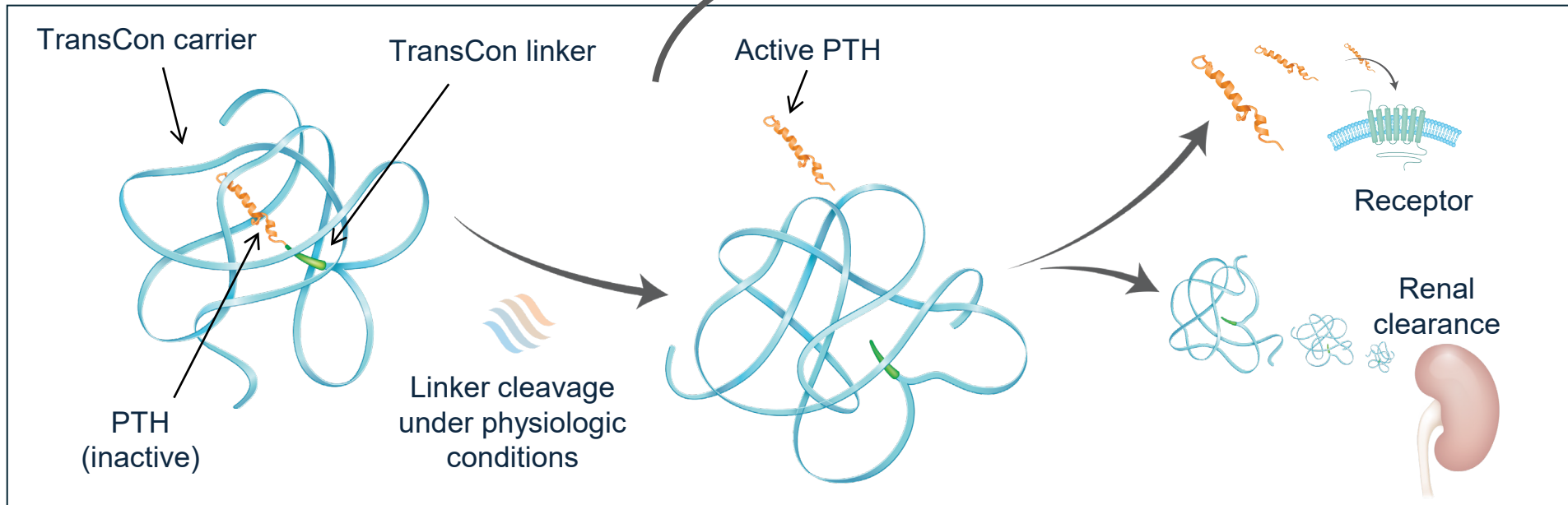
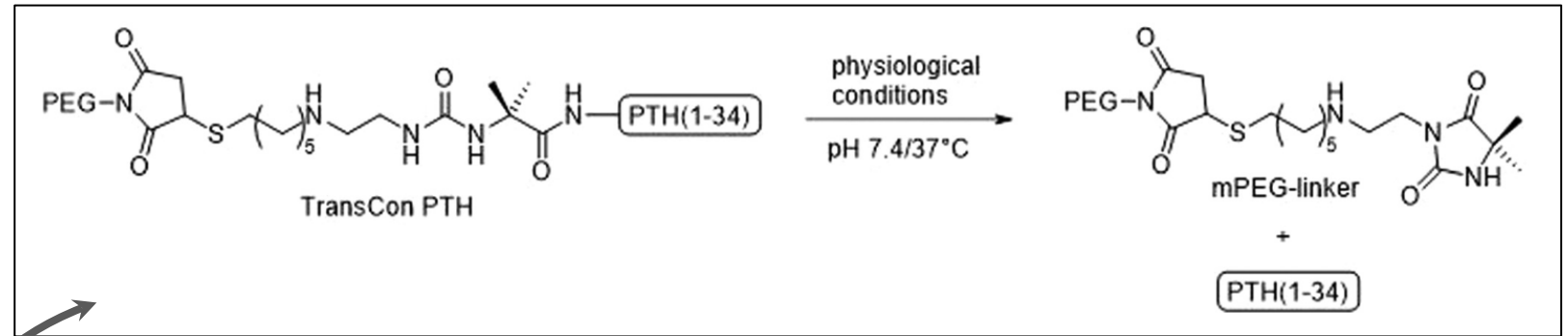
PTH(1-34) as continuous subcutaneous infusion

PTH(1-34) twice-daily injections achieved normalization of serum and urine calcium levels in many patients but with elevation of bone markers and high urine calcium excretion

Oral PTH(1-34) was an adjunctive medication to the standard therapy

PTH(1-84) has not demonstrated the ability to reduce the incidence of hypercalcemia, hypocalcemia, or hypercalciuria compared with SOC.

Il Palopegteriparatide (TransCon PTH)

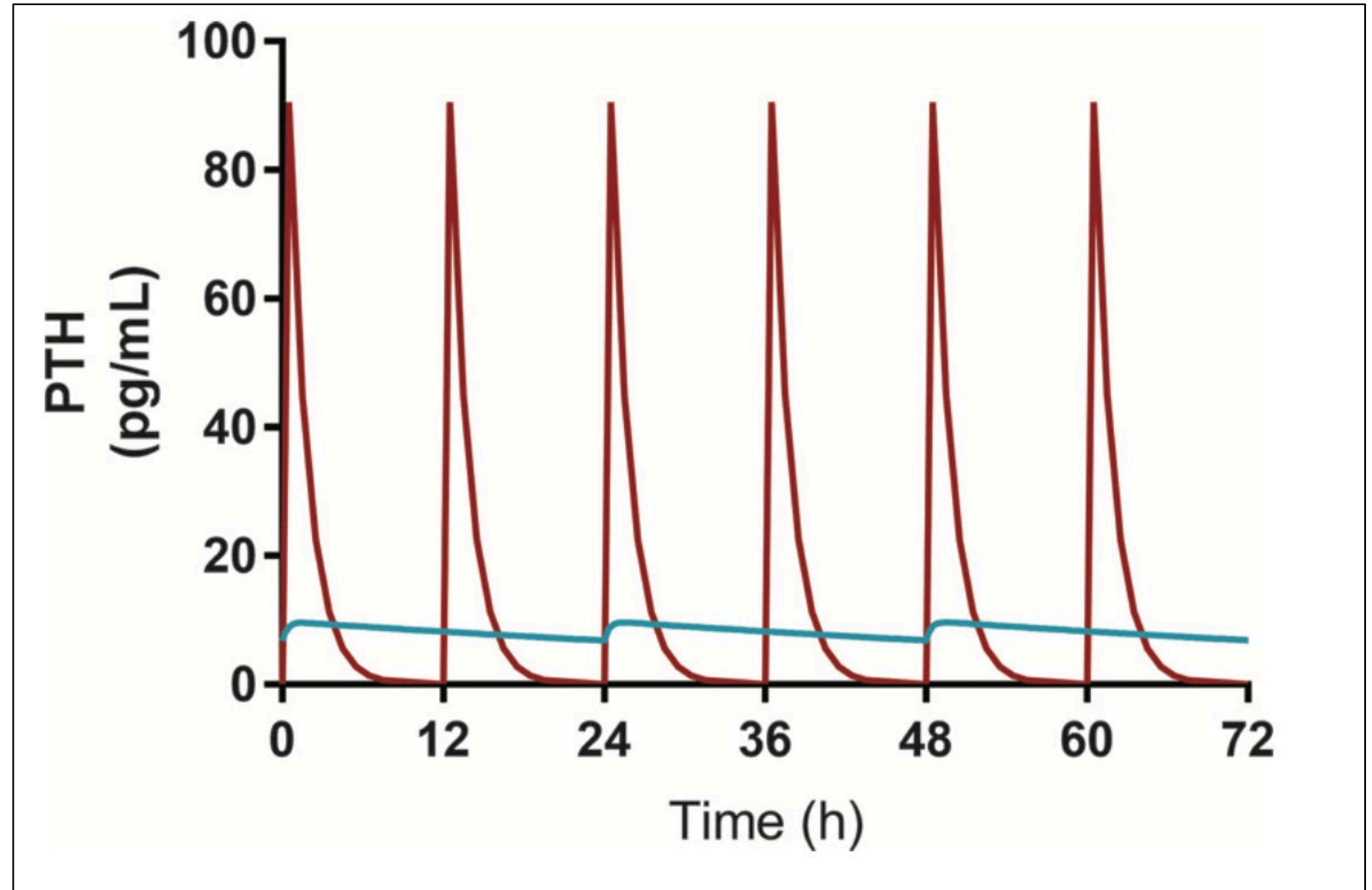


- TransCon PTH (palopegteriparatide) è un profarmaco del PTH(1-34), costituito da PTH(1-34) coniugato al vettore metossipolietylenglicole (mPEG) tramite un linker TransCon.
- PTH(1-34) ha un'affinità al PTHR1 ed attiva PTH1R in modo simile al PTH endogeno.
- TransCon PTH viene somministrato sottocute una volta al giorno
- In condizioni fisiologiche, il PTH viene scisso da palopegteriparatide in modo controllato per fornire un'esposizione sistemica continua del PTH attivo e mantenere i livelli di PTH nel range fisiologico negli adulti con ipoparatiroidismo.

Il Palopegteriparatide e il PTH(1-34)

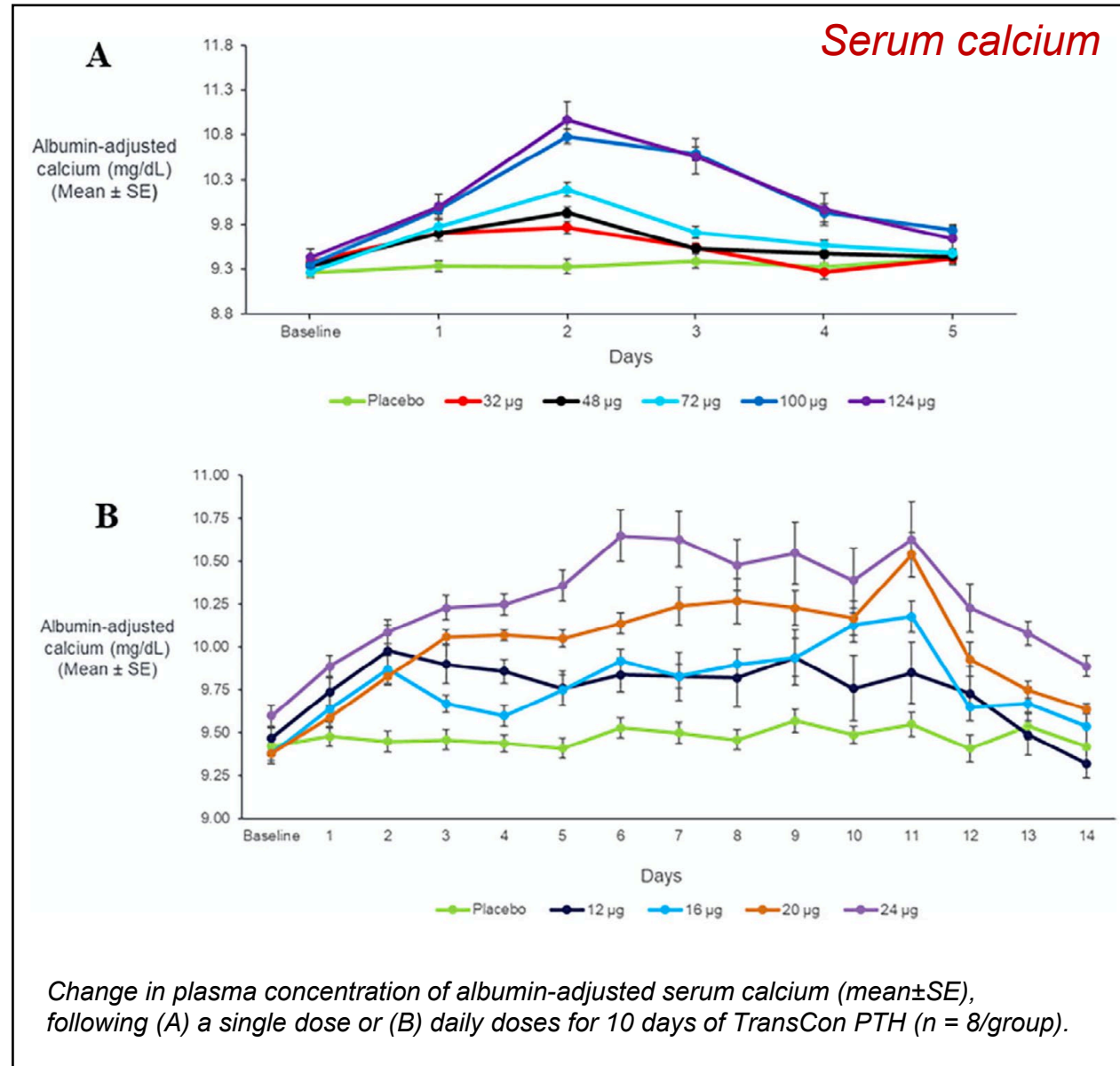
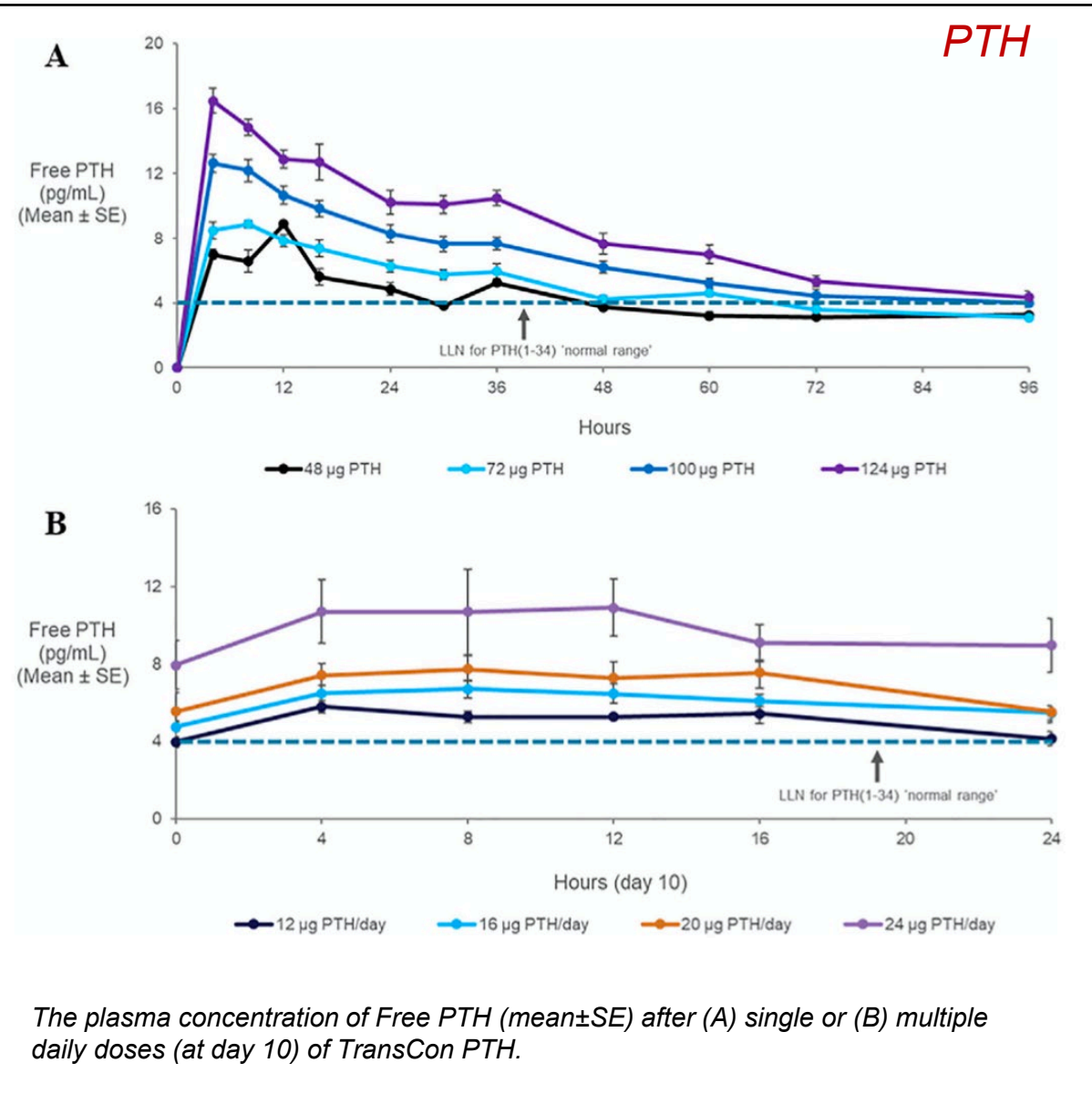
Il PTH rilasciato da palopegteriparatide è composto da PTH(1-34) e dal metabolita PTH(1-33) che ha attività simile alla molecola 1-34. Il PTH viene metabolizzato e eliminato a livello renale.

L'emivita apparente del PTH rilasciato da palopegteriparatide è di circa 60 ore.



Simulazione della concentrazione plasmatica di PTH dopo ripetute somministrazioni sottocute di 2.4 nmol teriparatide due volte die o TransCon PTH a 4.9 nmol una volta al giorno

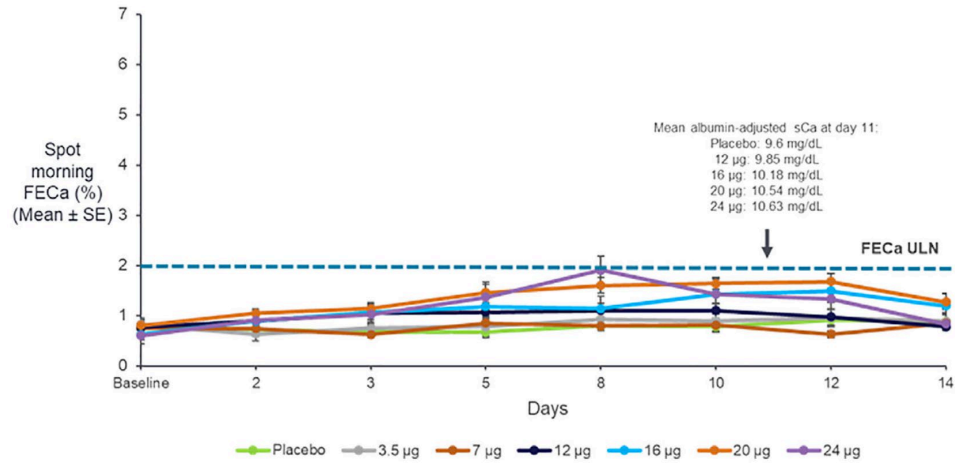
Phase 1 Trial of TransCon PTH in Healthy Adults



Phase 1 Trial of TransCon PTH in Healthy Adults

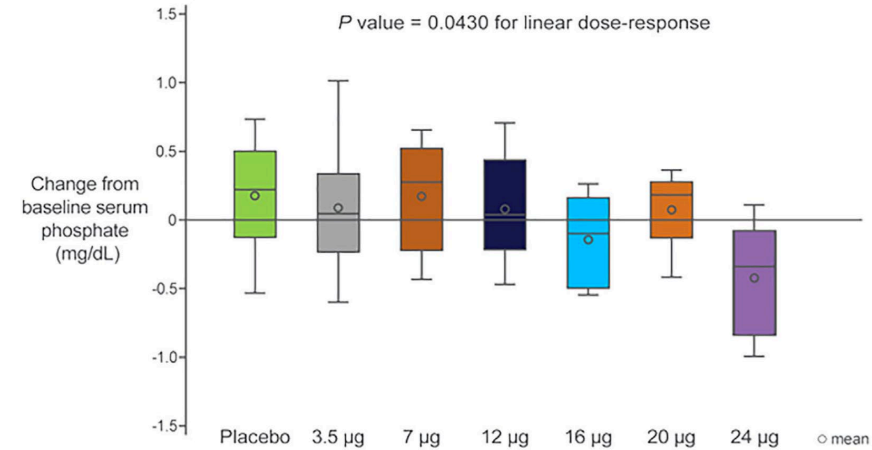
Calcium FE

Spot FECa with daily doses of TransCon PTH (n = 8/group) for 10 days. ULN = upper limit of normal.



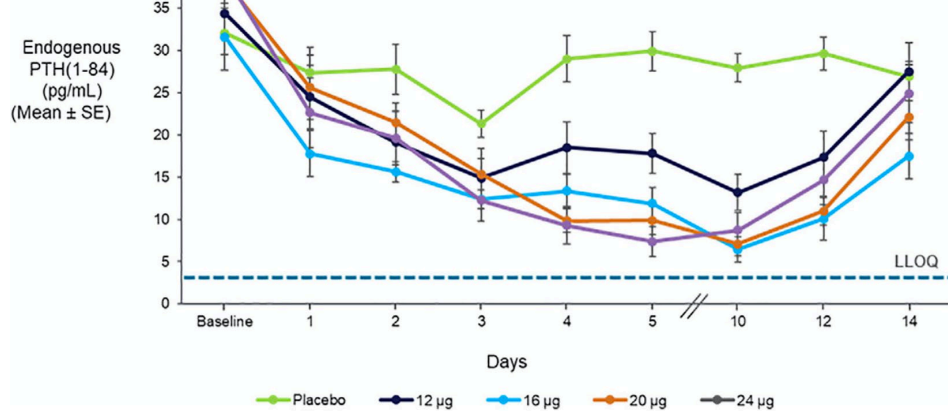
Serum phosphate

Phosphaturic effect with daily doses of TransCon PTH for 10 days (change from baseline over days 8 to 10).



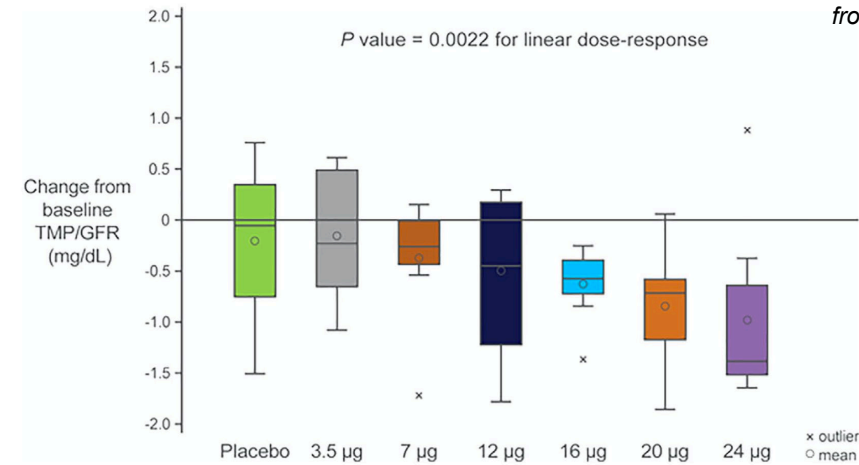
PTH

Suppression of intact endogenous PTH(1-84) with daily doses of TransCon PTH (n = 8/group) for 10 days. LLOQ = lower limit of quantification.



TmP/GFR

Box plots of the change of serum phosphate from baseline with daily doses of TransCon PTH for 10 days (change from baseline over days 8 to 10).



Criteri di somministrazione di palopegteriparatide

La dose iniziale raccomandata è di 18 µg una volta al giorno con successivi aggiustamenti della dose con incrementi di 3 µg ogni 7 giorni (dose massima 60 µg)

La 25(OH) vitamina D sierica deve rientrare nell'intervallo normale e il calcio sierico deve essere stabile e rientrare o essere leggermente inferiore all'intervallo normale



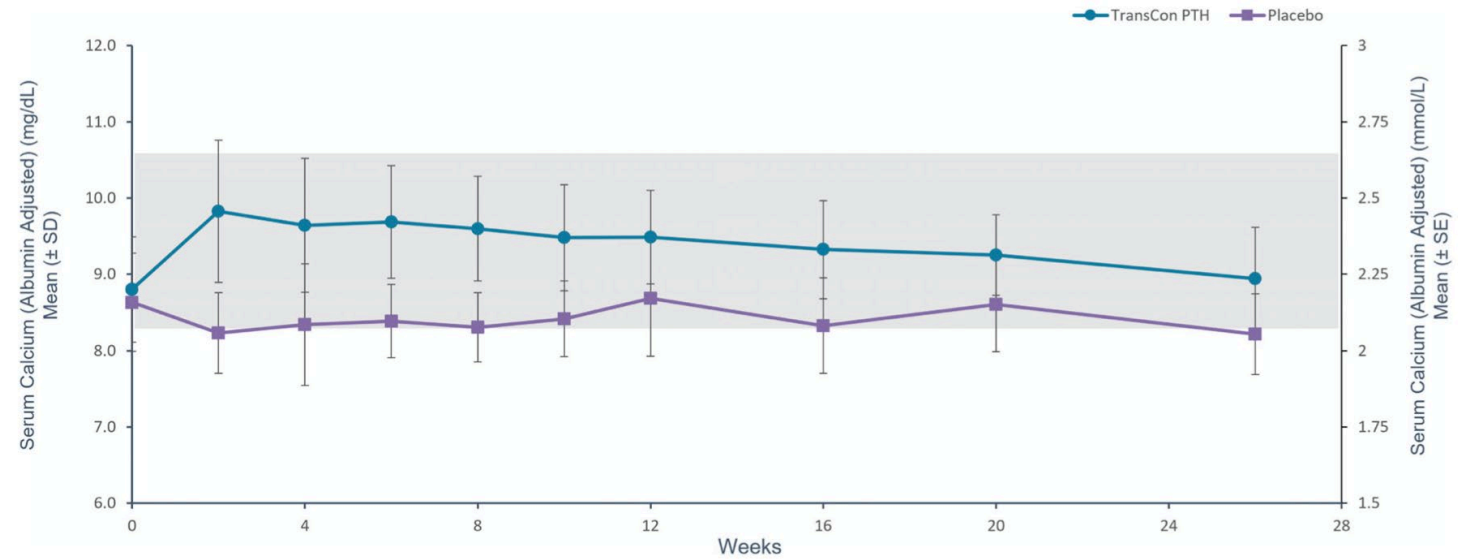
La dose ottimale dopo la titolazione è la dose minima richiesta per prevenire l'ipocalcemia e mantenere il calcio sierico entro l'intervallo normale senza la necessità di forme attive di integrazione di vitamina D o di calcio oltre all'integrazione alimentare raccomandata per la popolazione.

Phase 3 PaTHway Trial: PTH replacement With TransCon PTH

Serum calcium

In the TransCon PTH group, mean serum calcium values remained within the normal range at all study visits through week 26. Baseline mean serum calcium was 8.8 mg/dL (2.2 mmol/L) and 8.6 mg/dL (2.15 mmol/L) for TransCon PTH and placebo, respectively, and 8.9 mg/dL (2.22 mmol/L) and 8.2 mg/dL (2.05 mmol/L), respectively, at week 26.

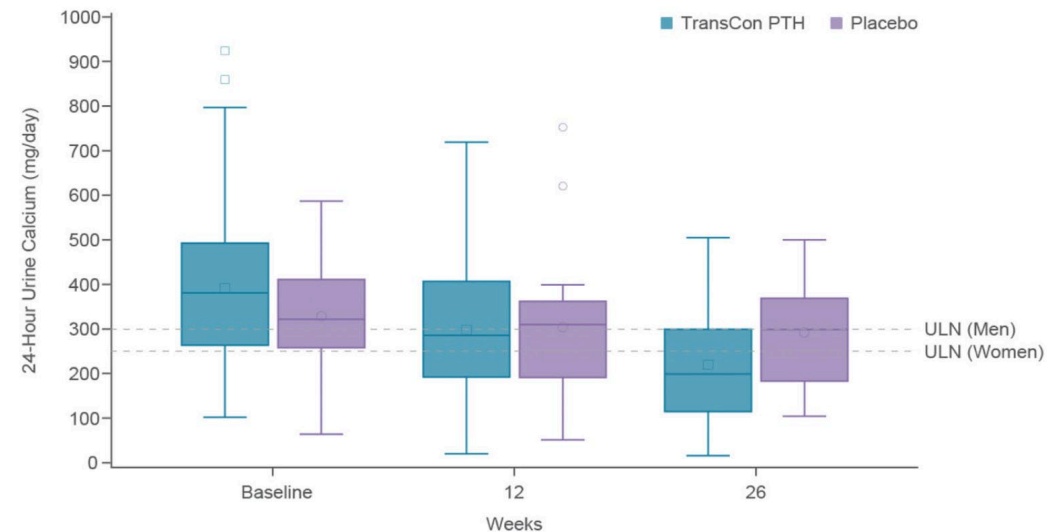
Participants receiving TransCon PTH maintained mean serum calcium levels in the normal range at all study visits



Urinary calcium

Mean 24-hour urine calcium values decreased from 390 mg/24 h at baseline to 220 mg/24 h in participants treated with TransCon PTH, and from 329 mg/24 h in participants who received placebo. The mean change from baseline was statistically significant in the TransCon PTH group ($p < 0.0001$) but not in the placebo group ($p = 0.24$).

Participants receiving TransCon PTH showed a significant reduction in urine calcium excretion than those on placebo from baseline to Week 26

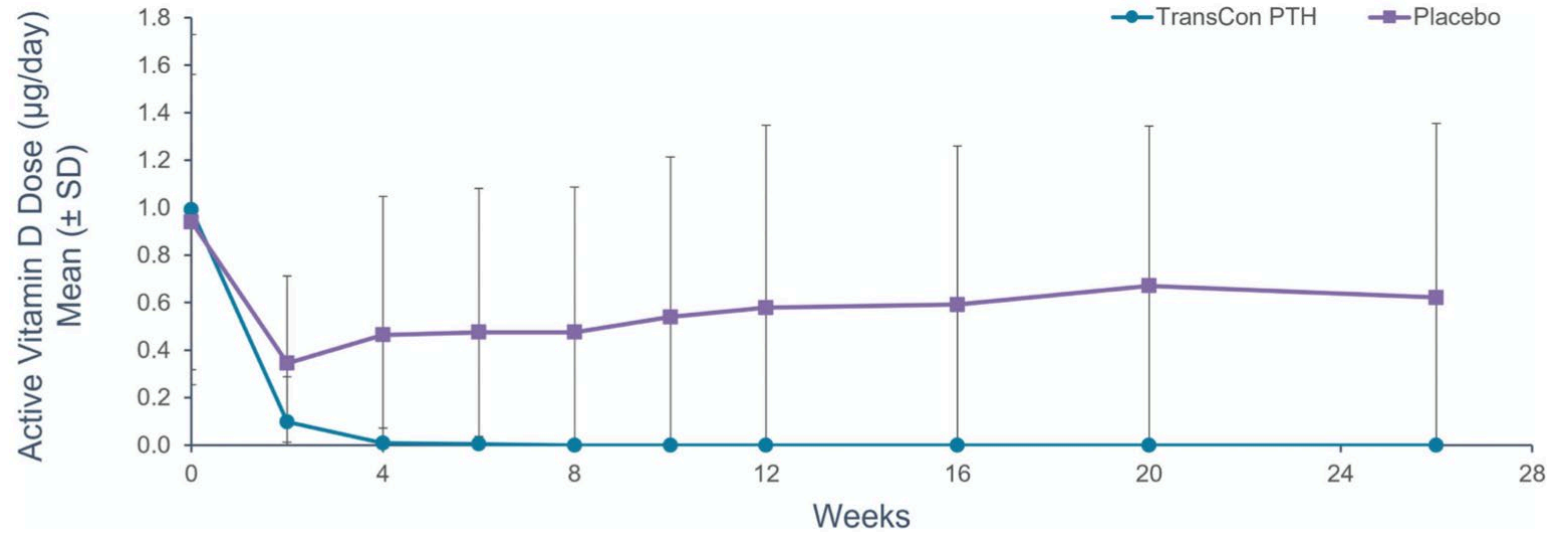


Phase 3 PaTHway Trial: PTH replacement With TransCon PTH

Therapy with vit D

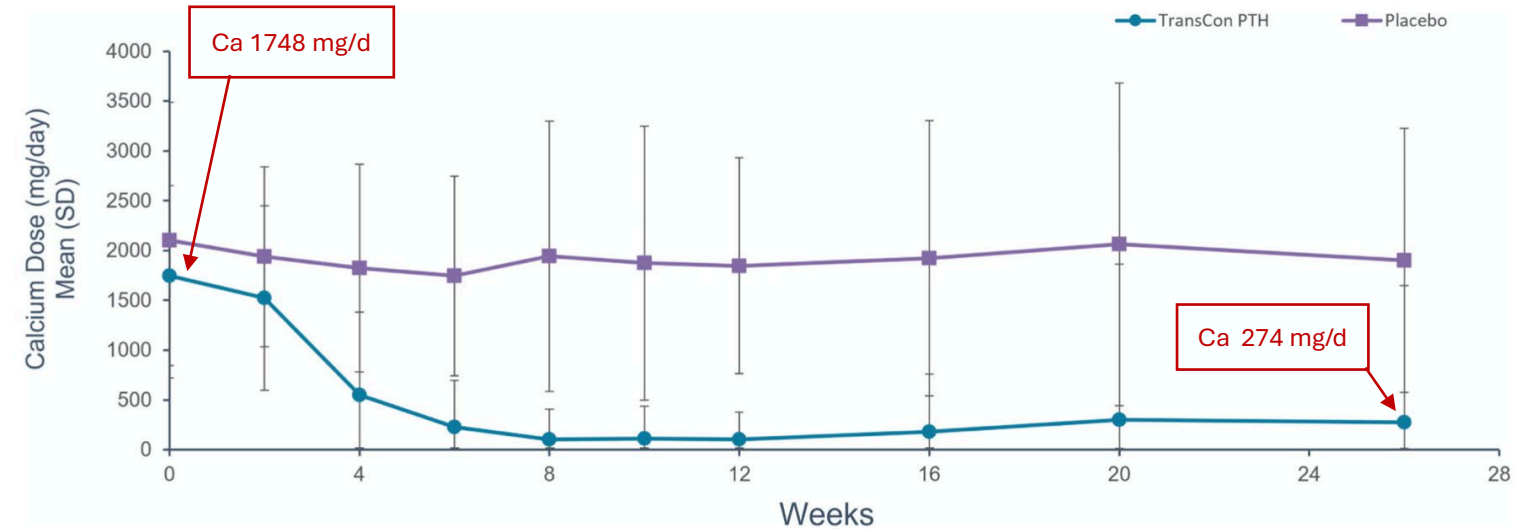
Per trial protocol, all participants decreased their active vitamin D dose by 33% to 50% (eg, by skipping the second dose of the day if taking 2 times daily (BID), skipping the final dose of the day if taking 3 times daily (TID), or reducing a once-daily dose of alfacalcidol $\geq 1.0 \mu\text{g}$ by 50% ($\geq 0.5 \mu\text{g}$) at the start of the blinded treatment period.

Within 4 weeks, the majority of participants treated with TransCon PTH discontinued active vitamin D.

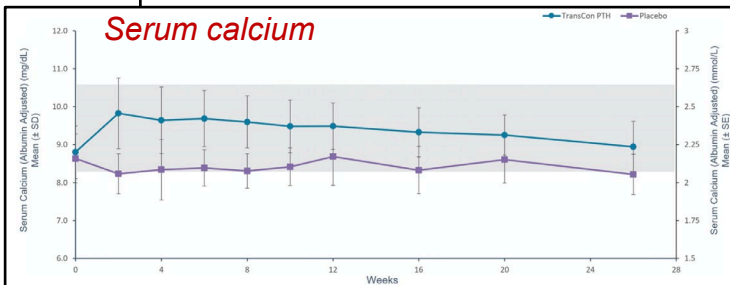


Therapy with calcium

After 4 weeks of treatment with TransCon PTH, elemental calcium intake decreased from a baseline mean (SD) of 1748.0 (903.9) mg/d to a dose of 548.8 (832.7) mg/d, which continued to decrease throughout the trial to a dose of 274.2 (1371.8) mg/d at week 26.



Serum calcium



Phase 3 PaTHway Trial: PTH replacement With TransCon PTH

This was a double-blind, placebo-controlled, 26-week, phase 3 study.

Participants (n = 84) were men and nonpregnant women (≥ 18 years of age) with chronic hypoparathyroidism of postsurgical, autoimmune, genetic, or idiopathic etiologies for a duration of at least 26 weeks treated with calcitriol ≥ 0.5 $\mu\text{g}/\text{d}$ or alfacalcidol ≥ 1.0 $\mu\text{g}/\text{d}$ in addition to elemental calcium ≥ 800 mg/d for at least 12 weeks before.

Urinary calcium excretion ≥ 125 mg/24 h and eGFR ≥ 30 mL/min was required for enrollment.

Participants were randomized 3:1 to once-daily TransCon PTH (initially 18 $\mu\text{g}/\text{d}$) or placebo, both co-administered with conventional therapy.

The composite primary outcome was

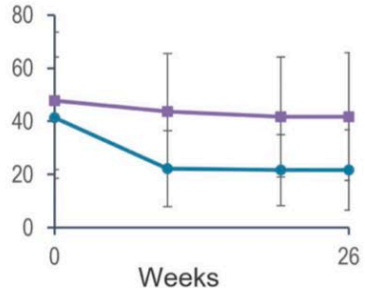
- the proportion of participants at week 26 who achieved albumin-adjusted serum calcium in the normal range (8.3– 10.6 mg/dL [2.07–2.64 mmol/L]),
- independence from active vitamin D, and
- independence from elemental calcium (>600 mg/d)
- with no increase in the prescribed study drug over the 4 weeks before week 26.

Findings at week 26	TransCon PTH (n = 61)	Placebo (n = 21)
No. participants meeting the primary endpoint criteria at week 26 (responders)	48	1
Proportion, % (95% CI)	79% (66, 88)	5% (0.1, 24)
Hypothesis test: p value (TransCon PTH versus placebo) ^a	<0.0001	
No. participants meeting each component		
Albumin-adjusted serum calcium within the normal range ^b	49 (80%)	10 (48%)
Independence from active vitamin D	60 (98%)	5 (24%)
Independence from therapeutic doses of calcium	57 (93%)	1 (5%)
No increase in prescribed study drug	57 (93%)	12 (5%)

- 79% (n=48/61) of participants treated with TransCon PTH met the primary multi-component efficacy endpoint at week 26 compared with 5% (n=1/21) in the placebo group
- 93% (n=57/61) of participants treated with TransCon PTH achieved independence from conventional therapy[‡]

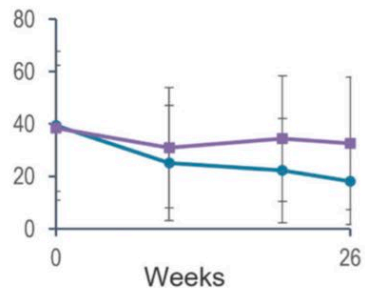
Phase 3 PaTHway Trial: PTH replacement With TransCon PTH

A HPES Symptom^a
Physical domain
Score



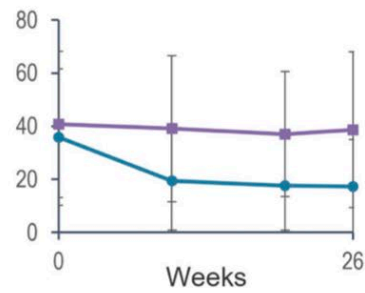
p-value = 0.0038^b

B HPES Symptom^a
Cognitive domain
Score



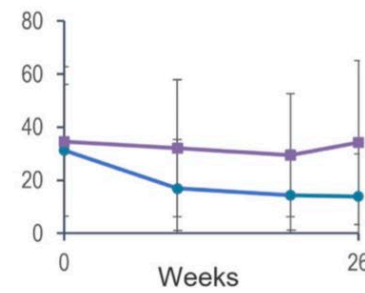
p-value = 0.0055^b

C HPES Impact^a
Physical Functioning
domain score



p-value = 0.0046^b

D HPES Impact^a
Daily Life domain
score



p-value = 0.0061^b

● TransCon PTH ■ Placebo

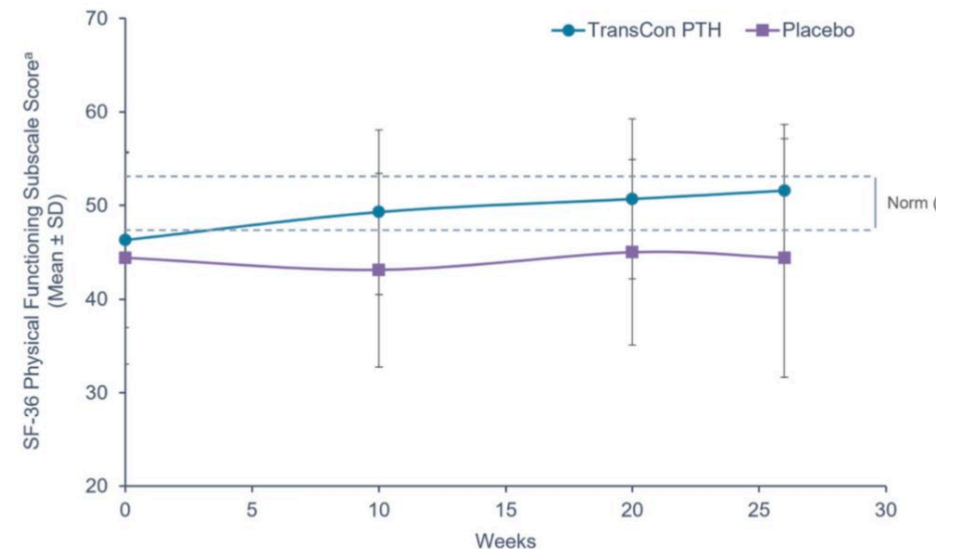
HPES, psychometrically score

The HPES is a psychometrically validated, disease-specific measure specifically designed to assess the symptoms and impact associated with hypoparathyroidism. A higher HPES score indicates greater symptom frequency or impact.

TransCon PTH treatment demonstrated a significant improvement compared with placebo at week 26 in HPES-Symptom domain scores

SF-36 physical functioning scores

Short Form Survey (SF-36) subscale score, a patient-reported survey (36-Item) that serves as a general measure of well-being. In the SF-36 subscale, lower scores are associated with a greater disease burden; increases in scores indicate improvement. The dashed lines indicate the upper (53) and lower (47) T-score bounds for the US general population's average level of functioning, with scores below 47 indicating impairment.



Phase 3 PaTHway Trial: PTH replacement With TransCon PTH

Adverse events

TEAE, <i>n</i> (%) ^a	TransCon PTH (<i>n</i> = 61)	Placebo (<i>n</i> = 21)
Any TEAE	50 (82)	21 (100)
Serious TEAE	5 (8)	3 (14)
Severity ^b		
Grade 1 TEAE	27 (44)	11 (52)
Grade 2 TEAE	21 (34)	9 (43)
Grade 3 TEAE	1 (2)	1 (5)
Grade 4 TEAE ^c	1 (2)	0
Treatment-related TEAE	30 (49)	8 (38)
Serious related TEAE	1 (2)	0
TEAE related to hypercalcemia or hypocalcemia leading to ER/urgent care visit and/or hospitalization	4 (7)	2 (10)
TEAE leading to discontinuation of study drug ^c	1 (2)	2 (10)
TEAE leading to death ^c	1 (2)	0

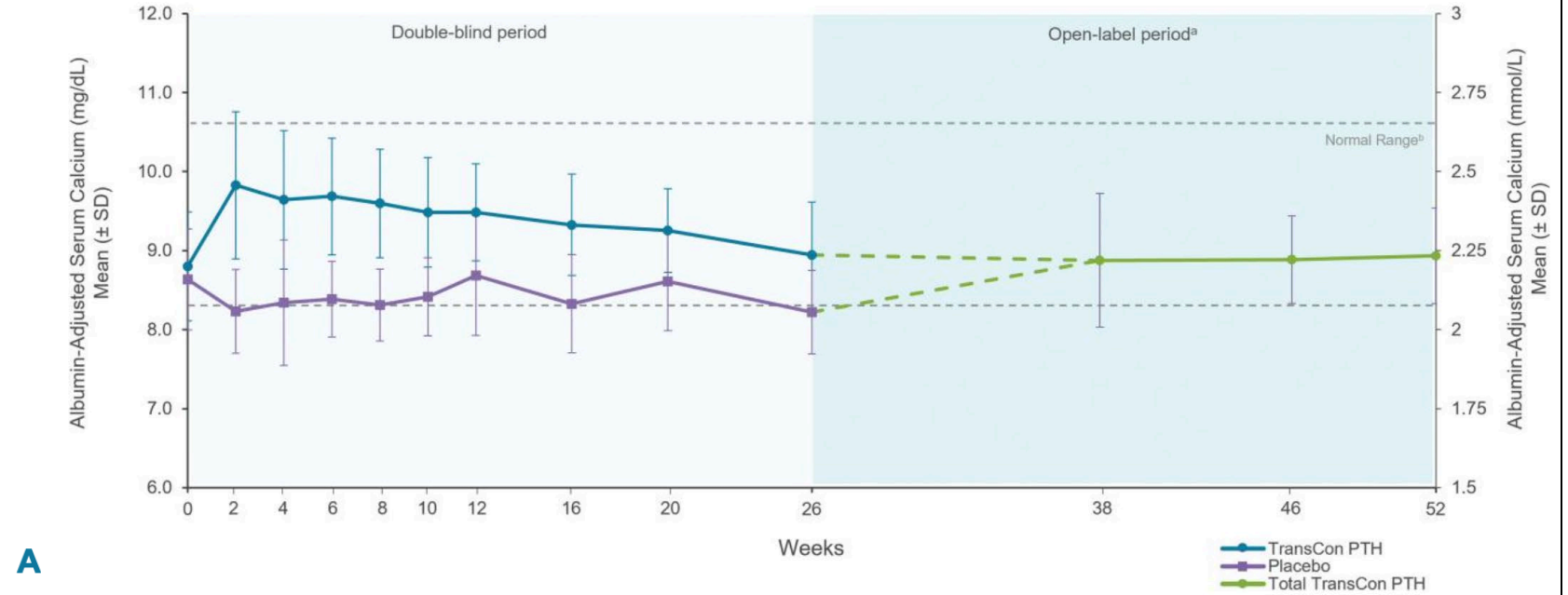
Abbreviations: ER, emergency room; PTH, parathyroid hormone; TEAE, treatment-emergent adverse event.

TEAEs by preferred term	TransCon PTH (<i>n</i> = 61)	Placebo (<i>n</i> = 21)
Participants with at least one TEAE, <i>n</i> (%) ^a	50 (82)	21 (100)
TEAEs, <i>n</i> (%)		
Injection site reaction	19 (31)	0
Headache	13 (21)	2 (10)
Hypocalcemia	6 (10)	9 (43)
Fatigue	9 (15)	5 (24)
Paresthesia	11 (18)	3 (14)
Muscle spasms	7 (12)	3 (14)
Nausea	7 (12)	2 (10)
Arthralgia	6 (10)	2 (10)
Diarrhea	6 (10)	1 (5)
Hypercalcemia	6 (10)	0
Constipation	4 (7)	1 (5)
Insomnia	4 (7)	1 (5)

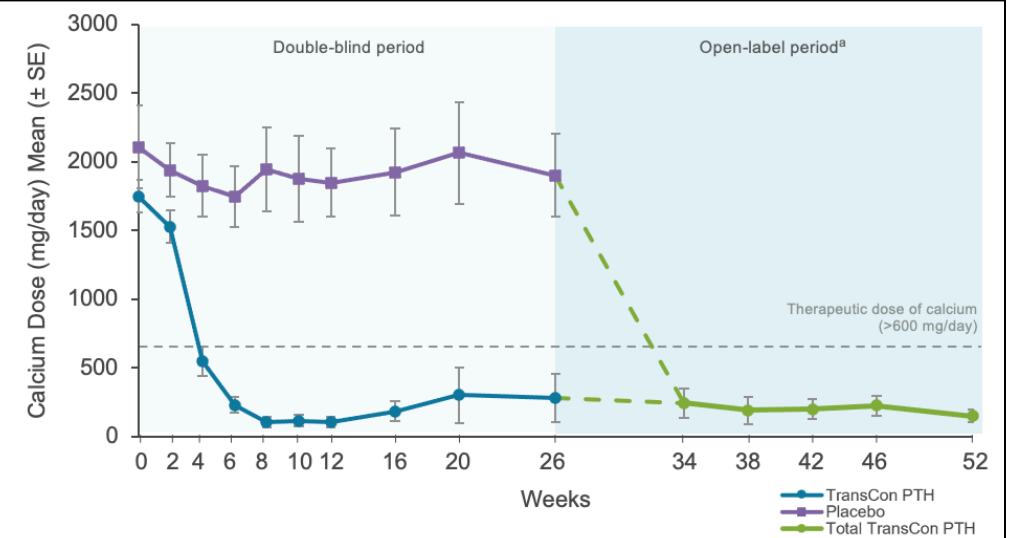
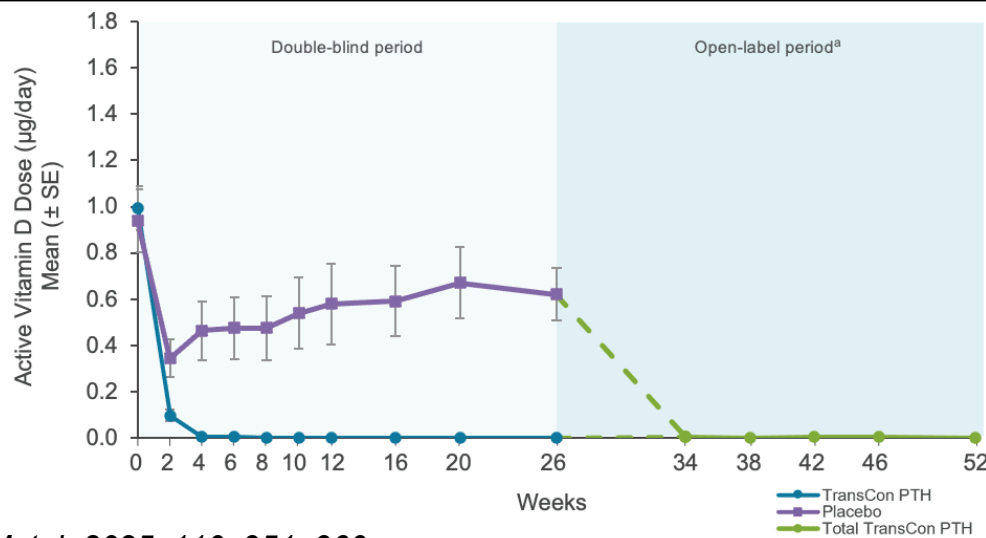
Abbreviations: PTH, parathyroid hormone; TEAE, treatment-emergent adverse event.

Phase 3 PaTHway Trial: open-label extension at 52 weeks

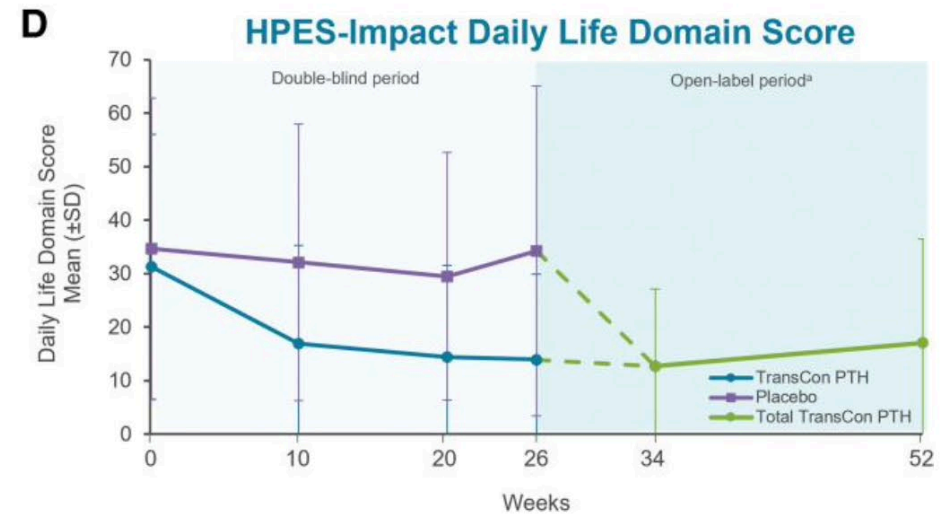
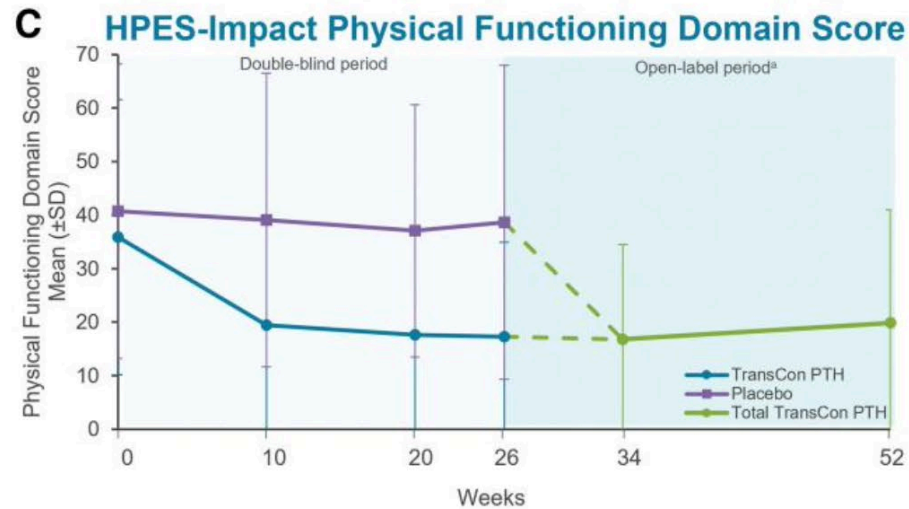
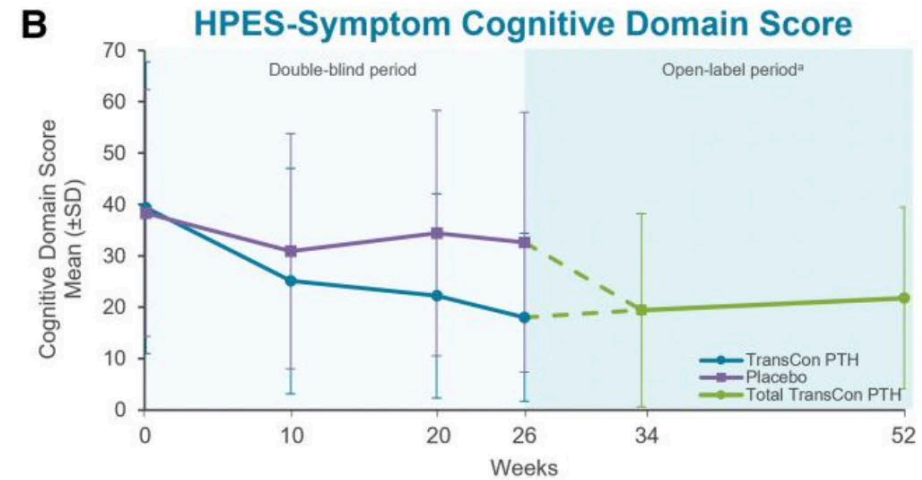
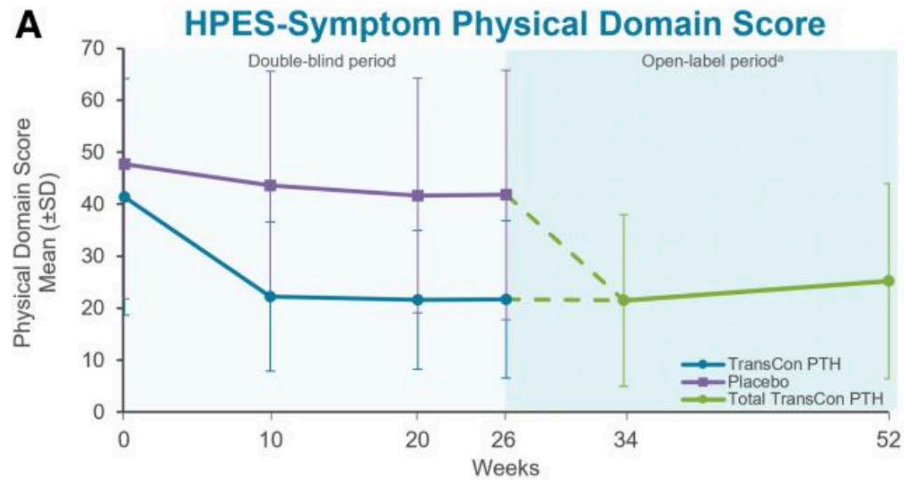
Serum calcium



Therapy with active VitD and calcium

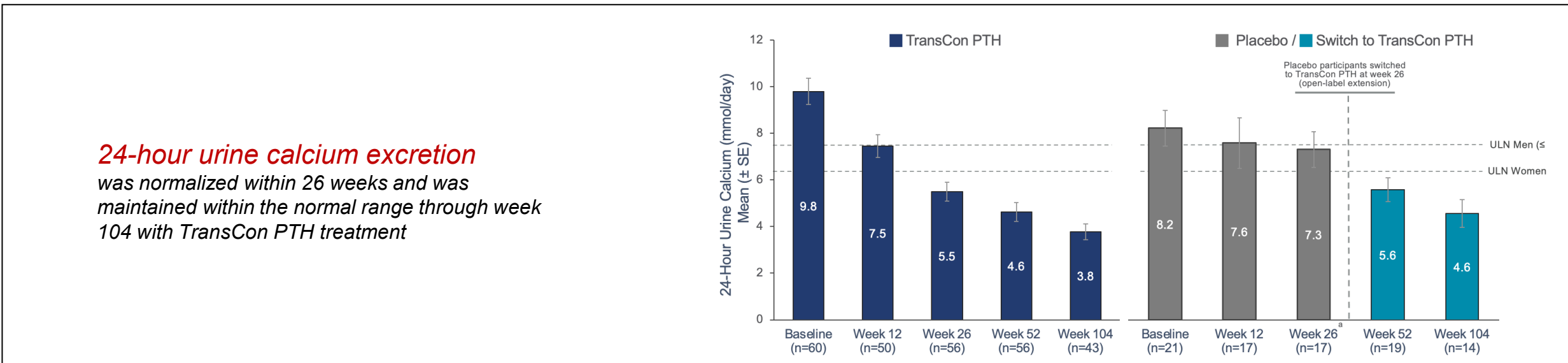
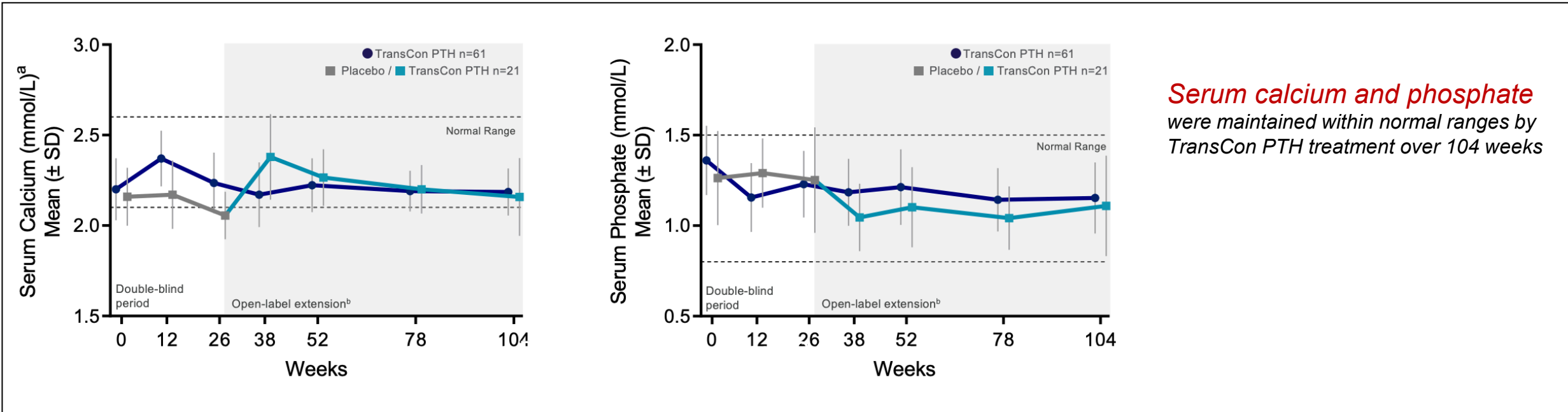


Phase 3 PaTHway Trial: open-label extension at 52 weeks

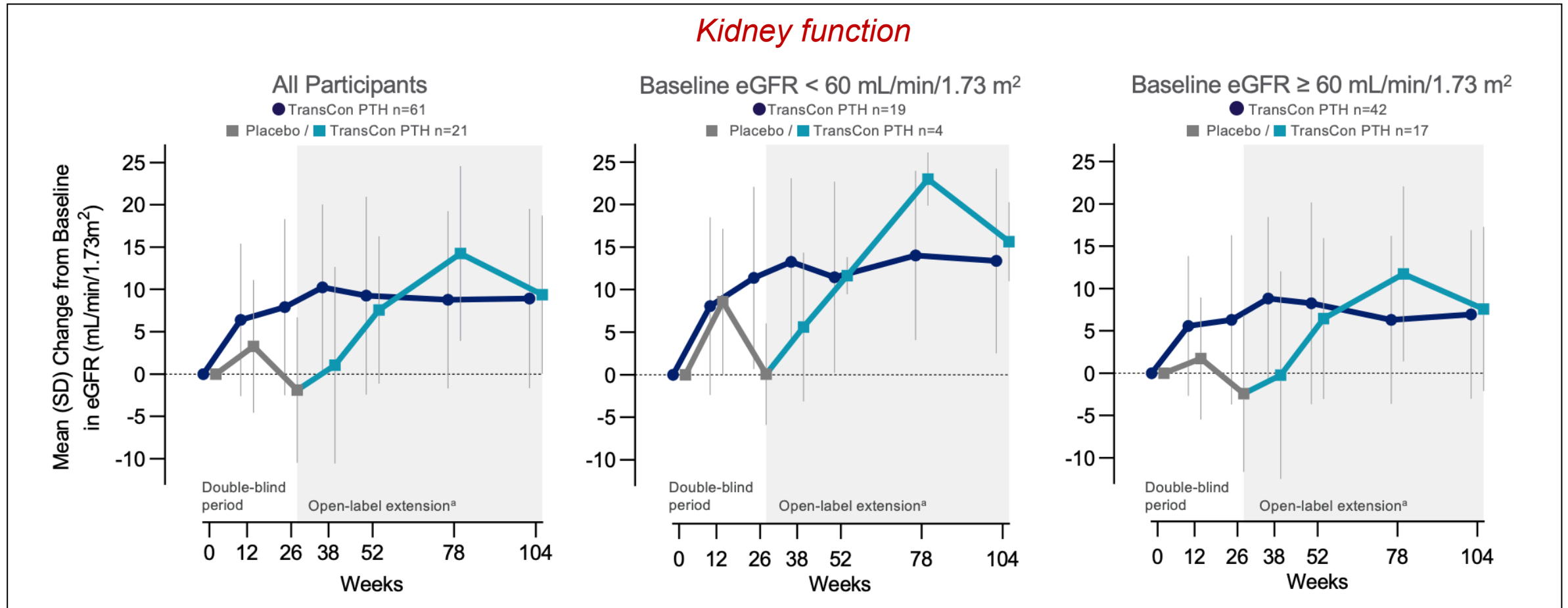


Patient-reported outcomes showed sustained improvements in quality of life, physical functioning, and well-being.

Phase 3 PaTHway Trial: open-label extension at 104 weeks



Phase 3 PaTHway Trial: open-label extension at 104 weeks



During the 26-week blinded period, treatment with palopegteriparatide resulted in statistically significant improvements in eGFR compared with placebo for all participants and for both baseline eGFR subgroups < 60 and ≥ 60 mL/min/1.73 m²

Does GFR improve during TransConPTH treatment ?

Phase 2 TransCon PTH Trial: open-label extension at 162 weeks



Primary Multi-Component Endpoint

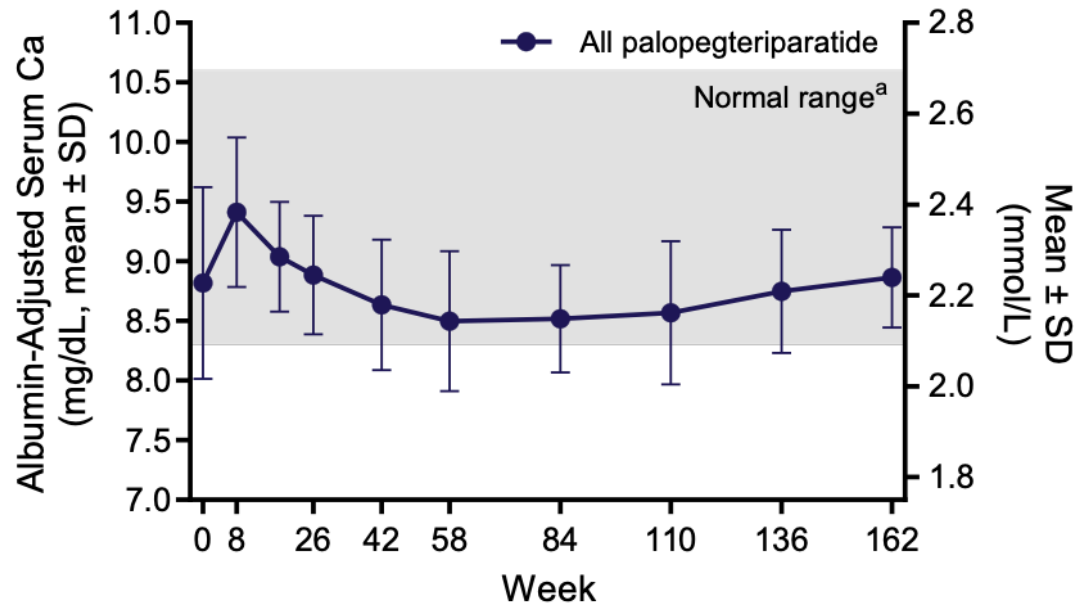
Proportion of participants with:

- Normal serum calcium; and
- Independence from active vitamin D; and
- Requiring $\leq 1,000$ mg/day oral calcium; and
- Normal fractional excretion of calcium (or at least 50% decrease from baseline)

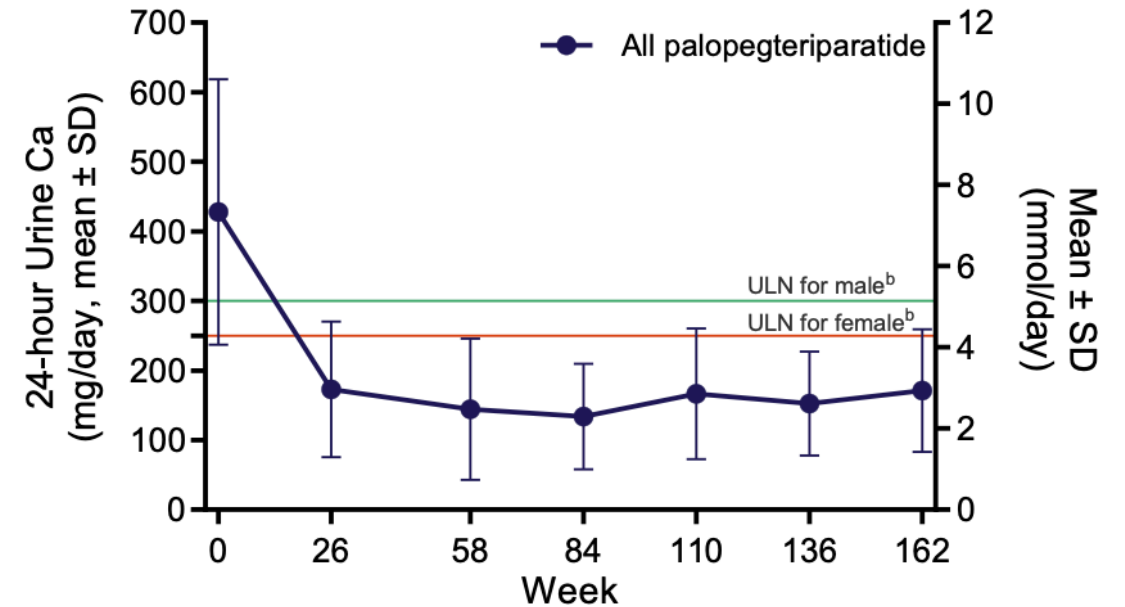
Of 57 participants, 52 (91%) achieved independence from conventional therapy at week 162

Phase 2 TransCon PTH Trial: open-label extension at 162 weeks

Mean Serum Calcium

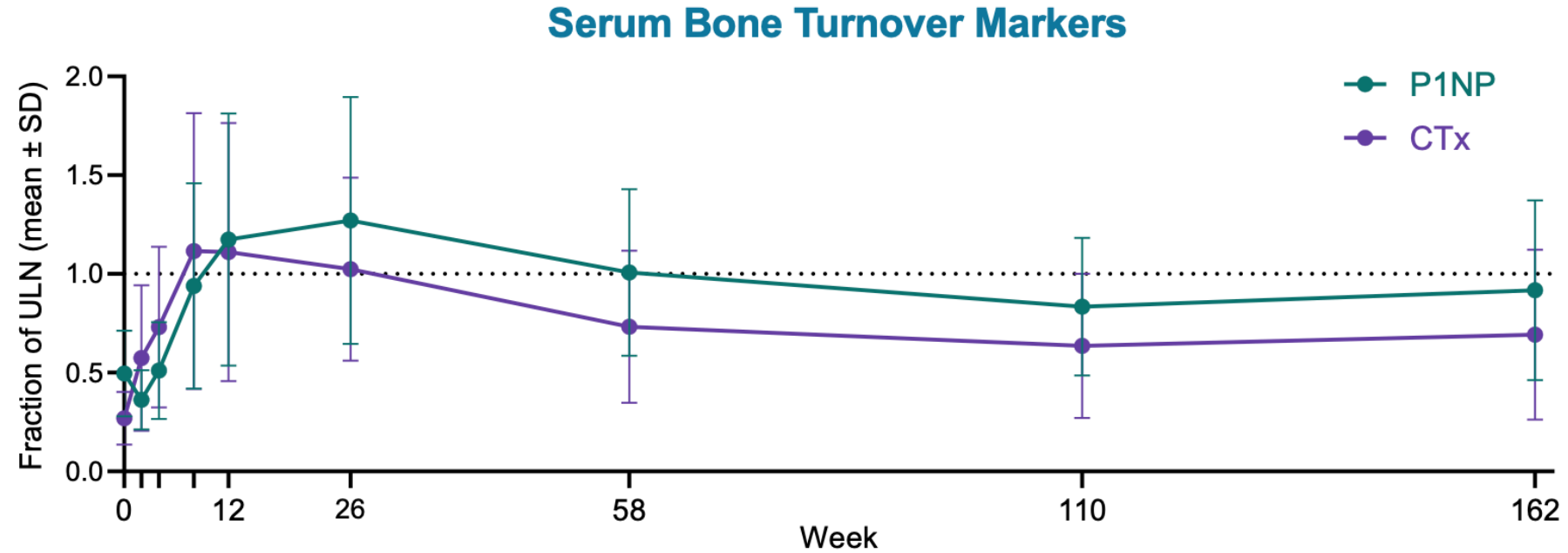


Mean 24-hour Urine Calcium



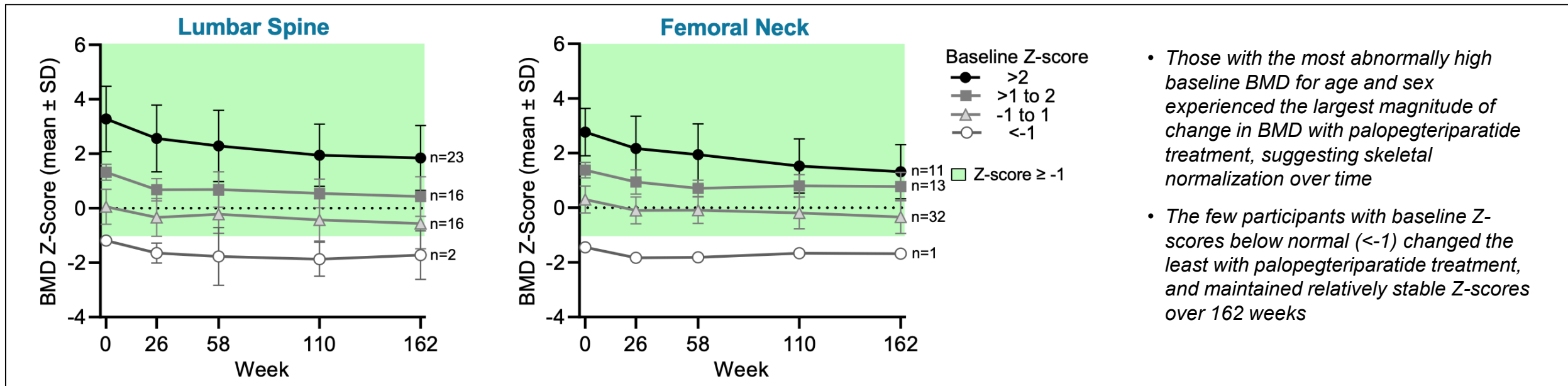
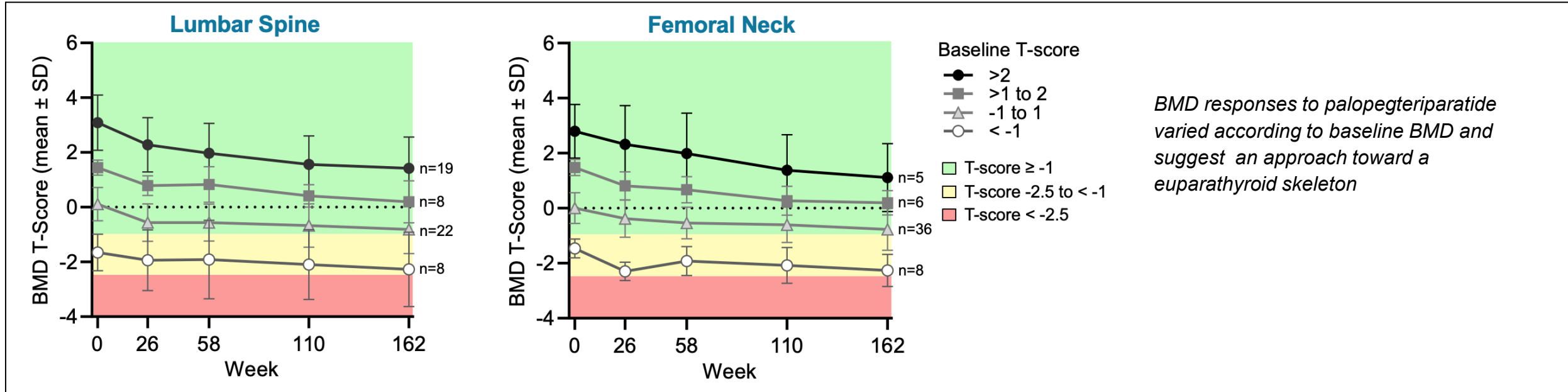
- Treatment with palopegteriparatide over 162 weeks maintained mean serum calcium within the normal range
- Mean 24-hour urine calcium excretion normalized within 26 weeks and was maintained within the normal range through Week 162 with palopegteriparatide treatment

Phase 2 TransCon PTH Trial: open-label extension at 162 weeks



- Mean serum bone turnover markers were transiently elevated above the ULN with the initiation of palopegteriparatide treatment and then remained below the ULN from Week 58 through Week 162
- The coupled bone resorption/formation response to treatment demonstrates the ability of palopegteriparatide to improve skeletal dynamics in adults with hypoparathyroidism

Phase 2 TransCon PTH Trial: open-label extension at 162 weeks



Efficacy of different PTH-like molecules in phase-3 studies

	TransConPTH	PTH(1-84)	PTH(1-34)
<i>Num.</i>	61	84	
<i>Weeks f-u</i>	26	24	
<i>Ref.</i>	<i>JBMR 2023</i>	<i>Lancet 2013</i>	<i>No phase-3 studies</i>
sCalcium in normal range	80%	87%	
Active Vit D	98%	42%	
Ca supplements < 1 g	93%	69%	
Composite end-points	79%	53%	
Calcium excretion	↓↓	↓	
<i>Ref</i>	<i>ASBMR 2024</i>	<i>JCEM 2016</i>	<i>JBMR 2012</i>
DXA lumbar spine	↓	↑	=
DXA total hip	↓	↑	↑
DXA femoral neck	↓	↑	=
DXA 1/3 radius	↓	↓	↓
<i>Bone istology</i>			
Trabecular number	-	-	↑
Cortical porosity	-	-	↑

Conclusioni

Palopegteriparatide è una terapia efficace e ben tollerata nei pazienti affetti da ipoparatiroidismo nelle sue diverse forme causali.

Esso mantiene normale la calcemia riducendo in modo sostanziale la necessità della terapia con vitamina D attiva e calcio.

Migliora così la qualità di vita dei pazienti migliorando la performance fisica e psichica.

Ci sono ancora aspetti della sua attività che rimangono da esplorare, tra questi l'effetto a lungo termine sullo scheletro e sulla funzione renale.