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Encaleret Restores Mineral Homeostasis in Autosomal Dominant Hypocalcemia Type 1 (ADH1): Primary Results from the Phase 3 CALIBRATE Trial

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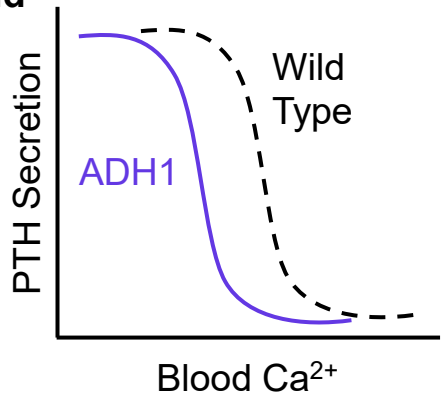
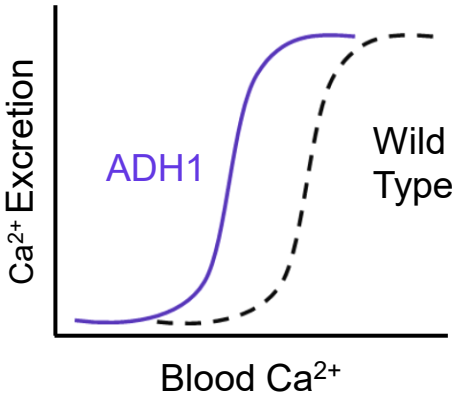
Activating variants in the CASR cause Autosomal Dominant Hypocalcemia Type 1 (ADH1)

Activating variants in the *CASR* increase tissue sensitivity to Ca^{2+} → **Hypersensitive CaSR causes dysregulation of Ca homeostasis** → **Clinical Manifestations**

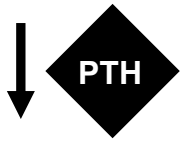
Parathyroid



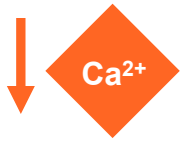
Kidney



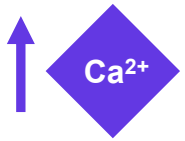
Roszko, et al. Front. Physiol. 2016.



Decreased PTH secretion



Decreased blood calcium



Increased urinary calcium

Acute symptoms

Hypocalcemic seizures

Paresthesia

Tetany

Muscle cramps

Long-term complications

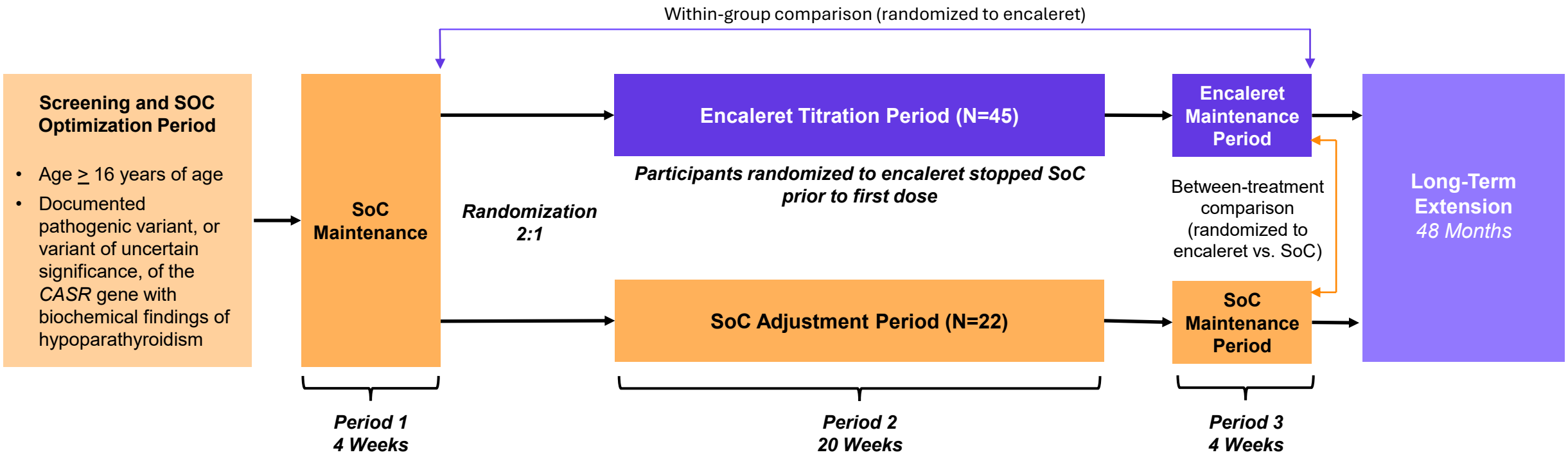
Nephrolithiasis

Nephrocalcinosis

Chronic Kidney Disease

Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

Phase 3 Study Design



Primary Composite Endpoint (within-group):

- Proportion of participants achieving:
  - cCa[1] within the target range of 2.08-2.68 mmol/L
    AND
  - 24-hour urine Ca within the reference range (<7.0 mmol/day for men & <6.25 mmol/day for women)

Additional Secondary Endpoints:

- Proportion of participants achieving iPTH above the lower limit of the reference range (key secondary)
- 1,25-$(OH)_2$ Vitamin D, magnesium, and phosphate
- Bone turnover markers
- Renal ultrasound and renal function

[1]Albumin-corrected serum calcium.
SoC = standard of care; a combination of oral activated Vitamin D and/or calcium supplements. *CASR* = calcium-sensing receptor gene. iPTH = intact parathyroid hormone.

Baseline Characteristics

Characteristic	Target range	SoC (N=22)	Encaleret (N=45)	All Participants (N=67)
Age, yr, mean (range)		37 (16-63)	44 (16-76)	42 (16-76)
Female, n (%)		11 (50%)	24 (53%)	35 (52%)
Intact PTH, pmol/L, mean (SD)	1.6-6.9	0.63 (0.49)	0.71 (0.82)	0.68 (0.73)
Serum Calcium[1], mmol/L, mean (SD)	2.08-2.68	1.97 (0.17)	2.09 (0.19)	2.05 (0.19)
24hr Urine Calcium, mmol/day, mean (SD)	<7.0(M)/6.25(W)	8.29 (4.89)	9.93 (4.44)	9.39 (4.62)
Phosphate, mmol/L, mean (SD)	0.81-1.55	1.63 (0.33)	1.54 (0.24)	1.57 (0.27)
Magnesium, mmol/L, mean (SD)	0.74–0.99	0.71 (0.06)	0.75 (0.07)	0.73 (0.07)
eGFR[2], mL/min/1.73 m^2, mean (range)	>60	77 (38-127)	83 (26-133)	79 (26-133)
Nephrocalcinosis/Nephrolithiasis[3], n(%)		17 (81%)	35 (80%)	52 (80%)
Conventional therapy[4]				
Elemental Calcium, mg/day, mean (SD)		1912 (2016)	1953 (2379)	1940 (2247)
Calcitriol, µg/day, mean (SD)		0.97 (0.86)	0.90 (0.45)	0.92 (0.60)
Alfacalcidol, µg/day, mean (SD)		2.06 (1.74)	2.82 (1.03)	2.62 (1.24)

43 unique *CASR* variants in study population

[1]Albumin-corrected serum calcium. [2]eGFR for N=63 participants ≥18 years determined via CKD-EPI. Mean (range) eGFR for participants <18 years (n=4) was 85.8 (69-108) determined via Schwartz. [3]Renal ultrasound performed at baseline in N=65 participants. Percentages are based on the number of participants with renal ultrasound available. [4]Average doses over Period 1.

76% of participants randomized to encaleret achieved serum cCa[1] and 24-hour urine calcium in the target ranges with restoration of iPTH secretion

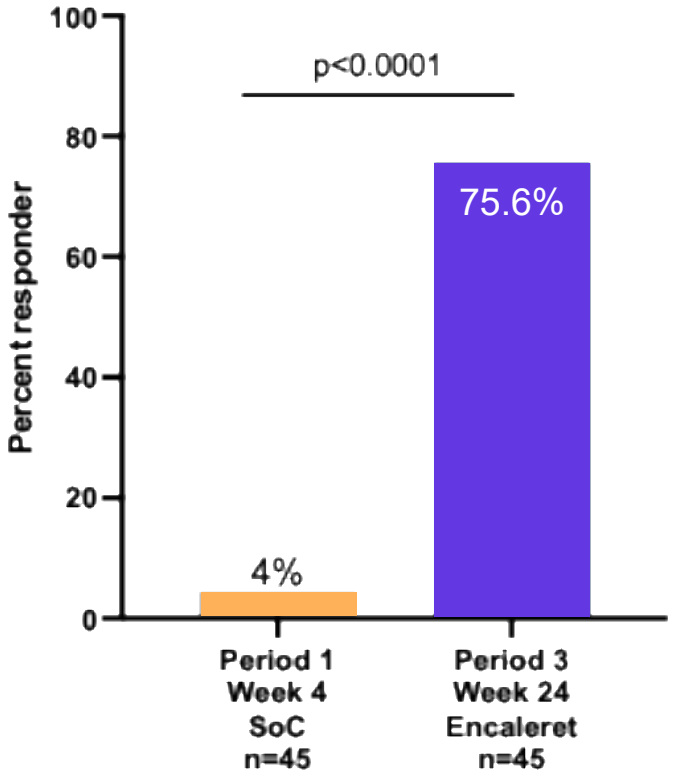
Primary Endpoint Responder Definition:

cCa 2.08-2.68 mmol/L

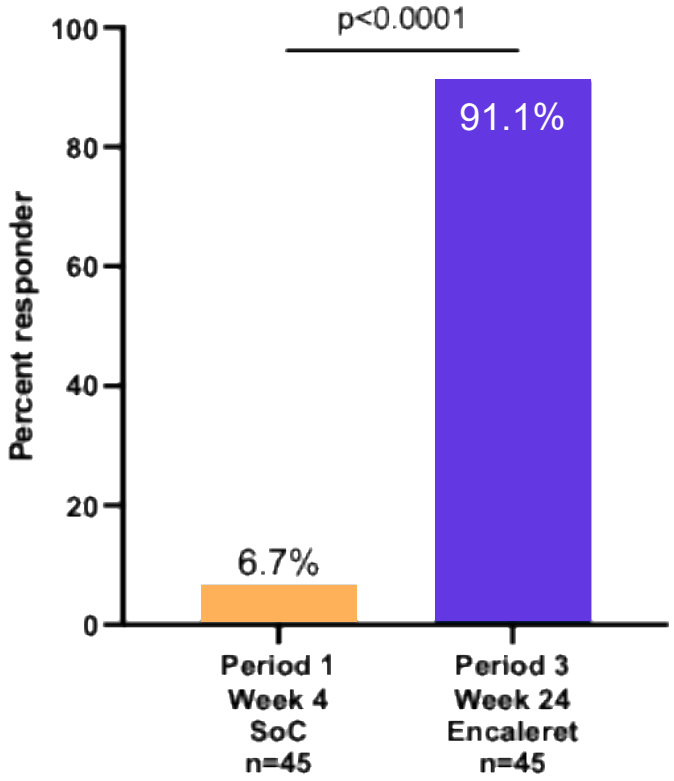
and

Normal 24hr UCa

Primary Endpoint Within-group comparison[2]
(randomized to encaleret)



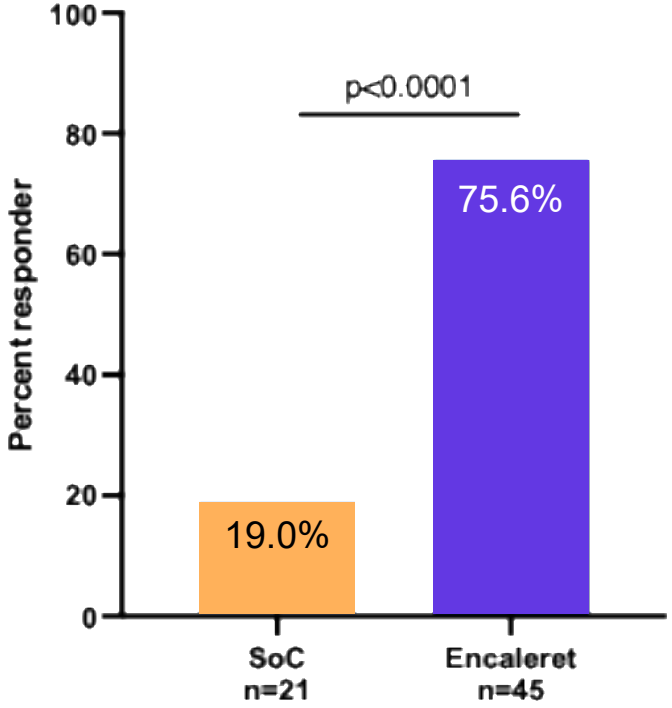
iPTH ≥ 1.6 pmol/L Within-group comparison[2]
(randomized to encaleret)



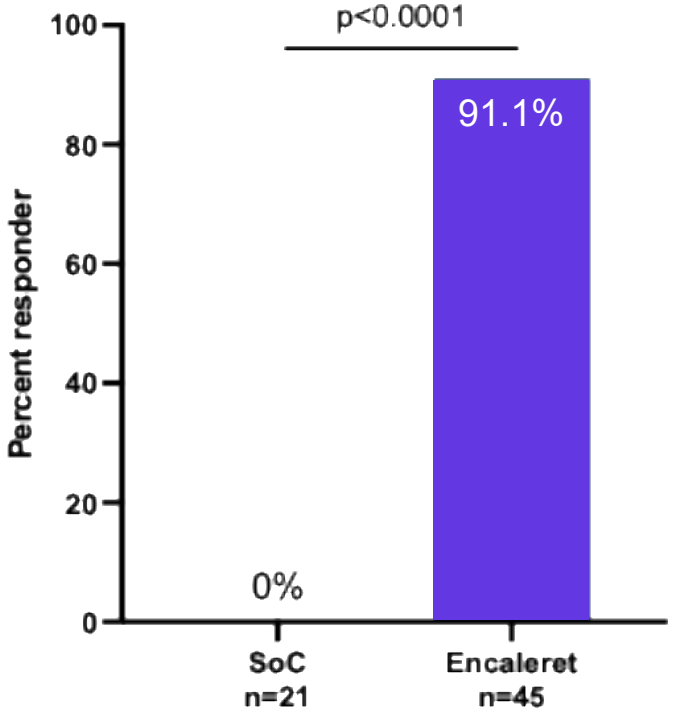
[1] Albumin-corrected serum calcium. [2]Analyzed by McNemar's test.

Statistically significant changes in cCa[1], 24-hour urine calcium and iPTH were also demonstrated in between-treatment comparisons

cCa 2.08-2.68 mmol/L
and
Normal 24-hour urine calcium
(encaleret vs. SoC[2])

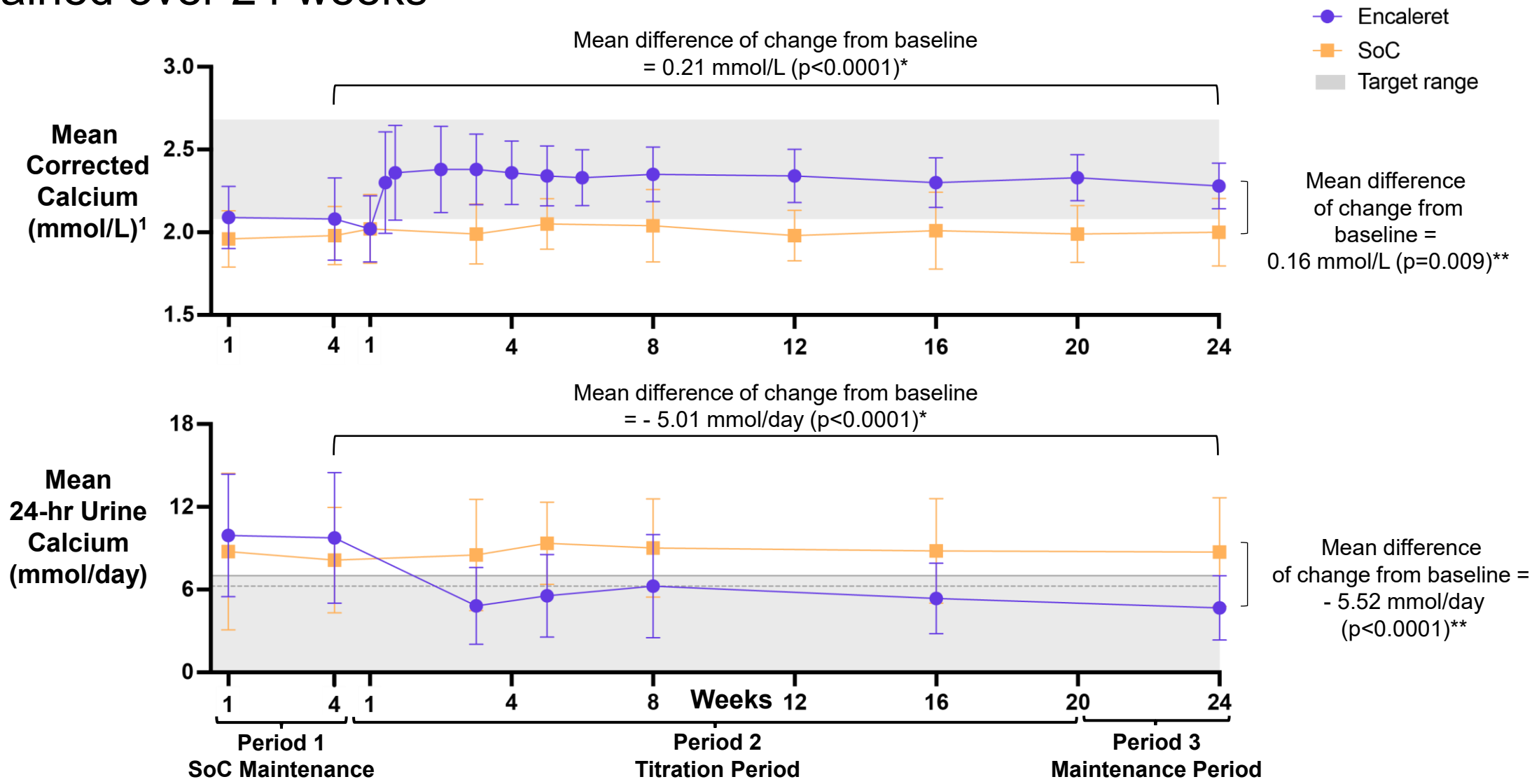


iPTH ≥ 1.6 pmol/L
(encaleret vs. SoC[2])



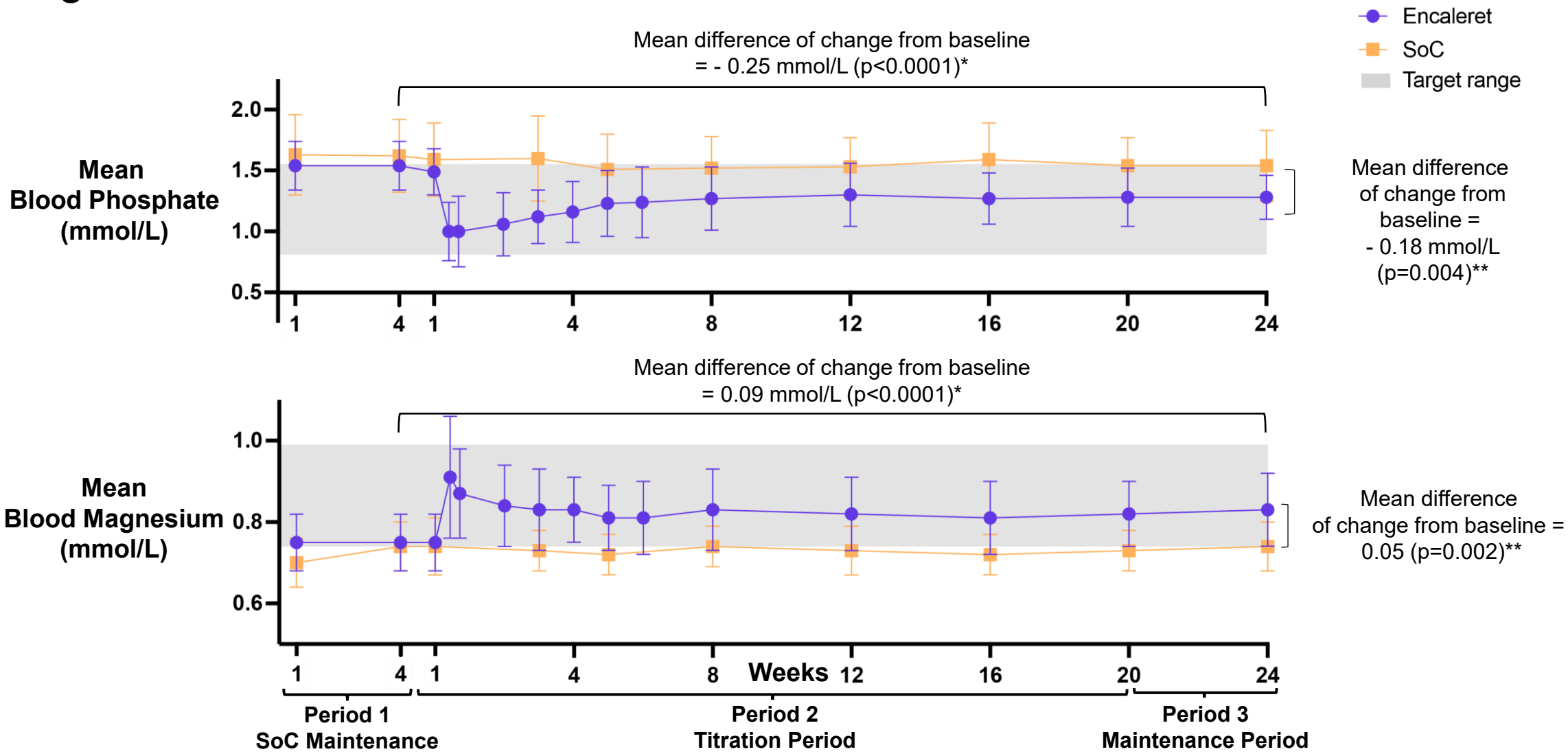
[1] Albumin-corrected serum calcium. [2]Analyzed by Barnard's unconditional exact test.

Encaleret increased serum calcium and decreased urine calcium with changes maintained over 24 weeks



[1]Albumin-corrected serum calcium. Data reported as mean±SD. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women.
*Within patient comparison of change from baseline of Week 4 vs Week 24. **Between group comparison of change from baseline of Period 3 Week 24.

Encaleret decreased serum phosphate and increased serum magnesium with changes maintained over 24 weeks



[1]Albumin-corrected serum calcium. Data reported as mean±SD. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women.
*Within patient comparison of change from baseline of Week 4 vs Week 24. **Between group comparison of change from baseline of Period 3 Week 24.

Encaleret was well-tolerated with no TEAEs resulting in encaleret or study discontinuation

	Period 1 SoC N=67	Periods 2 and 3 SoC N=22	Periods 2 and 3 Encaleret N=45
TEAE Leading to Study Discontinuation	0 (0%)	0 (0%)	0 (0%)
Participants experiencing any Serious TEAE	2 (3%)	3 (14%)	4 (9%)
Serious Related TEAE	1 (2%)	0 (0%)	1 (2%)
Participants experiencing any TEAE	30 (45%)	14 (64%)	40 (89%)
Mild	23 (34%)	6 (27%)	21 (47%)
Moderate	4 (6%)	6 (27%)	16 (36%)
Severe	3 (5%)	2 (9%)	3 (7%)
Related TEAE	4 (6%)	0 (0%)	16 (36%)
TEAEs in ≥5% of participants by preferred term			
Hypercalcemia	3 (4.5)	0	10 (22.2)
Headache	0	1 (4.5)	9 (20.0)
Constipation	0	2 (9.1)	5 (11.1)
Nausea	1 (1.5)	3 (13.6)	4 (8.9)
Fatigue	0	1 (4.5)	4 (8.9)
Hypertension	0	1 (4.5)	4 (8.9)
Hypocalcemia	4 (6.0)	3 (13.6)	3 (6.7)
Urinary tract infection	3 (4.5)	1 (4.5)	3 (6.7)
Sinusitis	0	2 (9.1)	2 (4.4)

For each category, participants are included only once, even if they experienced multiple events in that category. Relatedness assessed on the basis of the investigational product being administered in the respective study period reported.
TEAE = Treatment-Emergent Adverse Event

Summary

- 76% of participants with ADH1 randomized to encaleret achieved serum and urine calcium in the target range
  - Among encaleret responders at Week 24, none required conventional therapy during Period 3
- 91% of participants randomized to encaleret achieved restoration of endogenous iPTH
- Encaleret was well-tolerated with no discontinuations related to study drug
- In patients with ADH1, encaleret administered twice daily rapidly corrects and maintains mineral homeostasis within the normal range, as demonstrated by:
  - ✓ Increase in PTH
  - ✓ Correction of hypocalcemia
  - ✓ Normalization of mean 24-hr urine calcium
  - ✓ Reduction in mean serum phosphate
  - ✓ Increase in mean serum magnesium
- Trial in pediatric patients with ADH1 is ongoing

Acknowledgements

Thank you to the patients and their families,
the study sites and support staff