Encaleret normalizes mineral homeostasis and is associated with an increase in eGFR in patients with autosomal dominant hypocalcemia Type 1 (ADH1): 24-week phase 3 CALIBRATE results

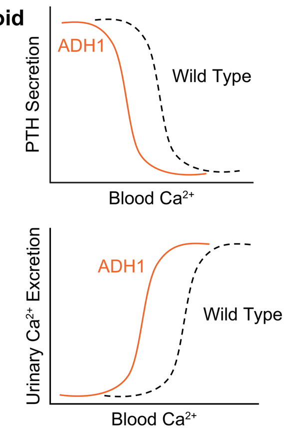
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BACKGROUND

ADH1 is caused by *CASR* gain-of-function variants increasing calcium sensitivity in the parathyroid and kidney[1,2]



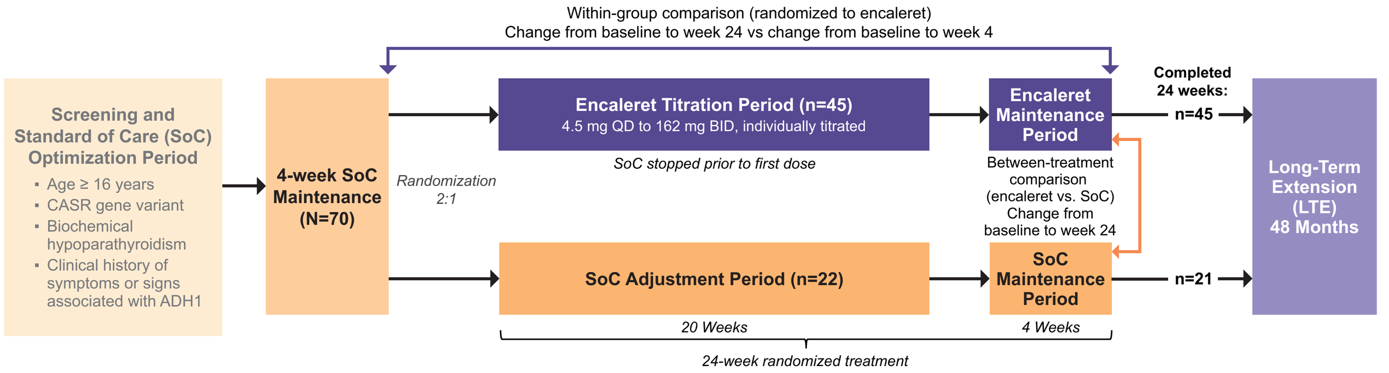
Parathyroid
PTH Secretion
ADH1
Wild Type
Blood Ca2+
Kidney
Urinary Ca2+ Excretion
ADH1
Wild Type
Blood Ca2+

Untreated ADH1 / conventional therapy	Goals of targeted therapy
Oversensitive CaSR	CaSR signaling normalized
Parathyroid: Low PTH secretion **Kidney:** Reduced tubular Ca^{2+} reabsorption	**Parathyroid:** PTH secretion restored **Kidney:** Tubular Ca^{2+} reabsorption increased
Chronic hypocalcemia and persistent hypercalciuria	Normalization of serum and urinary calcium
Hypocalcemia symptoms (eg, tetany, seizures, brain fog) and risk of nephrocalcinosis, nephrolithiasis, and impaired kidney function	Improved hypocalcemia symptoms and reduced long-term renal complications

Conventional therapy (calcium supplements and active vitamin D) does not correct the underlying pathophysiology and may leave patients exposed to hypocalcemia and renal complications

STUDY DESIGN AND PARTICIPANTS

Study Design: Phase 3 Study (CALIBRATE) – 25 sites, 9 countries



Within-group comparison (randomized to encaleret)
Change from baseline to week 24 vs change from baseline to week 4
Screening and Standard of Care (SoC) Optimization Period
• Age ≥ 16 years
• CASR gene variant
• Biochemical hypoparathyroidism
• Clinical history of symptoms or signs associated with ADH1
4-week SoC Maintenance (N=70)
Randomization 2:1
Encaleret Titration Period (n=45)
4.5 mg QD to 162 mg BID, individually titrated
SoC stopped prior to first dose
Encaleret Maintenance Period
Between-treatment comparison (encaleret vs. SoC) Change from baseline to week 24
SoC Adjustment Period (n=22)
SoC Maintenance Period
20 Weeks
4 Weeks
24-week randomized treatment
Completed 24 weeks:
n=45
n=21
Long-Term Extension (LTE) 48 Months

Primary Composite Endpoint at 24 weeks (within encaleret-treated group):
- Proportion of participants achieving:
 - cCa 8.3-10.7 mg/dL

 AND
 - UCa <300 mg/day (male)/<250 mg/day (female)

Additional Secondary and Exploratory Endpoints:
- cCa and 24-hour UCa between-treatment groups
- iPTH ≥ 15 pg/mL
- Phosphorus and magnesium
- **eGFR**
- **Nephrocalcinosis and nephrolithiasis assessed via renal ultrasound**

SoC = standard of care; a combination of oral active Vitamin D and/or calcium supplements. *CASR* = calcium-sensing receptor gene. iPTH = intact parathyroid hormone. eGFR = estimated glomerular filtration rate. cCa = albumin-corrected serum calcium; UCa = 24-hour urinary calcium. 99 participants were screened, 70 enrolled, and 67 randomized (June 2023–March 2025). Ultrasounds performed locally on prequalified equipment and read by a central reader blinded to study treatment and timepoint.

- **Current analysis:** Evaluation of the effect of encaleret, an investigational oral calcilytic, on renal endpoints — 24-hour urinary Ca^{2+}, eGFR, and renal ultrasound findings

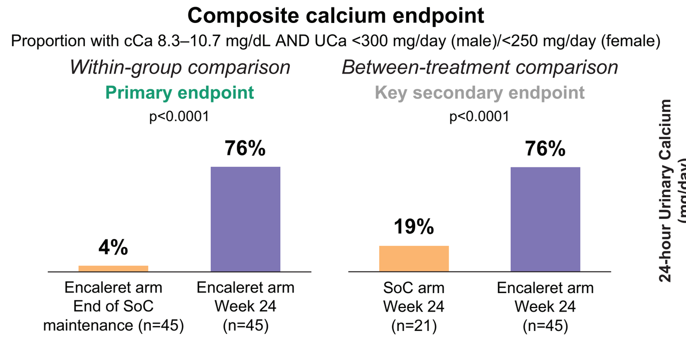
Baseline characteristics

Characteristic	Target / Reference Range	Encaleret (N=45)	SoC (N=22)
Age (years)	—	43.7 ± 16.0	36.8 ± 13.4
Female sex, n (%)	—	24 (53)	11 (50)
***CASR* variants, distinct*, n**	—	34	17
Mineral parameters			
cCa (mg/dL)	8.3–10.7	8.4 ± 0.8	7.9 ± 0.7
24-hour uCa (mg/day)	<300 men, <250 women	397 ± 178	331 ± 195
iPTH (pg/mL)	15–65	6.8 ± 7.8	6.0 ± 4.5
Phosphorus (mg/dL)	2.5–4.8	4.8 ± 0.7	5.0 ± 1.0
Magnesium (mg/dL)	1.8–2.4	1.8 ± 0.2	1.7 ± 0.1
Kidney function and imaging			
eGFR (CKD-EPI)** (mL/min/1.73 m^2)	≥ 90	77 ± 23 (n=42)	83 ± 27 (n=21)
eGFR (bedside Schwartz)** (mL/min/1.73 m^2)	≥ 90	82 ± 23 (n=3)	97 (n=1)
Nephrocalcinosis***, n (%)	—	35 (80)	17 (81)
Nephrolithiasis***, n (%)	—	0 (0)	1 (4.8)
History of nephrolithiasis, n (%)	—	10 (22)	4 (18)
Conventional therapy****			
Elemental calcium (mg/day)	—	1953 ± 2379 (n=40)	1912 ± 2016 (n=20)
Calcitriol (µg/day)	—	0.90 ± 0.45 (n=36)	0.97 ± 0.86 (n=17)
Alfacalcidol (µg/day)	—	2.82 ± 1.03 (n=11)	2.06 ± 1.74 (n=4)

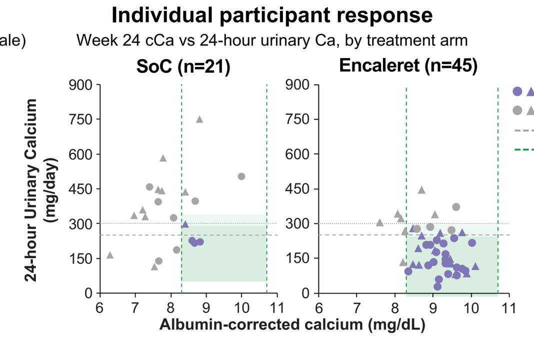
Data represent mean ± SD unless otherwise indicated. *Counts are of distinct *CASR* variants, not participants; 43 distinct variants were identified across the study population, of which 8 were represented in both treatment groups. **Determined via CKD-EPI for participants ≥18 years and via bedside Schwartz for the 4 participants <18 years. ***Assessed by renal ultrasound, performed at baseline in 65 participants (encaleret n=44, SoC n=21); percentages are based on participants with imaging available. Presence of nephrocalcinosis defined as grade 1 or higher. ****Mean total daily doses averaged over Period 1.

TREATMENT OUTCOMES

76% of participants met the primary endpoint after 24 weeks of encaleret

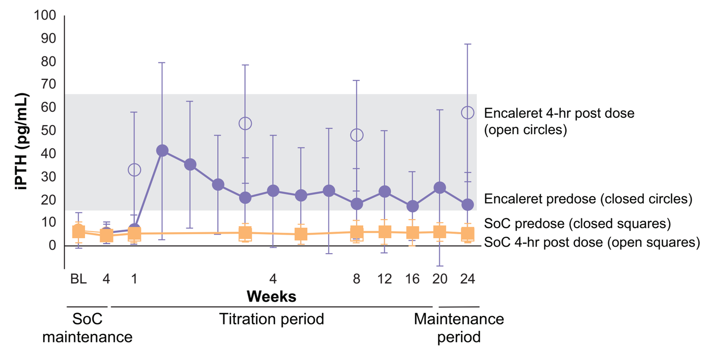


Composite calcium endpoint
Proportion with cCa 8.3–10.7 mg/dL AND UCa <300 mg/day (male)/<250 mg/day (female)
Within-group comparison
Primary endpoint
p<0.0001
4%
76%
Encaleret arm End of SoC maintenance (n=45)
Encaleret arm Week 24 (n=45)
Between-treatment comparison
Key secondary endpoint
p<0.0001
19%
76%
SoC arm Week 24 (n=21)
Encaleret arm Week 24 (n=45)

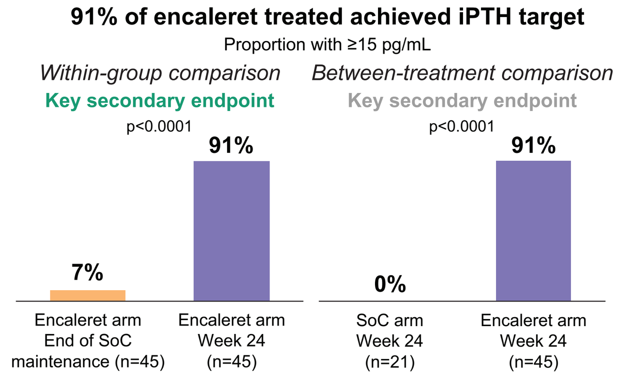


Individual participant response
Week 24 cCa vs 24-hour urinary Ca, by treatment arm
SoC (n=21)
Encaleret (n=45)
24-hour Urinary Calcium (mg/day)
Albumin-corrected calcium (mg/dL)
Responder (F, M)
Non-responder (F, M)
uCa upper limit: 250 F, 300 M
cCa 8.3–10.7 mg/dL

Encaleret restored PTH secretion, with changes maintained over 24 weeks



iPTH (pg/mL)
Weeks
SoC maintenance
Titration period
Maintenance period
Encaleret 4-hr post dose (open circles)
Encaleret predose (closed circles)
SoC predose (closed squares)
SoC 4-hr post dose (open squares)



91% of encaleret treated achieved iPTH target
Proportion with ≥15 pg/mL
Within-group comparison
Key secondary endpoint
p<0.0001
7%
91%
Encaleret arm End of SoC maintenance (n=45)
Encaleret arm Week 24 (n=45)
Between-treatment comparison
Key secondary endpoint
p<0.0001
0%
91%
SoC arm Week 24 (n=21)
Encaleret arm Week 24 (n=45)

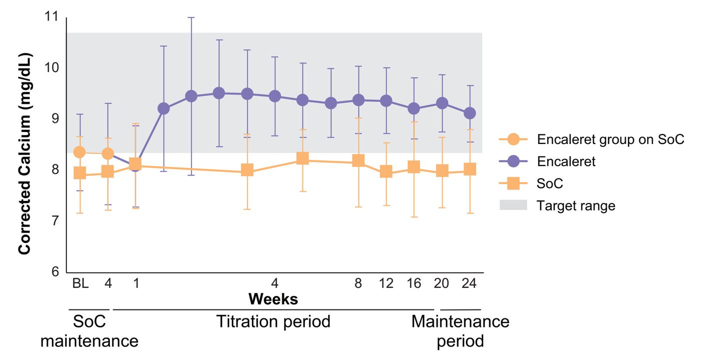
iPTH Week 24 ΔBL: Encaleret 50.8 ± 29.1 vs SoC -1.3 ± 3.1 pg/mL

Between-group difference 52.2 (SE 4.7), p<0.0001

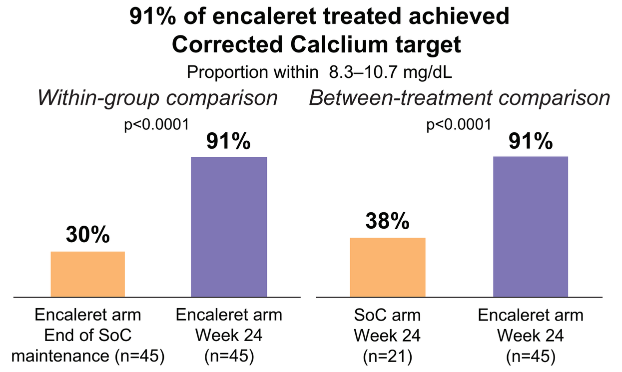
Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

Data reported as mean ± SD. Gray shading denotes the target or reference range.

Encaleret increased serum calcium, with changes maintained over 24 weeks



Corrected Calcium (mg/dL)
Weeks
SoC maintenance
Titration period
Maintenance period
Encaleret group on SoC
Encaleret
SoC
Target range



91% of encaleret treated achieved Corrected Calclium target
Proportion within 8.3–10.7 mg/dL
Within-group comparison
p<0.0001
30%
91%
Encaleret arm End of SoC maintenance (n=45)
Encaleret arm Week 24 (n=45)
Between-treatment comparison
p<0.0001
38%
91%
SoC arm Week 24 (n=21)
Encaleret arm Week 24 (n=45)

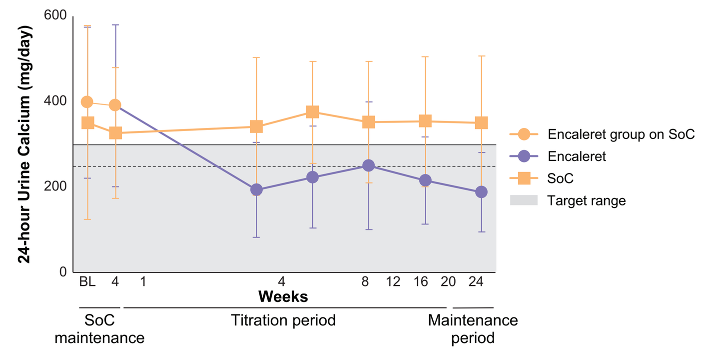
cCa Week 24 ΔBL: Encaleret +0.7 ± 0.9 vs SoC +0.1 ± 0.9 mg/dL

Between-group difference 0.6 (SE 0.2), p<0.01

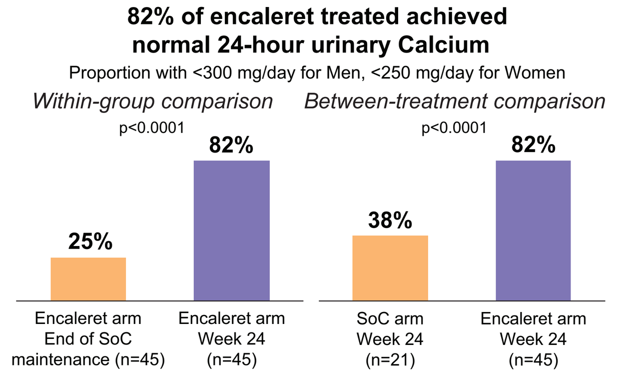
Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

Data reported as mean ± SD. Gray shading denotes the target or reference range.

Encaleret decreased 24-hour urinary calcium over the study period



24-hour Urine Calcium (mg/day)
Weeks
SoC maintenance
Titration period
Maintenance period
Encaleret group on SoC
Encaleret
SoC
Target range



82% of encaleret treated achieved normal 24-hour urinary Calcium
Proportion with <300 mg/day for Men, <250 mg/day for Women
Within-group comparison
p<0.0001
25%
82%
Encaleret arm End of SoC maintenance (n=45)
Encaleret arm Week 24 (n=45)
Between-treatment comparison
p<0.0001
38%
82%
SoC arm Week 24 (n=21)
Encaleret arm Week 24 (n=45)

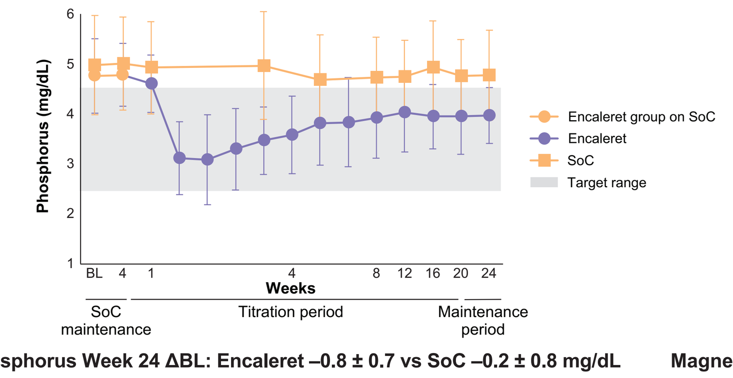
24-hour uCa ΔBL at Week 24: Encaleret –207 ± 174 vs SoC +11 ± 186 mg/day

Between-group difference –221 (SE 47), p<0.0001

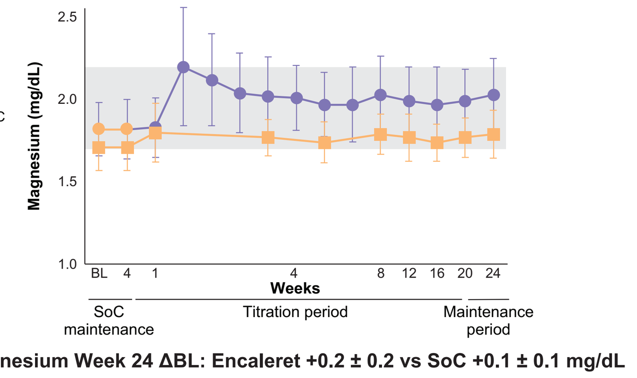
Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

For 24-hour urine calcium, the solid line reflects the upper limit for men and the dashed line the upper limit for women.

Encaleret reduced serum phosphorus and increased serum magnesium over 24 weeks



Phosphorus (mg/dL)
Weeks
SoC maintenance
Titration period
Maintenance period
Encaleret group on SoC
Encaleret
SoC
Target range



Magnesium (mg/dL)
Weeks
SoC maintenance
Titration period
Maintenance period

Phosphorus Week 24 ΔBL: Encaleret –0.8 ± 0.7 vs SoC –0.2 ± 0.8 mg/dL

Between-group difference –0.6 (SE 0.2), p<0.01

Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

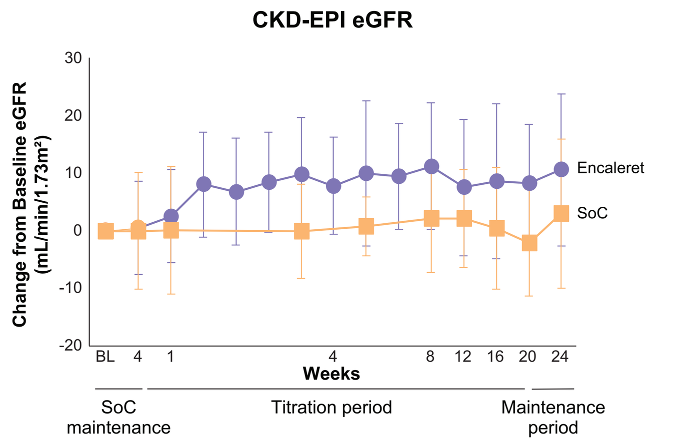
Magnesium Week 24 ΔBL: Encaleret +0.2 ± 0.2 vs SoC +0.1 ± 0.1 mg/dL

Between-group difference 0.13 (SE 0.04), p<0.01

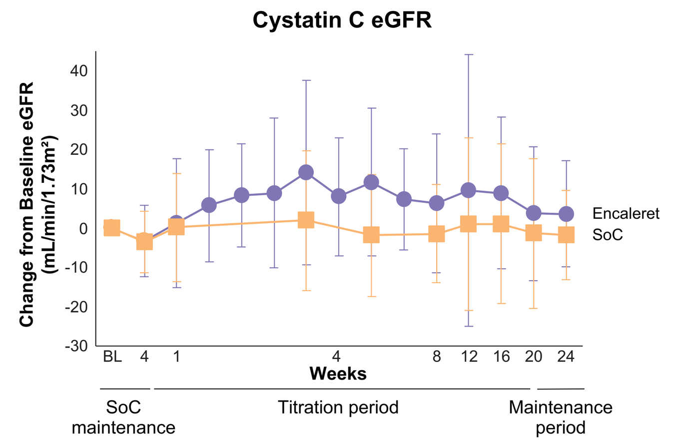
Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

Data reported as mean ± SD. Gray shading denotes the reference range.

Encaleret increased eGFR over the study period



CKD-EPI eGFR
Change from Baseline eGFR (mL/min/1.73m²)
Encaleret
SoC
Weeks
SoC maintenance
Titration period
Maintenance period



Cystatin C eGFR
Change from Baseline eGFR (mL/min/1.73m²)
Encaleret
SoC
Weeks
SoC maintenance
Titration period
Maintenance period

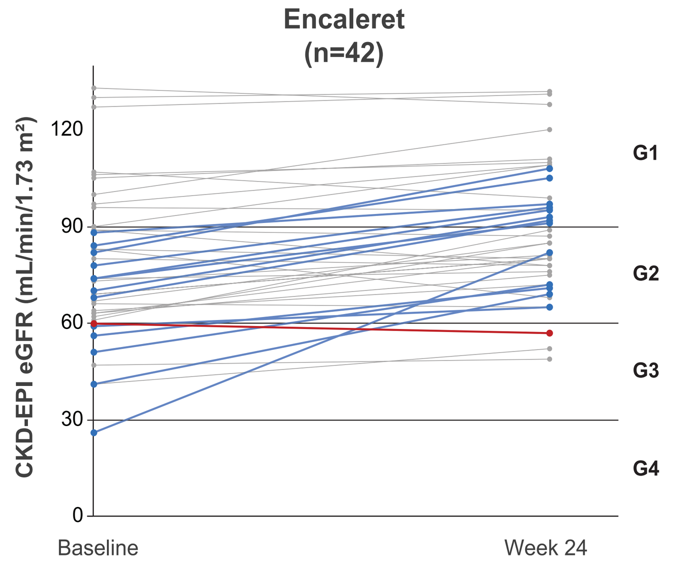
Week 24 ΔBL: Encaleret +11±13 vs SoC +3±13 mL/min/1.73m²

Between-group difference 7.6 (SE 3.6), p<0.05

Encaleret within-arm: ΔBL to W24 vs ΔBL to W4 on SoC maintenance, p<0.0001

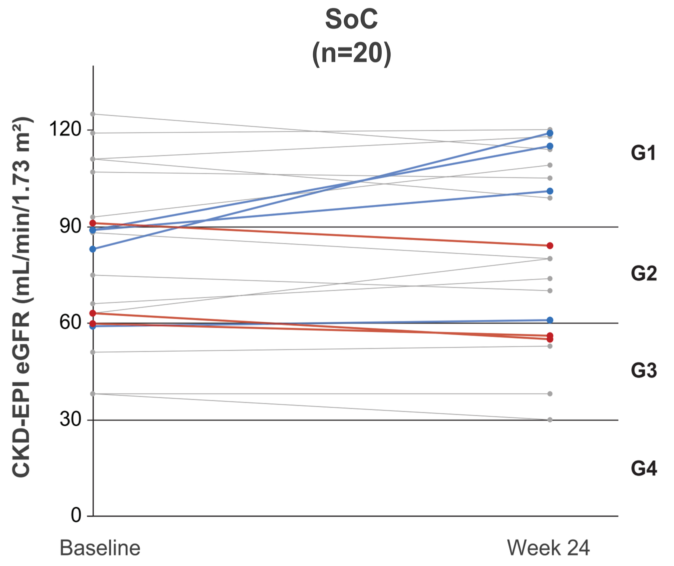
Line graphs represent mean ± SD throughout the study for change from baseline in eGFR calculated by CKD-EPI; data from four participants <18 years whose eGFR was calculated via bedside Schwartz were excluded. Samples were collected following an 8-hour fast and prior to the morning encaleret or SoC dose.

eGFR CKD stage improved or remained stable in 98% of encaleret participants vs 85% with SoC



Encaleret (n=42)
CKD-EPI eGFR (mL/min/1.73 m²)
G1
G2
G3
G4
Baseline
Week 24

Improved 13 (31%) Unchanged 28 (67%) Worsened 1 (2%)

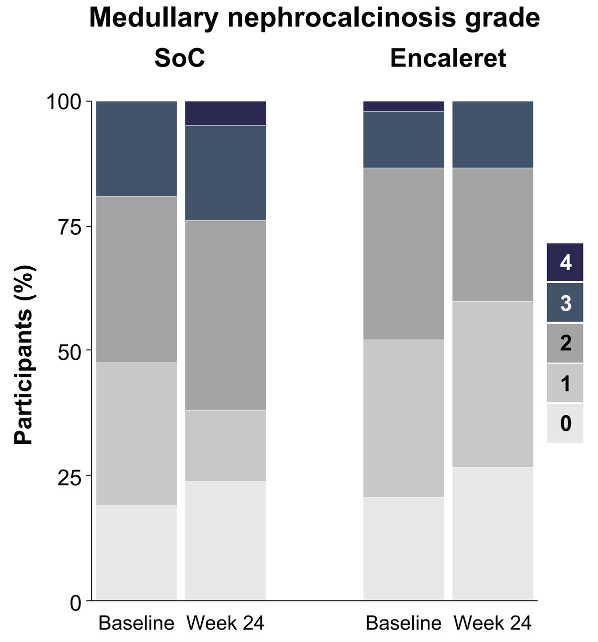


SoC (n=20)
CKD-EPI eGFR (mL/min/1.73 m²)
G1
G2
G3
G4
Baseline
Week 24

Improved 4 (20%) Unchanged 13 (65%) Worsened 3 (15%)

CKD stage boundaries at eGFR 90, 60 and 30 mL/min/1.73 m²; line color shows direction of CKD stage change from baseline to Week 24. Participants <18 years (bedside Schwartz) and one SoC participant without a Week 24 value are excluded.

Nephrocalcinosis and nephrolithiasis assessed via renal ultrasound over 24 weeks

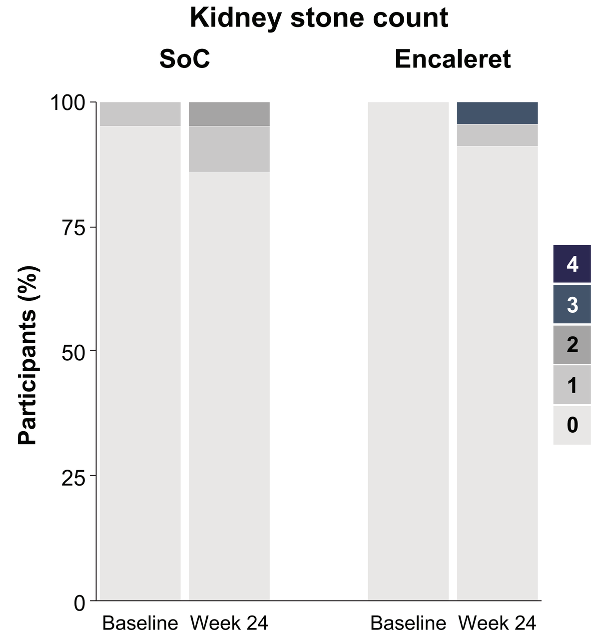


Medullary nephrocalcinosis grade
SoC
Encaleret
Participants (%)
Baseline
Week 24
4
3
2
1
0

Any nephrocalcinosis: 81% → 76% | 80% → 73%

Grade improved: 15% | 23%

Grade worsened: 25% | 9%



Kidney stone count
SoC
Encaleret
Participants (%)
Baseline
Week 24
4
3
2
1
0

Any stones: 5% → 14% | 0% → 9%

Proportion of participants with each finding on renal ultrasound. Percentages are based on participants with imaging available (encaleret n=44 at baseline, n=45 at Week 24; SoC n=21). Stone count is the total across both kidneys; nephrocalcinosis grade is the highest grade in either kidney. Grade 4 was defined as diffuse calcifications with accumulation at the tips of nearly all renal pyramids. Nephrolithiasis was defined as a cortical stone or an isolated calcification within or at the tip of a pyramid when the remaining pyramids did not meet Grade 4 criteria. Imaging outcomes are descriptive and no between-group statistical comparison was performed.

- Overall nephrocalcinosis prevalence remained stable; kidney stone findings involved few participants, most of whom had history of nephrolithiasis
 - Nephrolithiasis: encaleret 0 to 4 participants; SoC 1 to 3 participants

No TEAEs led to encaleret discontinuation during randomized treatment

Overall safety

	SoC Maintenance (4 weeks)	Randomized treatment (24 weeks)	
	N = 67 n (%)	SoC N = 22 n (%)	Encaleret N = 45 n (%)
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)
Serious TEAE	2 (3)	3 (14)	4 (9)
Related TEAE			
Any	4 (6)	0 (0)	16 (36)
Serious	1 (2)	0 (0)	1 (2)
Study Discontinuation	0 (0)	0 (0)	0 (0)
Hypercalcemia	3 (4.5)	0 (0)	10 (22.2)
Headache	0 (0)	1 (4.5)	9 (20.0)
Constipation	0 (0)	2 (9.1)	5 (11.1)
Nausea	1 (1.5)	3 (13.6)	4 (8.9)
Fatigue	0 (0)	1 (4.5)	4 (8.9)
Hypertension	0 (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 (0)	2 (9.1)	2 (4.4)

TEAE = Treatment-Emergent Adverse Event. For each category, participants are included only once, even if they experienced multiple events in that category. Relatedness considered by the investigator as related to investigational product being administered in the respective study period reported. *Hypocalcemia was reported as TEAE if considered by investigator to have worsened from baseline. Data extracted on 15Oct2025.

CONCLUSIONS

- Encaleret normalized mean blood and urine calcium in most participants and was associated with an increase in mean eGFR in individuals with ADH1 at Week 24
 - Nephrocalcinosis was stable in both arms over 24 weeks
- Consistent with inhibition of the oversensitive renal CaSR, encaleret corrected hypocalcemia while also decreasing urinary calcium
- Follow-up is needed to assess encaleret's long-term impact on renal calcifcations and function
 - Encaleret has the potential to become the first personalized therapy for ADH1, directly targeting the underlying mechanism of the disease

REFERENCES: 1. Roszko KL, et al. *Front Physiol.* 2016. **2.** Riccardi D, et al. *Nat Rev Nephrol.* 2016;12(7):414-425.

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