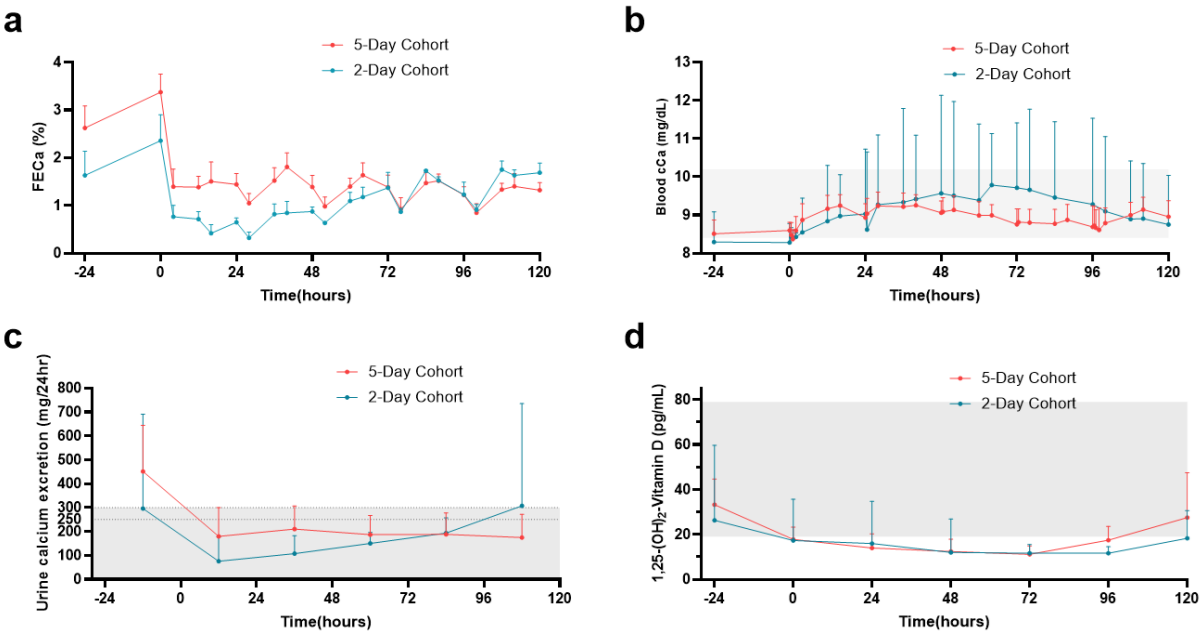
Supplementary Materials

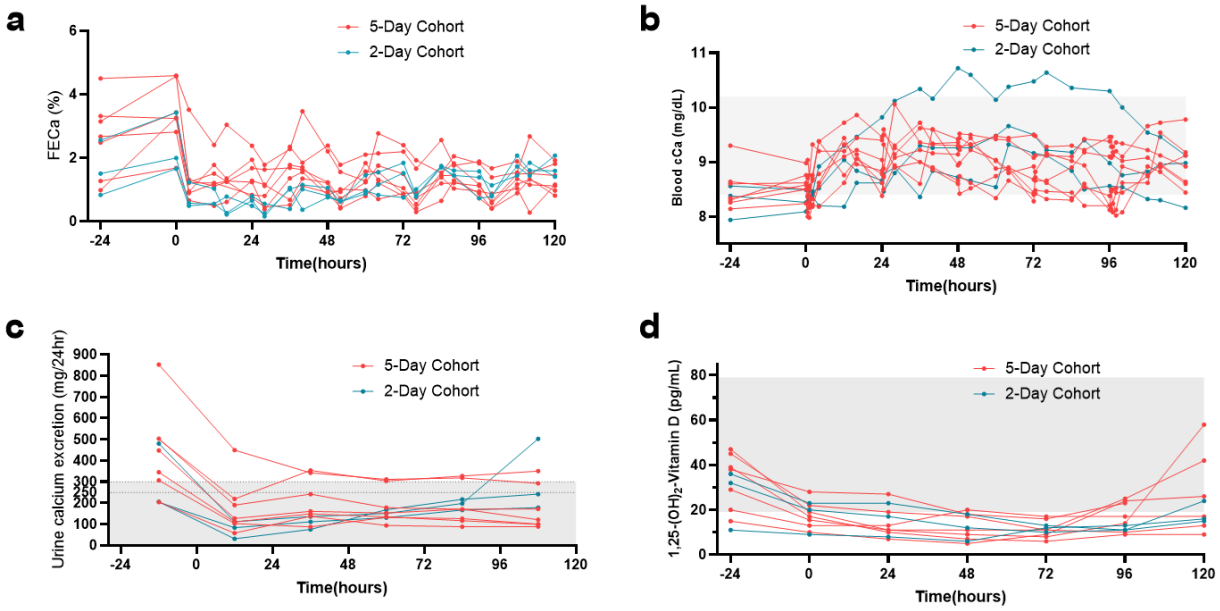
Supplemental Figure 1: Response of calcium homeostasis by treatment duration

Panels a-d present the same panels shown in Figure 2a-d, with data separated by treatment duration (5-day cohort in red, 2-day cohort in blue). In the 5-day cohort, FECa and 24h-Uca increased slowly following the first missed dose at 48h. Data is presented as mean ± 95% confidence intervals (CI).



Supplemental Figure 2: Individual participant data showing encaleret's effect on calcium homeostasis

Panels a-d show individual participant data which were used to derive summary results in Figure 2a-d in the manuscript. Each line represents a single participant (5-day cohort in red; 2-day cohort in blue).

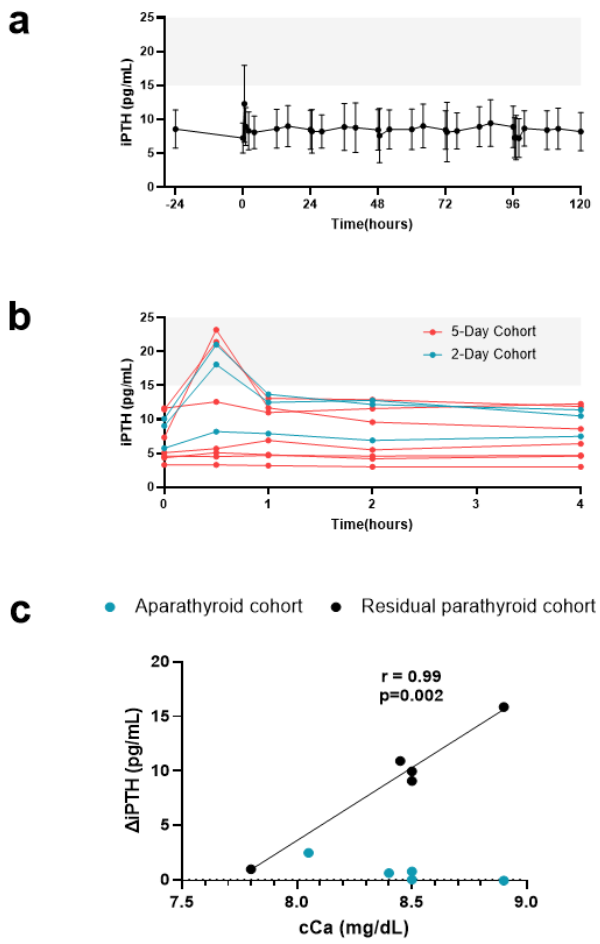


Supplemental Figure 3: Effects of encaleret on PTH

(a) Mean± 95%CI iPTH levels over time.

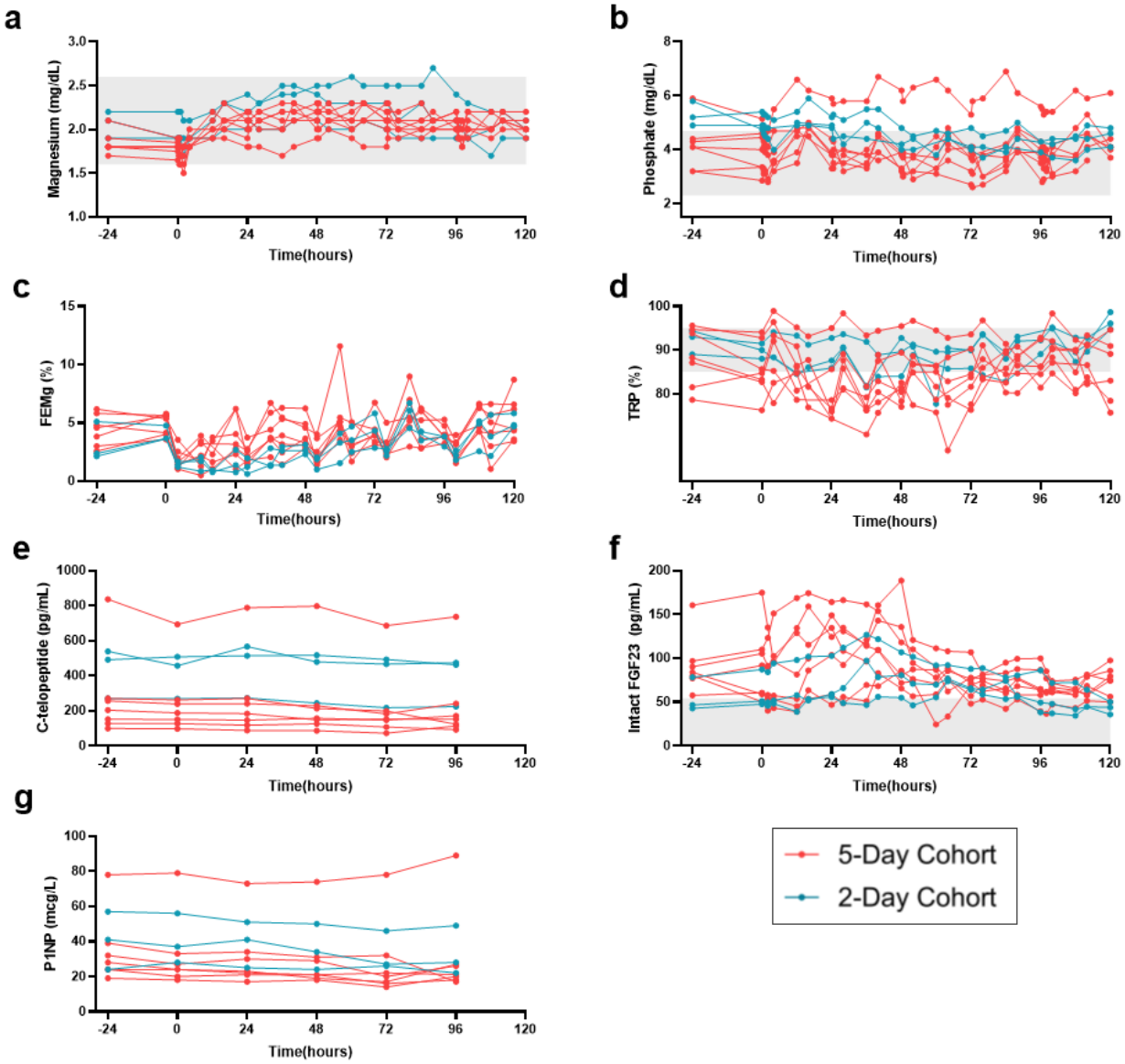
(b) Individual iPTH concentrations during the first 4 hours following the initial encaleret dose, allowing for visualization of the transient iPTH peak at 30 minutes for each participant (5-day cohort in red, 2-day cohort in blue, gray shaded region represents normal range)

(c)Relationship between the change in iPTH from time 0h to time 30 minutes and cCa at the time of encaleret administration (0h). Participants classified as belonging to the aparathyroid cohort (blue) or the residual parathyroid cohort (black). A linear regression line is shown for participants with residual parathyroid function (r=0.99, p=0.002)



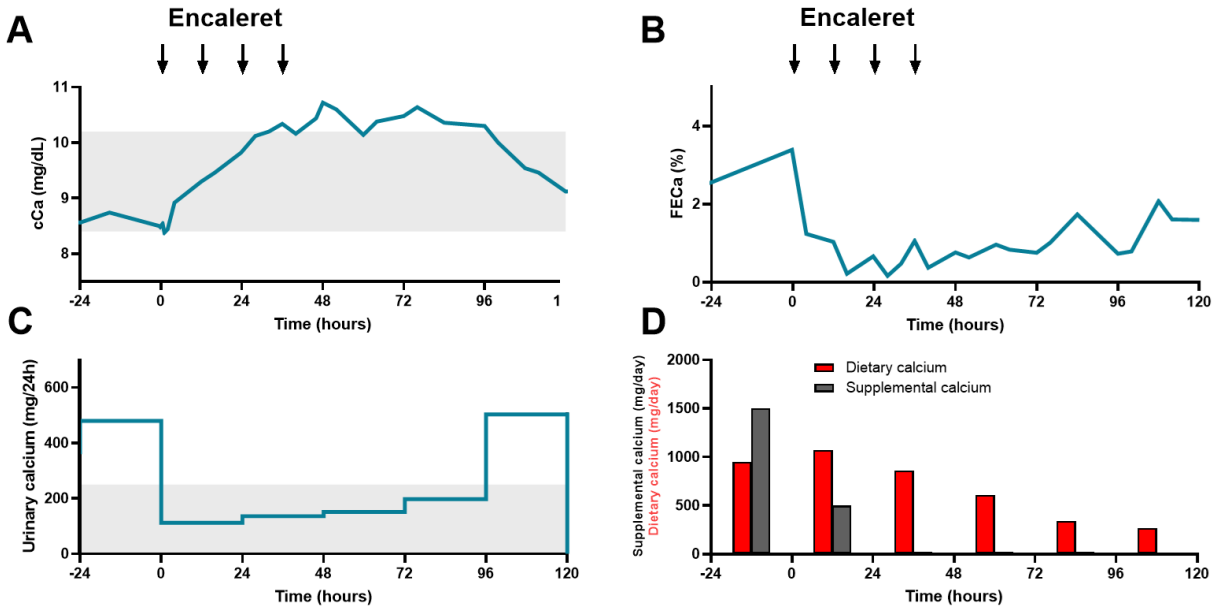
Supplemental Figure 4: Individual participant data showing encaleret's effect on magnesium, phosphate, and bone turnover markers.

Panels a-g show individual participant data which were used to derive summary results in Figure 3a-f. C-telopeptide and P1NP are graphed separately. Each line represents a single participant (5-day cohort in red, 2-day cohort in blue).



Supplemental Figure 5: Individual response in calcium homeostasis for participant who experienced hypercalcemia prompting early encaleret discontinuation.

This participant's biochemistry during the admission is shown including (a) cCa, (b) FECa, (c) 24h-Uca, (d) exogenous calcium supplementation (gray) and estimated dietary calcium intake (red). The participant did not receive any calcitriol during the admission. Encaleret administration is indicated by black arrows. Notably, following drug discontinuation, blood cCa remained stably elevated despite cessation of calcium supplementation and restriction of dietary calcium intake. This participant's 24h-Uca and FECa remained suppressed while the patient was hypercalcemic for several days. By day 5, more than 60 hours after the final encaleret dose, blood cCa decreased, accompanied by increases in FECa and 24h-Uca.



Supplemental Table 1: Adverse Events

Body System Preferred Term	Participants N=10 n (%)	AE Count Total 33
Endocrine disorders		1
Hypothyroidism, exacerbation	1(10%)	
Eye Disorders		
Conjunctivitis	1 (10%)	1
Gastrointestinal disorders		
Inguinal hernia*	1(10%)	1
Nausea	2(20%)	2
General Disorders and Administration Site Conditions		
Fatigue	2(20%)	2
Hepatobiliary Disorders		
Gallbladder polyps	1(10%)	1
Infections and Infestations		
Lung infection	1(10%)	1
Injury, poisoning, and procedural complications		
Abdominal Pain **(**Post-operative pain)*	1(10%)	1
Blood creatine phosphokinase increased	1(10%)	1
Metabolism and Nutrition Disorders		
Hypercalcemia	1(10%)	1
Symptomatic hypocalcemia	8(80%)	11
Symptomatic hypocalcemia*	1(10%)	1
Musculoskeletal and Connective Tissue Disorders		
Back pain	1(10%)	1
Nervous System Disorders		
Headache	2(20%)	3
Paresthesia	1(10%)	1
Skin and subcutaneous tissue disorders		
Contact dermatitis	1(10%)	1
Impetigo	1(10%)	1
Vascular disorders		
Superficial Thrombophlebitis	2(20%)	2

The n reflects the number of participants who experienced at least one event within a particular category (row). Only participants who received study drug were included in this table. Participants who did not receive study drug did not report any AEs while on study.

*Baseline (occurring after screening and before study drug administration)

Adverse Events of Special Interest

The protocol was written to collect information about hypocalcemic events either symptomatic hypocalcemia or asymptomatic severe hypocalcemia (cCa < 7 mg/dL) as an AE of special interest (AESI) because these are common occurrences in participants with hypoparathyroidism. Hypocalcemic symptoms were not considered AEs unless the participant noted it was worse than baseline, or their symptoms had resolved and then worsened. Twelve AESI events in eight participants occurred which were all symptomatic. One AESI occurred prior to the treatment phase of the study, three occurred in two patients during the treatment phase of the study, and eight occurred after the treatment phase of the study. All symptoms of hypocalcemia were mild and not significantly different in magnitude from baseline symptoms.