The Effects of Encaleret (CLTX-305) on Mineral Physiology in Autosomal Dominant Hypocalcemia Type 1 (ADH1) Demonstrate Proof-of-Concept: Early Results from an Ongoing Phase 2B, Open-Label, Dose-Ranging Study

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NIH National Institute of Dental and Craniofacial Research

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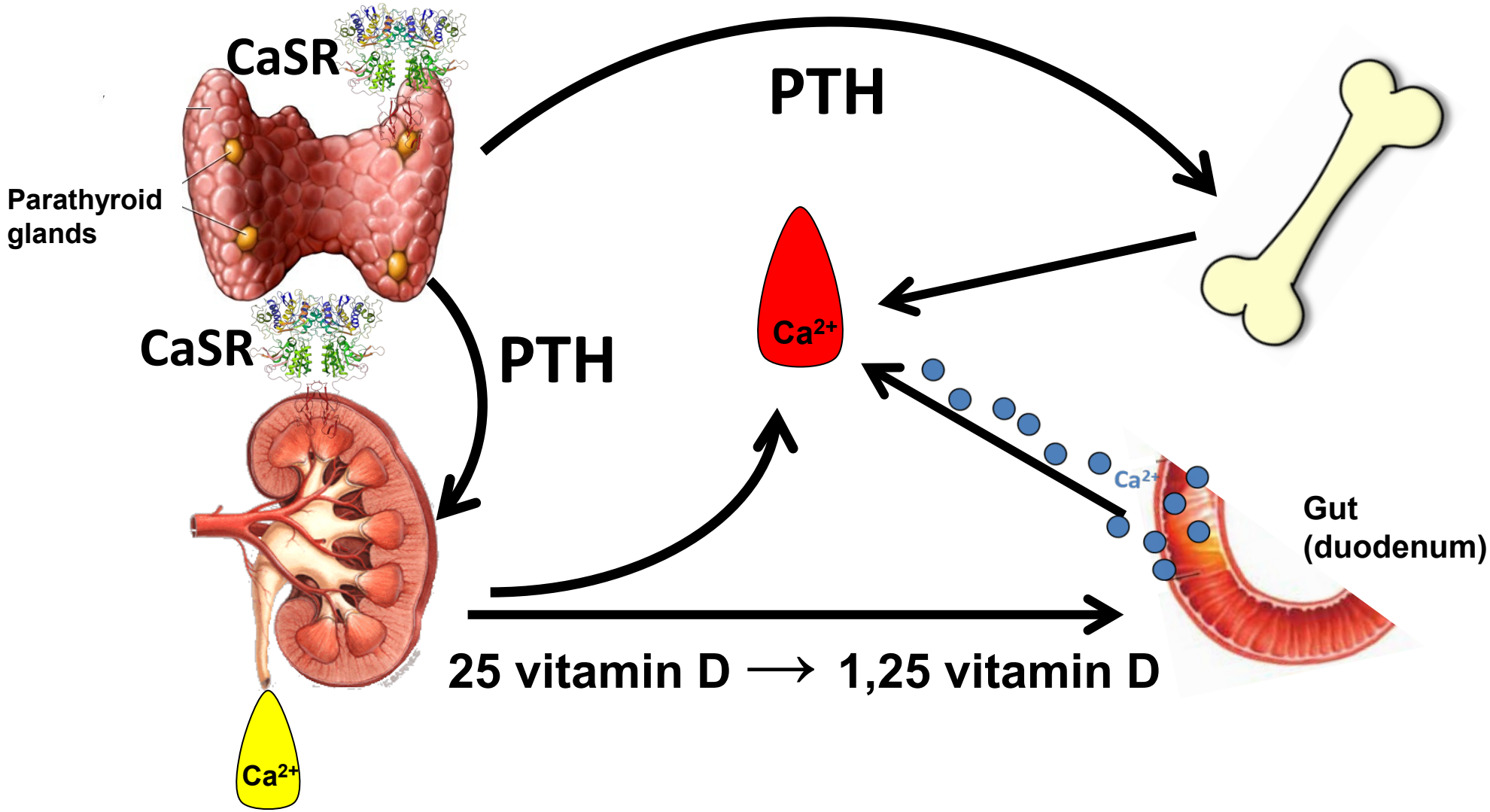
Disclosures

- This study was supported by a public/private partnership between the NIDCR Intramural Research Program and BridgeBio affiliate Calcilytix Therapeutics, Inc.
- Non-FDA approved investigational agent will be discussed

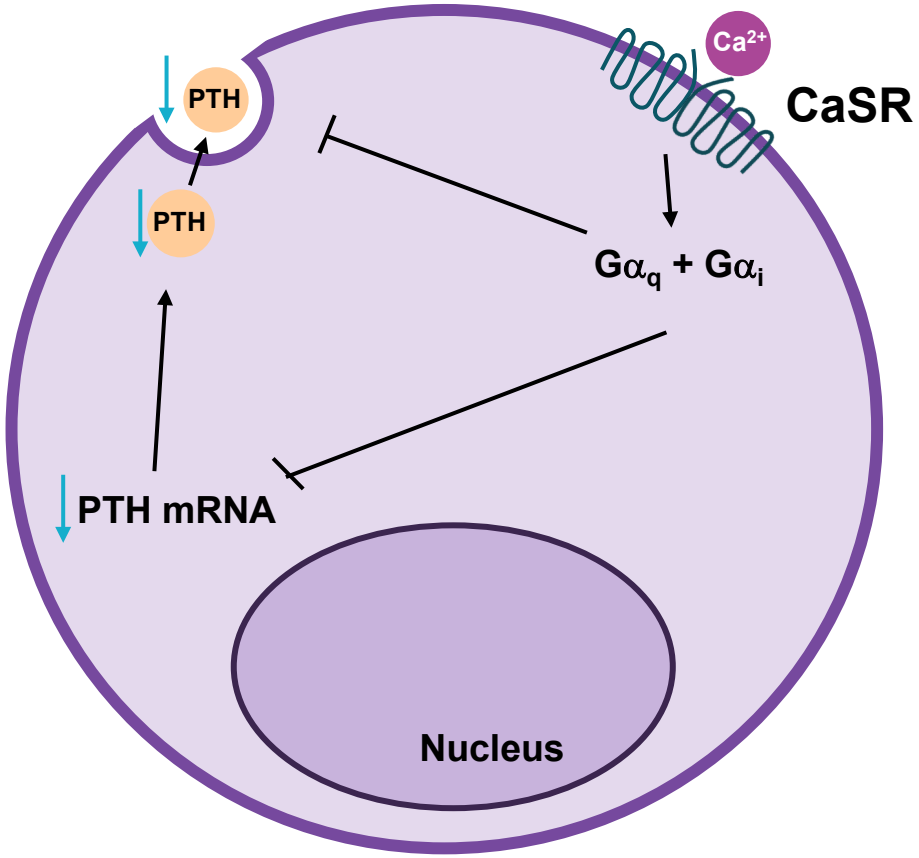
Blood calcium is maintained by four organs regulated by PTH and the CaSR



PTH = parathyroid hormone; CaSR = calcium-sensing receptor

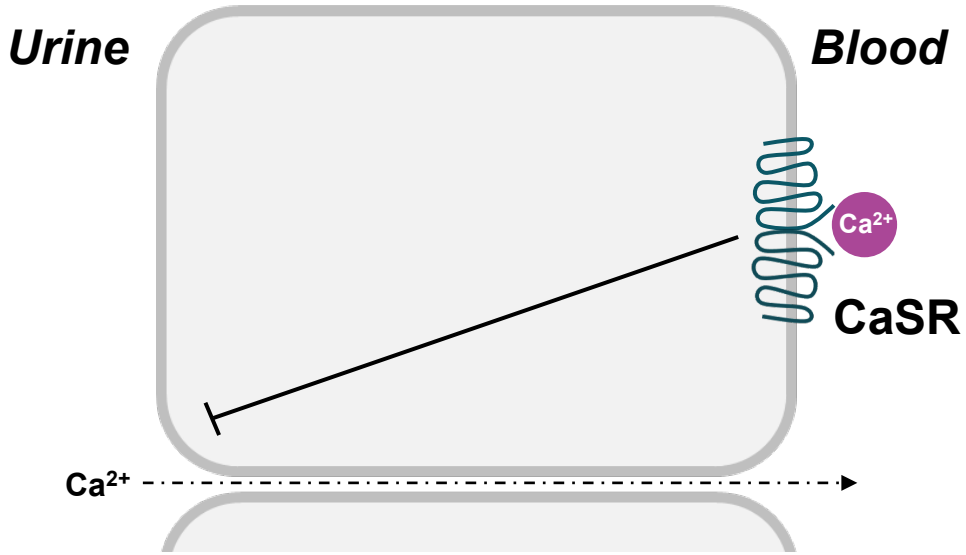
CaSR maintains physiological calcium homeostasis primarily through its activity in the parathyroid cell and renal tubule

Parathyroid cell



CaSR decreases PTH synthesis and secretion in response to ↑ blood Ca^{2+}

Renal Tubule

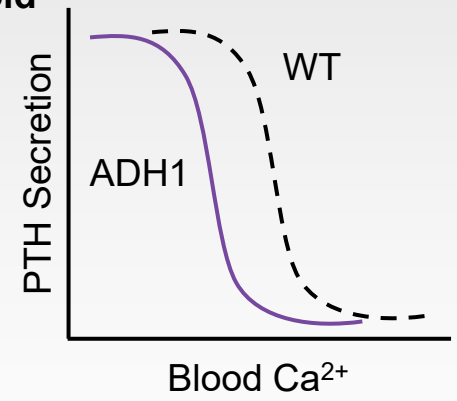


CaSR decreases renal tubular Ca^{2+} reabsorption in response to ↑ blood Ca^{2+}

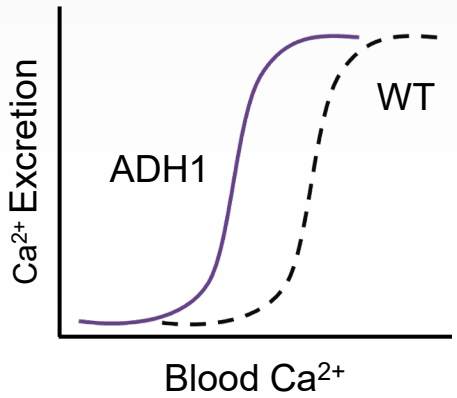
Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia (ADH1)

Activating variants in the *CASR* increase tissue sensitivity to Ca^{2+}

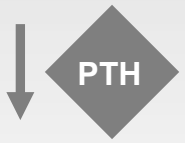
Parathyroid



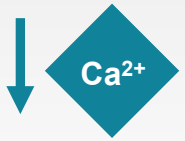
Kidney



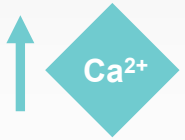
Hyperactive CaSR causes dysregulation of Ca homeostasis



Decreased parathyroid hormone (PTH) secretion



Decreased blood calcium



Increased urinary calcium

Clinical Manifestations

Acute symptoms

Hypocalcemic seizures

Paresthesia

Tetany

Muscle cramps

Long-term complications

Nephrolithiasis

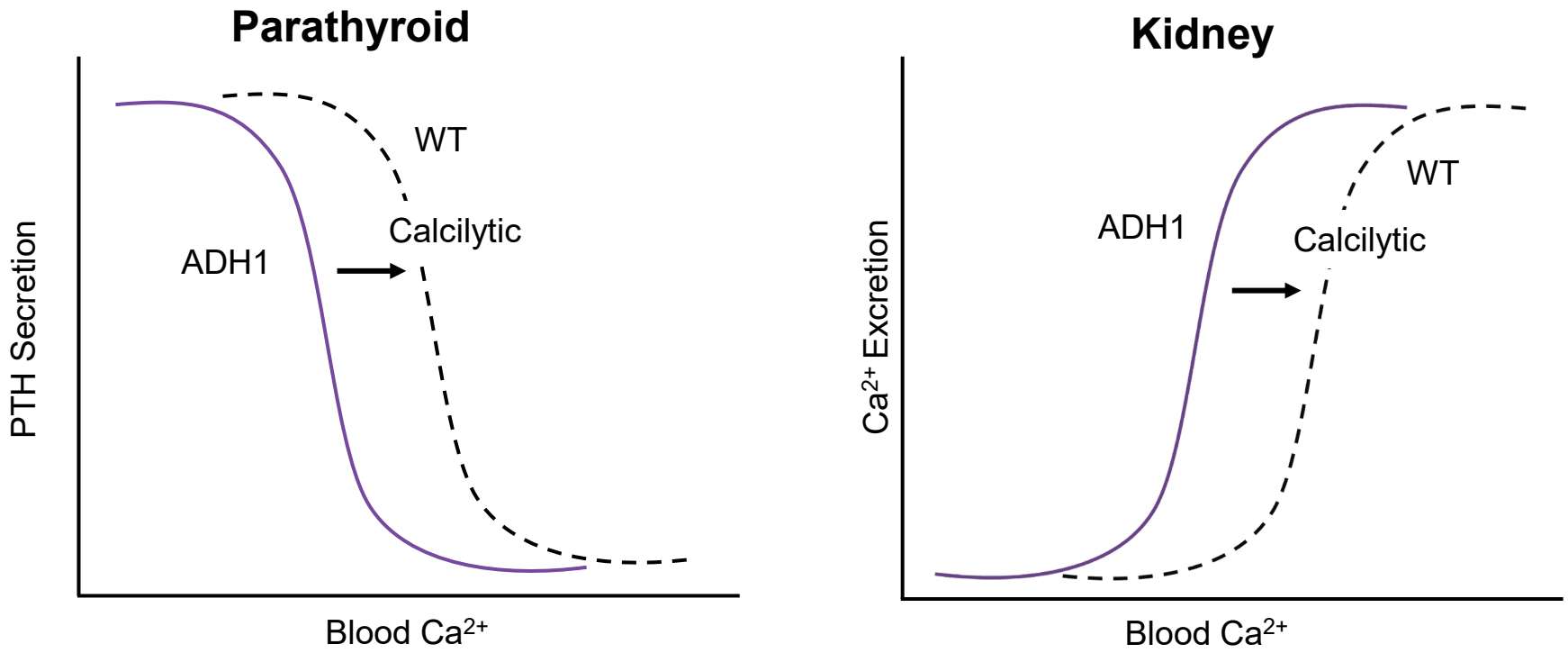
Nephrocalcinosis

Chronic Kidney Disease

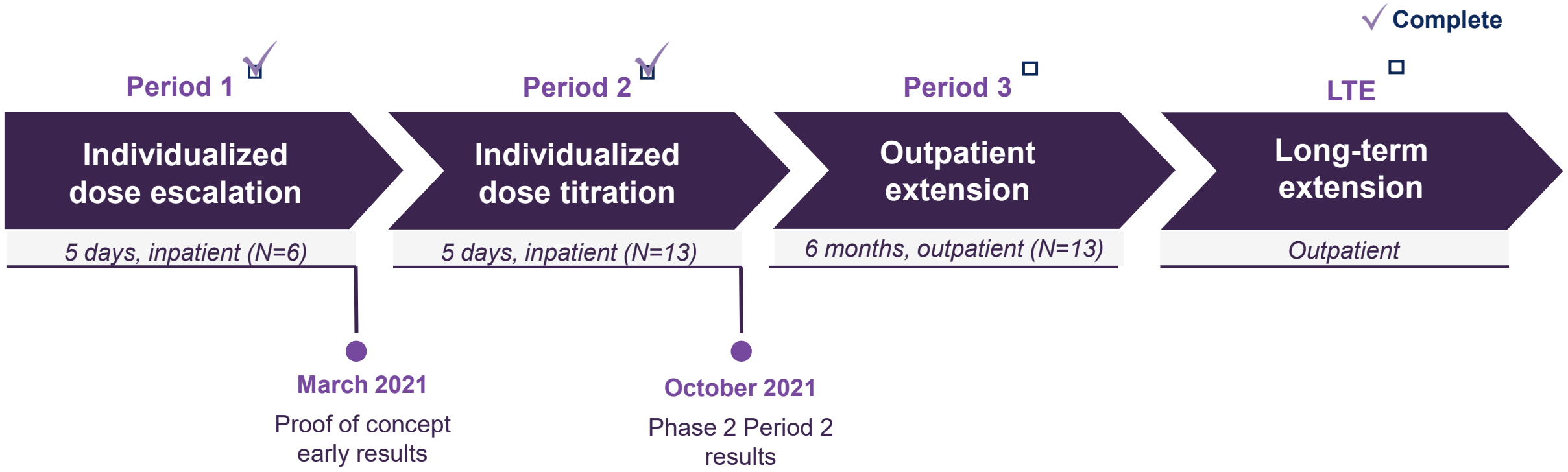
Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

Encaleret, an investigational oral calcilytic, may be a potential treatment for ADH1

- Calcilytics are negative allosteric modulators of the CaSR
- Encaleret decreases CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1



Encaleret Phase 2B Study Design – CLTX-305-201



Key study objectives:

- Safety and tolerability
- Blood calcium concentration
- Urine calcium concentration
- Intact parathyroid hormone concentration

Additional measures:

- Blood 1,25-$(OH)_2$ Vitamin D, magnesium, and phosphate
- Urine creatinine, cAMP, citrate, phosphate, sodium, magnesium
- Bone turnover markers (serum collagen C-telopeptide, serum procollagen Type 1 N-propeptide)

Baseline Characteristics

Characteristic	Study Population (N = 13)	*Normal Range*
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Nephrocalcinosis, n (%)	10 (77%)	
ECG QT_cB (msec)	452 ± 16	*< 440*
Calcium[1] (mg/dL)[2]	8.0 ± 0.7	*8.4 –10.2*
Intact PTH (pg/mL)[2]	2.8 ± 3.4	*15 – 65*
Phosphate (mg/dL)[2]	5.1 ± 1.1	*2.3 – 4.7*
Magnesium (mg/dL)[2]	1.8 ± 0.1	*1.6 – 2.6*
24h Urine Calcium (mg/24h)	425 ± 253	*< 250-300*
Supplements		
Elemental Calcium (mg/day) [mean (range)]	2628 (750-4800)	
Calcitriol (µg/day) [mean (range)]	0.8 (0.2-2.0)	
***CASR* Variants**	C131Y (2), P221L (2), E604K (1), A840V (3), F788C (1), T151M (1), Q245R (1), I692F (1), E228K (1)	

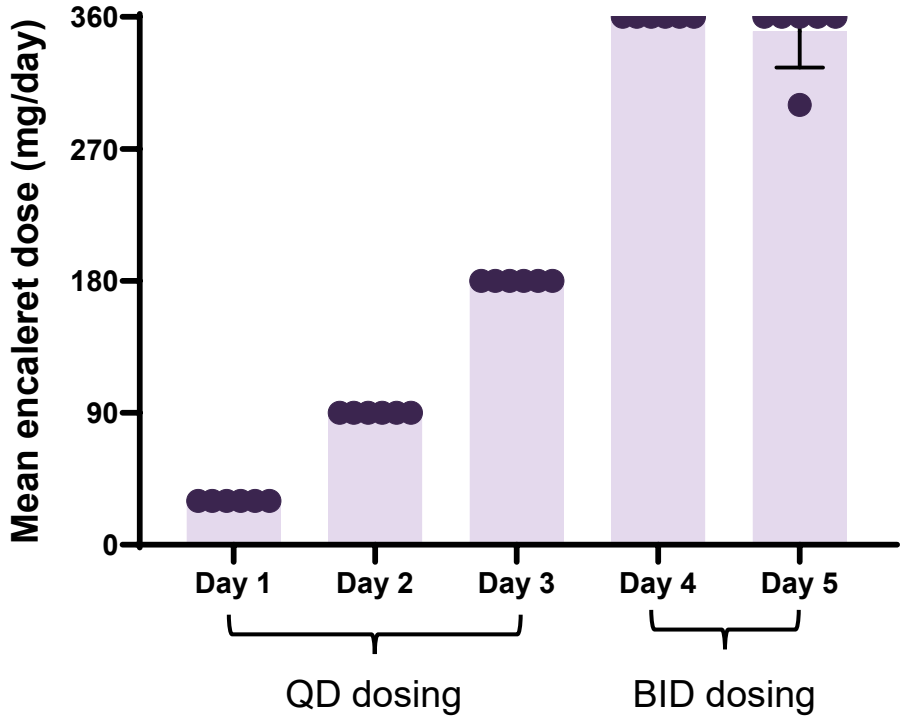
Data reported as mean±SD. ECG QTcB = electrocardiogram Bazett-corrected Q-T interval.
1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1 in Period 1 or Period 2.

Period 1 and Period 2 Oral Encaleret Dosing Summary

Period 1 Dosing

Defined dose escalation

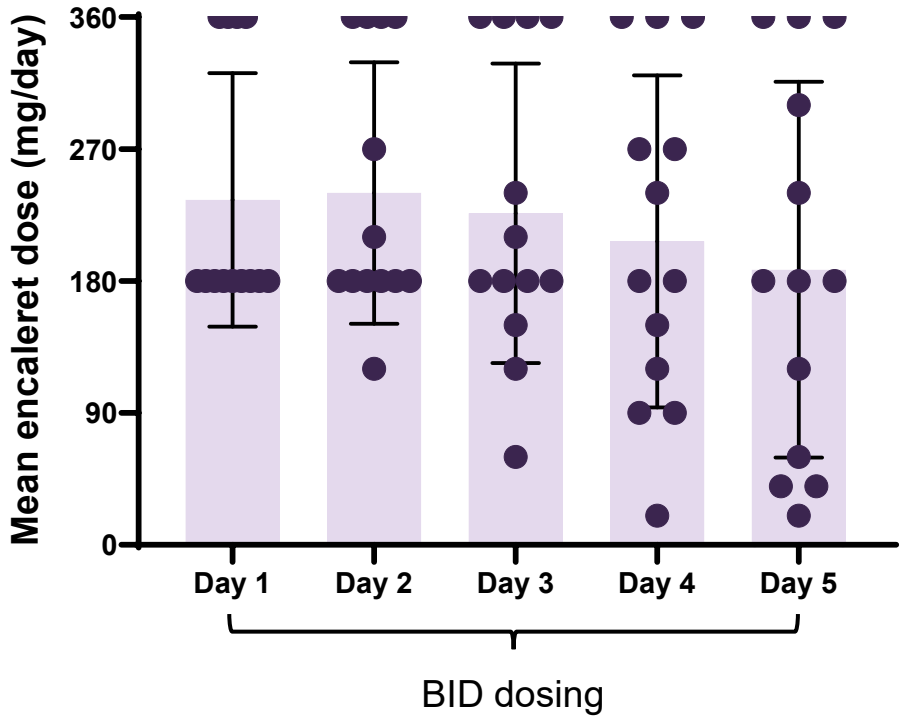
Day 5 Mean: 350.0±22.4 mg/day



Period 2 Dosing

Individualized dose titration

Day 5 Mean: 187.7±128.2 mg/day



Data reported as mean±SD.

Encaleret was well-tolerated with no serious adverse events reported

	Period 1 N = 6	Period 2 N=13
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**	**0 (0%)**
Number of subjects experiencing any Adverse Event	**6 (100%)**	**10 (77%)**
Mild	6 (100%)	10 (77%)
Moderate	1 (17%)	0 (0%)
Severe	0 (0%)	0 (0%)
Number of Adverse Events Reported	**19**	**12**
Mild	18 (95%)	12 (100%)
Moderate	1 (5%)	0 (0%)
Severe	0 (0%)	0 (0%)
Treatment-related Adverse Events*	**3 (16%)**	**8 (67%)**
Hypocalcemia	1 (33%)	0 (0%)
Hypophosphatemia	2 (67%)	7 (88%)
Hypercalcemia	0 (0%)	1 (12%)

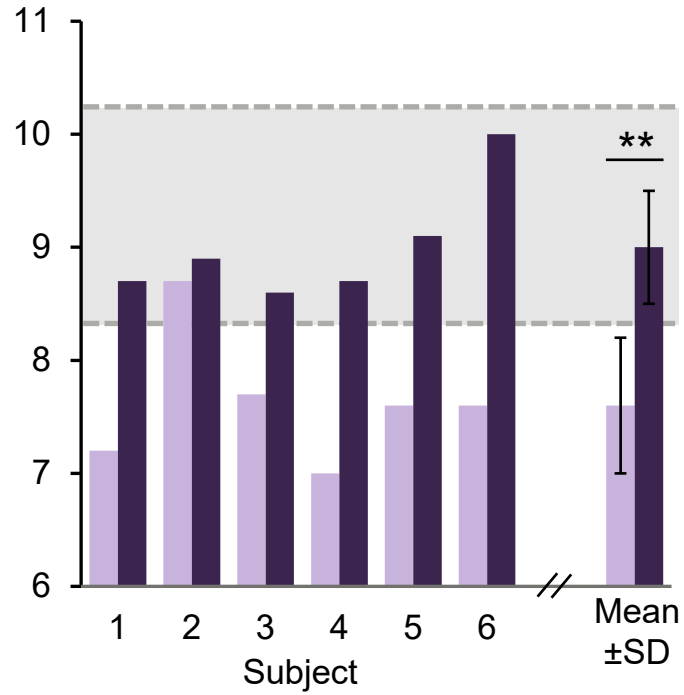
*Treatment-related adverse events were transient and resolved either spontaneously or with adjustment of the encaleret dose.
Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs.

Period 1 Results (n=6): Encaleret increased PTH secretion and normalized blood and urine calcium

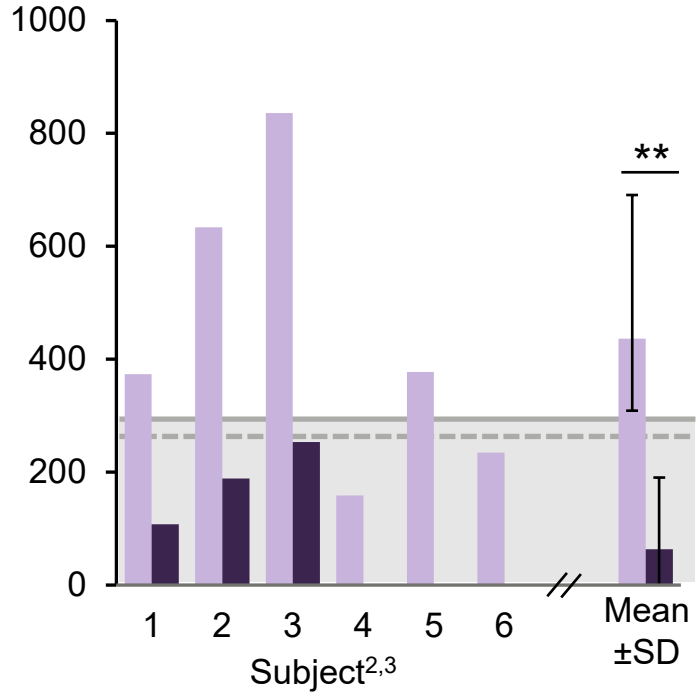
Baseline Value (Day 1)

Mean Value (Day 5) on encaleret 180 mg BID[1]

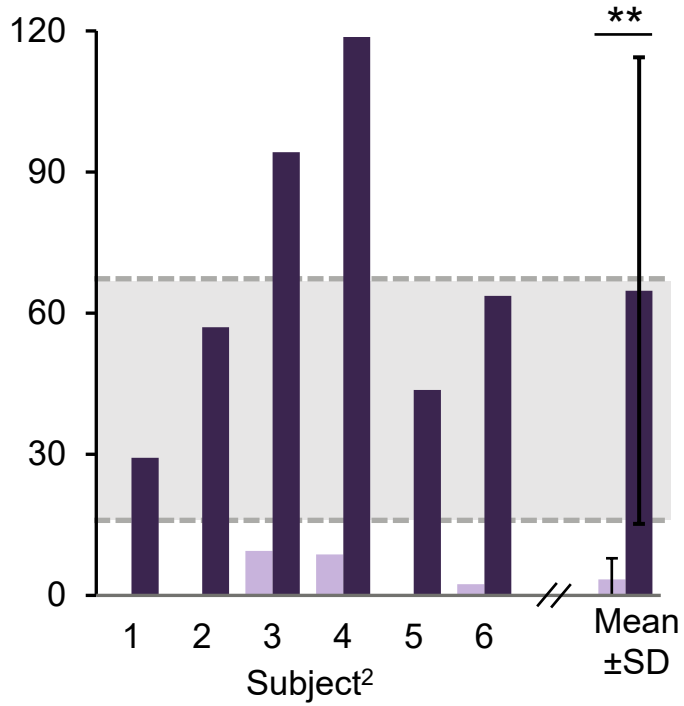
Albumin-corrected blood calcium
mg/dL



Urine calcium
mg/day

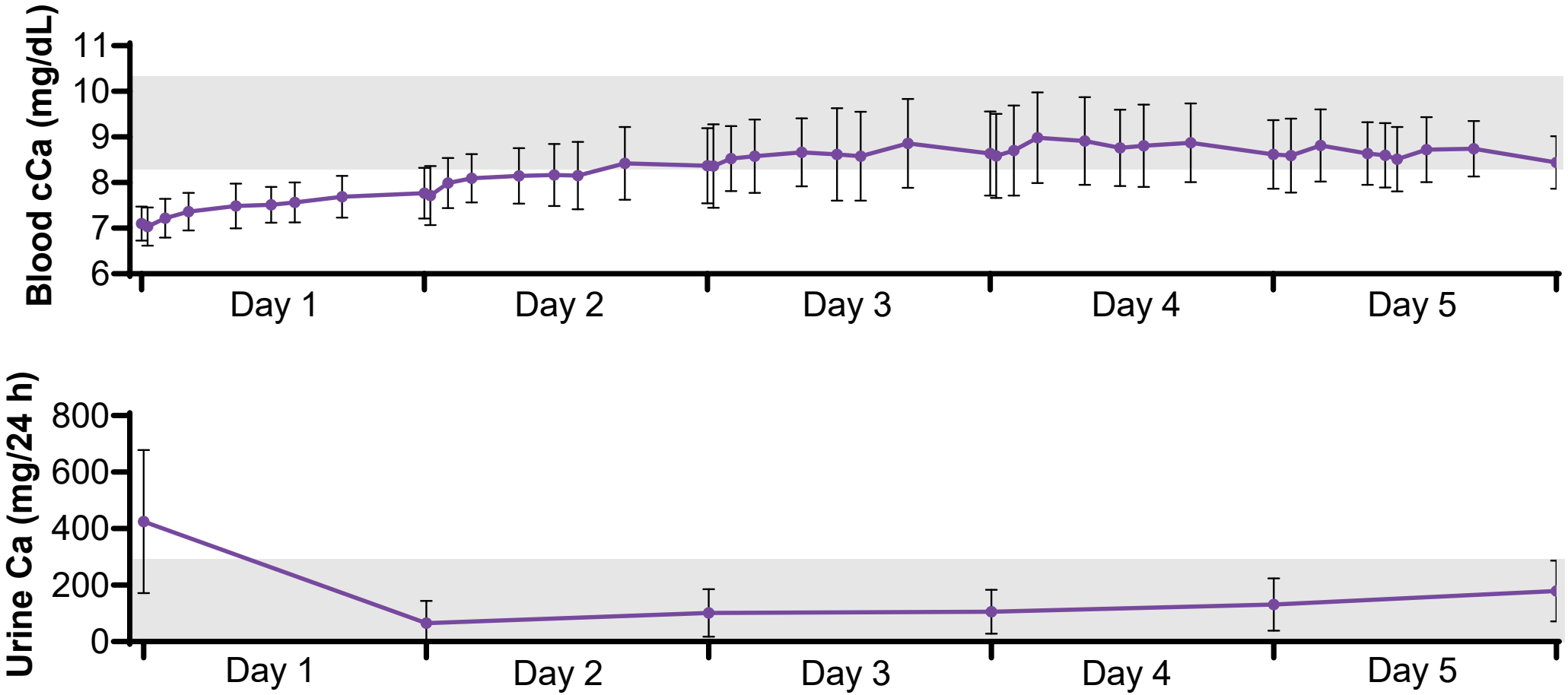


Intact parathyroid hormone
pg/mL



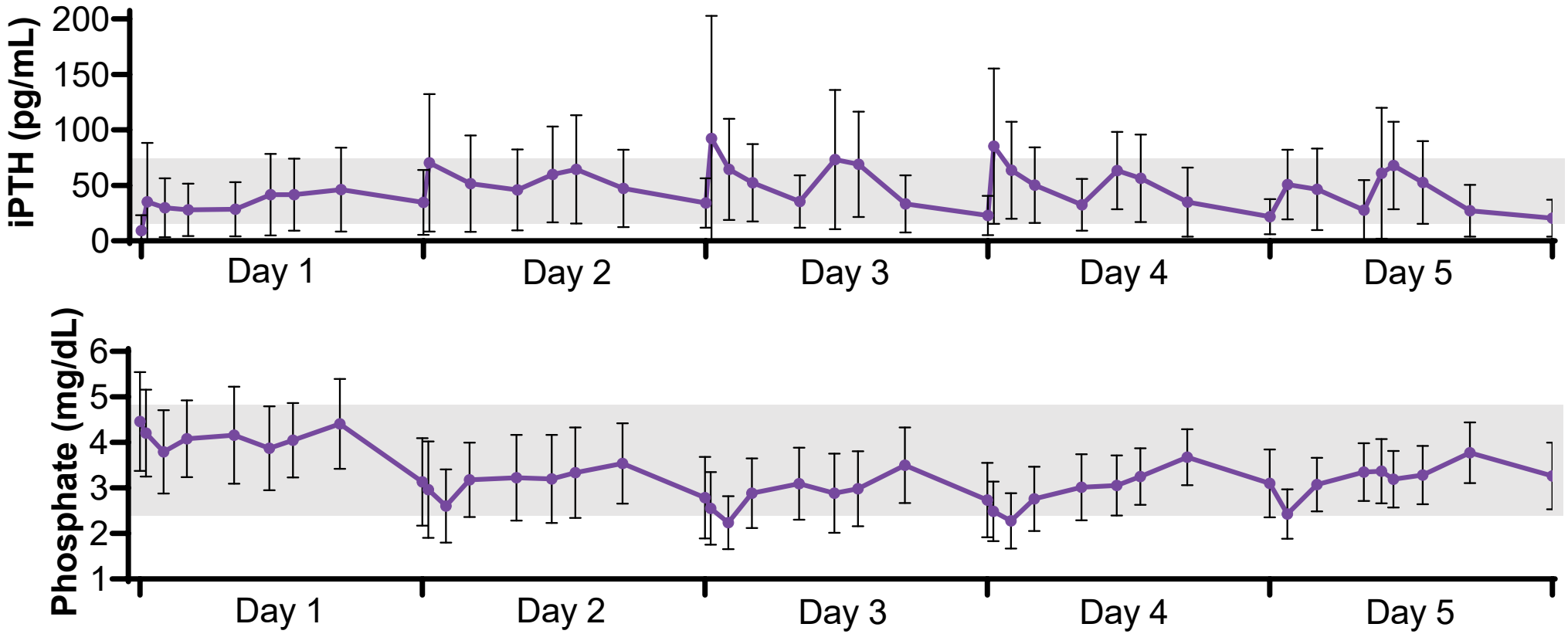
1. Encaleret dose adjusted to 180/120 in 1 subject on Day 5. 2. Values below limit of assay quantitation recorded as “0”.
3. Day 4 values used in two subjects given Day 5 values unavailable. Gray shading reflects normal range. ** p-value < 0.01.

Period 2 Results (n=13): BID Encaleret normalized mean blood and urine calcium



Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range.
Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women.

Period 2 Results (n=13): BID encaleret increased mean PTH and decreased mean blood phosphate



Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range.

Summary

- In 13 participants, encaleret normalized mean corrected blood calcium and 24-hour urine calcium excretion during Periods 1 and 2
- Mean PTH increased and phosphate decreased into the normal range during Periods 1 and 2
- Compared with Period 1, individualized BID dosing in Period 2 resulted in a decrease in the mean Day 5 dose
- Encaleret was well-tolerated when administered once or twice daily over 5 days, with no serious adverse events reported

Conclusions

- Consistent improvements in mineral homeostasis suggest encaleret may become an effective treatment for ADH1
- Outpatient evaluation of encaleret in this Phase 2b study remains ongoing
- Data support further investigation of encaleret in ADH1 patients

Acknowledgements

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