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Encaleret Proof-of-Concept in ADH1

March 2021

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(the "Company", "we" or "our") in 2021, including positive pivotal data in a multibillion-dollar market and positive proof-of-concept data in multiple blockbuster indications; the timing and success of the Company's four major clinical data readouts in 2021 for each of encaleret, acoramidis, infigratinib and BBP-631; early results from the Company's ongoing Phase 2b proof-of-concept, open-label study of encaleret for the treatment of Autosomal Dominant Hypocalcemia Type 1 ("ADH1") being indicative of final data from the Phase 2b study of encaleret; the potential prevalence of the target patient population with a rare genetic form of hypoparathyroidism caused by pathogenic variants in the calcium-sensing receptor (*CaSR)* gene; the inability of current standard of care therapies to treat ADH1; encaleret continuing to be well-tolerated with no serious adverse events and no adverse events of moderate or severe intensity reported in the Company's ongoing Phase 2b proof-of concept, open-label study; tolerability and consistent mineral responses following encaleret administration in all six ADH1 trial participants continuing to demonstrate proof-of-concept that encaleret may be an efficacious therapy option for ADH1; the Company's ability to complete enrollment of Cohort 2 in the ongoing Phase 2b study of encaleret; the timing and success of the Company's meetings with regulatory health authorities, including the U.S. Food and Drug Administration ("FDA"), in 2021 to discuss potential paths to registration prior to initiation of a Phase 3 registrational study of encaleret in patients with ADH1; the design, timing and success of a Phase 3 registrational study of encaleret in patients with ADH1; the ability of encaleret to be the first approved targeted oral dosing therapy option indicated specifically for the treatment of ADH1; encaleret's ability to treat ADH1 at its source by normalizing CaSR sensitivity; the exploration of encaleret's potential use in patients with other forms of hypoparathyroidism; the unknown future impact of the COVID-19 pandemic delay on the Company's ongoing clinical trials and/or the Company's operations or operating expenses; expected manufacturing capabilities; strategy; future financial position; projected costs; prospects; plans; objectives of management; and the Company's ability to complete certain milestones. 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These risks, uncertainties, and other factors include, among others: early data from our ongoing Phase 2b proof-of-concept, open-label study of encaleret for the treatment of ADH1 not being indicative of final data; our ability to complete enrollment of Cohort 2 in the ongoing Phase 2b study of encaleret; the potential size of the target patient population for ADH1 not being as large as anticipated; encaleret not being well-tolerated, with serious adverse events and adverse events of moderate or severe intensity being reported in the final Phase 2b study data; encaleret not continuing to demonstrate that it may be an efficacious therapy option for ADH1 based on the final Phase 2b data; encaleret not being the first approved therapy option indicated specifically for the treatment of ADH1, if the development program is not successful or if a competing therapy option is approved; the design and success of ongoing and planned clinical trials, future regulatory filings, approvals and/or sales; despite having ongoing and future interactions with the FDA or other regulatory agencies to discuss potential paths to registration prior to initiation of a Phase 3 registrational study of encaleret in patients with ADH1, the FDA or such other regulatory agencies may not agree with our regulatory approval strategies, components of our filings, such as clinical trial designs, conduct and methodologies, or the sufficiency of data submitted; the inability of encaleret to be used in patients with other forms of hypoparathyroidism; potential adverse impacts due to the global COVID-19 pandemic such as delays in regulatory review, manufacturing and supply chain interruptions, adverse effects on healthcare systems and disruption of the global economy; and those risks and uncertainties described under the heading "Risk Factors" in the Company's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission ("SEC") and in subsequent filings made by the Company with the SEC, which are available on the SEC's website at www.sec.gov. 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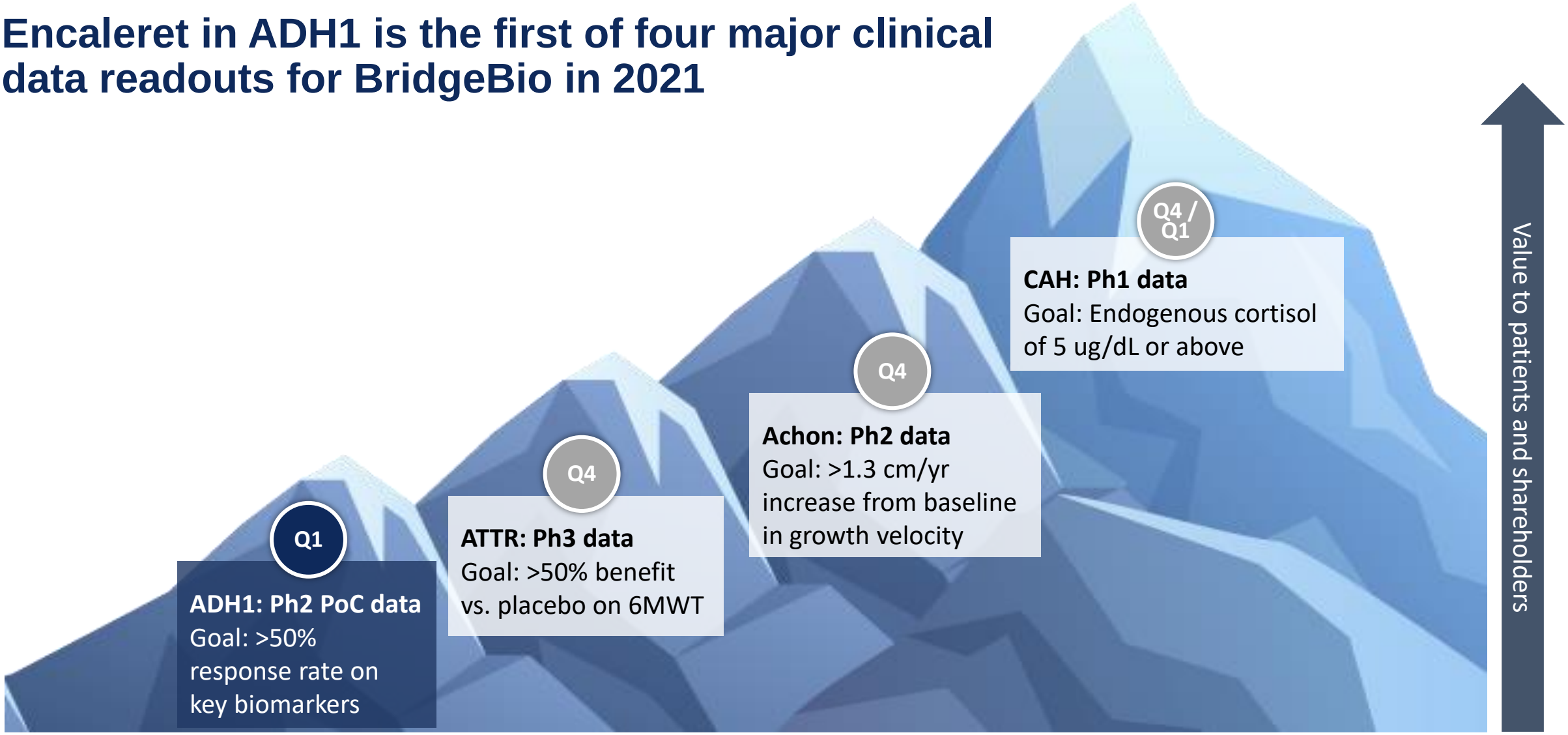
Encaleret in ADH1 is the first of four major clinical data readouts for BridgeBio in 2021



Growth potential this year:

- Positive pivotal data in a multibillion-dollar market
- Positive POC data in multiple blockbuster indications

Alexis and Jackson
ADH1 patients

Encaleret for autosomal dominant hypocalcemia type 1 (ADH1) overview

ADH1 overview

Prevalence

12K individuals harboring variants in US[1]

Genetic driver

Calcium-sensing receptor (CaSR) hyperactivation

Pathophysiology

Decreased blood calcium, elevated urine calcium, and lower parathyroid hormone secretion [2]

Features of a potential best-in-class medicine for ADH1

Direct targeting of CaSR

Normalization of all downstream effects of CaSR hyperactivity

Potential to address most common symptoms

arising from altered calcium and parathyroid hormone dysregulation

Oral dosing, the first targeted therapy for ADH1 in a convenient form for patients and families

1 Dershem et al., Amer Jour of Hum Genetics, 2020; 2 Lienhardt, et al., JCEM, 2001

Alexis and Jackson
ADH1 patients

ADH1 Overview

Phase 2 Clinical Study Update

Program Next Steps

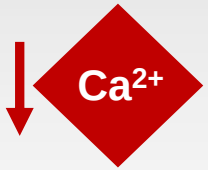
Encaleret is designed to treat ADH1 at its source by normalizing CaSR sensitivity

ADH1 disease mechanism

CaSR senses and regulates blood Ca levels

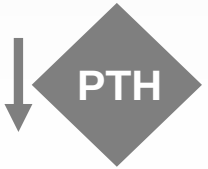
ADH1-causing variants hyperactivate CaSR

Hyperactive CaSR causes dysregulation of Ca homeostasis



Decreased blood calcium

Increased urinary calcium



Decreased parathyroid hormone (PTH) secretion

Acute symptoms and long-term complications

Presenting symptoms

Hypocalcemic seizures

Loss of consciousness

Paresthesia

Tetany

Muscle cramps

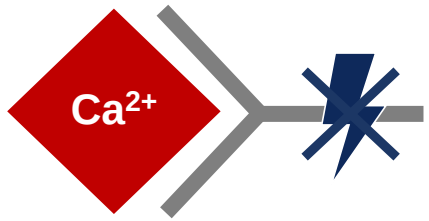
Long-term complications

Nephrolithiasis

Nephrocalcinosis

Chronic Kidney Disease

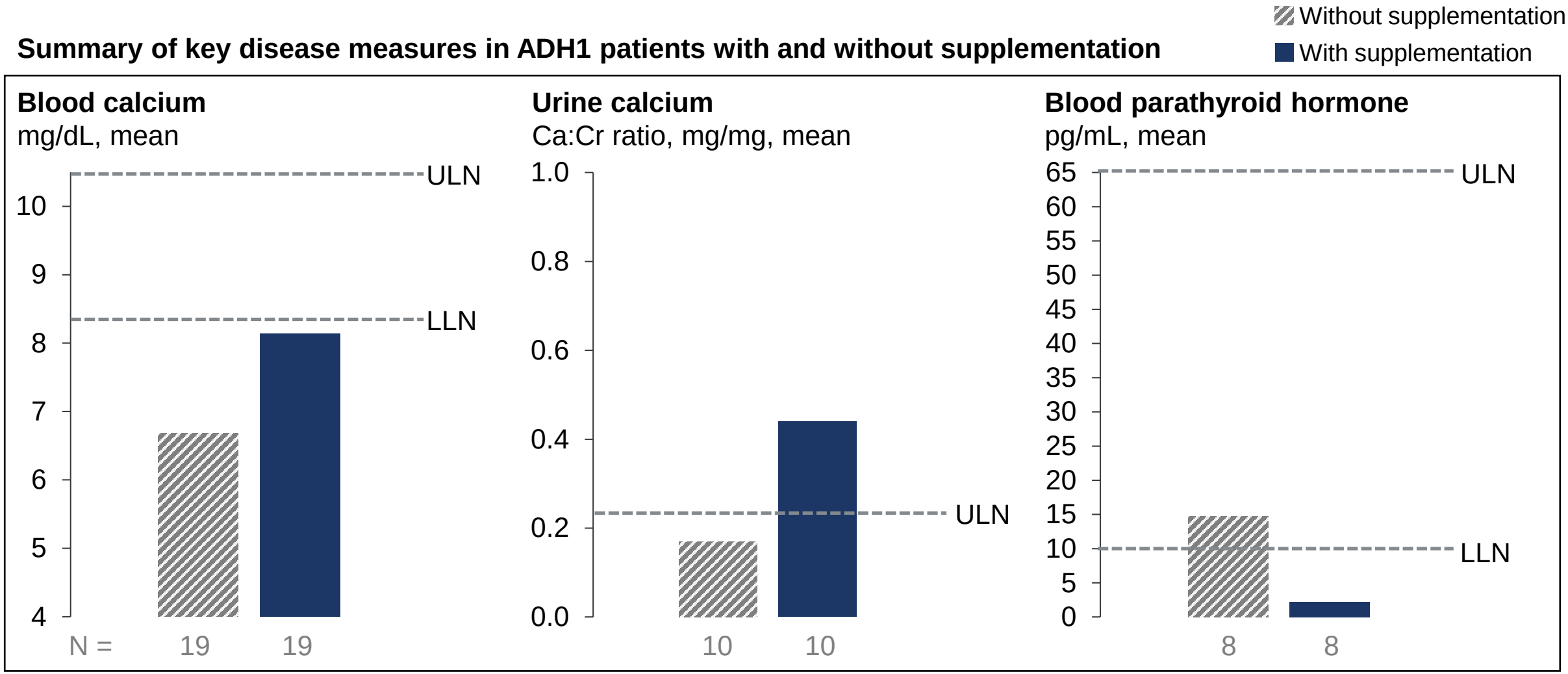
Therapeutic hypothesis



Normalizing CaSR sensitivity to Ca will normalize blood Ca, urine Ca, and PTH levels in ADH1, potentially resolving symptoms

Current therapy for ADH1 (oral calcium, activated Vitamin D) raises blood Ca but does not address disease mechanism; increases UCa, suppresses PTH

Summary of key disease measures in ADH1 patients with and without supplementation

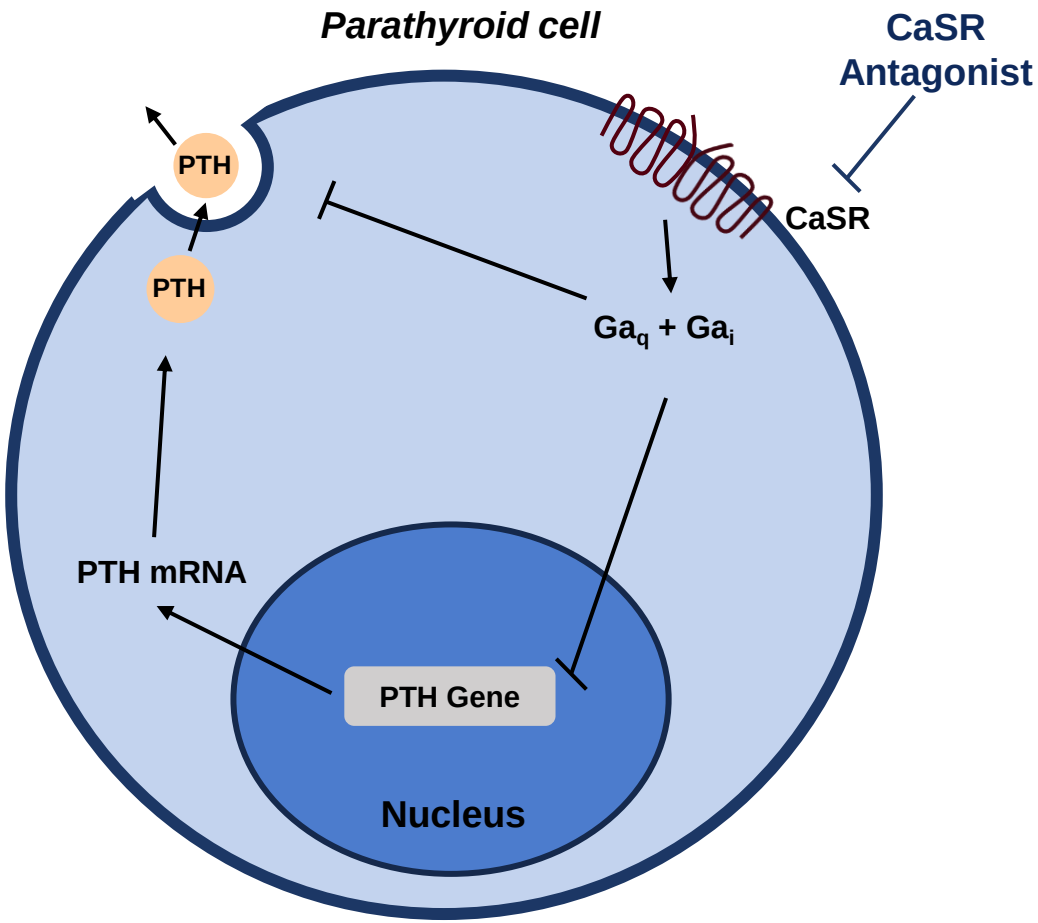


Objective of treatment with encaleret is to normalize all three disease measures simultaneously

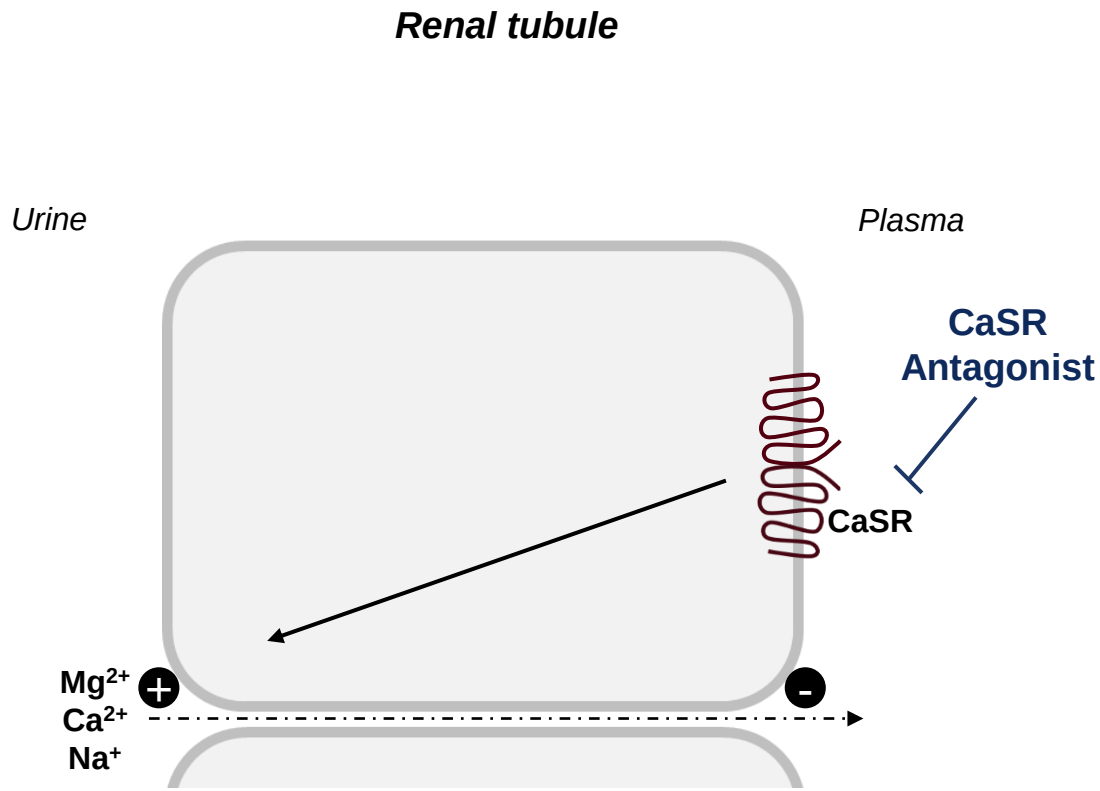
ULN = Upper-limit of normal; LLN = Lower-limit of normal; Ca:Cr ratio = calcium-creatinine ratio

Source: Pearce et al. Clin Endocrinol (Oxf).1996. PTH values reported as below detection limit or undetectable were recorded as “0”.

CaSR antagonists increase PTH secretion and renal calcium reabsorption



Antagonizing CaSR increases PTH synthesis and secretion

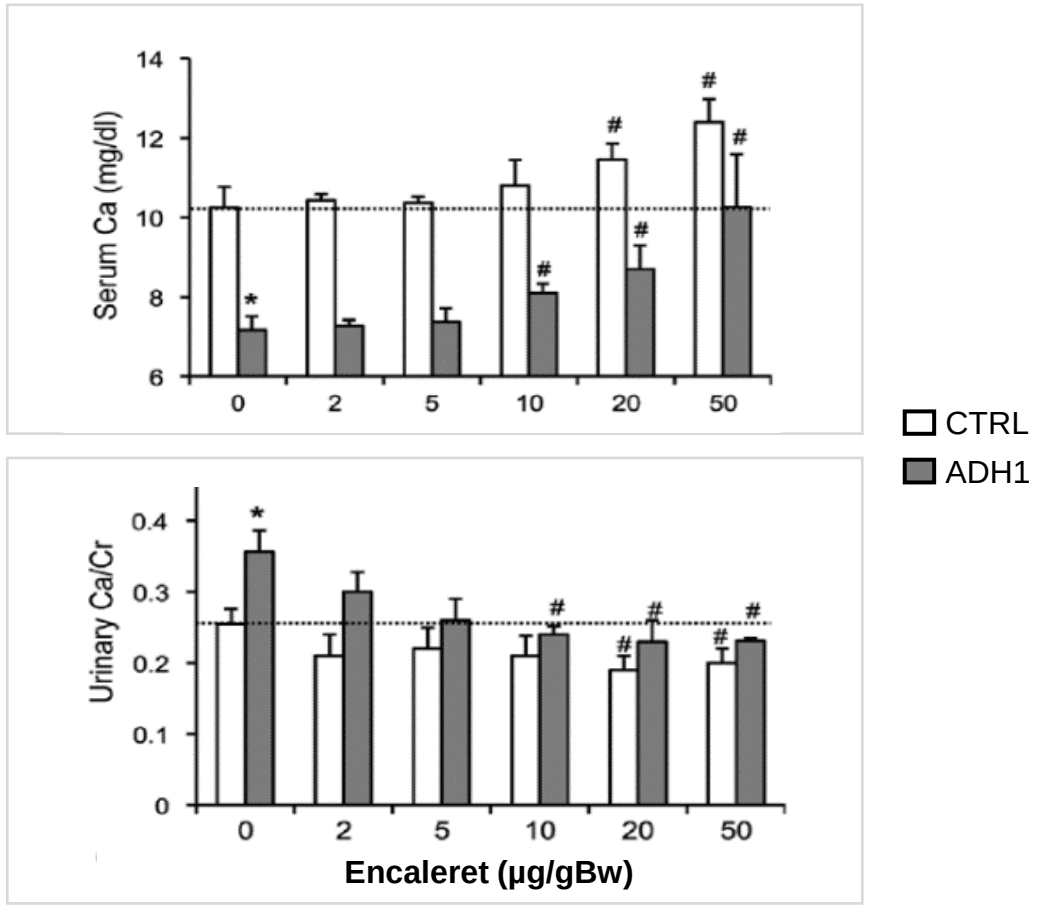


Antagonizing CaSR increases renal calcium reabsorption, decreasing excretion, independent of PTH

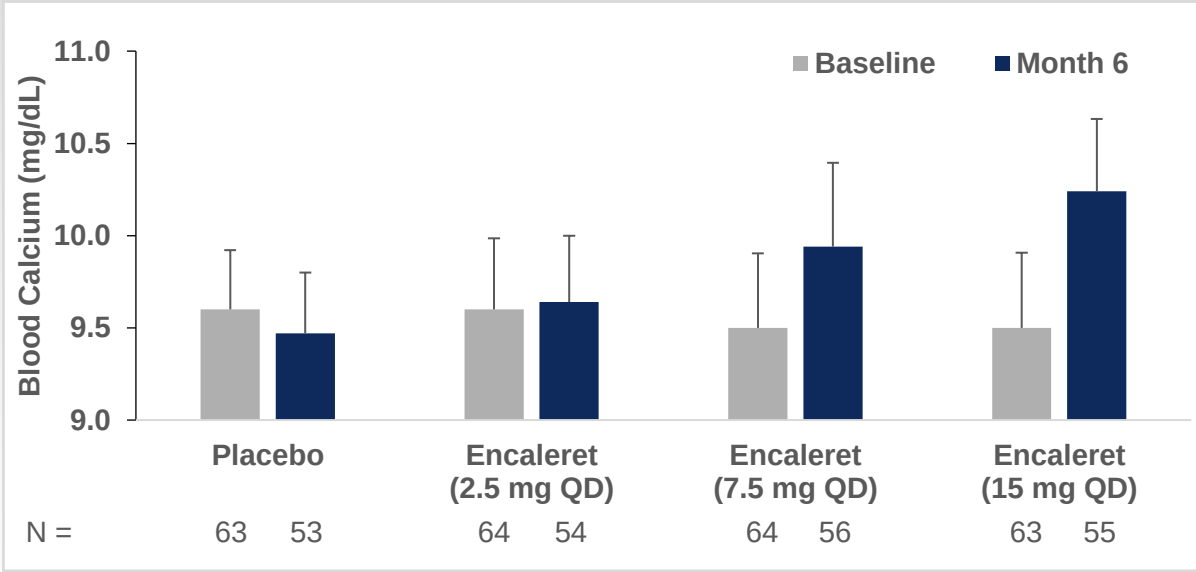
Figures adapted from: 1 Berne and Levy Physiology, 6th ed. Chapter 39; 2 Toka, H.R., et al. Physiology. 2015.

Encaleret proof of mechanism in a mouse model of ADH1 and in humans with wild-type CaSR

Encaleret normalized blood and urine calcium in the ADH1 (CaSRv knock-in) mouse[1]



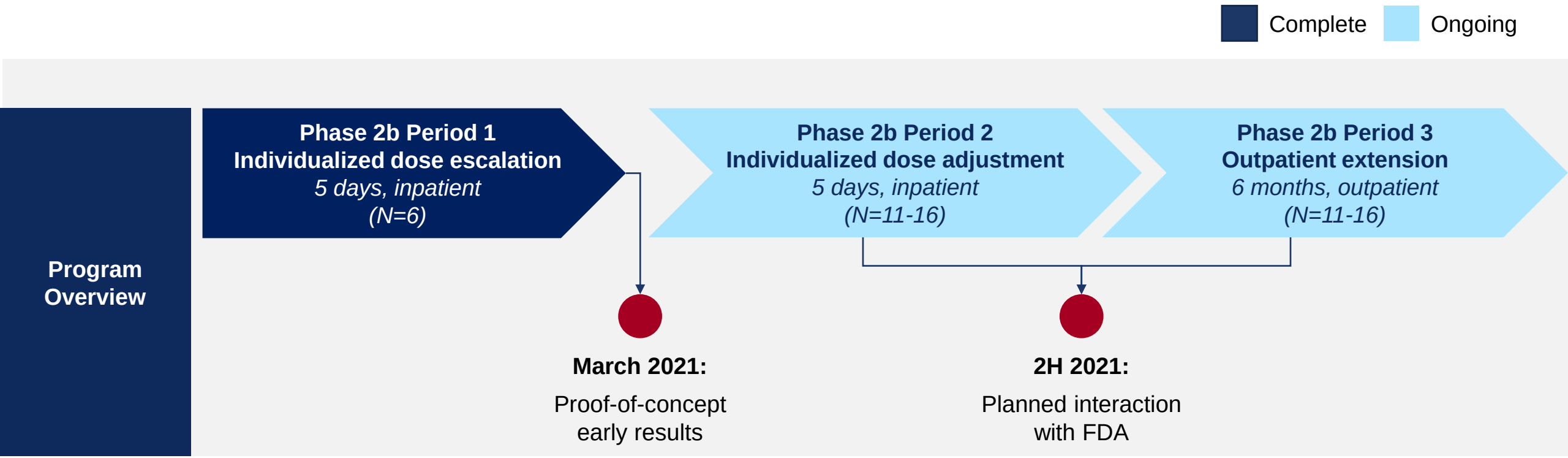
Encaleret was well-tolerated except for increased blood calcium in osteoporosis patients[2,3]



- **In prior osteoporosis development program (>1,200 participants), dose-dependent increases in mean serum calcium were observed**
- **Encaleret was well-tolerated; hypercalcemia events were more frequent among participants receiving higher doses**
- **Increasing serum calcium levels is target effect in ADH1**

1 Dong B., et al. J Bone & Min 2015; #p<0.05 compared to baseline data; *p<0.05 compared to control animals; 2 Halse J., et al. J Clin Endocrinol Metab 2014; 3 Data on File; 4 Cosman F., et al. Osteoporos Int 2015

Phase 2b study will continue as we plan the Phase 3 study



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)

Alexis and Jackson
ADH1 patients

ADH1 Overview

Phase 2 Clinical Study Update

Program Next Steps

Presenter's Disclosures

The NIDCR receives/received research funding from two BridgeBio affiliates:

- QED for research in Tumor-induced Osteomalacia
- Calcilytix for research in ADH1

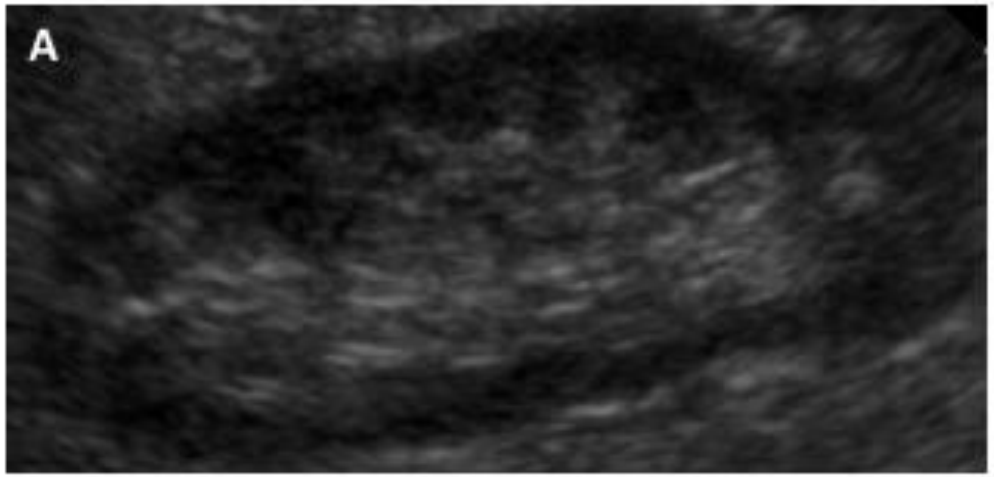
Case

- 40-year-old man
- Tetany as a newborn, seizures at age 4-5 years, muscle cramps, paresthesia – no evaluation or treatment
- Diagnosed with idiopathic hypoparathyroidism at age 24 – started on calcium/calcitriol plus intermittent hydrochlorothiazide
- Came to NIH in 2010 to participate in a PTH 1-34 trial – genetic testing identified a *CASR* variant (E604K)

	Pre-PTH 1-34	1 year of PTH 1-34 BID
Corrected Ca (mg/dL) (8.4-10.2)	7.5	8
Intact PTH (pg/mL) (15-65)	<3	4.5
Phosphate (mg/dL) (2.5-4.5)	4.5	5.1
Calcium excretion (mg/day) (<300)	285	**425**
eGFR (mL/min/1.73 m^2) (>60)	70	**80**

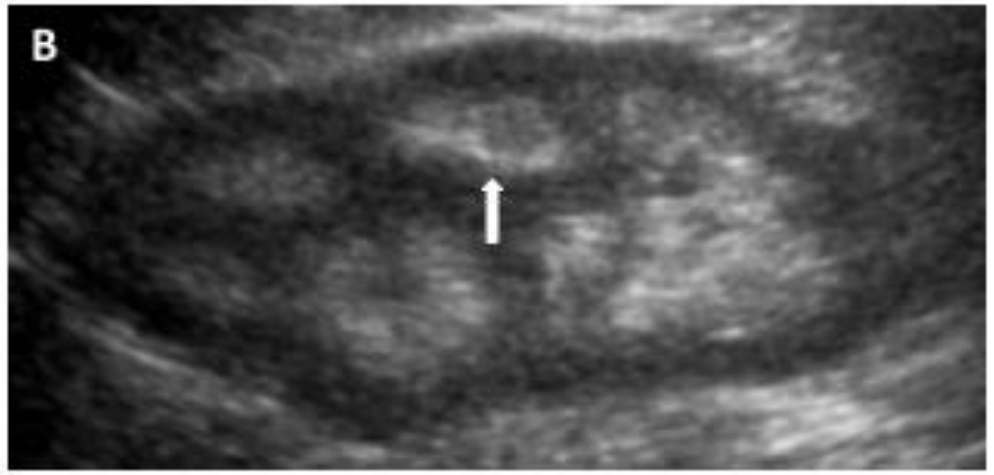
While on PTH 1-34 replacement, patient developed significant nephrocalcinosis

Baseline



Normal kidney ultrasound

One year of PTH 1-34 BID



Medullary nephrocalcinosis

Both conventional therapy and PTH 1-34 BID were inadequate in managing his hypocalcemia and hypercalciuria or preventing renal morbidity

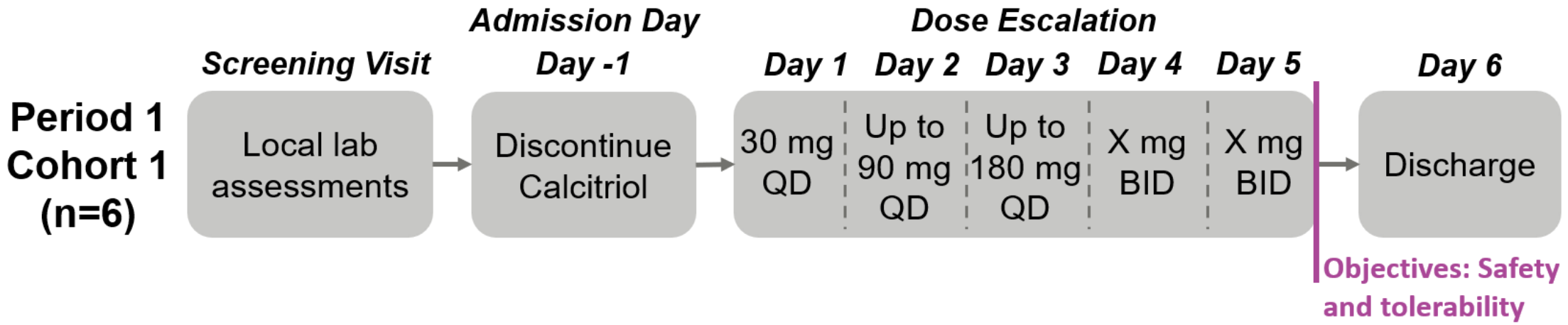
Gafni et al, JBMR, 2018.

Case

- Now aged 50 years
- Treated with PTH 1-34 for almost 5 years, resumed conventional therapy in 2015
- Returned to NIH in 2020 to participate in the encaleret trial

	Pre-PTH 1-34	1 year of PTH1-34 BID	Pre-encaleret (Oct 2020)
Corrected Ca (mg/dL) (8.4-10.2)	7.5	8	7.9
Intact PTH (pg/mL) (15-65)	<3	4.5	<1.2
Phosphate (mg/dL) (2.5-4.5)	4.5	5.1	5.2
Calcium excretion (mg/day) (<300)	285	**425**	**377**
eGFR (mL/min/1.73 m^2) (>60)	70	80	**57**

Period 1 Schema



Baseline characteristics

Characteristic	Encaleret N = 6	*Normal Range*
Age, mean (range)	40 (22-60)	
Female, n (%)	3 (50%)	
Nephrocalcinosis, n (%)	4 (67%)	
ECG QT_cB (msec)	452 ± 9	*< 440*
Corrected Calcium (mg/dL)*	7.6 ± 0.6	*8.4 –10.2*
Intact PTH (pg/mL)*	3.4 ± 4.5	*15 – 65*
Phosphate (mg/dL)*	4.5 ± 0.7	*2.5 – 4.5*
Magnesium (mg/dL)*	1.6 ± 0.4	*1.6 – 2.6*
24h Urine Calcium (mg/24h)	436 ± 255	*< 250-300*
Supplements		
Elemental Calcium (mg/day) [mean (range)]	2317 (800-4000)	
Calcitriol (µg/day) [mean (range)]	0.9 (0.5-2.0)	
***CASR* Variants**	C131Y (2), P221L (2), E604K (1), A840V (1)	

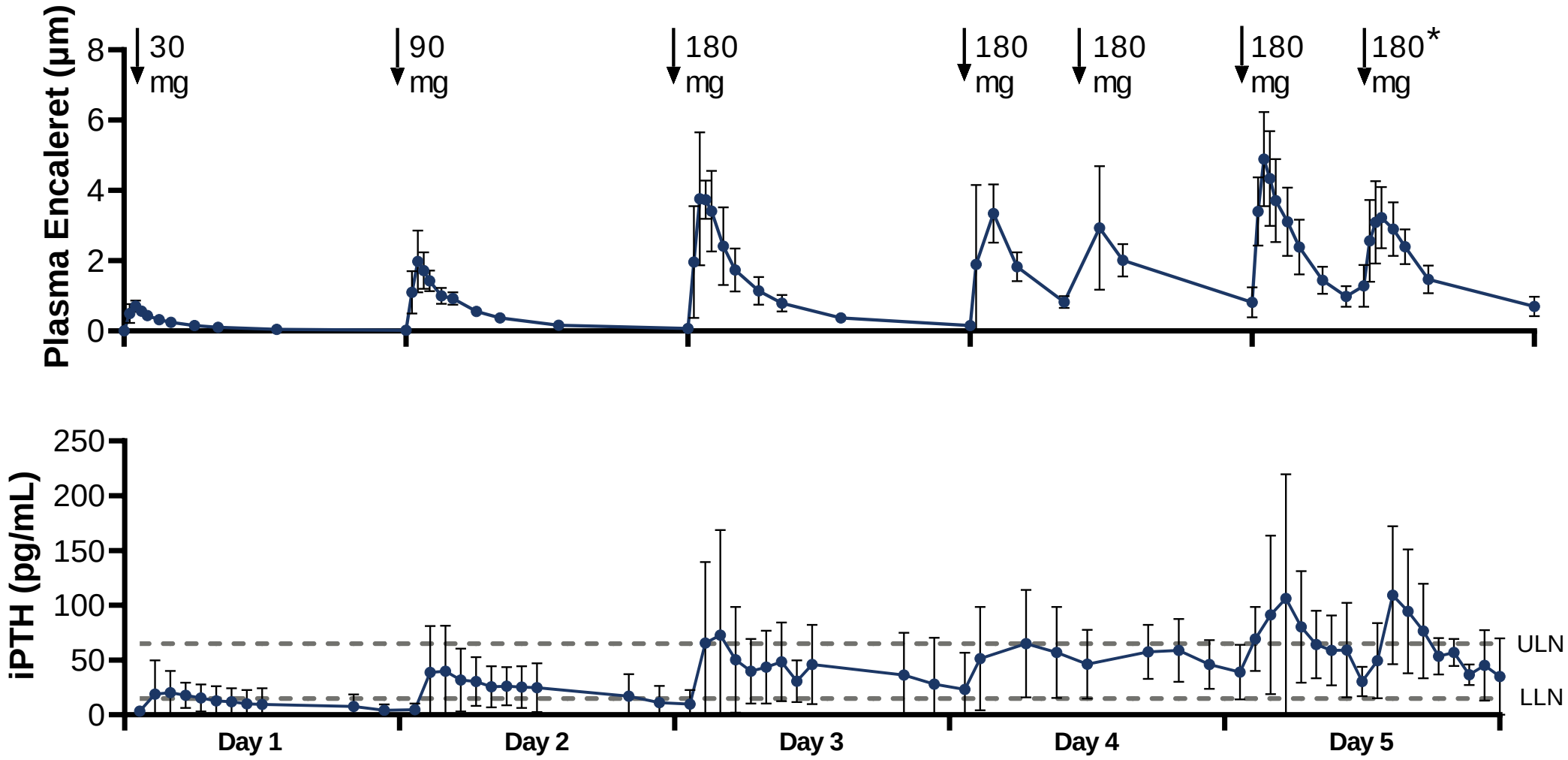
ECG QT_cB = electrocardiogram Bazett-corrected Q-T interval
*Measurements taken pre-dose Day 1 (mean ± SD).

Encaleret was generally well-tolerated with no serious adverse events reported after 5 days

	N = 6
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**
Number of subjects experiencing any Adverse Event	**5 (83%)**
Mild	5 (83%)
Moderate	0 (0%)
Severe	0 (0%)
Number of Adverse Events Reported	**9**
Mild	9 (100%)
Moderate	0 (0%)
Severe	0 (0%)

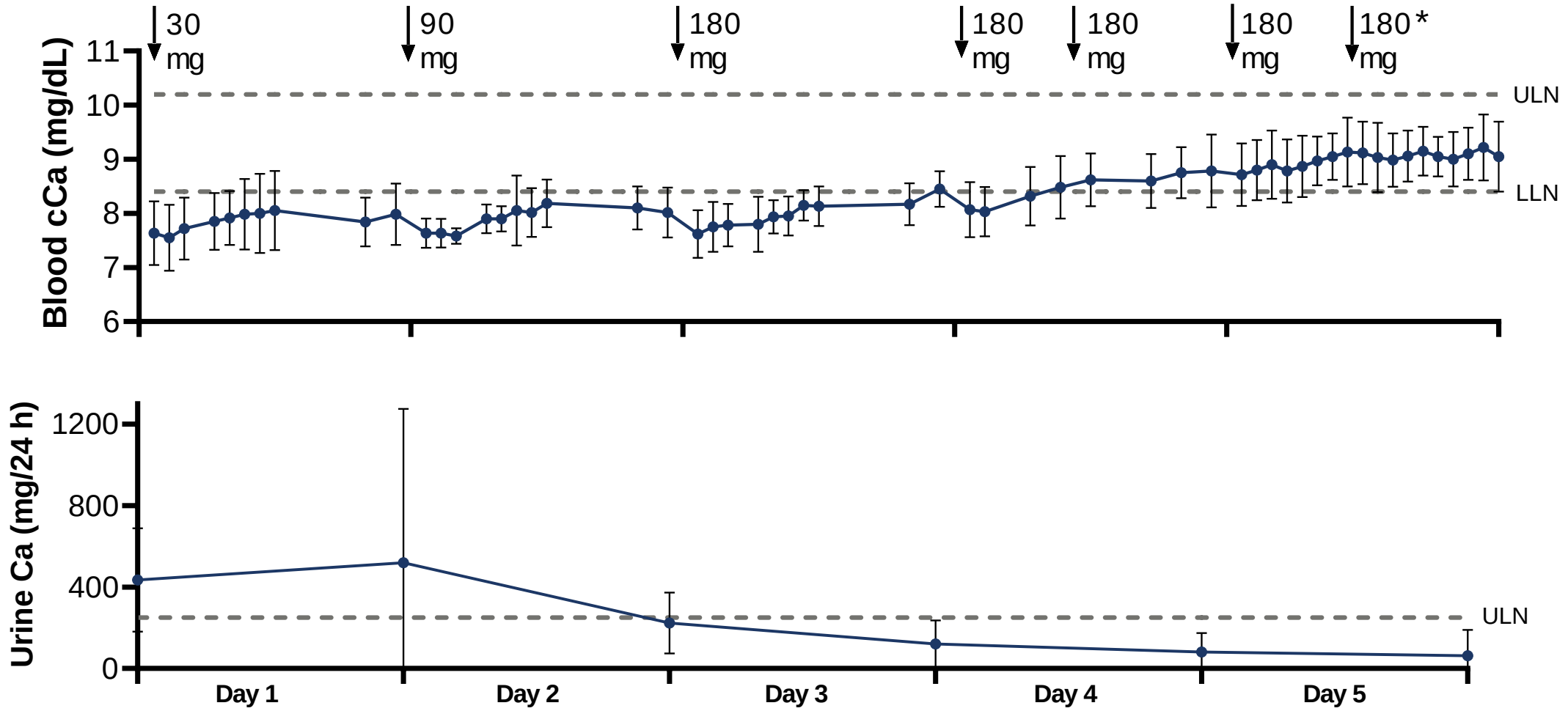
Only treatment-related AE was mild, transient, asymptomatic hypophosphatemia (<2 mg/dL) in 2 subjects

Dose dependent-increases in PTH mirrored encaleret levels



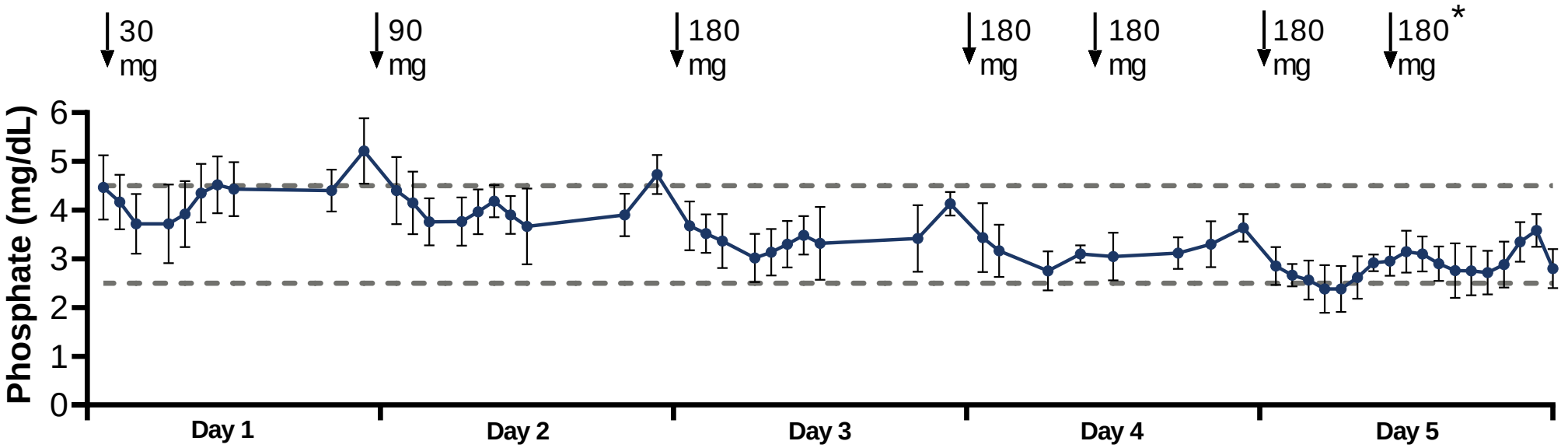
Data shown as mean ± SD. *One subject reduced second dose on Day 5 to 120 mg. Dashed line reflects normal range of PTH 15-65 pg/mL.

Encaleret normalized blood and urine calcium



Data shown as mean ± SD. Values below limit of assay quantitation were marked as “0”. *One subject reduced second dose on Day 5 to 120 mg.
Dashed line reflects normal ranges: calcium, 8.4-10.2 mg/dL; 24-hr urine calcium, < 250-300 mg/day.

Encaleret reduced blood phosphate

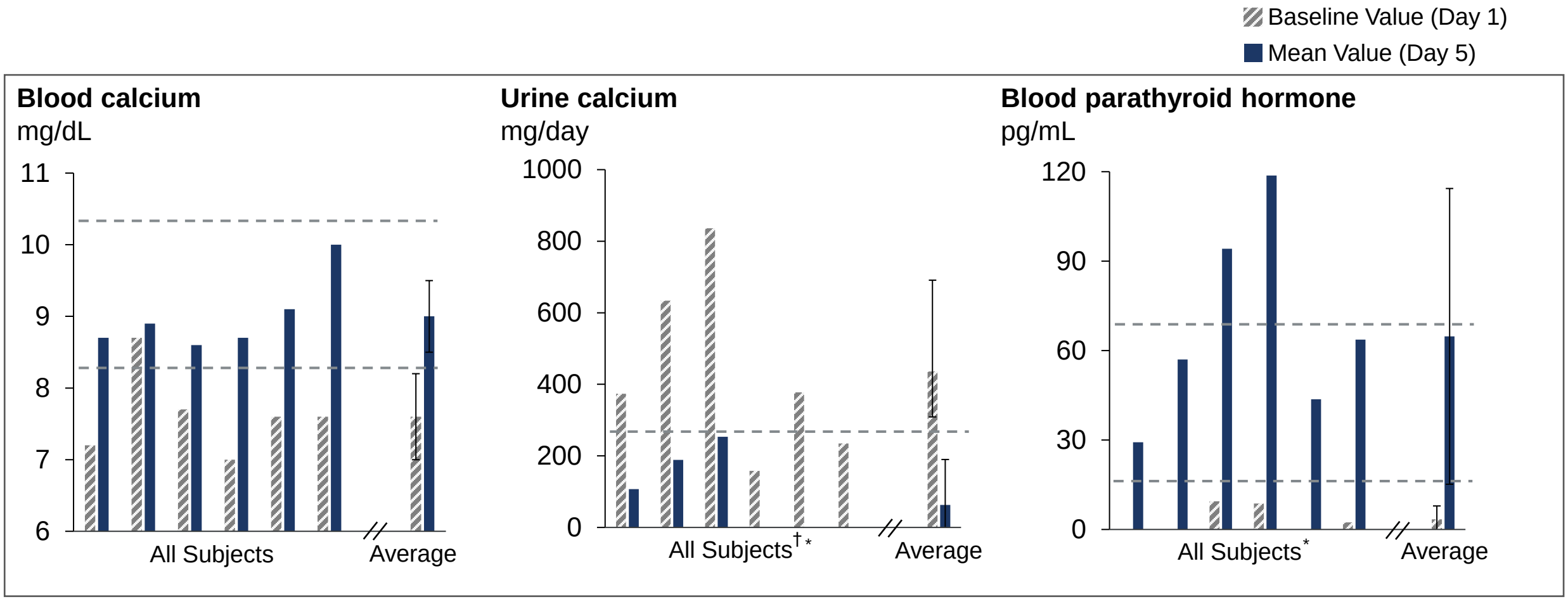


Additional findings:

- Blood magnesium normalized
- Baseline prolonged QT_cB normalized on Day 5

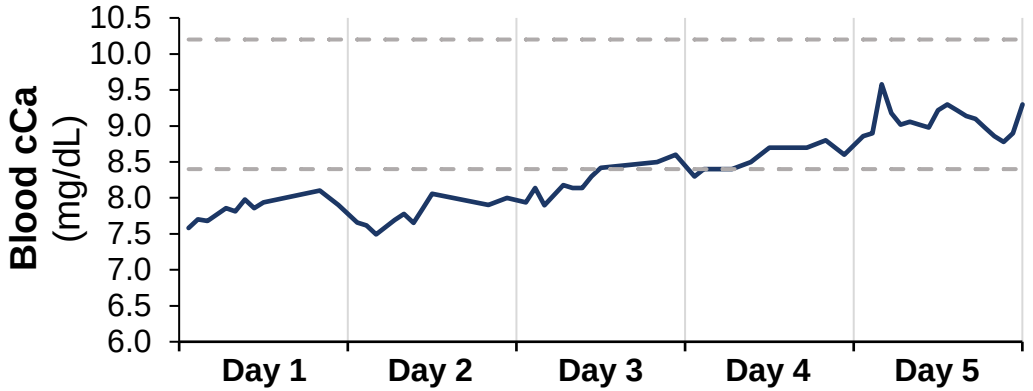
Data shown as mean ± SD. *One subject reduced second dose on Day 5 to 120 mg. Dashed line reflects normal range of blood phosphate 2.5-4.5 mg/dL.

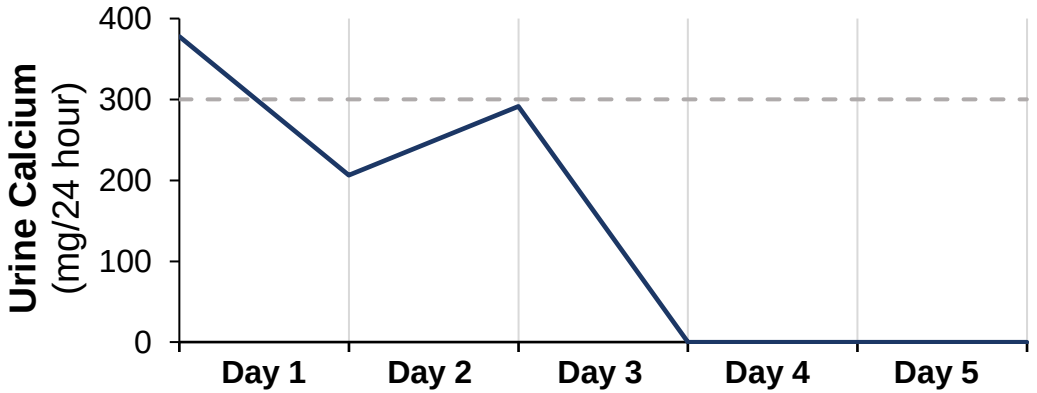
Individual and mean responses on Day 1 and 5 of Period 1

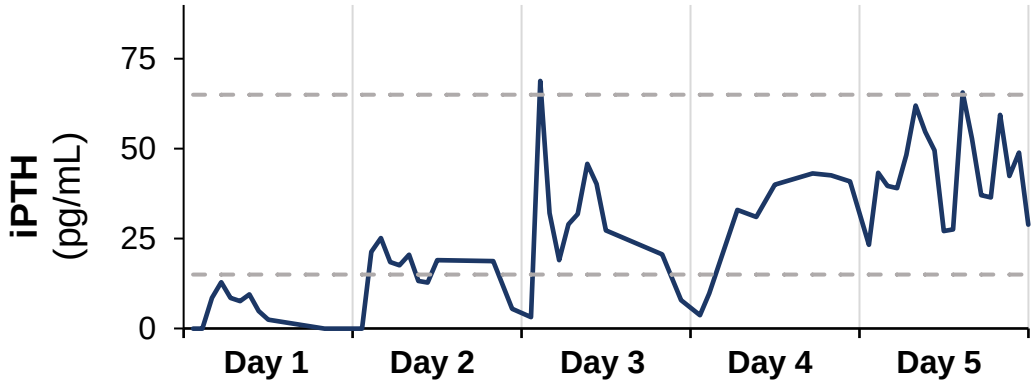


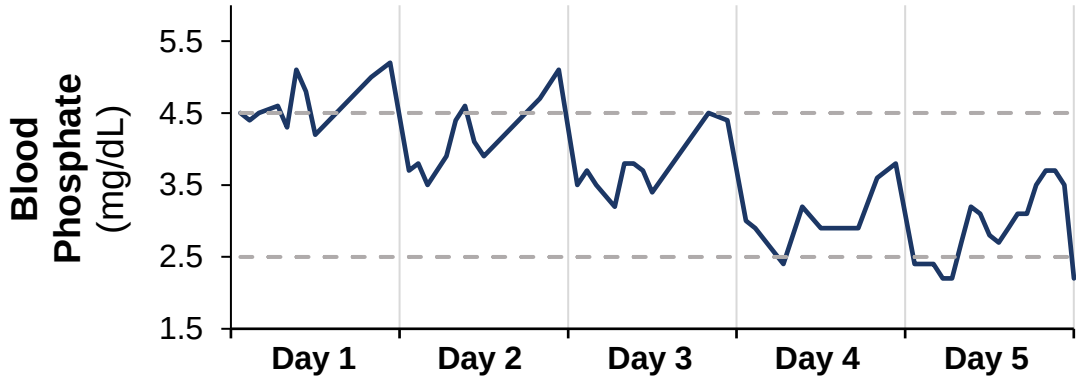
*Values below limit of assay quantitation recorded as “0”. † Day 4 values used in two subjects given Day 5 values unavailable.
Dashed lines reflect normal ranges.

Back to our case's individual response









PTH, blood and urine calcium, and blood phosphate normalized over the course of Period 1

*Values below limit of assay quantitation recorded as "0". Dashed lines reflect normal ranges.

Conclusions

- Encaleret was well-tolerated when administered in escalating oral doses once or twice daily over 5 days, with no serious adverse events reported and no adverse events of moderate or severe intensity
- Blood calcium, PTH, and phosphate were normalized and maintained within the normal range on average by day 5
- Urinary calcium excretion was reduced to below the upper limit of normal or undetectable in all participants while on encaleret and eucalcemic
- Consistent changes from baseline in blood and urine mineral measurements provide proof-of-concept data that encaleret may be an effective treatment for ADH1
- Data support further development of encaleret in ADH1

Acknowledgements

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NIH National Institute of Dental and Craniofacial Research

Alexis and Jackson
ADH1 patients

ADH1 Overview

Phase 2 Clinical Study Update

Program Next Steps

Next steps for encaleret include generating further evidence in ongoing Phase 2b study

2020

- ✓ Initiate Phase 2b study in ADH1
- ✓ Receive ODD from FDA for ADH

2021

- ✓ Report Phase 2b proof-of-concept results
- ❑ Complete enrollment of Cohort 2 in Phase 2b study
- ❑ Interaction with FDA

Planned activities

- Phase 3 registrational study in ADH1
- Pediatric development program in ADH1
- Evaluation of encaleret in non-genetic hypoparathyroidism

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Questions and Answers