Eneboparatide Development Update

ENDO – June 16th, 2023

Mission Statement

*Amolyt Pharma, a global, clinical-stage company, is building on its team's established expertise to **transform the lives** of patients suffering from **rare endocrine** and **related diseases**.*

Generating Near-Term Milestones from our Product Portfolio

Program (Indication)	Pre-clinical	IND-enabling	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Commercial Rights
Eneboparatide Hypoparathyroidism						• Phase 3 clinical trial topline data by end **2024**	AMOLYT PHARMA
AZP-3813 Acromegaly						• Phase 1 clinical trial data in Q**1 2024**	AMOLYT PHARMA
AZP-40XX PHP[1] / HHM[2]						• Drug candidate selection	Exclusive option to license

Additional pipeline expansion opportunities

[1] PHP: Primary Hyperparathyroidism
[2] HHM: Humoral Hypercalcemia of Malignancy

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Agenda

Eneboparatide, a Novel PTHR1 Agonist Dr Mark Sumeray, CMO Amolyt Pharma	8:30-8:50am
Eneboparatide Phase 2 Trial Results Dr Aliya Khan, Professor of Clinical Medicine, Divisions of Endocrinology and Metabolism and Geriatrics, McMaster University	8:50-9:10am
Eneboparatide Phase 3 Trial Design Dr Mark Sumeray, CMO Amolyt Pharma	9:10-9:25am
Hypoparathyroid Patient Voice Patty Keating, Chairwoman HypoPARA Patient Association	9:25-9:40am
General Q&A	9:40-10:00am

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ENEBOPARATIDE, A PTH1 RECEPTOR AGONIST FOR HYPOPARATHYROIDISM

Mark Sumeray, Chief Medical Officer - Amolyt Pharma

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Hypoparathyroidism is Characterized by a Deficiency in PTH

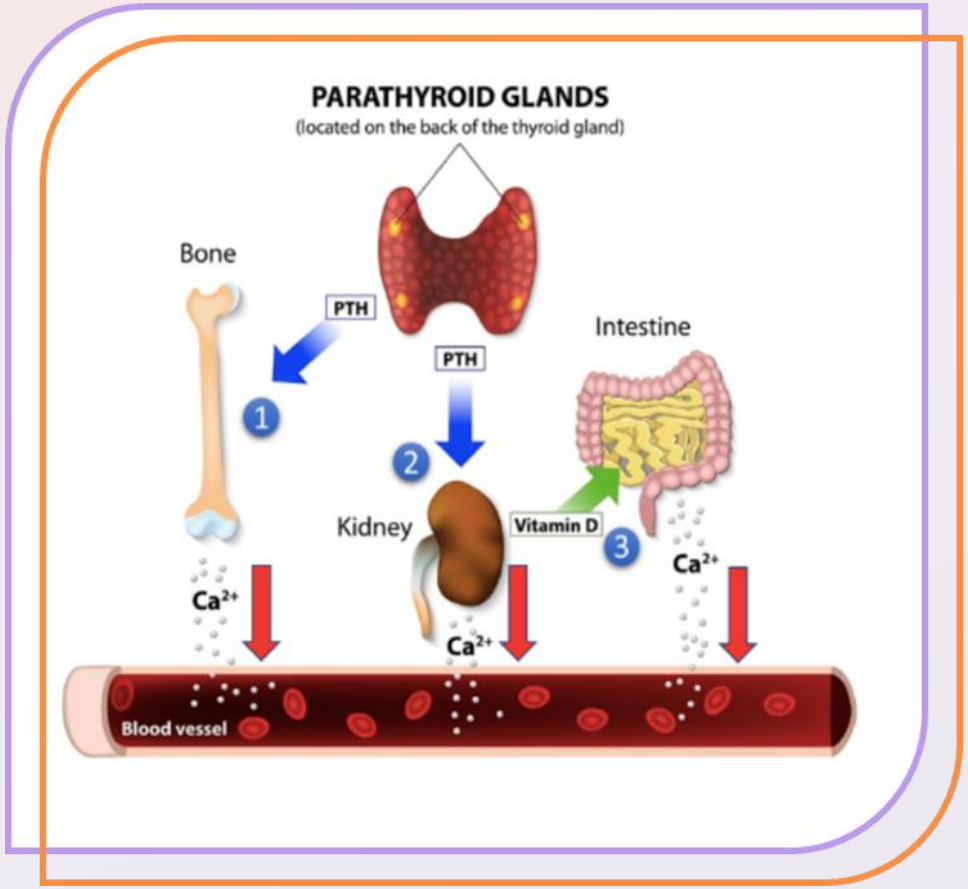
Hypoparathyroidism (HP) is a rare endocrine disorder characterized by a ***deficiency in parathyroid hormone (PTH)*** that results in ***dysregulation of serum calcium (sCa) and phosphorus***[1]

Most commonly occurs due to ***damage or removal*** of the ***parathyroid glands*** during thyroid surgery

Hypoparathyroidism is the **sole** remaining classic endocrine deficiency disease for which the **replacement hormone** is not the standard of care yet

For decades, ***conventional therapy (SoC)*** has aimed at ***short-term symptom management*** with large doses of oral calcium (Ca) and active vitamin D (VitD) supplementation

PTH Plays Key Role in Calcium Metabolism Across a Number of Organs



[1]Gafni R, et al. *New England Journal of Medicine*. 2019.

Despite Conventional Treatments, Patients with HP Experience Life Altering Symptoms and Often Develop Complications

Symptoms (neuromuscular, brain fog)
- ***72%***[3] of patients report an average of **16** different symptoms
  - Severe: ***31%***[3]
  - Moderate or severe ***79%***[3]

Therapeutic goal #1 - Normalization of Serum Calcium Levels and Symptom Relief
- Sustained and stable sCa levels within normal range over full 24 hours to:
  - Eliminate Ca/VitD supplementation
  - Decrease frequency and severity of symptoms

Kidney Disease
- > **50%**[5] have hypercalciuria
- ***26%***[1] have CKD
- ***4.8-fold***[4] increased risk of kidney stones

Therapeutic goal #2 - Preserve Kidney Function
- Decrease in urinary Ca (uCa) excretion, in particular in patients with elevated uCa

Bone
- ***17%***[1] have osteopenia or osteoporosis
- ***53%***[2] are peri- or post-menopausal women

Therapeutic goal #3 - Ensure Bone Safety
- Neutral impact on the bone; ideally restore normal and physiological bone turnover without bone loss

The current SoC, as well as HP treatments in development, ***do NOT achieve all of these therapeutic goals***

[1]Proprietary quantitative Market Research, 2021
[2]Proprietary retrospective Natural History Study, 2020
[3]Hadker and al., Endocrine Practice, Volume 20 No. 7 July 2014
[4]Underbjerg L. et al. *J Bone Miner Res.* 2013 Nov; 28(11): 2277-2285
[5] Based on Clinical baseline patient data (Amolyt, Ascendis)

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Parathyroid hormone – replacement should mimic physiological effects

Hypoparathyroidism is the “sole remaining classic endocrine deficiency disease for which the replacement hormone is not available”

Normal PTH levels reflect background “tonic” secretion with superimposed pulses for fine control of serum calcium levels

Neither ‘infusion-like’ continuous levels of PTH nor short exposure administration mimic normal physiology

- Multiple pre-clinical models demonstrate excessive bone loss with continuous, non-pulsatile exposure to PTH
- Continuous, non-pulsatile elevation of PTHrP demineralizes bone in certain malignancies
- Short exposure with intermittent administration of PTH increases bone volume however clinical experience with rhPTH(1-84) shows
  - Lack of 24-hour control and elevated urinary calcium excretion in many subjects
  - Adverse events, including hyper/hypocalcemia and vasoactive events

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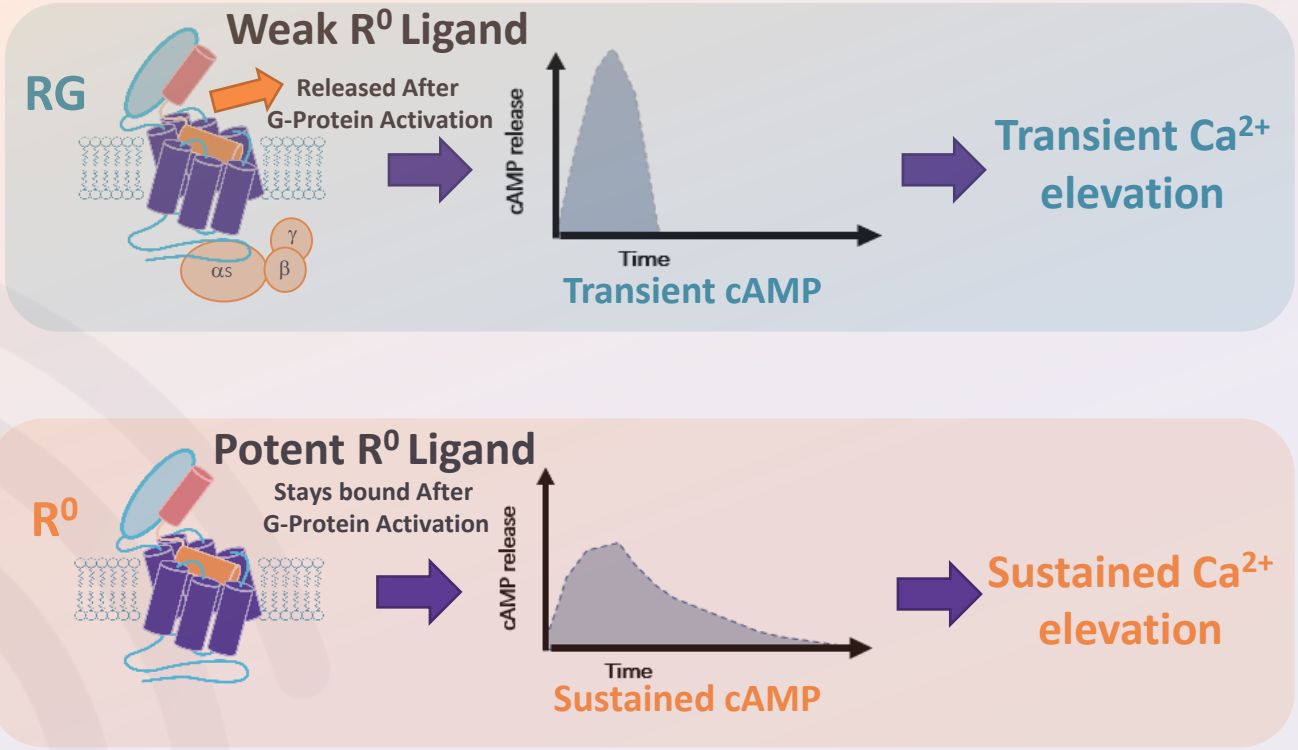
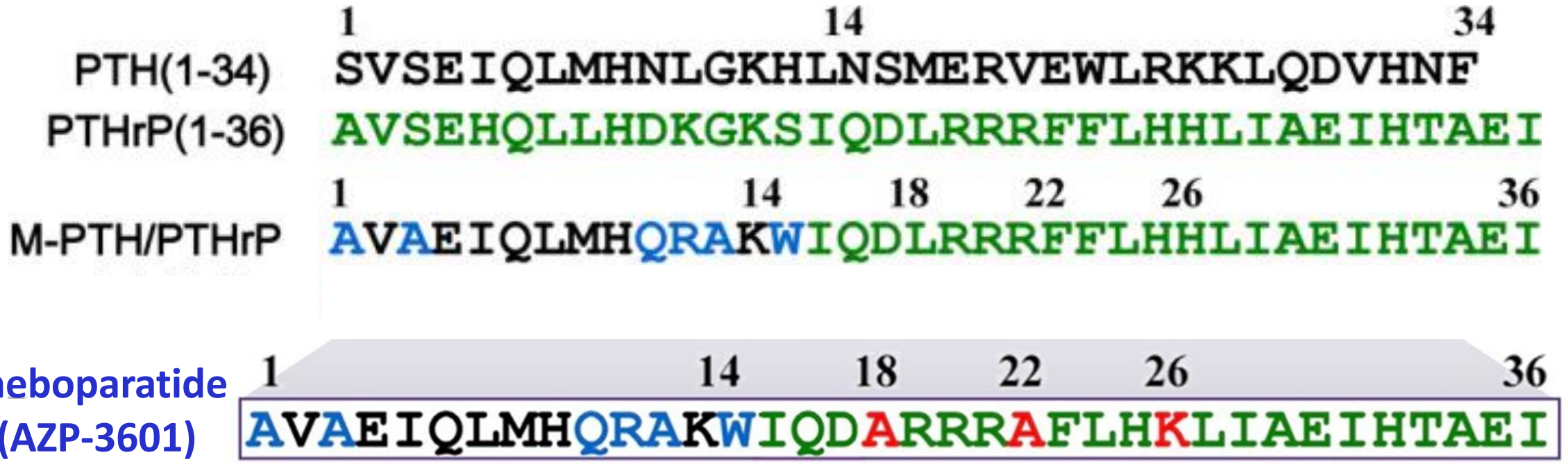
Eneboparatide Designed to Achieve Continuous Calcium Control, Restore Normal Renal Calcium Handling and Activate Normal Bone Turnover

- **Eneboparatide was specifically designed to bind with high affinity to the R^0 conformation**



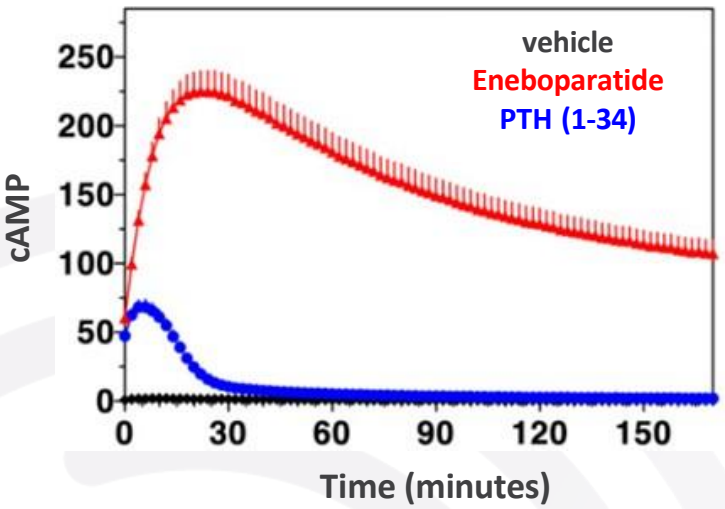
Eneboparatide is a Unique Hybrid Analog of PTH and PTHrP Engineered for High Affinity for the R^0 Conformation of the PTH1 Receptor



Adapted from Noda et al. JBMR Plus 4:e10367 2020

High Affinity for R^0 Conformation Translates to Enhanced and Prolonged Signaling Resulting in a Sustained Biological Response

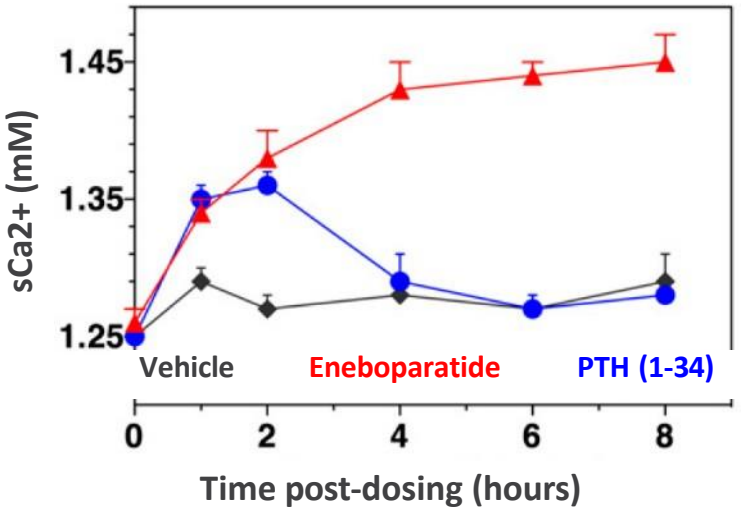
cAMP signaling
after ligand washout



Sustained cAMP signal with Eneboparatide

Compared with PTH(1-34) in HEK293 (kidney) cell line expressing the hPTH1 receptor

Mouse serum Ca^{2+}



Sustained sCa^{2+} with Eneboparatide

Blood ionized calcium responses in mice

Eneboparatide and PTH(1-34) have comparable in vivo half-lives

Shimizu M et al., *JBMR.* 2016
Gardella TJ et al., *Pharmacol. Rev.* 2015

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Eneboparatide Phase 1 Trial Design

Completed

Phase 1 - Part A
Single Ascending Dose Cohort
Healthy volunteers
7 cohorts
n= 52

Completed

Phase 1 - Part B
Multiple Ascending Dose Cohort
Healthy volunteers
5 cohorts
n= 52

Study Objectives

- Safety & tolerability following single and 2-week multiple ascending doses
- Efficacy as measured by sCa, uCa, bone biomarkers

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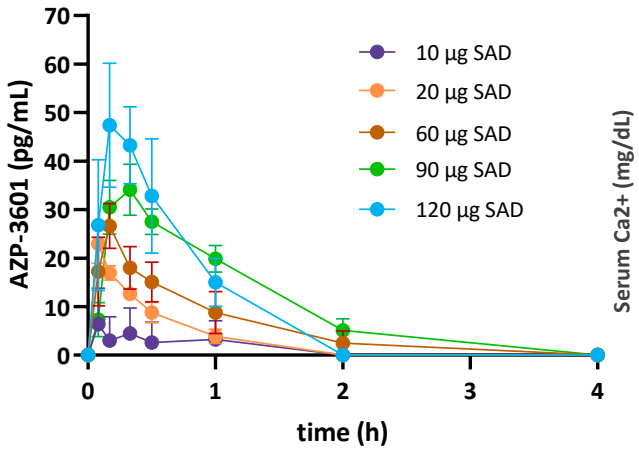
Clinical Data in Healthy Volunteers Confirm Eneboparatide MOA

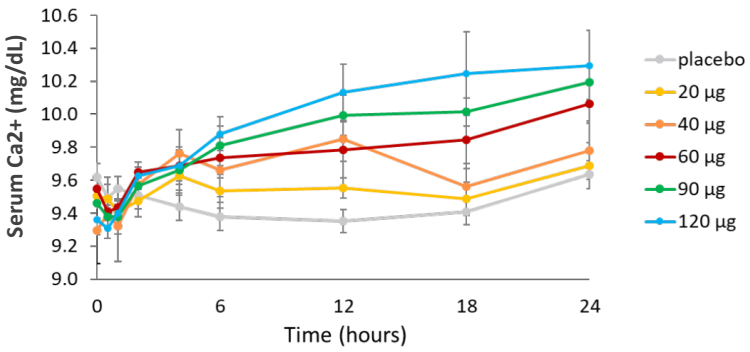
- Safety & tolerability following single and 2-week multiple ascending doses
- Efficacy as measured by sCa, uCa, bone biomarkers

Part A
Single Ascending Dose Cohort
Healthy volunteers
7 cohorts / n= 52

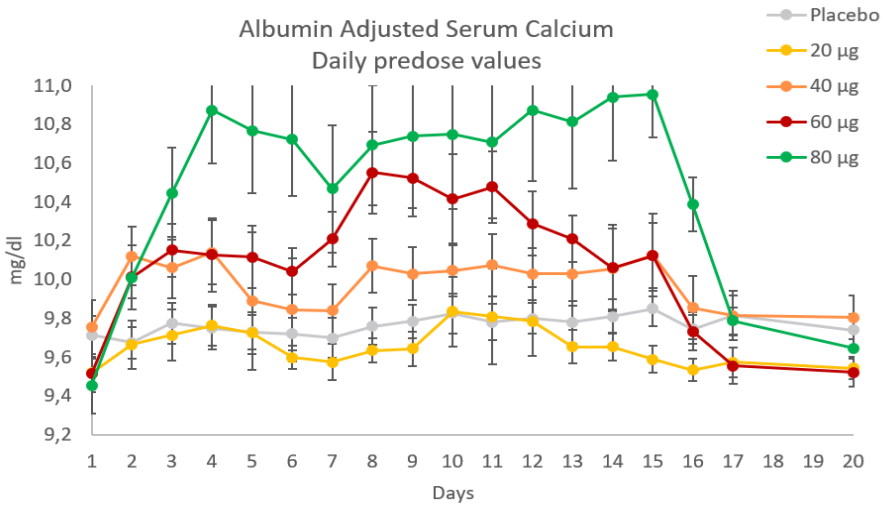
Part B
Multiple Ascending Dose Cohort
Healthy volunteers
5 cohorts / n= 50



Short PK



Long PD



Dose Dependent and Sustained Impact on Serum Calcium Levels

ENEBOPARATIDE, PHASE 2A CLINICAL TRIAL

Aliya Khan, Professor of Clinical Medicine; Director, Calcium Disorders Clinic - McMaster University

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Eneboparatide Phase 2a Trial Design

- 3-month multicenter open label study to evaluate the safety and efficacy of eneboparatide
- 2 consecutive cohorts of patients with chronic HP
  - Cohort 1: 20 µg/day as starting dose, individual titration up to 60 µg/day
  - Cohort 2: 10 µg/day as starting dose, individual titration up to 80 µg/day
- Objectives
  - Safety, tolerability, PK
  - Efficacy as measured by sCa, Ca/Vit D supplement withdrawal, urinary Ca
  - Bone safety as measured by bone biomarkers and BMD (Cohort 2 only)

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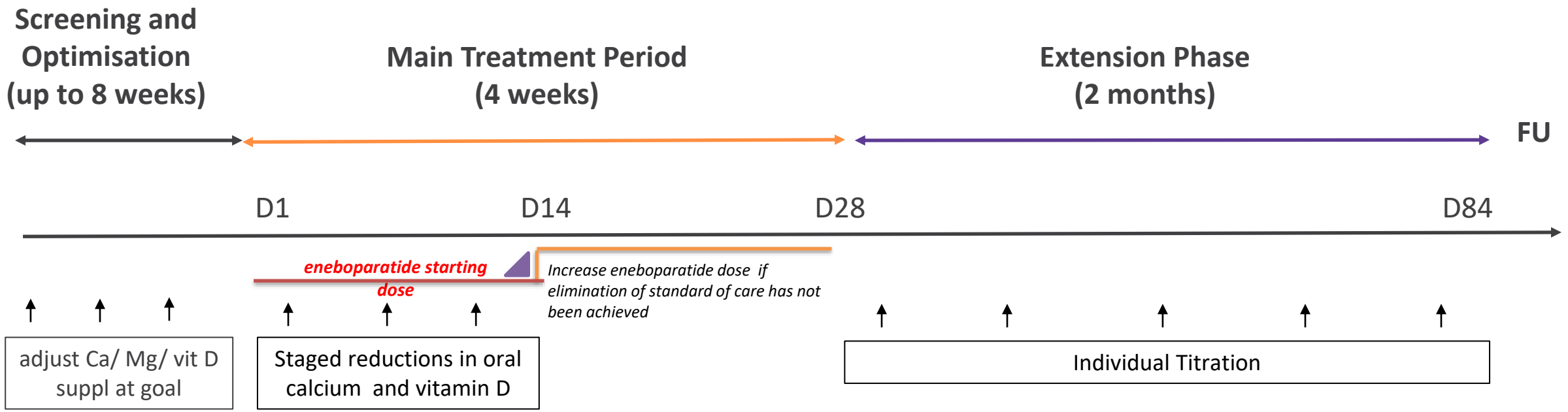
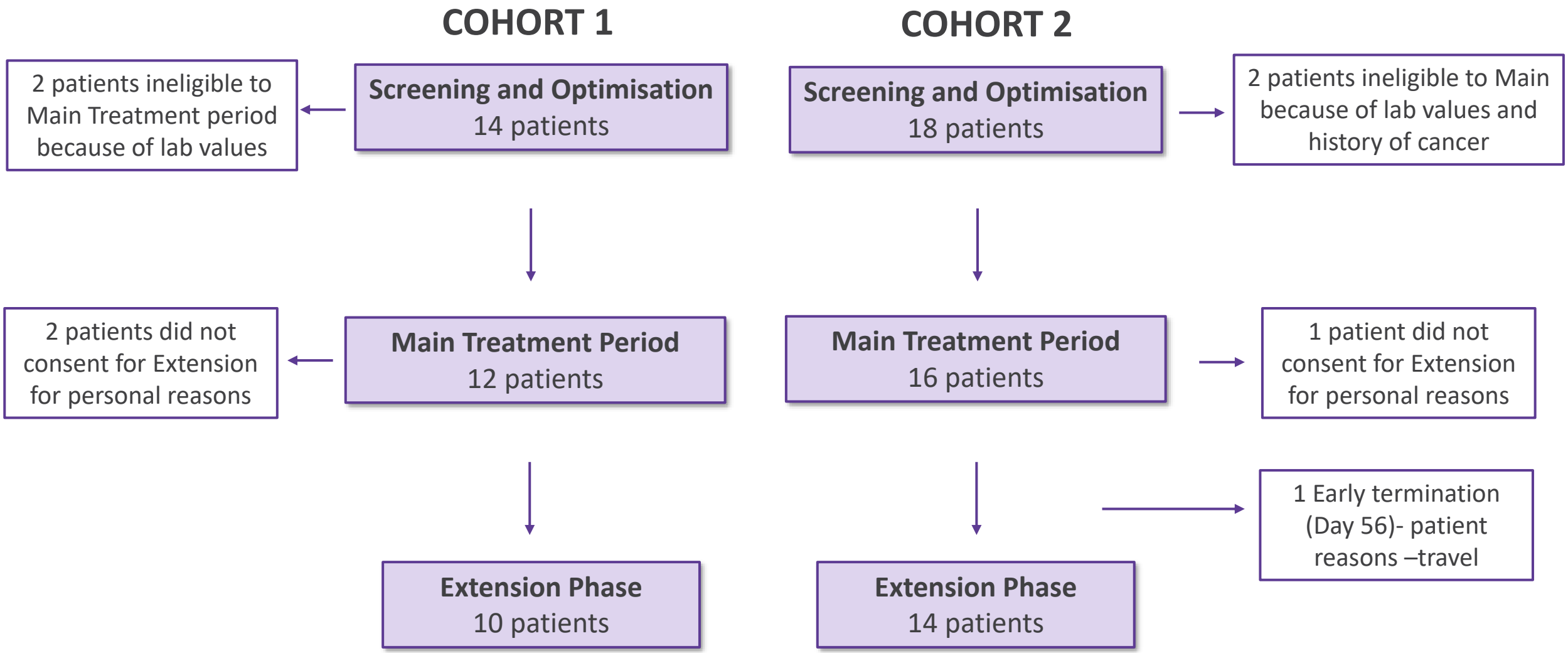
Phase 2a Trial Design



Target range for serum calcium defined as 7.8 to 9 mg/dL (1.95-2.25 mmol/L)

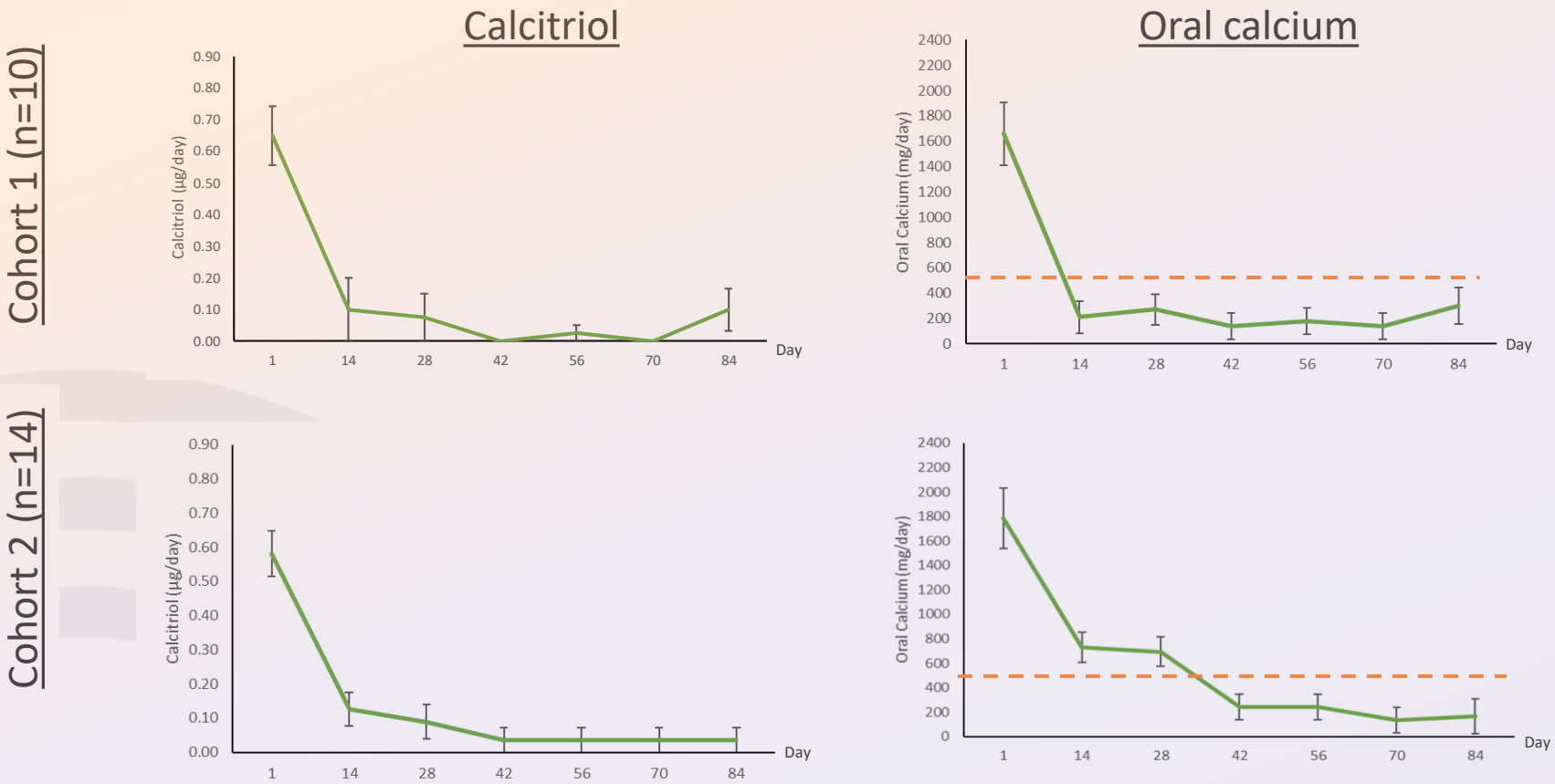
FLOW CHART



BASELINE CHARACTERISTICS

	Cohort 1 N=12	Cohort 2 N=16	All N=28
Mean age, yrs (SD), min-max	62.7 (9.7), 44-72	54 (11.2), 26-72	57.7 (11.3), 26-72
Female, n (%)	9 (75%)	12 (75%)	21 (75%)
Mean BMI, kg/m^2 (SD), min-max	28.3 (4.4), 23.0-37.1	29.1 (5.4), 19.6-38	28.8 (4.9), 19.6-38
Post-menopausal women, n (%)	7 (58.3%)	7 (43.8%)	14 (50%)
Mean time since menopause, yrs, min-max	20.1, 10-33	13.5, 2-20	17.1, 2-33
Mean time since HP diagnosis, yrs, min-max	12.8, 2-31	12.3, 3-50	12.5, 2-50
Mean time since HP diagnosis (women), yrs, min-max	13, 2-31	13, 3-50	13, 2-50
Etiology of hypoparathyroidism **Post-surgery, n (%)** **Idiopathic, n (%)** **Genetic, n (%)**	 10 (83.3%) 2 (16.7%) -	 13 (81.3%) 2 (12.5%) 1 (6.3%)	 23 (82.1%) 4 (14.3%) 1 (3.6%)
Mean oral vitamin D dose, ug/day, min-max	0.67, 0.25-1	0.60, 0.25-1	0.63, 0.25-1
Mean oral calcium dose, mg/day, min-max	1,625, 1,000-3,500	1,688, 1,000-7,800	1,661, 1,000-7,800
Mean Alb-adjusted serum calcium, mg/dL, min-max	8.67, 8.10-9.20	8.70, 7.72-9.6	8.71, 7.72-9.6
Mean 24-hour urinary calcium, mg/24h, min-max	329, 143-614	331, 57-729	330, 57-729
CKD-EPI (mL/min/1.73m^2)- eGFR	71.15, 46.1-90.0 (n=10)	70, 38-109 (n=11)	70.55, 38-109 (n=21)

Eneboparatide Demonstrated Potential to Eliminate Standard of Care Treatment



- Active Vitamin D was rapidly discontinued (8/10 and 13/14 patients were off at Day 84 in C1 and C2, respectively)
- Oral calcium supplementation was brought to ≤ 500mg/day (8/10 and 13/14 patients in C1 and C2, respectively)

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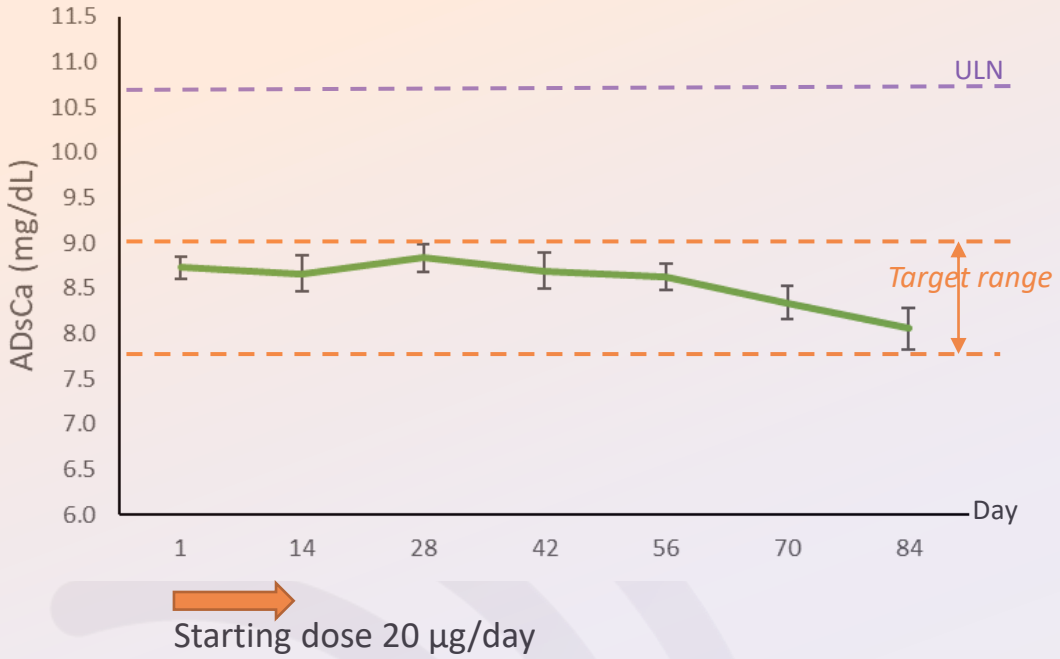
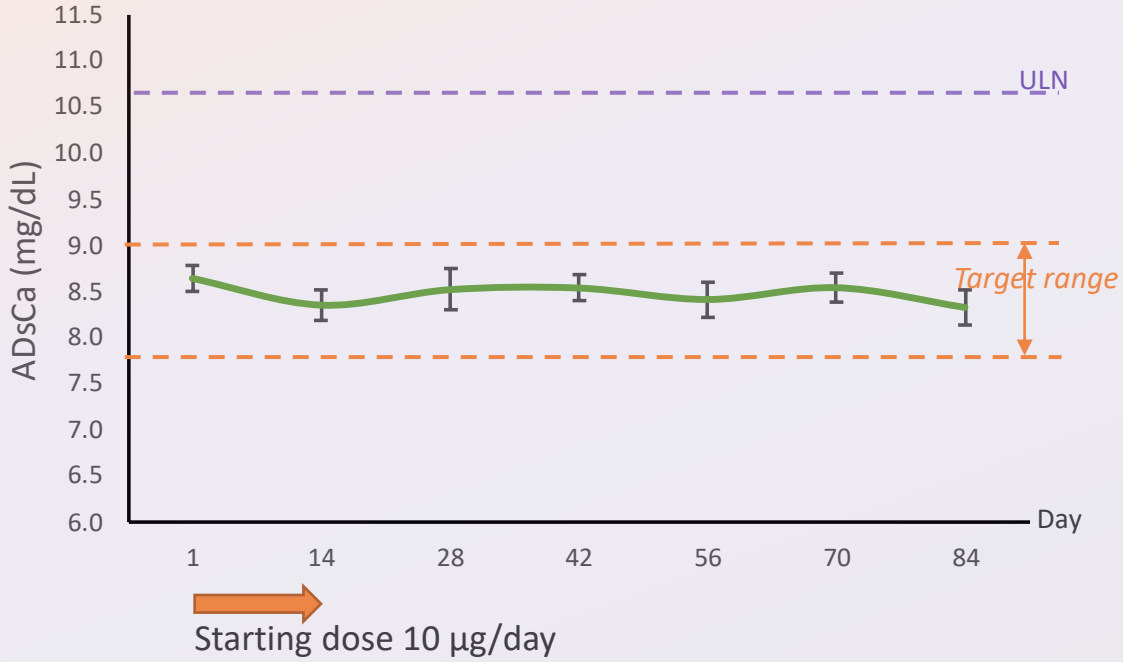
Maintained Target Mean Serum Calcium Throughout the Study Duration

C1 Patients who completed Extension Period, N=10



Starting dose 20 µg/day

C2 Patients who completed Extension Period, N=14



Starting dose 10 µg/day

Therapeutic Goal #1

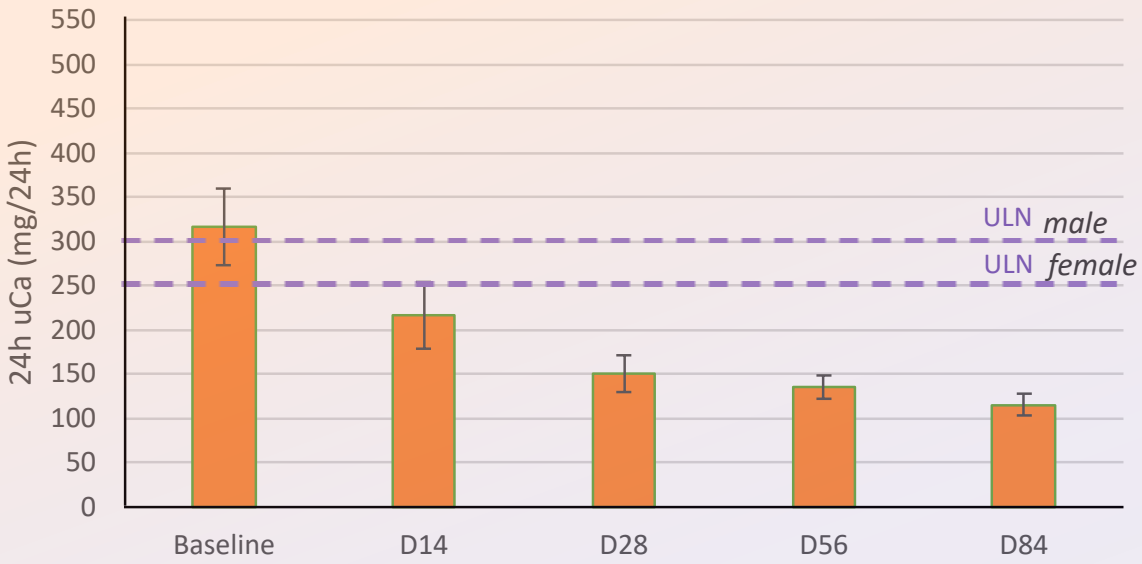
Normalization of Serum Calcium Levels and Discontinuation of SoC

ACHIEVED

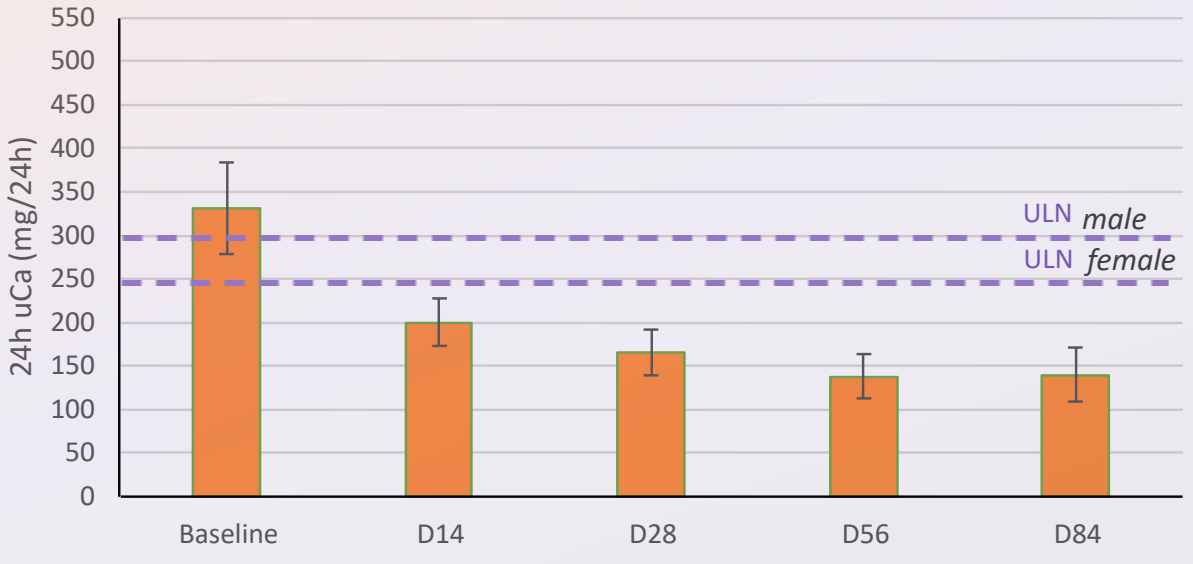
Data are presented as mean ± SEM

Induced a Rapid, Profound and Sustained Normalization of Mean 24-Hour Urine Calcium

C1 Patients who completed Extension Period, N=10



C2 Patients who completed Extension Period, N=14



Therapeutic Goal #2

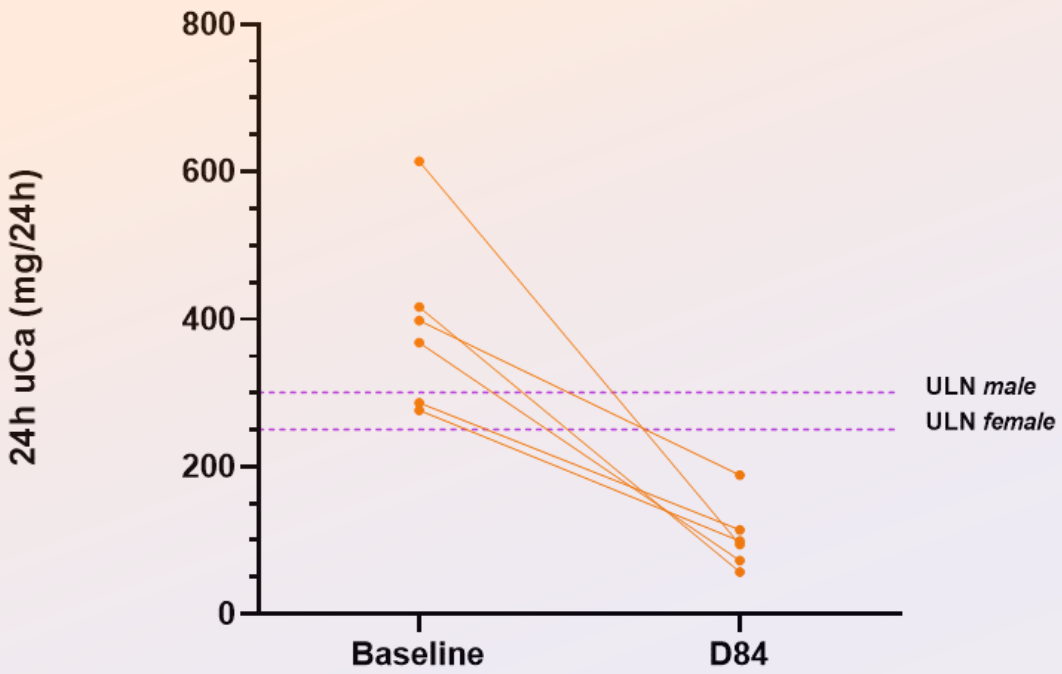
Preserve Kidney Function

ACHIEVED

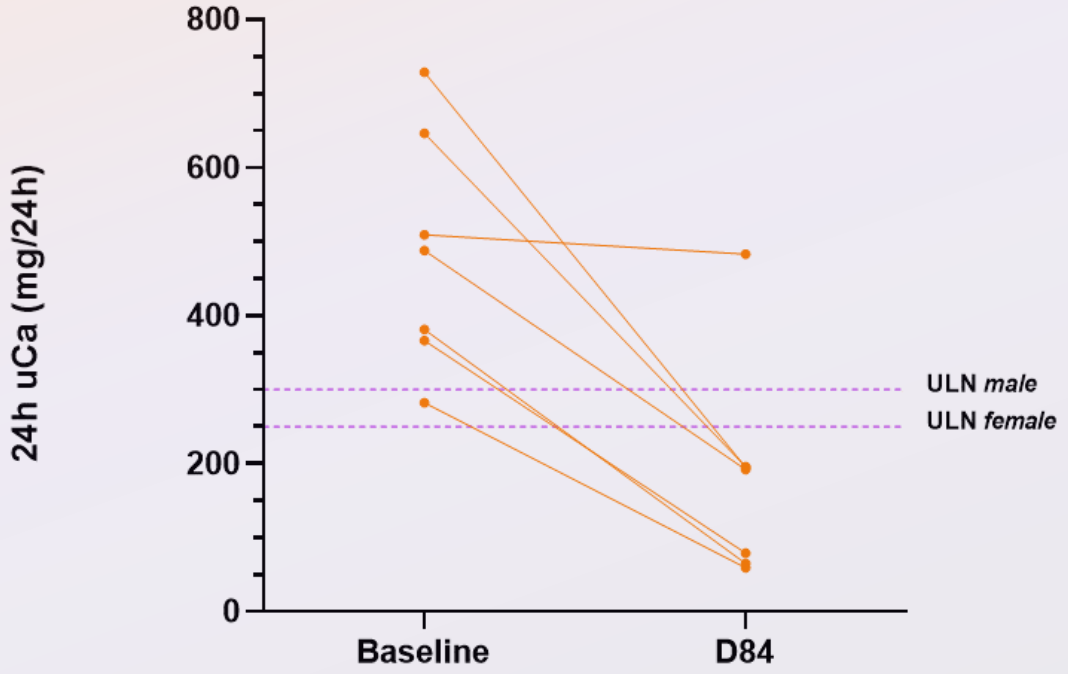
Data are presented as mean ± SEM

Mean 24h-Urinary Calcium – Patients with Elevated Urinary Ca at Baseline

C1 Patients with hypercalciuria at baseline, N=6



C2 Patients with hypercalciuria at baseline, N=7



In 12/13 (92%) patients with elevated urinary calcium at baseline, eneboparatide induced rapid, profound and sustained normalization of 24-hour urine calcium

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SAFETY SUMMARY

Adverse Event	Cohort 1 N=12 n (n/N %)	Cohort 2 N=16 n (n/N %)	Total N=28 n (n/N %)
SAEs	0	0	0
AEs	36	77	113
Mild	25 (69%)	67 (87%)	92 (81%)
Moderate	11 (31%)	10 (13%)	21 (19%)
Severe	0	0	0
ISRs	4 in 4 patients	14 in 9 patients	18 in 13 patients
Hypocalcemia*	2	9	11
Hypercalcemia	3	0	3

- Eneboparatide treatment was well tolerated
- No SAEs or AEs leading to withdrawal
- All AEs mild or moderate in intensity

*Hypocalemia was more common in Cohort 2 likely due to lower starting dose (10 μg/d)

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Showed Promising Effect on Bone Safety

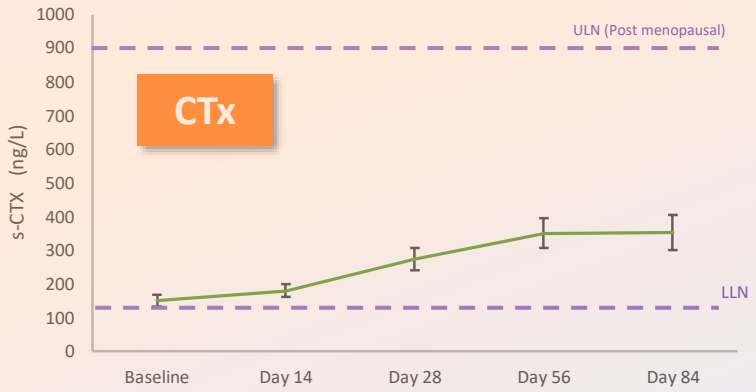
- Treatment with eneboparatide induced a gradual and mild increase in both anabolic and catabolic bone markers to the mid-normal level by 4-8 weeks
- Findings support eneboparatide's mechanism of action targets urinary calcium reabsorption rather than bone resorption
- This may be an important clinical benefit as 17-43% of patients with HP have osteopenia or osteoporosis; 53% are peri- or post-menopausal women
- At 3 months – not seeing significant catabolic effect – consistent with short half- life ~45mins

Therapeutic Goal #3

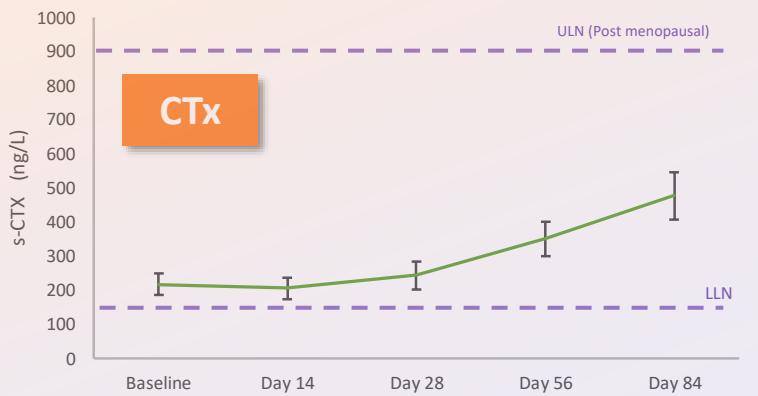
Ensure Bone Safety

ACHIEVED

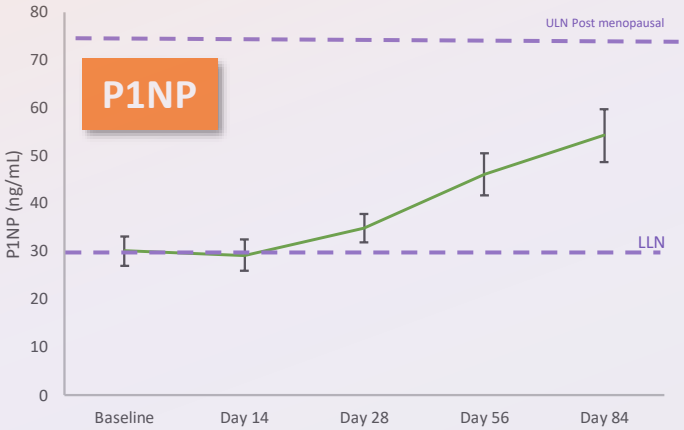
C1 Patients who completed Extension Period, N=10



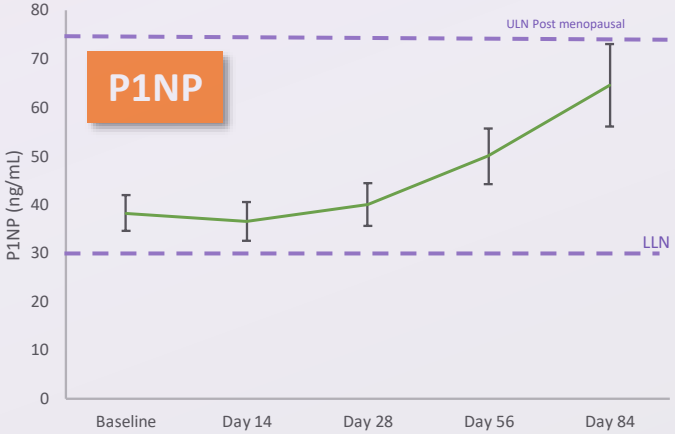
C2 Patients who completed Extension Period, N=14



C1 Patients who completed Extension Period, N=10



C2 Patients who completed Extension Period, N=14



Data are presented as mean ± SEM

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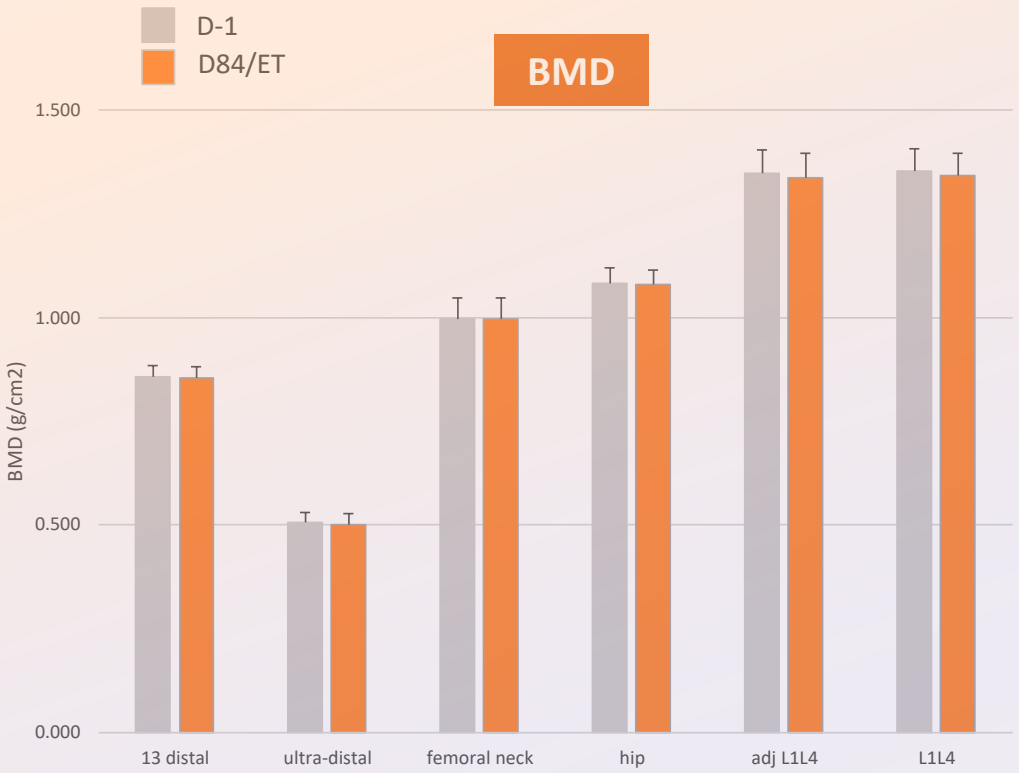
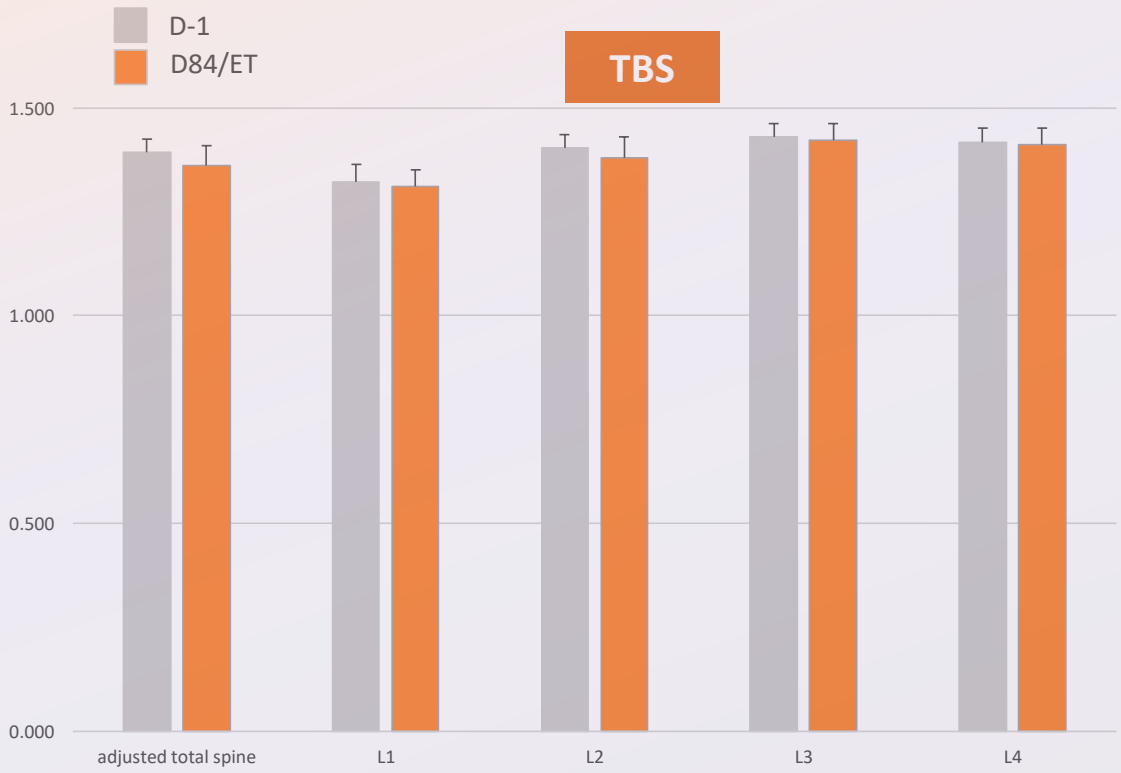
Bone Mineral Density and Trabecular Bone Score Remained Stable

C2 Patients who completed Extension Period, N=14



C2 Patients who completed Extension Period, N=14



Consistent with a balanced increase in bone biomarkers, ***Bone Mineral Density and Trabecular Bone Score remained stable***

Data are presented as mean ± SEM

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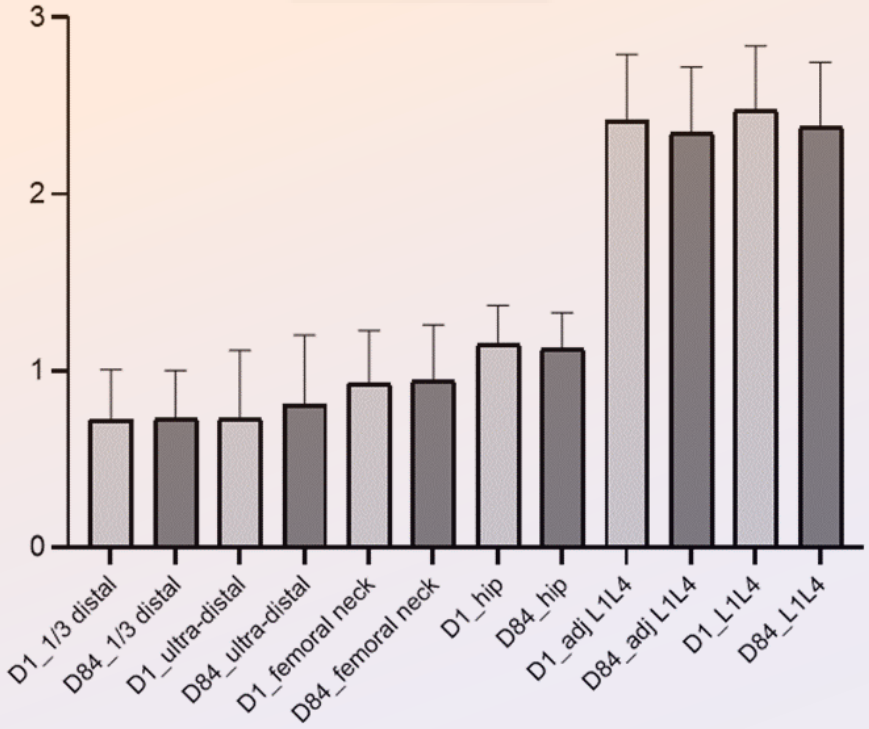
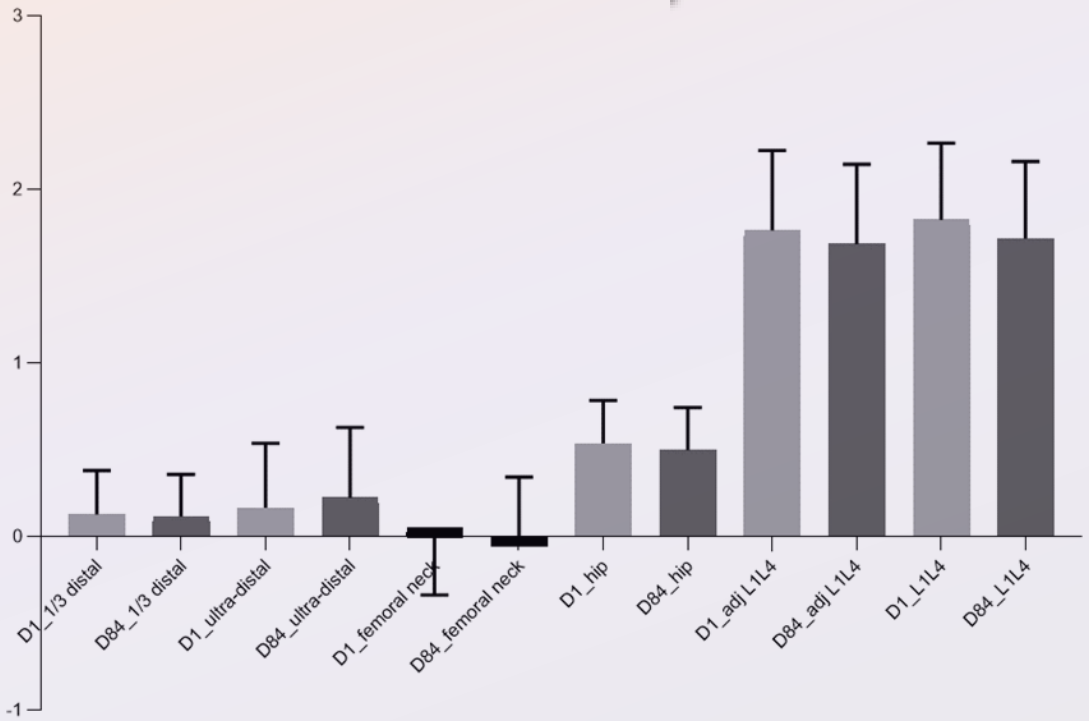
Showed Promising Effect on Bone for Patients at Risk of Bone Disease

Z-Score



T-Score



- Consistent with a balanced increase in bone biomarkers, ***Z-score and T-score remained stable, including in patients with osteopenia***
- ***6/14 patients (43%) were osteopenic*** at baseline: radius (3), femoral (2), radius+femoral (1)

Data are presented as mean ± SEM

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Key Takeaways

The only therapeutic, either available or in development, that can effectively address ALL THREE key therapeutic goals

1

Eneboparatide was well-tolerated at all doses administered

- No drug-related serious treatment adverse events (TEAEs) were reported
- No TEAEs leading to discontinuation of study drug

2

Subjects appeared to establish physiological calcium metabolism

- Independence from vitamin D and oral calcium achieved in most patients -80-93% (13/14)
- Urinary calcium decreased and normalized in 12/13 patients with hypercalciuria
- Bone biomarkers and BMD suggestive of restoration of balanced bone turnover

3

Next steps in Development

- Launched Phase 3 clinical trial in May 2023

ENEBOPARATIDE, PHASE 3 CLINICAL TRIAL DESIGN

Mark Sumeray, Chief Medical Officer - Amolyt Pharma

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Calypso Study Design

CALYPSO STUDY

Primary Composite Endpoint (Primary Efficacy Analysis) at Week 24

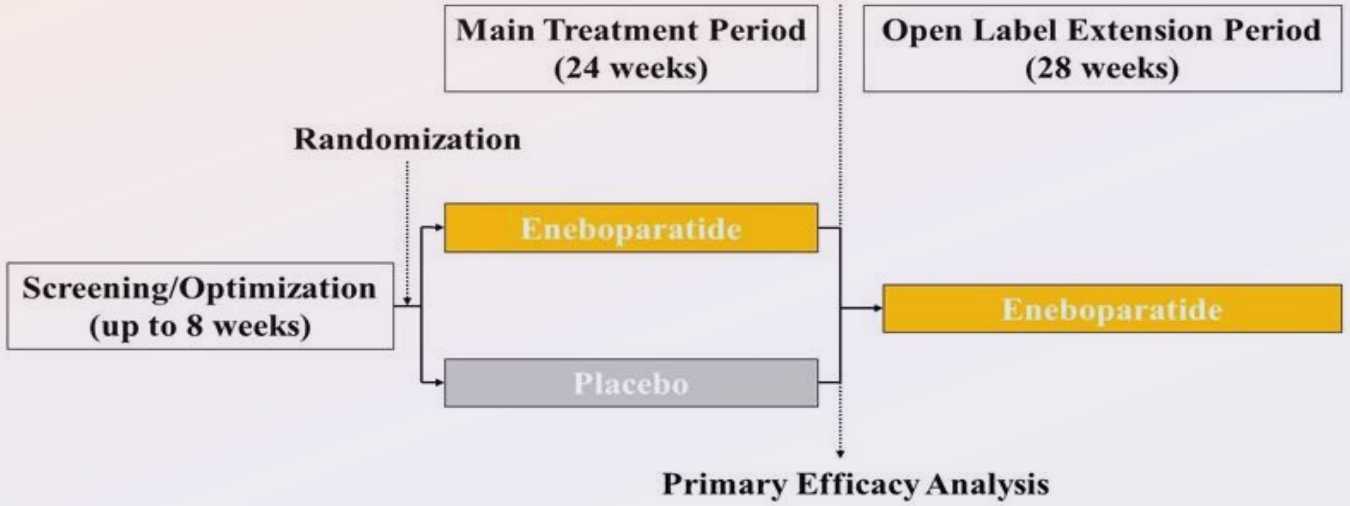
- Proportion of patients with AdsCa within the normal range and achieving independence from supplements

Key Secondary Endpoints at Week 24

- Normalization of the 24-hour urinary calcium in patients with hypercalciuria at baseline
- Disease-specific patient reported outcomes

Safety Endpoints

- Bone safety: biomarkers, BMD, TBS, HRpQ CT
- PK, ADA, AEs, Labs etc



- 165 patients to be randomized (2:1 eneboparatide : placebo)
- Minimum of 75 patients with hypercalciuria
- Stratification on etiology of chronic hypoparathyroidism (surgery vs non-surgery)

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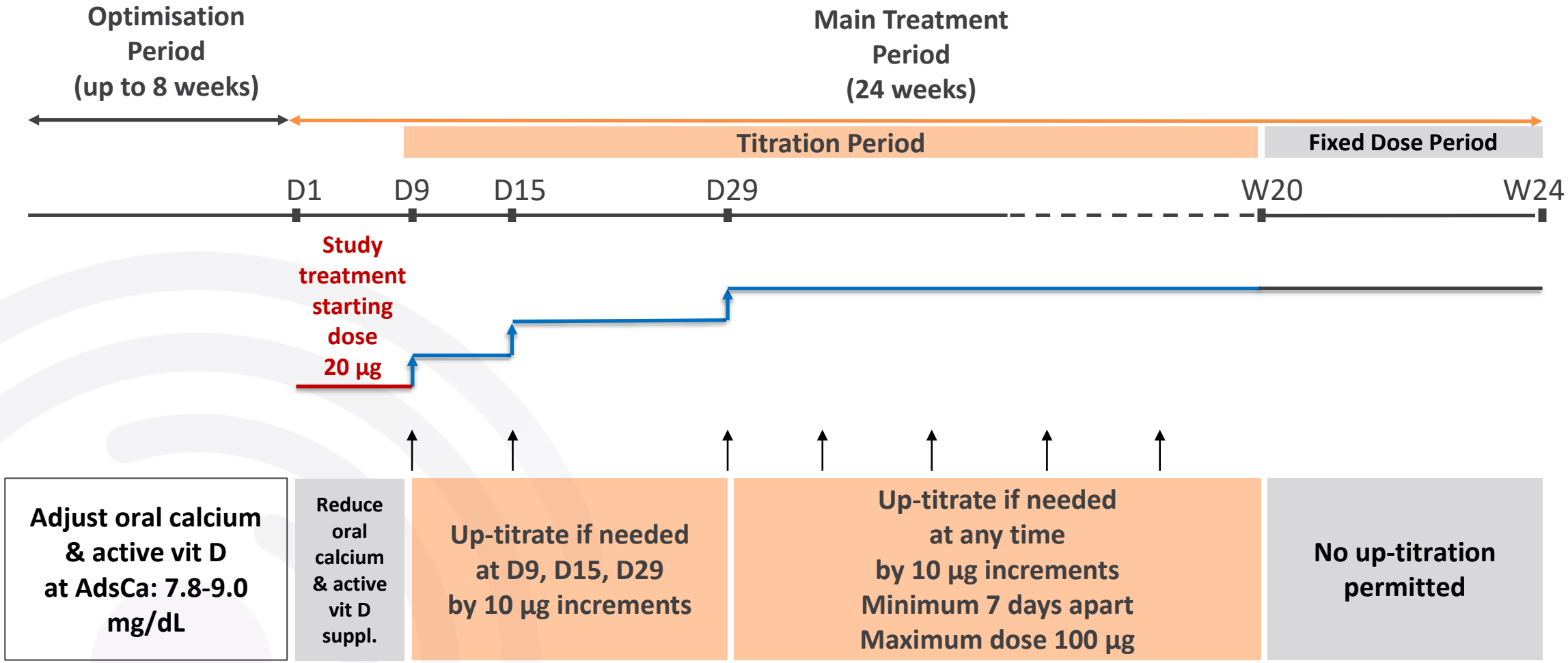
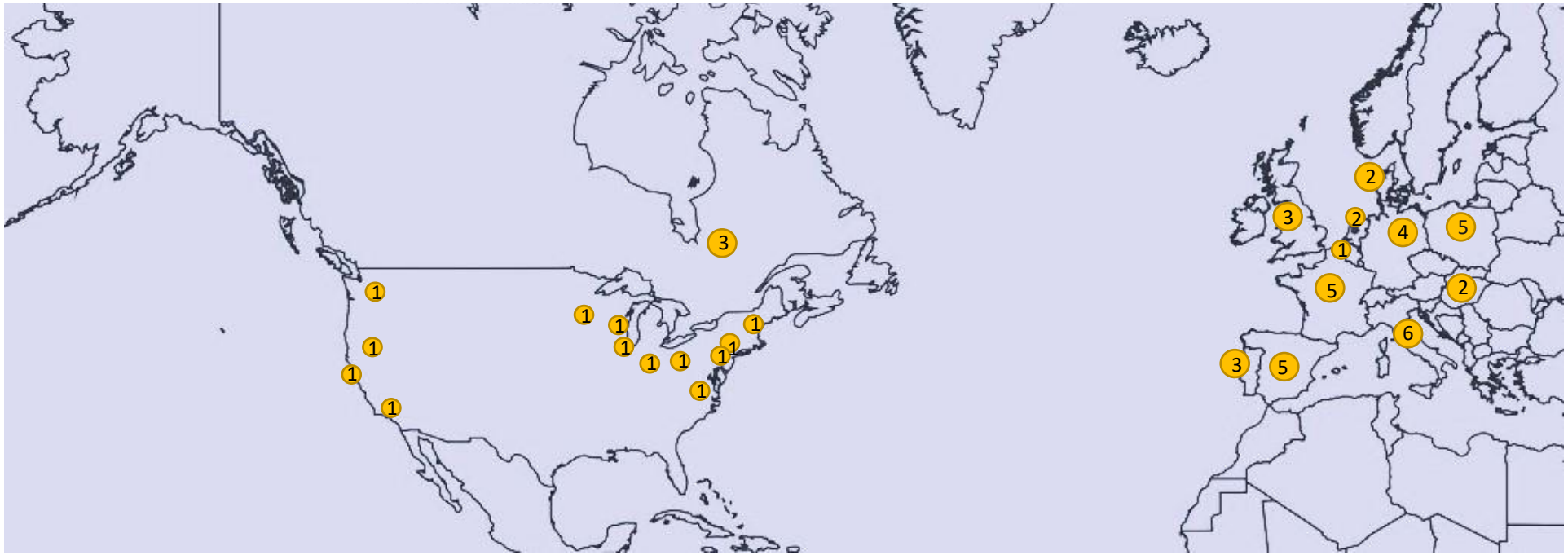
Study Treatment Schematic

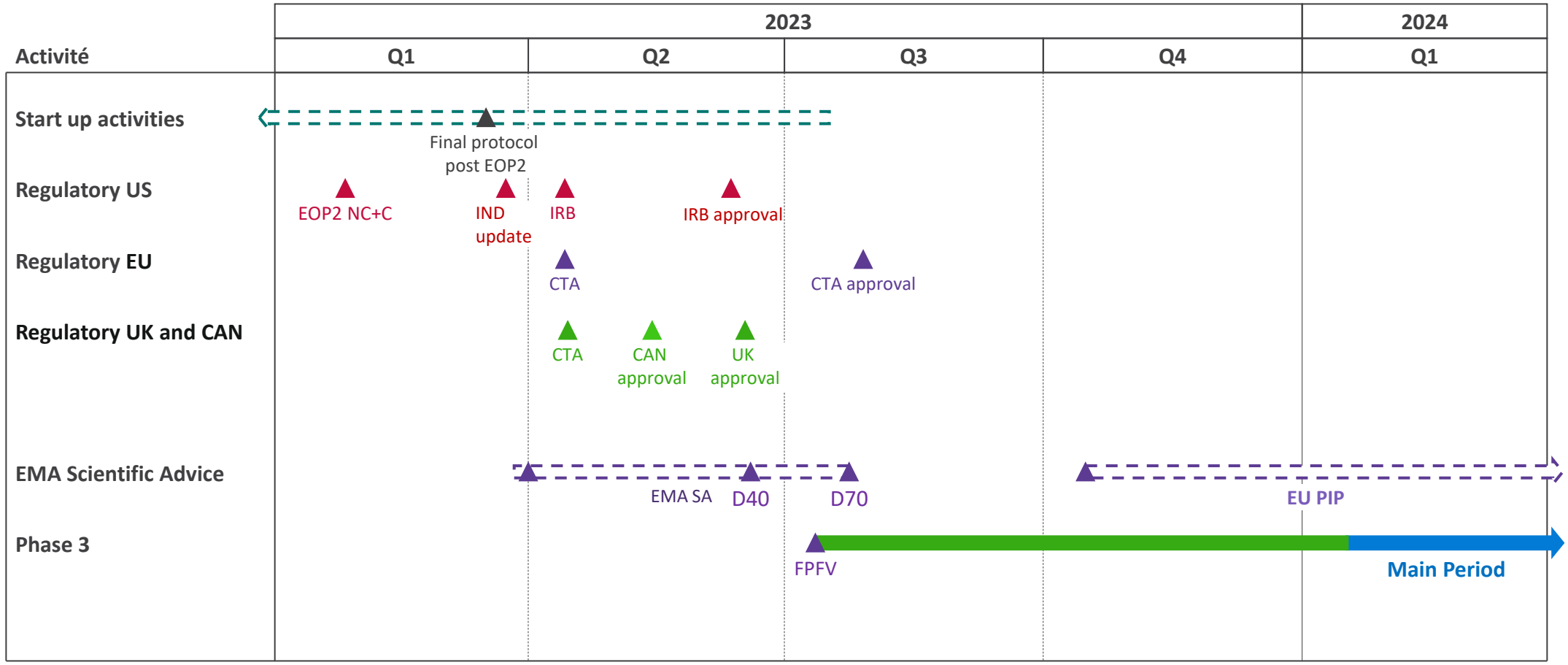


Feasibility and Site Selection for Calypso Trial

- Target number of patients: 165 patients randomized
- Target number of sites: 50+ sites
- Target countries : US, EU countries, UK and Canada
- 54 sites selected (13 countries): US (13), EU with central submission (35), UK (3), Canada (3)
- Currently investigating a few additional sites in US



Eneboparatide Expected Clinical and Regulatory Timelines



Assumptions:

- CTA: 106 days (queries)
- FPFV 1 month following IRB approval
- If no questions EMA SA obtained at D40
- 6 months recruitment
- 50+ sites, 165 patients
- Main period includes 8 weeks for optimization

Calypso Trial Provides Data Expected to Support Differentiated Labeling

CALYPSO STUDY

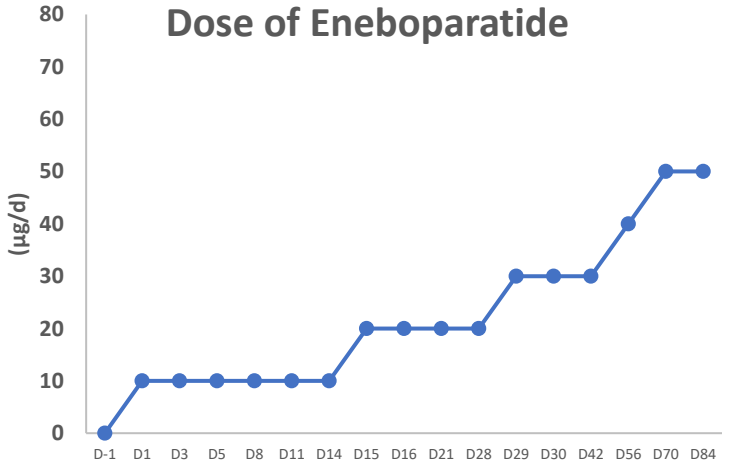
- Sample size (n=150 completers) expected to generate highly statistically significant results
- Primary efficacy endpoint supports monotherapy indication (control of calcium in absence of supplements)
- All key secondary endpoints expected to support labeling claims (adjusted for multiple comparisons generating inferential P values)
  - First key secondary efficacy endpoint is normalization of urinary calcium excretion (major driver of complications and costs)
  - Others focused on disease-specific patient reported outcomes (physical, cognitive function, quality of life)
- Bone safety (imaging and biomarkers) expected to reflect neutral impact on turnover
- Label expected to support differentiation vs other PTH products (efficacy on normalization of urinary calcium, bone safety)

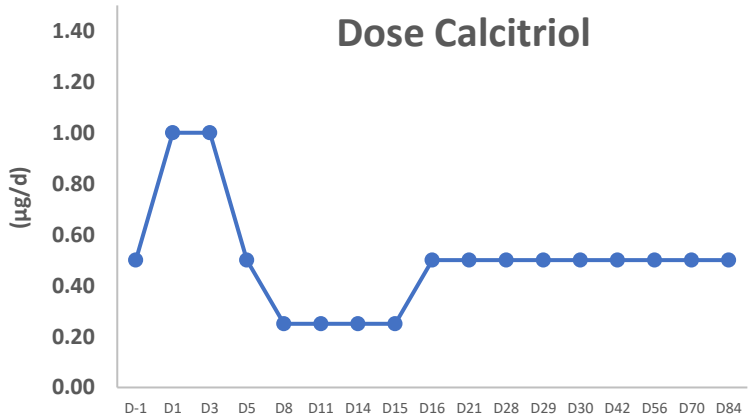
AMOLYT PHARMA

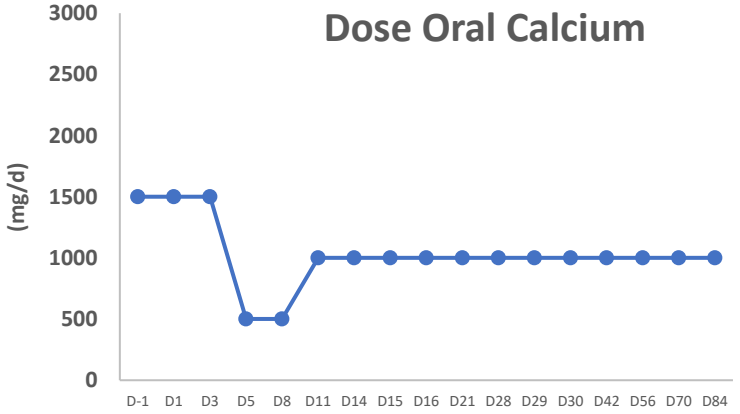
HYPOPARATHYROIDISM PATIENT VOICE

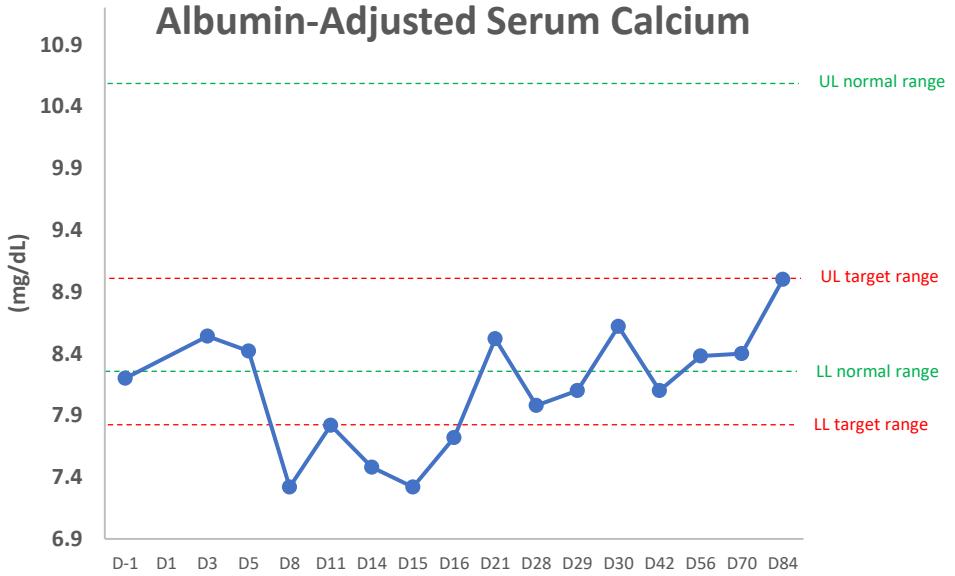
Patty Keating, Patient and Chairwoman - HypoPARA Patient Association

AMOLYT PHARMA









47yrs man
85 kg
10 yrs post-Surgery