OR23-04 - TREATMENT OF CHRONIC HYPOPARATHYROIDISM WITH ENEBOPARATIDE (AZP-3601), A NOVEL PTH 1 RECEPTOR AGONIST: RESULTS FROM A PHASE 2 TRIAL

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CONFLICT OF INTEREST

Peter Kamenicky, MD, PhD

- **Co-investigator**

Shire / Takeda	SHP634-401
Amolyt Pharma	AZP-3601-CLI-001, AZP-3601-CLI-002
Calcylitix Pharmaceutics	CLTX-305-301

- **Speaker's honoraria, congress invitations**

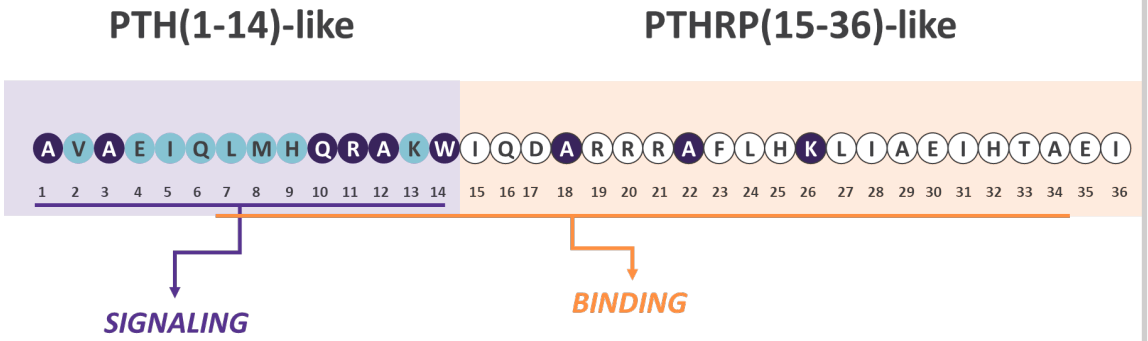
Shire / Takeda
Amolyt Pharma

- **Advisory board:**

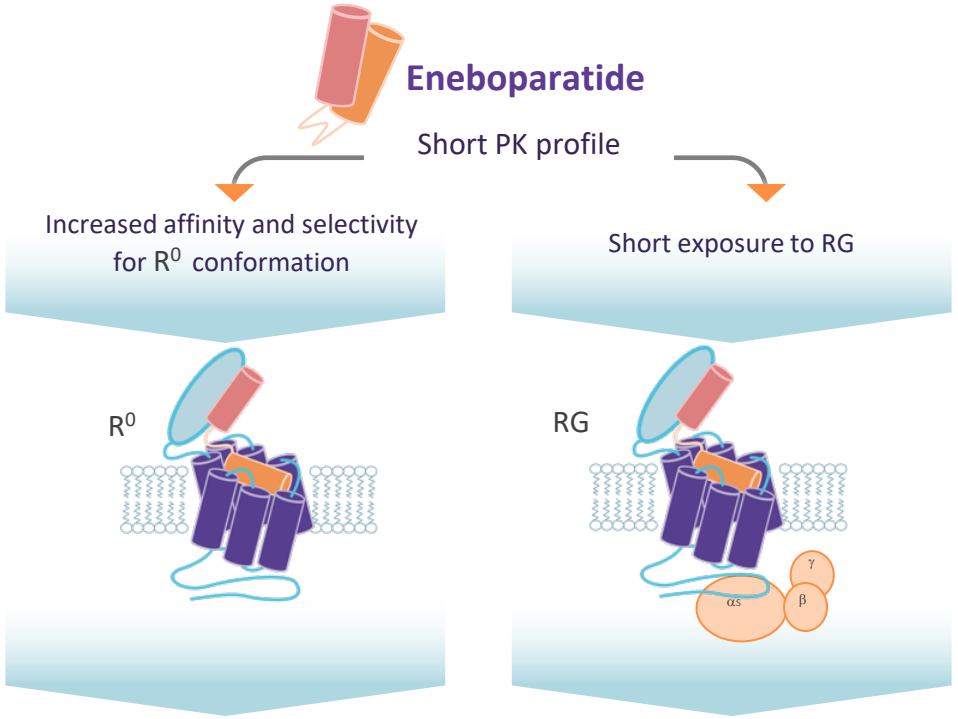
Ascendis Pharma

Eneboparatide (AZP-3601): a peptide that preferentially binds the R^0 conformation of the PTH1 receptor

Multiple PTH/PTHrP Hybrid Peptides were assessed for desired structure activity relationship 'SAR'

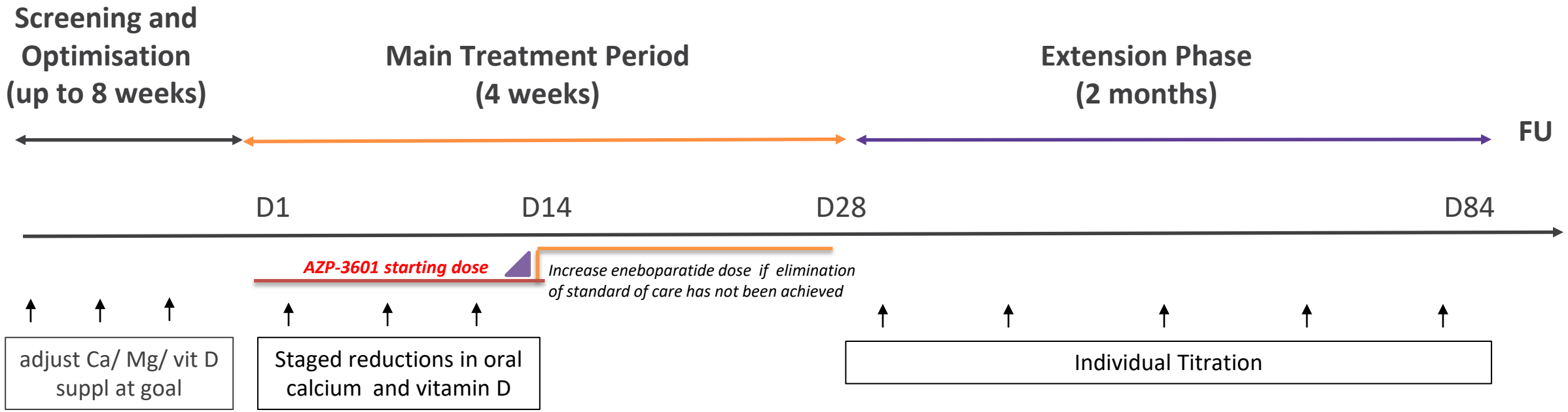


Eneboparatide has higher affinity for R^0 conformation of the receptor vs other PTH1R agonists



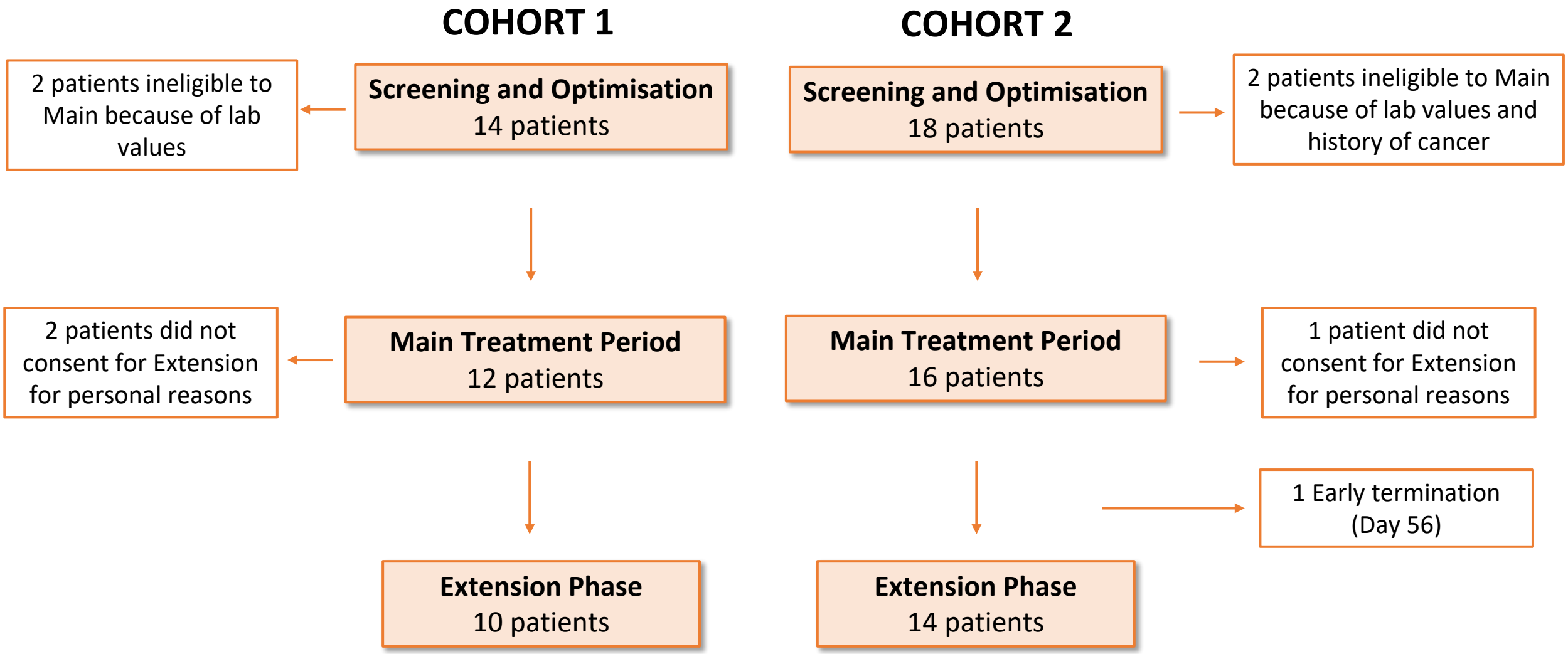
Study Design

- 3-month multicenter open label study to evaluate the safety and efficacy of eneboparatide
- 2 consecutive cohorts of patients with chronic HP
  - Cohort 1 (n=12): 20 µg/day as starting dose (individual titration up to 60 µg/day)
  - Given the effectiveness and tolerability of dose 20 µg, dose 10 µg was selected for Cohort 2 (n=16) as a starting dose in order to further explore dose relationship (individual titration up to 80 µg/day)



Target range for serum calcium defined as 7.8 to 9 mg/dL

Patient Flow through both Cohorts



Baseline Characteristics

	Cohort 1 N=12	Cohort 2 N=16
Mean age, years (SD), min-max	62.7 (9.7), 44-72	54 (11.2), 26-72
Female, n (%)	9 (75%)	12 (75%)
Mean BMI, kg/m^2 (SD), min-max	28.3 (4.4), 23.0-37.1	29.1 (5.4), 19.6-38
Post-menopausal women, n (%)	7 (58.3%)	7 (43.8%)
Mean time since menopause, years, min-max	20.1, 10-33	13.5, 2-20
Mean time since cHP diagnosis *(overall population)*, **years, min-max**	12.8, 2-31	12.3, 3-50
Mean time since cHP diagnosis *(women only)*, **years, min-max**	13, 2-31	13, 3-50
Etiology of cHP **Post-surgery, n (%)** **Idiopathic, n (%)** **Genetic, n (%)**	 10 (83.3%) 2 (16.7%) -	 13 (81.3%) 2 (12.5%) 1 (6.2%)
Mean oral vitamin D *(calcitriol dose equivalent)*, **µg/day, min-max**	0.67, 0.25-1	0.60, 0.25-1
Mean oral calcium dose, mg/day, min-max	1,625, 1,000-3,500	1,688, 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
Mean 24-hour urinary calcium, mg/24h, min-max	329, 143-614	331, 57-729

AMOLYT PHARMA

Eneboparatide Was Well-Tolerated with a Good Safety Profile

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

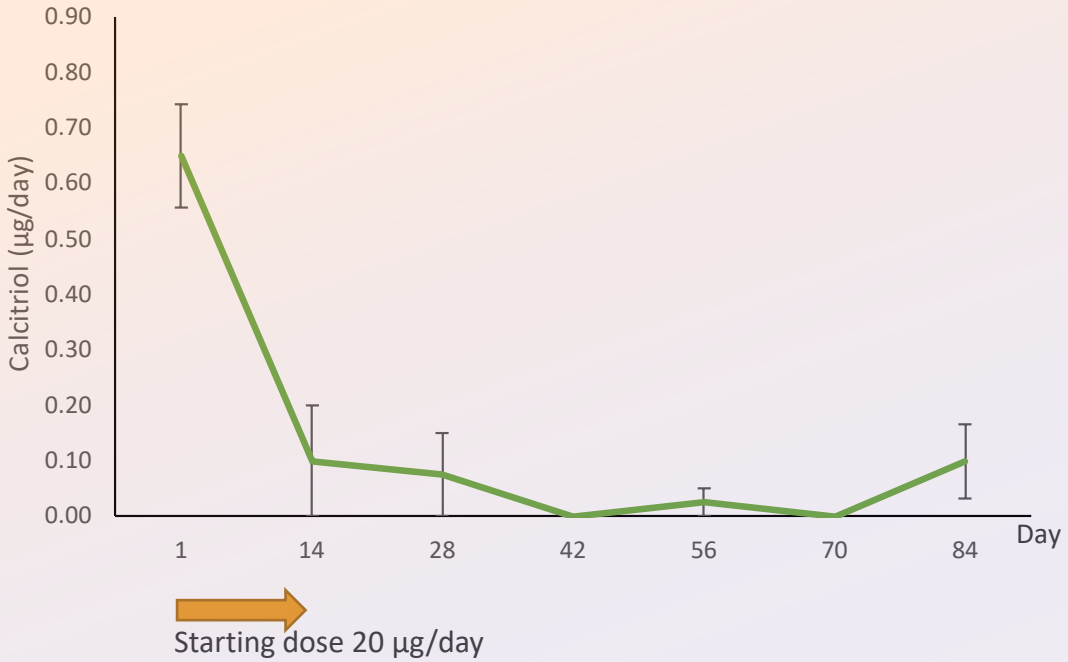
- Eneboparatide treatment was well tolerated
- No SAEs
- Good safety profile with no safety concerns

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

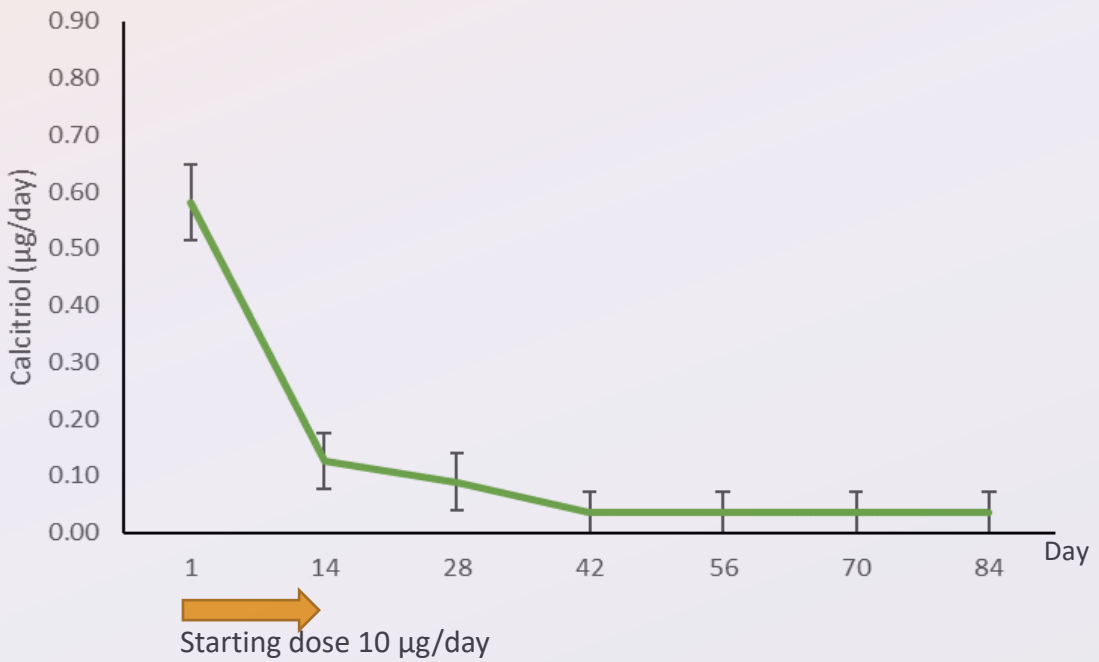
AMOLYT PHARMA

Demonstrated Potential to Eliminate Standard of Care Treatment - Calcitriol

C1 Patients who completed Extension Period, N=10



C2 Patients who completed Extension Period, N=14



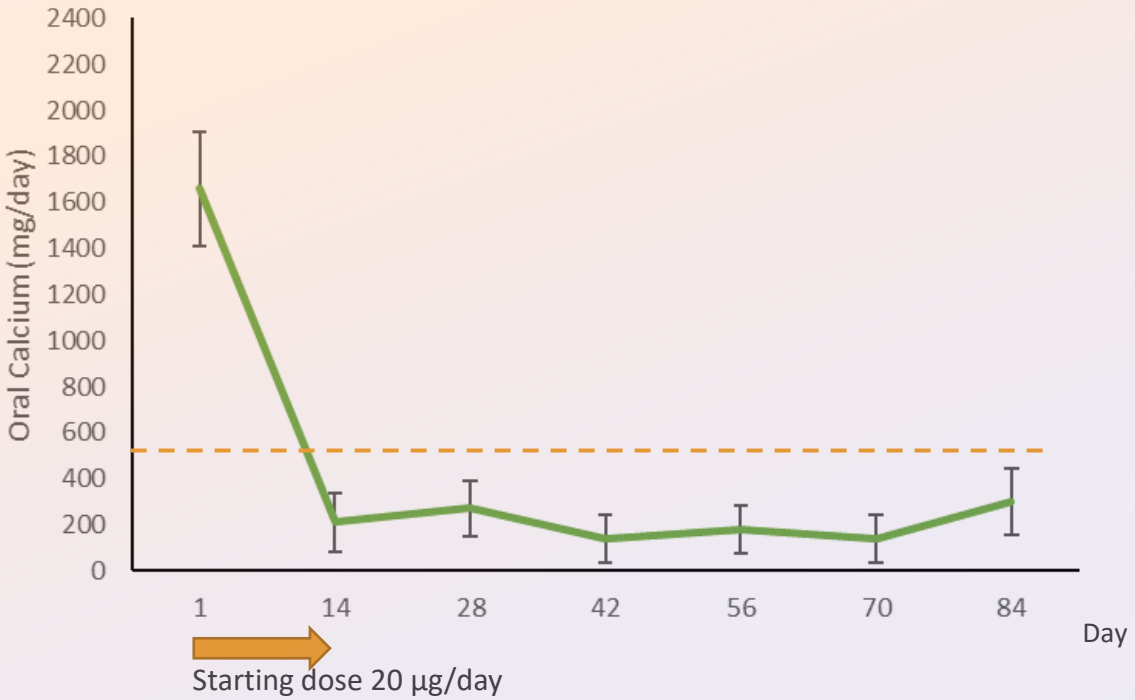
For one patient, calcitriol was reintroduced at D84 instead of D85 due to a misunderstanding of the protocol

Eneboparatide enabled ***discontinuation of Vitamin D*** within two weeks of treatment initiation

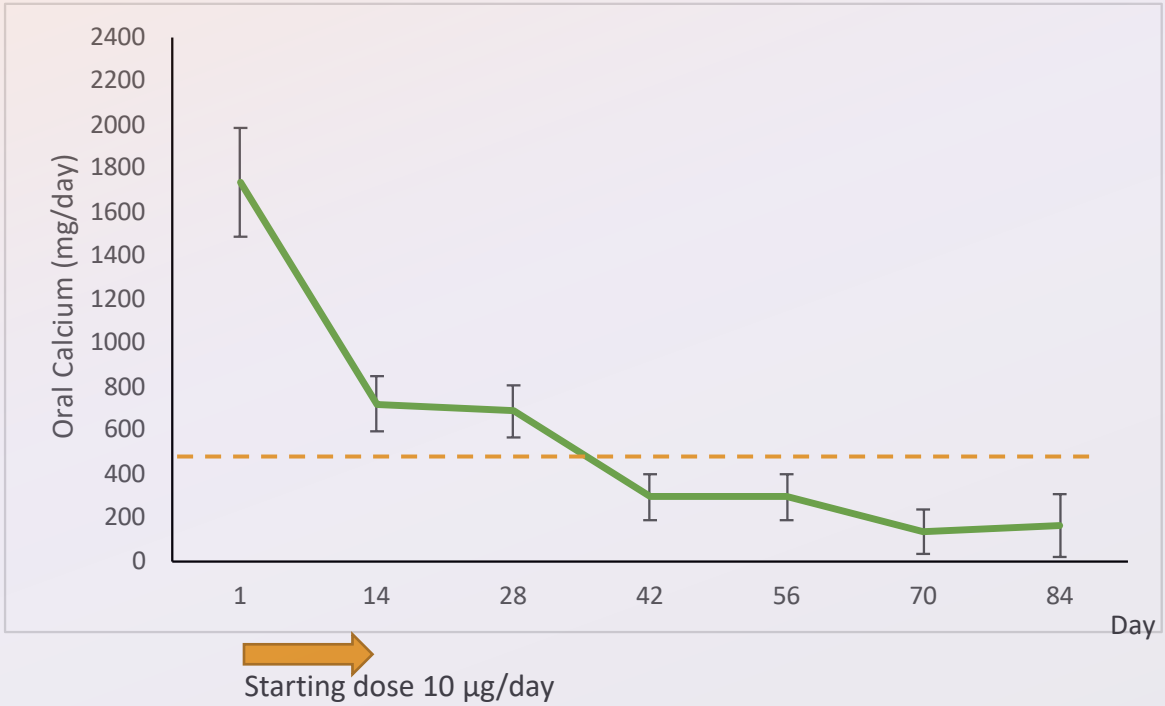
Data are presented as mean ± SEM

Demonstrated Potential to Eliminate Standard of Care Treatment – Oral Calcium

C1 Patients who completed Extension Period, N=10



C2 Patients who completed Extension Period, N=14



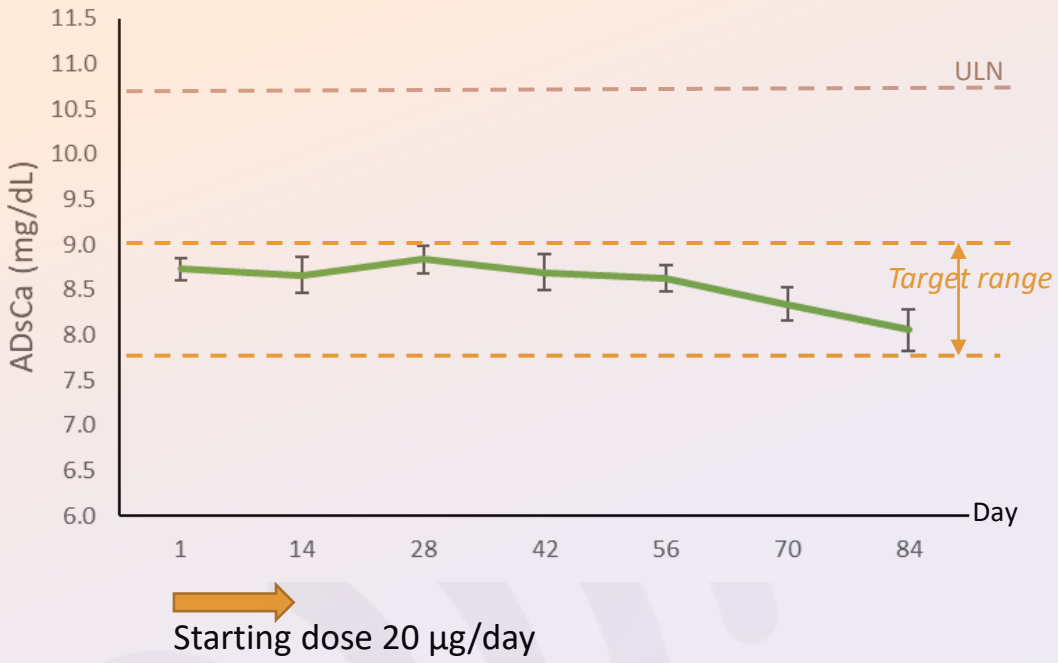
In both cohorts, eneboparatide enabled ***sustained reduction in oral calcium supplementation*** below 500mg/d. In Cohort 2, discontinuation of oral calcium supplementation was delayed and required up-titration due to the lower starting dose, supporting a ***dose-related effect***

Data are presented as mean ± SEM

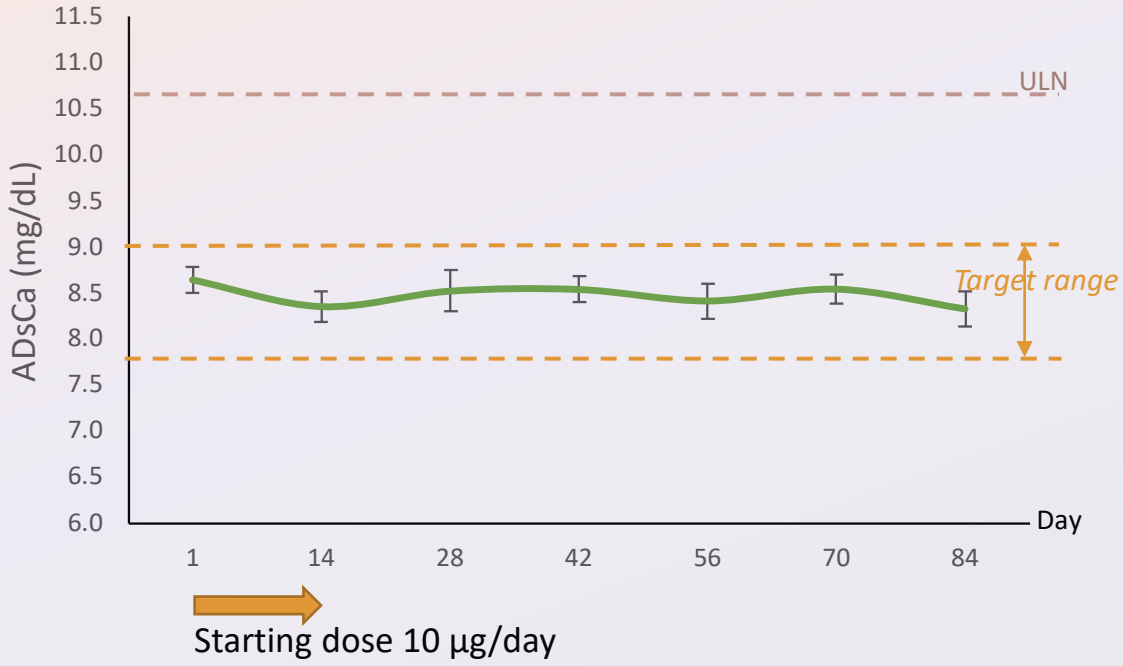
AMOLYT PHARMA

Maintained Target Mean Serum Calcium Throughout the Study Duration

C1 Patients who completed Extension Period, N=10



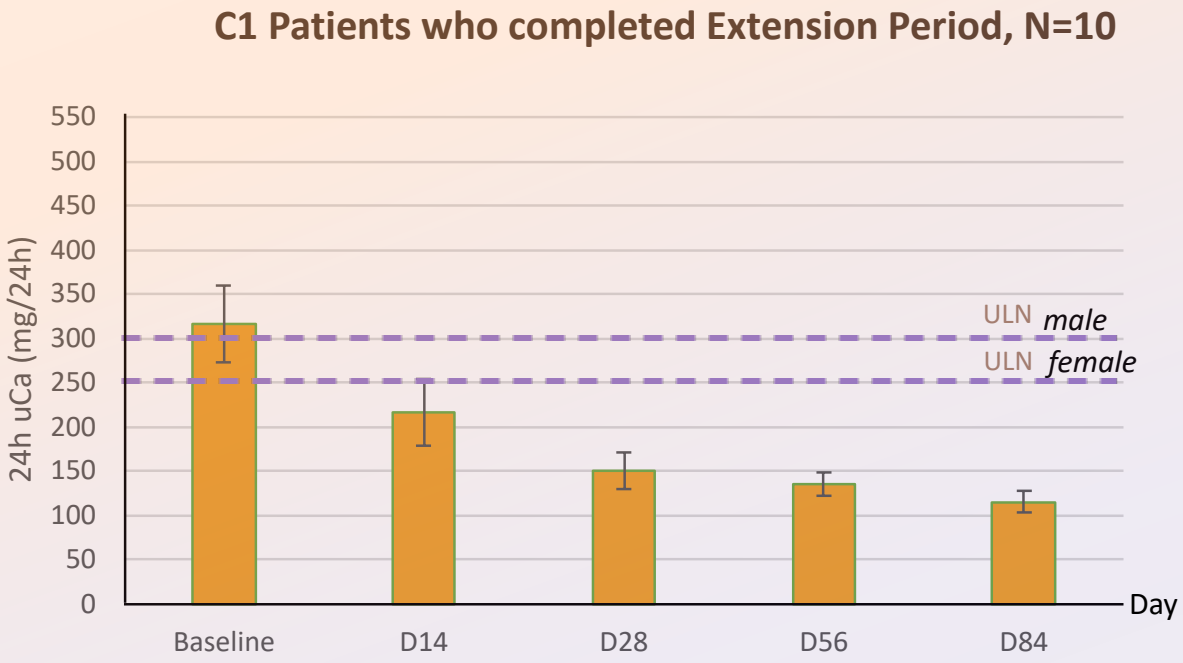
C2 Patients who completed Extension Period, N=14

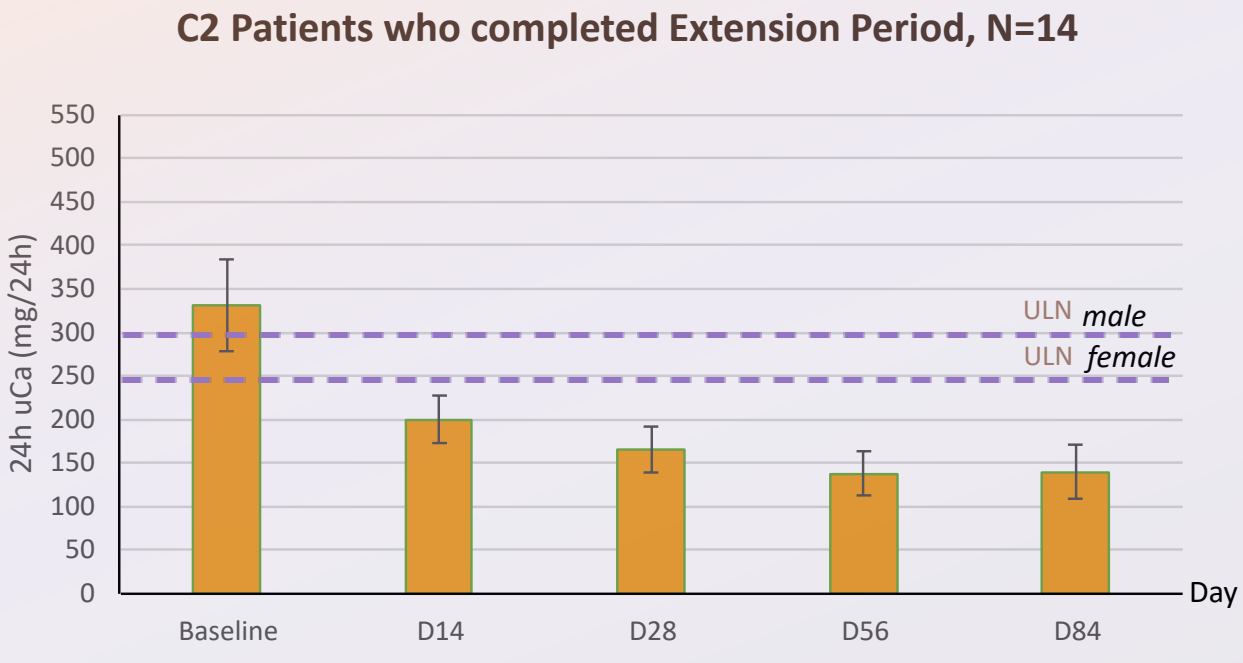


Eneboparatide mean (SD) dose at Day 84 was 28(15) µg/d in C1 and 43(18) µg/day in C2

Data are presented as mean ± SEM

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

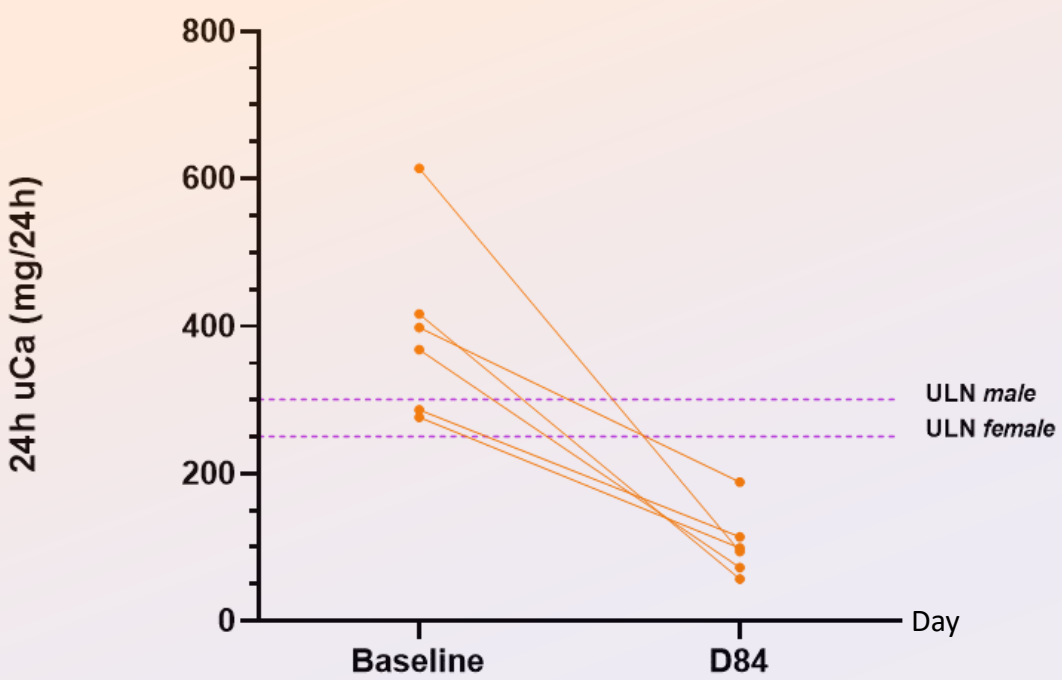




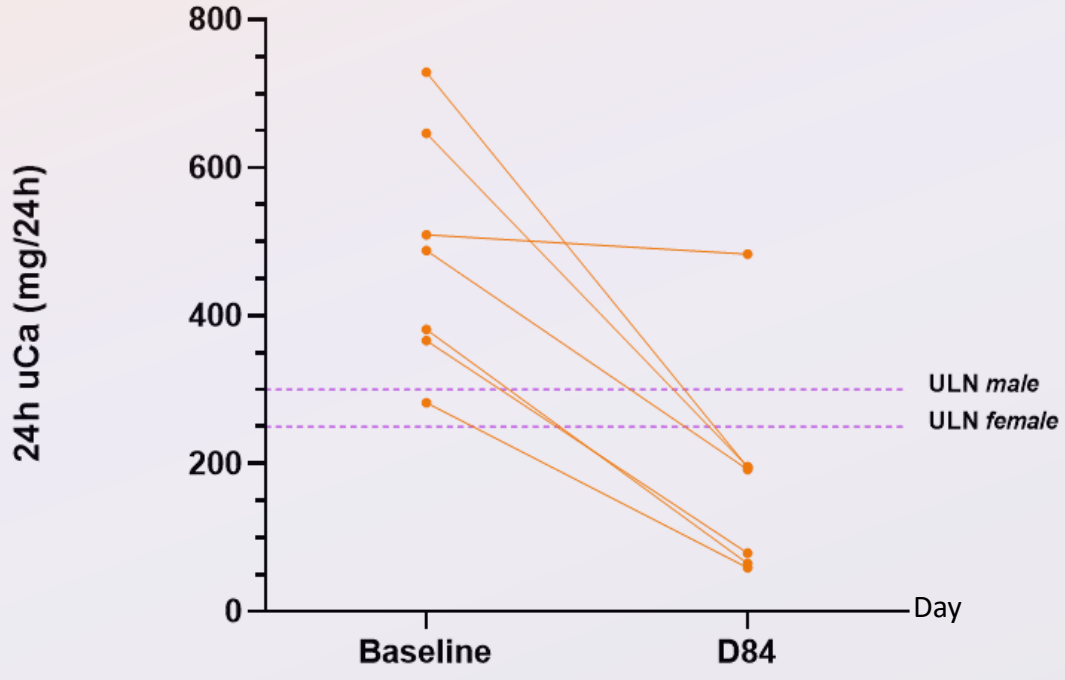
Data are presented as mean ± SEM

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

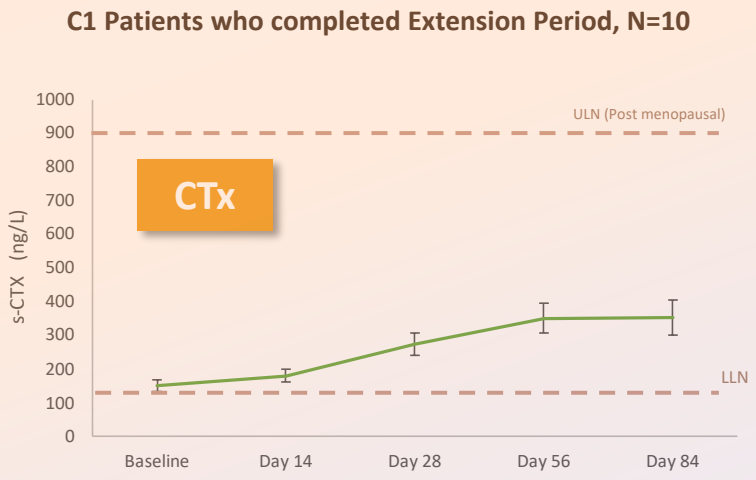


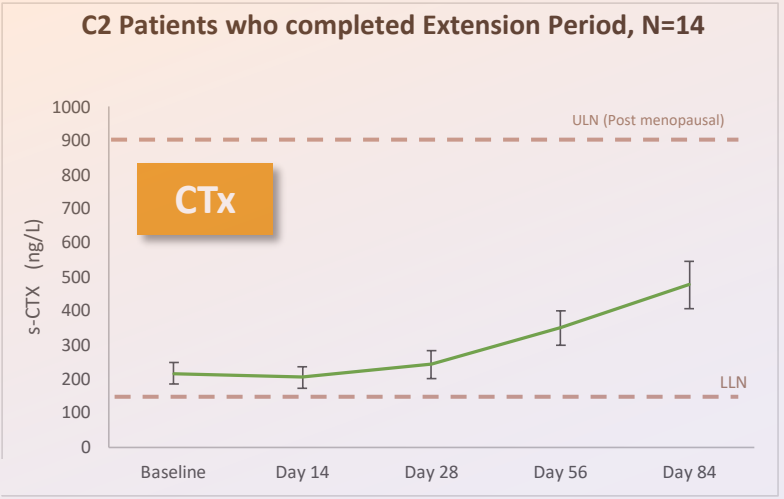
In 12/13 (92%) patients with elevated urinary calcium at baseline, efficacy of eneboparatide demonstrated by rapid, profound and sustained normalization of 24-hour urine calcium

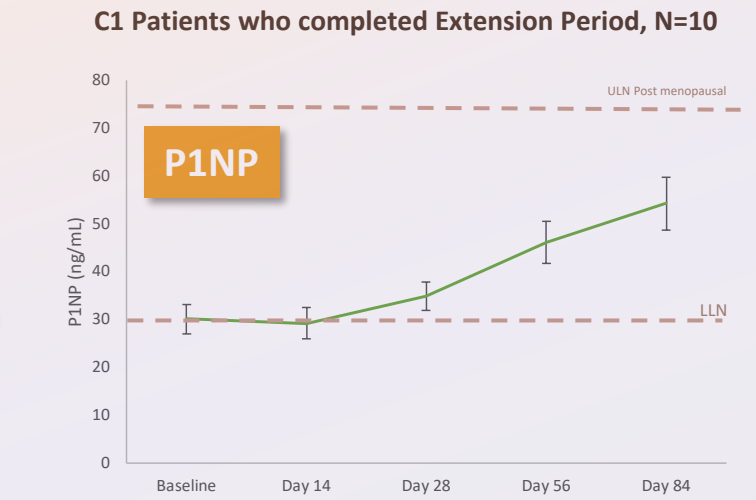
AMOLYT PHARMA

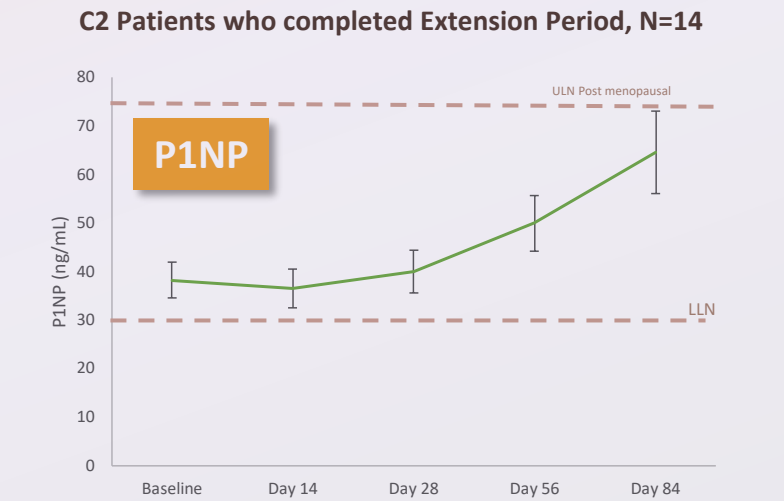
Eneboparatide Stimulated a Balanced Resumption of Bone Turnover

- 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 effect if confirmed in longer term studies since 17-43% of patients with HP have **osteopenia or osteoporosis**; 53% are peri- or post-menopausal women







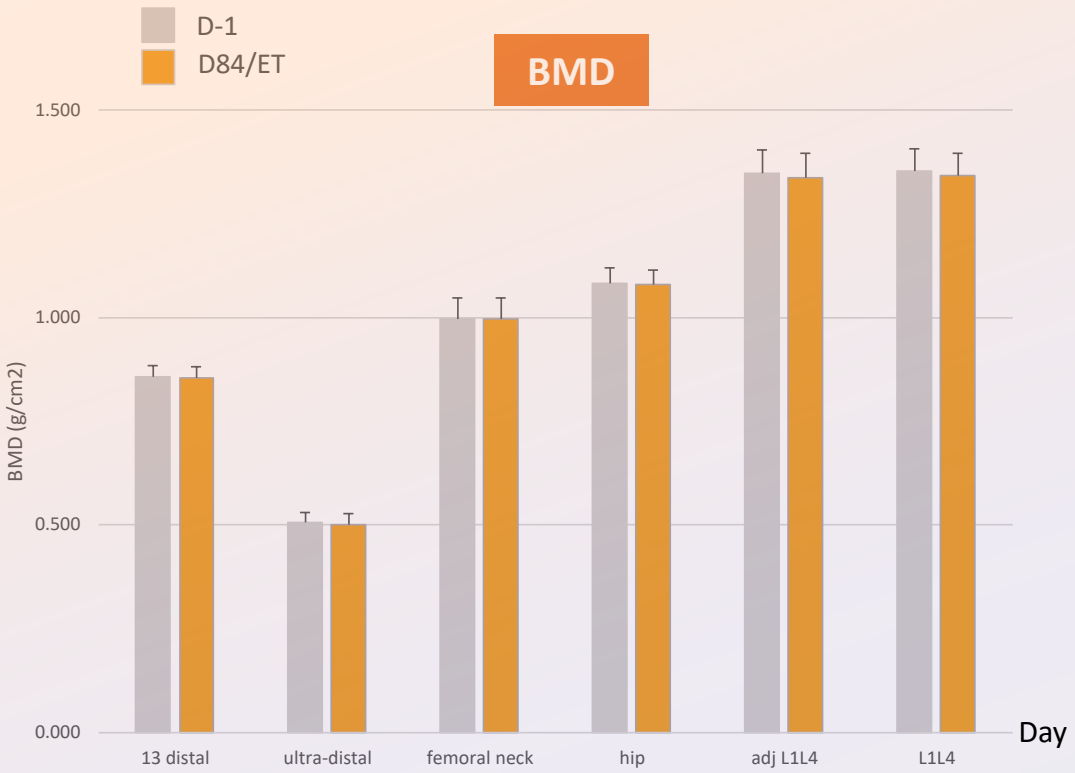


Data are presented as mean ± SEM

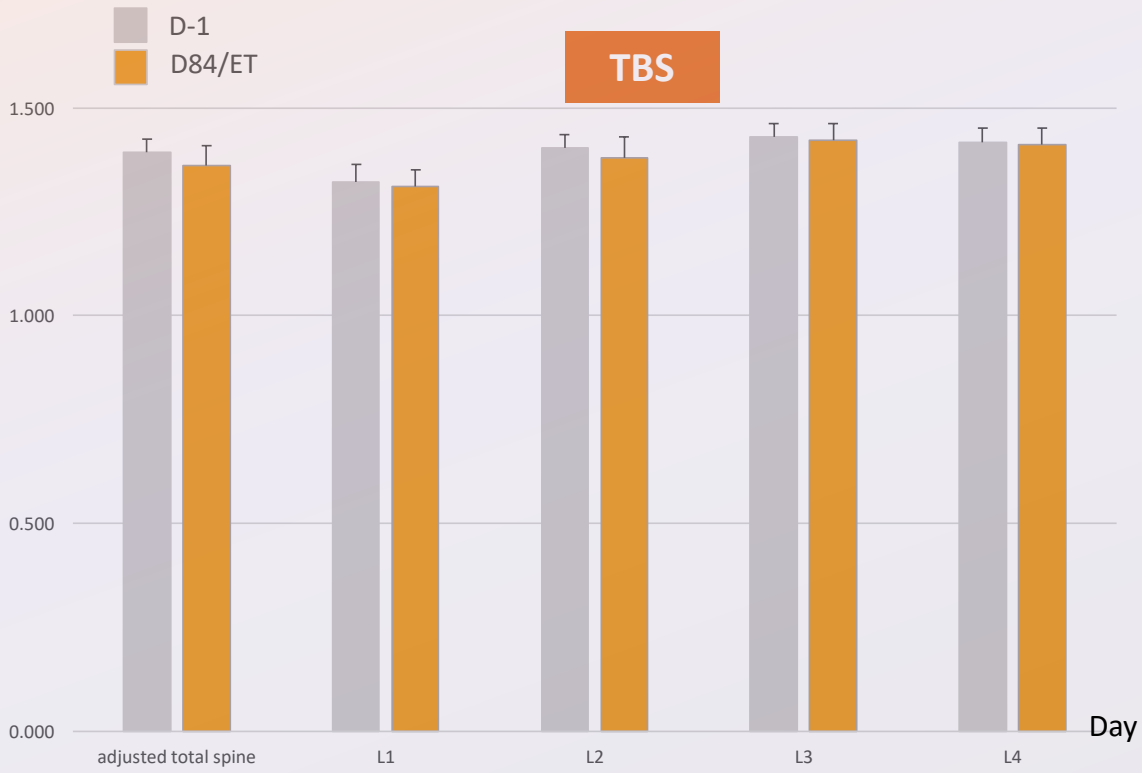
AMOLYT PHARMA

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



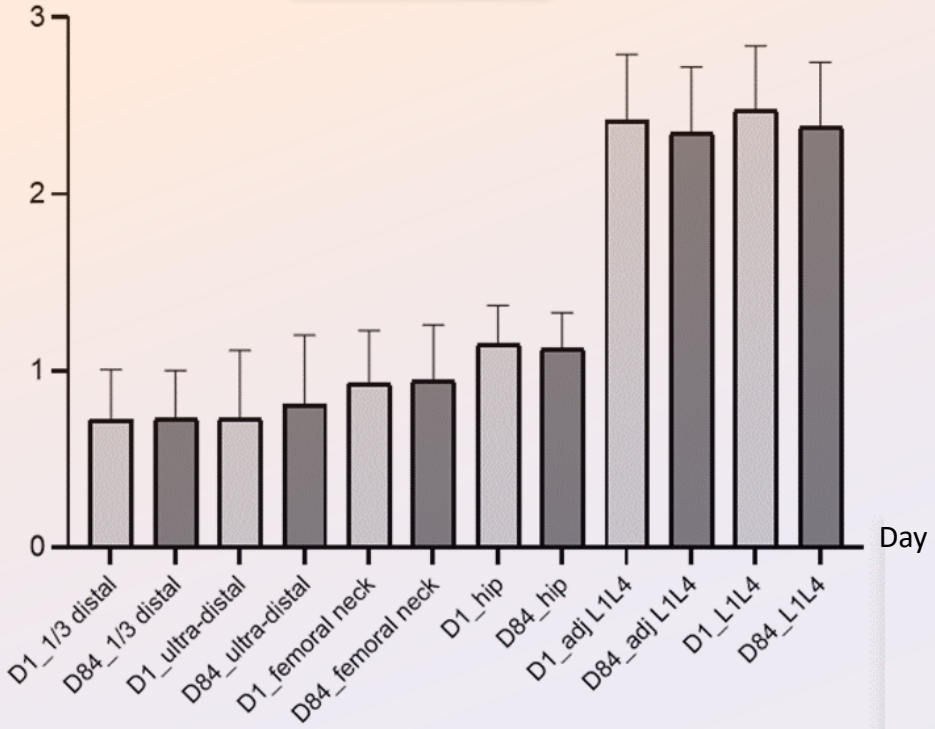
Consistent with a balanced increase in bone biomarkers, ***Bone Mineral Density and Trabecular Bone Score remained stable***

Data are presented as mean ± SEM

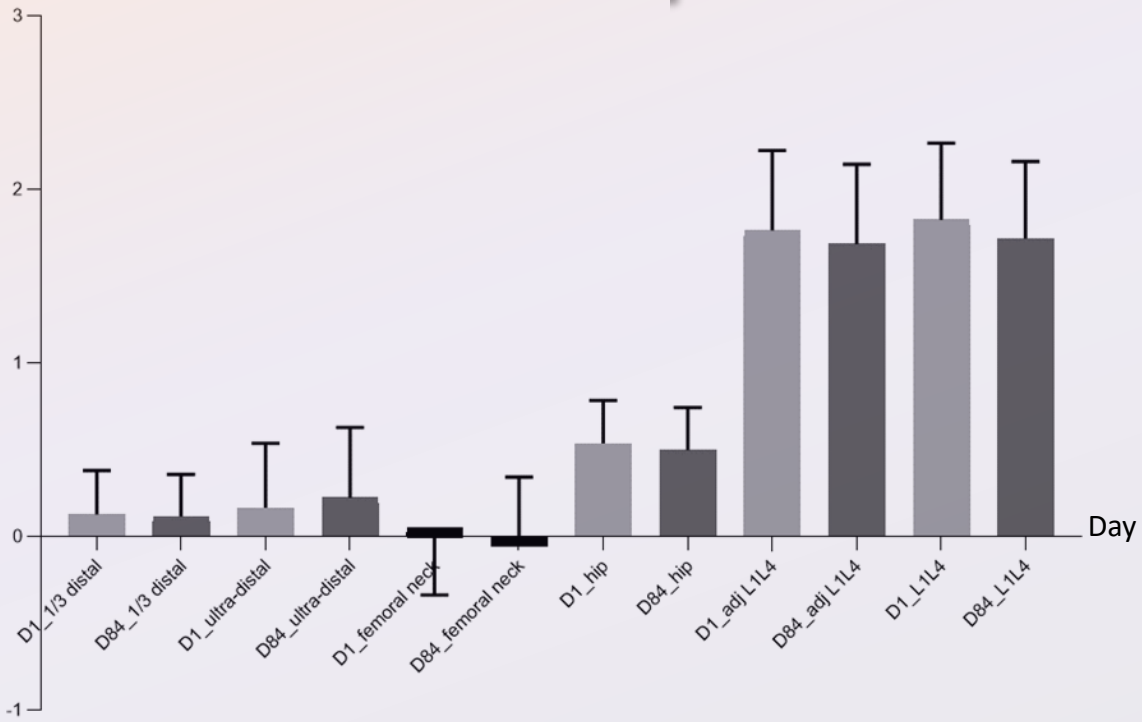
AMOLYT PHARMA

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

AMOLYT PHARMA

SUMMARY AND CONCLUSION

- Eneboparatide treatment for 3 months was well tolerated with no safety concerns.
- Standard of care (active vitamin D and oral calcium supplementation) was rapidly eliminated while mean ADsCa was maintained within the target range.
- Mean urinary calcium decreased to within the normal range including in patients with hypercalciuria at baseline.
- Bone biomarker data were consistent with a balanced resumption of bone turnover.
- Cohort 1 and Cohort 2 data support eneboparatide as a potential treatment of chronic hypoparathyroidism targeting urinary calcium reabsorption rather that bone resorption, and advancement to Phase 3 with 20 µg as the starting dose.
- A multicenter, randomized, placebo-controlled, double-blind Phase 3 study is underway in North America and Europe (CT.gov Id: NCT05778071).

CALYPSO STUDY

AMOLYT PHARMA