

Pharmacokinetic Clinical Studies Of An Orally Delivered Recombinant PTH Analog

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The Unigene logo is located in the bottom right corner of the slide. It features the word "unigene" in a lowercase, green, sans-serif font. The letter "u" is stylized with a small dot above it. The background of the slide includes a graphic of a glass vial tilted to the left, with several white, oval-shaped pills spilling out onto a light blue surface.

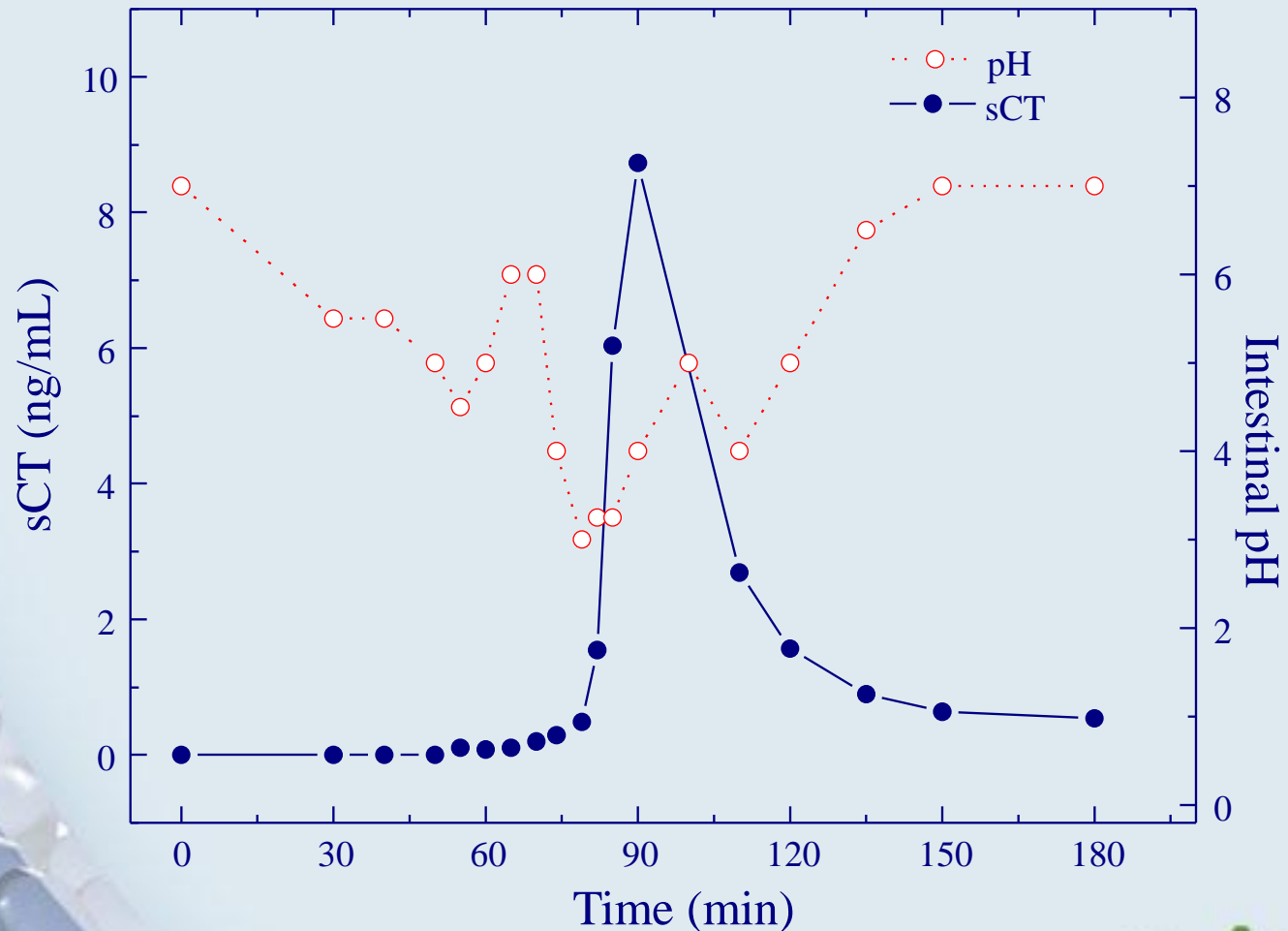
Goals of the Oral PTH Analog Program

- Overall Goal of Program is to Develop a Safe, Effective, and Cost-Efficient Orally Delivered Tablet Formulation of a PTH Analog
- Goal of Phase I PK Studies is to
 - Demonstrate blood levels sufficient for bone anabolic activity
 - Demonstrate PK variability consistent with requirements for efficacy and safety
 - Optimize the solid dosage form and evaluate its contribution to PK variability

Components of Unigene's Standard Solid Dosage Oral Delivery Formulation

Component Category	Tablet Contents
Protease Inhibitor	Organic Acid
Enhancer	Acylcarnitine
Enteric Coat	Eudragit L30D-55
Sub Coat	Kollicoat IR
Active Ingredient	Peptides and Small Proteins

Administration of Enteric-Coated sCT Capsule and Heidelberg Capsule in Dogs



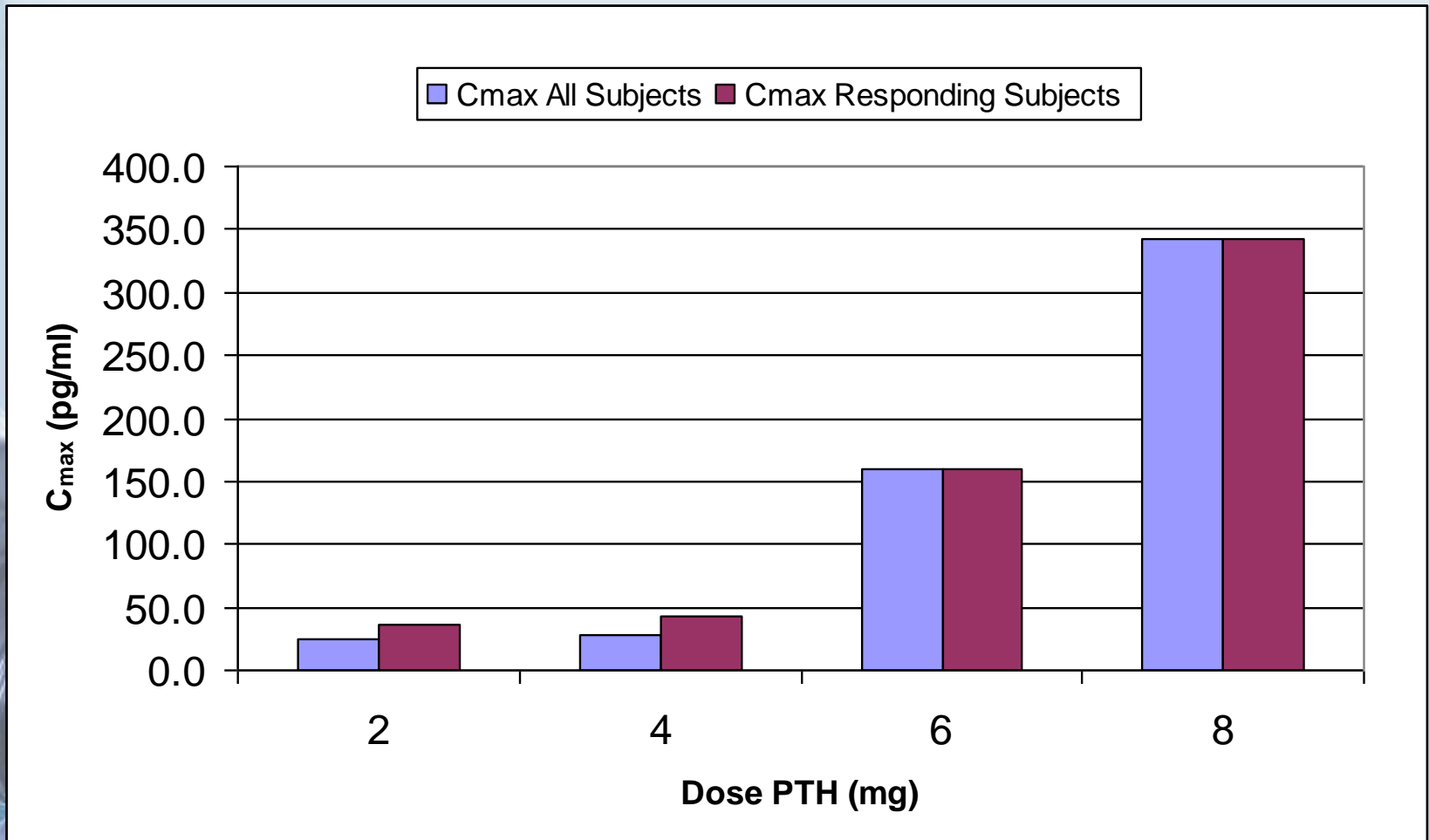
Objectives of Clinical Studies UGL-OR0802 and UGL-OR0901 with PTH Analog

- Measure PTH Analog Plasma Levels with a Sandwich ELISA That Measures Only the Intact Molecule
- Determine Whether Blood Levels and PK Profile are Adequate for Bone Anabolic Effect
 - UGL-OR0802 : Dose Finding Study
 - UGL-OR0901: Two-Period Replicate Dose Study to Determine Inter- and Intra-Subject Variability
- Determine Safety of Orally Administered PTH

Phase I Study UGL OR0802: PK and Safety Assessment of 4 Escalating Doses of rhPTH Analog

- *Design:* Single-blind, Placebo Controlled, 2 Period, Crossover Study With Two Cohorts
- *Study Medication:* PTH Analog in Formulated Tablets for Oral Delivery
- *Doses:* 2 mg, 4 mg, 6 mg and 8 mg of PTH Analog per Tablet and Placebo
- *Subjects:* 24 Healthy Postmenopausal Female Volunteers
- *Dosing:* Each Subject Randomized To A Two-period Dosing Schedule And Received A Single Dose Or Placebo At Each Period. Dosing was done in the morning following an overnight fast
- *Assessment:*
 - Measurement of Orthostatic Hypotension, ECG. Continuous Dual-Lead Cardiac Monitoring, Vital Signs, Laboratory Safety Events
 - Pharmacokinetic Parameters Measured by ELISA

UGL-OR0802: Mean C_{max} Values



Phase I Study UGL OR0802: PK and Safety Assessment of Escalating Doses (2, 4, 6, and 8 mg) of rhPTH Analog

- There was a linear dose response at the higher doses (4, 6 and 8 mg doses)
- The overall variability in the data was somewhat higher than anticipated
- Examination of the data indicated that the rate of elimination of the peptide was faster than would be predicted by the known subcutaneous half-life (~ 1 hour)
- Further examination led us to conclude that the half life of oral PTH is shorter (~ 15 min) and this is supported by the literature
- The primary reason for the higher than anticipated variability resulted from the infrequent blood collection intervals (every 30 min)
- First pass metabolism may also contribute to variability

Phase I Study UGL-OR0901: An Open Label , Randomized, Two-Period Replicate Dose Study of rhPTH Analog Tablets

- **Objectives:**

- To assess the safety and tolerability of orally administered rhPTH Analog in healthy volunteers
- To assess the between-subject pharmacokinetic variability
- To assess the intra-subject pharmacokinetic variability

- **Number of Subjects**

- 24 postmenopausal women were enrolled

- **Dose**

- Treatment A: 6 mg tablets; Treatment B: 2x4 mg tablets
- Subjects were dosed in the morning following an overnight fast

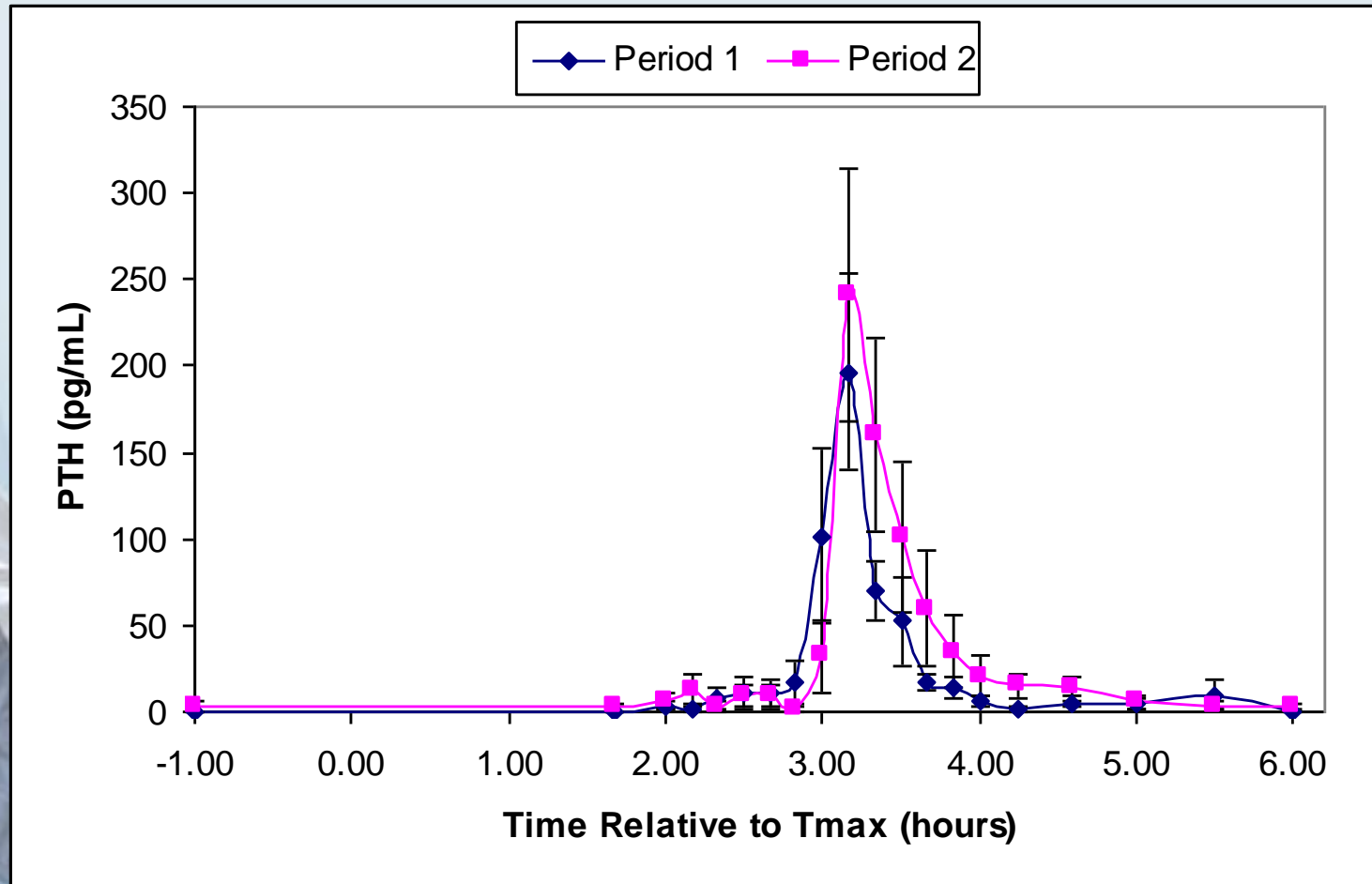
- **Sampling**

- Blood samples were taken at 10 min intervals between 2 and 5 hours following each dose

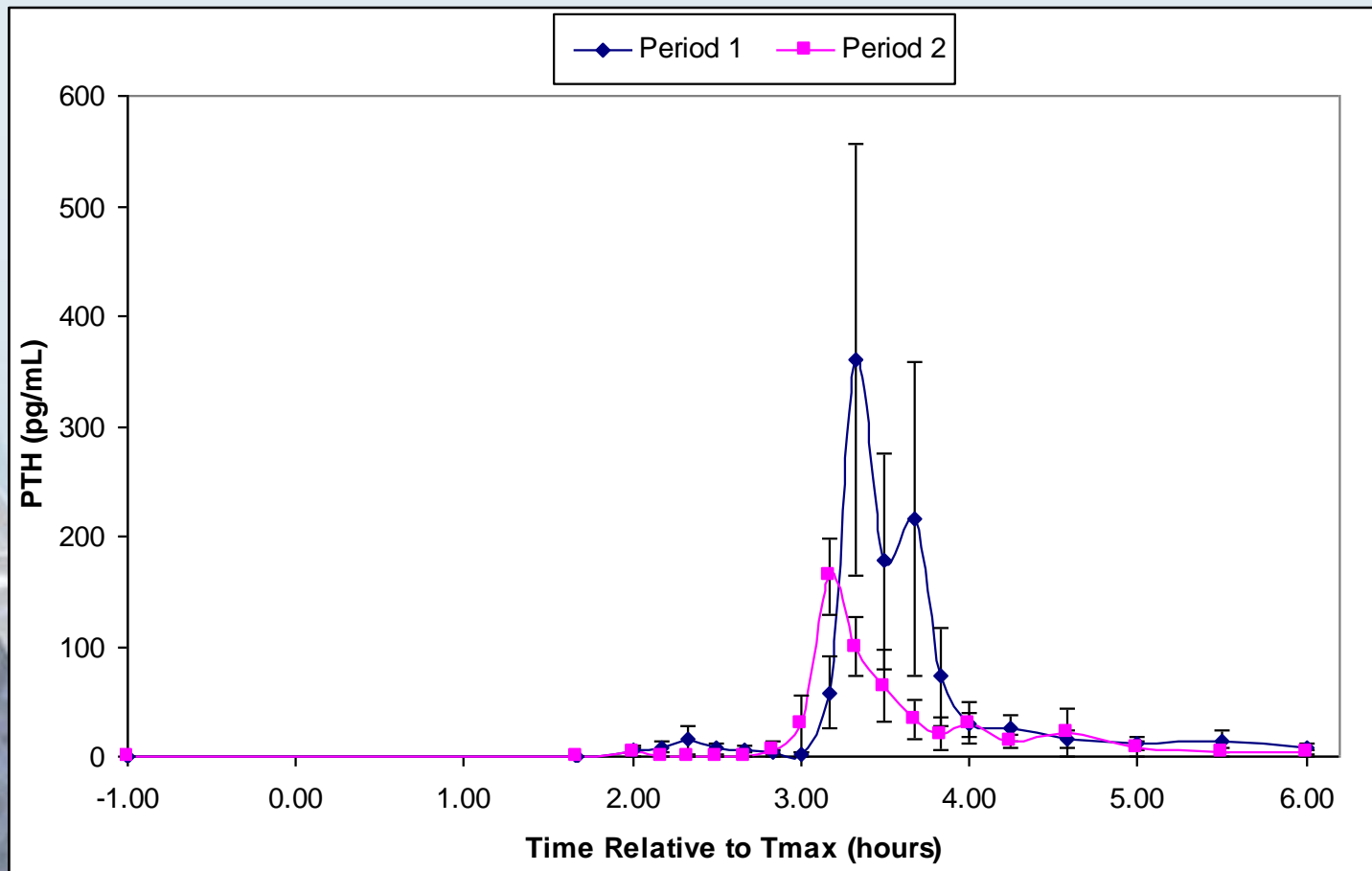
- **Assessment:**

- Measurement of ECG, Dual-Lead Cardiac Monitoring (Holter), Mobile Cardiac Telemetry, Vital Signs, Laboratory Safety Events
- Pharmacokinetic Parameters Measured by Sandwich ELISA Assays

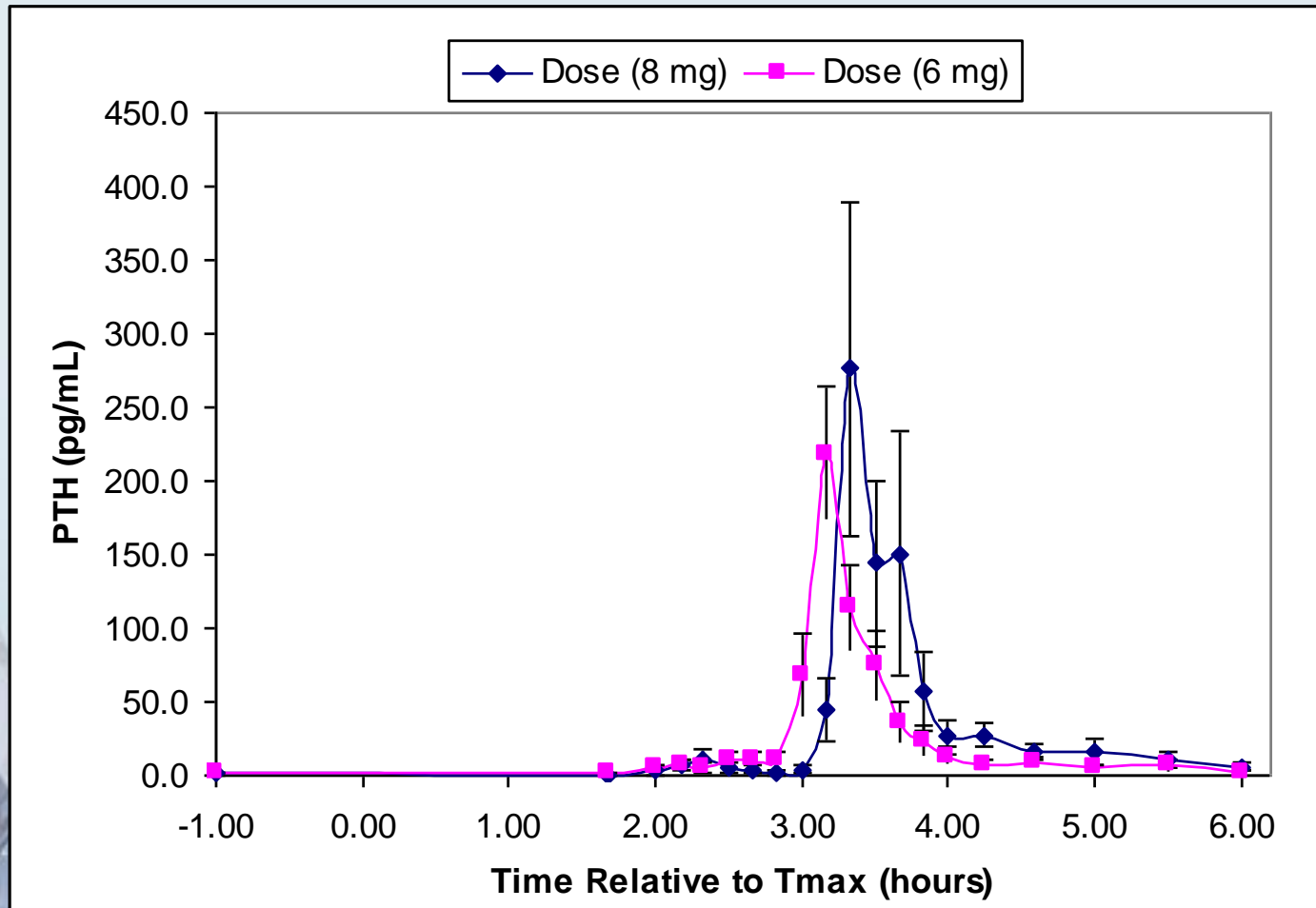
Period 1 vs Period 2 Intra-subject Variability 6 mg Dose



Period 1 vs Period 2 Intra-subject Variability 2x4 mg Dose



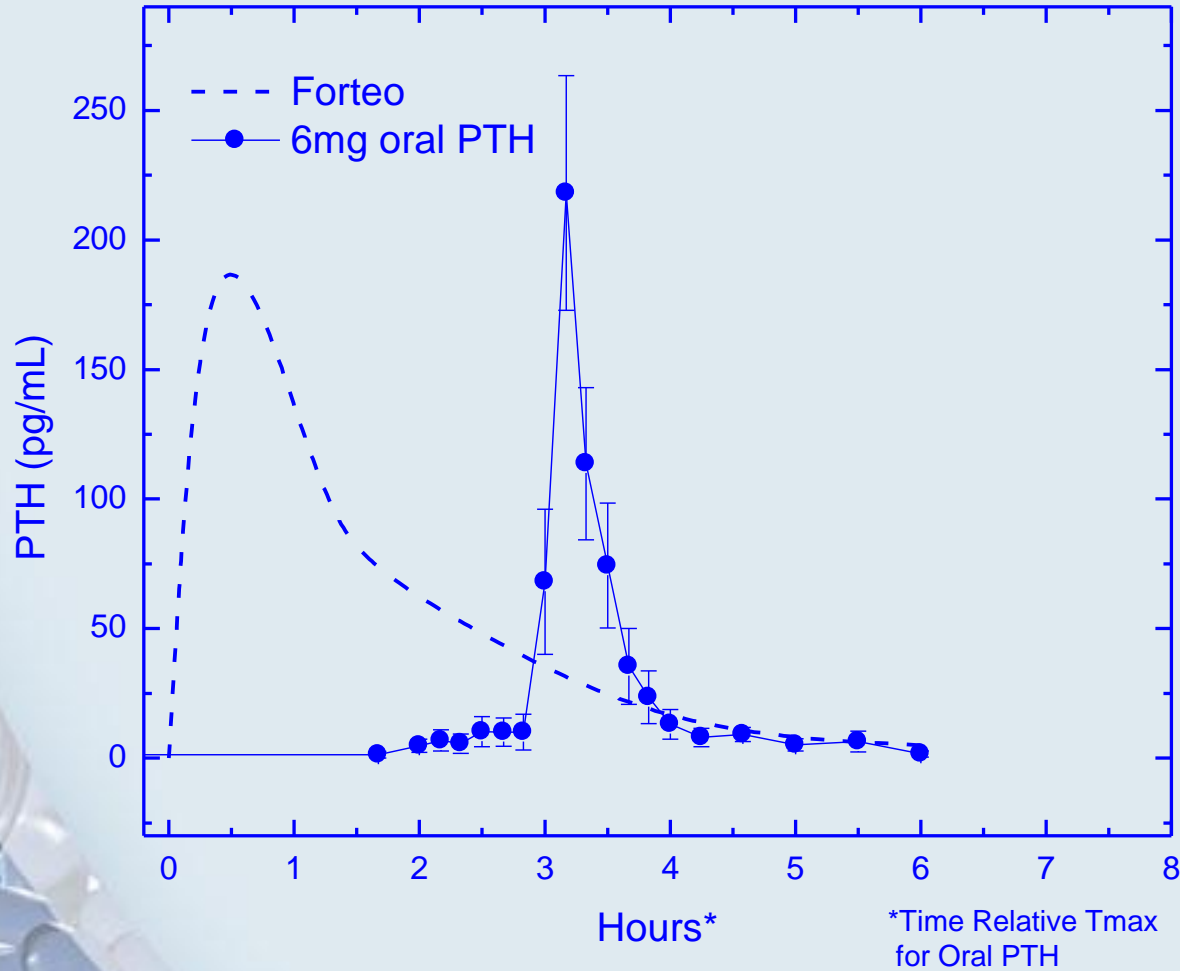
Mean Results Period 1 and 2 Combined 6 mg vs 2x4 mg Dose



PK Data from UGL OR0901

Dose (mg)	AUC (pg*hr/mL) Period 1	AUC (pg*hr/mL) Period 2	Cmax	Max to Mean Ratio
6	513	683	219	3.45
2x4	1002	468	276	6.0

Comparison of PK Profiles of Forteo[®] vs 6mg Dose of Oral PTH Analog



Conclusions from Phase I Study UGL-OR0901

PK Parameters

- The mean exposure per mg of oral dose was significantly increased compared to previous oral studies with PTH Analog
 - Mean Cmax of 218 pg/mL at the 6 mg dose is significantly higher than reported for teriparatide at the 20 µg dose (80 -175 pg/mL depending on study)
- The AUC values from this study are comparable to those reported for Forteo® and hence should be consistent with the PK profile required for bone anabolic activity
- The variability (Max to Mean ratio) for Cmax values for the 6 mg dose has been reduced by more than 50% compared to the previous study at the same dose

Serum Calcium (mg/dL) Periods 1&2 (Mean \pm SD)

Lab Reference Range: 8.5 – 10.1 mg/dL

PERIOD 1						
Dose	Baseline	1 hr	2 hr	4 hr	8 hr	24 hr
6 mg	9.5 \pm 0.3	9.1 \pm 0.2	9.2 \pm 0.2	9.1 \pm 0.2	9.1 \pm 0.2	8.8 \pm 0.3
2X4 mg	9.5 \pm 0.5	9.2 \pm 0.5	9.2 \pm 0.4	9.1 \pm 0.6	9.1 \pm 0.5	8.9 \pm 0.6

PERIOD 2						
Dose	Baseline	1 hr	2 hr	4 hr	8 hr	24 hr
6 mg	9.5 \pm 0.3	9.1 \pm 0.3	9.0 \pm 0.3	9.2 \pm 0.2	9.3 \pm 0.4	8.9 \pm 0.3
2X4 mg	9.5 \pm 0.5	9.2 \pm 0.7	9.2 \pm 0.9	9.3 \pm 0.8	9.4 \pm 0.6	9.0 \pm 0.5

Conclusions from Phase I Study UGL-OR0901

Safety Parameters

- There were no cardiac events as measured by ECG, Holter monitoring and telemetry at either the 6 mg or 2x4 mg dose
- There was one transient episode of symptomatic orthostatic hypotension at each dose level
- There were no serious AEs reported during the study, and no clinically significant changes were seen in total Ca, as well as PO₄, Mg and endogenous PTH

Path Forward

- An oral PTH analog formulation with acceptable bioavailability, variability and safety has been demonstrated
- Anabolic potential of oral PTH Analog will be confirmed in an multi-dose study in postmenopausal osteoporotic women where the primary endpoints will be serum P1NP and spine BMD
- Based on the current data, single tablet doses between 4 mg and 6 mg will be assessed in this study

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 - Musculoskeletal Diseases Group

Backup slides



Adverse Events vs C_{max} after Administration of Two 4 mg Tablets

Subject Number	Total Adverse Events		Cmax (pg/mL)	Clammy	Diaphoretic	Diarrhea	Dry heaves or vomited	Elevated blood pressure	Headache	Hot flashes	Lightheaded	Nausea	Orthostatic hypotension	Stomach cramps	Syncope
1	2	P1	31						1					1	
	4	P2	101				1	1				1		1	
5	None	P1	195												
	1	P2	152											1	
8	None	P1	64												
	3	P2	278						1			1		1	
9	3	P1	80		1						1		1		
	None	P2	57												
17	7	P1	1661		1	1	3		1	1		2		1	
	Dropout	P2													
18	None	P1	164												
	None	P2	148												
22	None	P1	597												
	Dropout	P2													
23	None	P1	95												
	None	P2	244												

Individual Results from UGL OR0901 (Responders)

Subject	UGNE	
	Period 1	Period 2
	6 mg dose	
	Cmax (pg/ml)	
3	113	34
4	429	524
6	93	675
7	861	77
10	247	688
11	499	781
12	102	259
13	17	NQ
14	128	40
15	70	260
16	37	35
19	88	56
20	140	69
21	295	Withdrew
24	NQ	120
Mean	223	278
sdev	234	285
CV	105%	102%
Median	120	120
Geomean	139	151
Min	17	34
Max	861	781

Endogenous PTH (pg/mL) Periods 1&2 Mean ± SD

Dose	Baseline	1 hr	2 hr	4 hr	8 hr	24 hr
6 mg	35.5 ± 14.8	27.0 ± 12.4	28.8 ± 12.1	27.5 ± 10.6 P<0.05	28.2 ± 11.8	36.4 ± 11.4
2X4 mg	36.4 ± 16.1	22.7 ± 17.3	28.0 ± 16.0	25.5 ± 16.3	24.2 ± 10.8	33.0 ± 16.8
Dose	Baseline	1 hr	2 hr	4 hr	8 hr	24 hr
6 mg	35.5 ± 14.8	32.7 ± 12.3	32.7 ± 9.5	25.6 ± 7.9	28.2 ± 11.8	25.5 ± 11.5
2X4 mg	36.4 ± 16.1	37.1 ± 12.6	33.8 ± 15.6	36.0 ± 17.7	33.5 ± 13.0	42.3 ± 19.2