PHARMACOKINETICS AND PHARMACODYNAMICS OF SUBCUTANEOUSLY (SC) ADMINISTERED DOSES OF BA058, A BONE MASS DENSITY RESTORING AGENT IN HEALTHY POSTMENOPAUSAL WOMEN

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OBJECTIVE

- Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue which leads to enhanced fragility and increased risk of fractures.[1]
- Normally, the process of bone turnover is a dynamic process consisting of bone mineralization and resorption. In addition to age, a number of underlying pathological mechanisms result in an imbalance in this process leading to the clinical sequelae of osteoporosis.
- Current therapeutic options used in the treatment of osteoporosis include:
  - Estrogens
  - Selective estrogen receptor modulators (SERMs)
  - Calcitonin (salmon)
  - Bisphosphonates
  - Monoclonal Antibodies (e.g. denosumab)
- A relatively new pharmacologic approach is the use of human parathyroid hormone (hPTH) and related analogues and peptides:
  - The 34-amino acid terminal fragment of hPTH, known as hPTH(1-34), appears to contain the full biological activity of native PTH(1-84) with regard to restoration of bone.[2] Teriparatide (Forteo®; Eli Lilly and Co., Indianapolis, Indiana), a recombinant human PTH (rhPTH(1-34)), was approved by the FDA in 2002 as a new therapy for osteoporosis. Teriparatide can stimulate bone formation, increase bone mass and reduce the risk of fractures.[3]
  - Human PTH-related peptide (hPTHrP) is related to the PTH family, is secreted endogenously, and is partially homologous with the sequence of hPTH at the amino-terminus, where 8 of the first 13 amino acids are identical in both peptides.[4]
  - hPTHrP has also been shown to have an important role in calcium homeostasis[4], normal skeletal development[5] and to restore bone mass in people when administered in an intermittent pattern.[6]
  - BA058 is a 34-amino acid analog of hPTHrP (1-34) with molecular modifications of specific amino acids.
  - BA058 is expected to have similar or greater efficacy in restoring bone mineral density in individuals with osteoporosis than hPTH(1-34), but with less risk of causing hypercalcemia. Initial *in vitro* and *in vivo* studies identified BA058 as displaying such properties.[7-10]
- The objective of the present investigation was to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) of multiple doses of BA058 when given by sc injection to healthy postmenopausal women.

METHODOLOGY

- This was a randomized, double-blind, placebo-controlled, multiple-dose safety, tolerability, and PK/PD study of sc administered BA058 in healthy postmenopausal women, conducted at 2 sites.
- A total of 39 eligible subjects were sequentially enrolled into 1 of 4 study groups (receiving 5, 20, 40, and 80 μg of BA058) consisting of 10 subjects each, with the exception of Group 2 which had only 9 subjects. Within each study group of 10 subjects, 8 were randomly assigned to receive BA058 and 2 were randomly assigned to receive placebo (Group 2 had only 1 placebo). All subjects received a single sc dose of study medication (BA058 or placebo) for 7 days. After a dose level had been determined to be well tolerated, subsequent cohorts of subjects were enrolled in the next study group.
- The demographic information of the subjects who were enrolled in the study is presented in Table 1.
- Pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, T_{last}, CL/F, k_{el}, $t_{1/2}$, and accumulation index [AI]) were calculated from plasma BA058 data on Days 1 and 7 using WinNonlin® Version.5.01 (Pharsight Corporation, Mountain View, CA). Moreover, $AUC_{0-\tau}$ and ratio of AUC_{0-t} to $AUC_{0-\infty}$ (AUCR) were computed for Day 1 and AI was computed for Day 7.
- Dose proportionality of BA058 PK parameters (C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, and $AUC_{0-\tau}$) was evaluated using the power model using PROC MIXED of SAS®. Version 8.2 (SAS Institute Inc., Cary, NC).
- Descriptive statistics for BA058 plasma concentrations and PK parameters and PD concentration data in serum (total and ionized calcium, phosphorus: PTH(1-84),1, 25-dihydroxyvitamin D [vitamin D], procollagen type 1 N-propeptide [P1NP-marker of bone formation], and C-telopeptide type 1 collagen [CTX- marker of bone resorption], and anti-BA058 antibody) and urine (calcium, phosphorus, cyclic AMP [c-AMP], and creatinine) were calculated using SAS®.

RESULTS

Pharmacokinetics:

- The mean plasma BA058 concentrations-time profile following BA058 doses are presented in Figure 1.
- Plasma BA058 PK parameters following BA058 doses for Days 1 and 7 are summarized in Tables 2 and 3.
- BA058 was characterized by a rapid absorption following sc administration with a mean C_{max} occurring within approximately 1 hour postdose.
- BA058 exhibited a short half-life with mean $t_{1/2}$ values of 1.05 to 2.59 hours.
- Apparent clearance was 28.56 L/hr following the lowest dose (5 μg) and ranged from 82.74 L/hr to 103.9 L/hr following the 20, 40, and 80 μg doses.
- The results indicated that exposure to BA058 was relatively comparable between Days 1 and 7 for each BA058 dose.
- Mean AI values ranged from 0.844 to 1.12 following multiple dosing of BA058. Moreover, mean PK parameters values of T_{max}, $t_{1/2}$, and CL/F were comparable between Days 1 and 7.
- Dose proportionality was concluded for C_{max} and AUC following the BA058 doses investigated (Table 4 and Figures 2 and 3. Note: $AUC_{0-\infty}$ and $AUC_{0-\tau}$ are presented as AUC_{0-inf} and AUC_{0-tau}, respectively in the figures).

Pharmacodynamics:

- The mean baseline-adjusted total and ionized calcium, phosphorus: PTH(184), vitamin D, P1NP, and CTX following BA058 doses and placebo are presented in Figures 4 and 5.
- The mean urinary excretion rate of calcium, phosphorus, c-AMP, and creatinine following BA058 doses and placebo are presented Figure 6.
- Compared to placebo and predose levels, repeated sc administration of BA058 doses resulted in a small transient increase in serum calcium that remained within the normal laboratory ranges (normal range for total calcium: 8.4 to 10.4 mg/dL, normal range for ionized calcium: 1.11 to 1.37 mmol/L).
- Serum phosphorus levels temporarily decreased following the sc administration of BA058 doses compared to placebo and predose levels (normal range: 2.6 to 4.7 mg/dL).
- Consistent with physiological expectations, serum PTH (1-84) concentrations marginally and briefly decreased and vitamin D concentrations slightly increased following BA058 doses compared to placebo and predose levels.
- Serum P1NP concentrations rose above baseline for all dose groups by Day 8 in an apparent but non-significant dose-dependent manner.
- Serum CTX fluctuated around baseline values without any apparent dose-proportionality.
- While mean urinary excretion rates of c-AMP increased immediately following BA058 administration; those of calcium, phosphorus, and creatinine generally stayed at the predose levels.
- The majority of observed changes in the levels of PD markers in serum and urine were small in magnitude and remained within 1 SD of the mean.
- No antibodies to BA058 were detected prior to or following the administration of BA058 or placebo doses.

Table 1: Demographic Summary of Subjects Enrolled in the Current Investigation

Treat		5 μg	20 μg	40 μg	80 μg	Pooled Active	Pooled Placebo	Total
Gender	Female	8	8	8	8	32	7	39
Race	Black	1	3	0	0	4	0	4
	Caucasian	4	3	8	8	23	7	30
	Hispanic	3	2	0	0	5	0	5
Frame Size	Small	2	1	1	0	4	0	4
	Medium	5	7	4	8	24	5	29
	Large	1	0	3	0	4	2	6

Table 2: Summary of Plasma BA058 Pharmacokinetic Parameters Following 5 μg Through 80 μg BA058 Doses - Day 1

	Treatment A	Treatment B	Treatment C	Treatment D
Pharmacokinetic Parameters	Mean± SD (N)	Mean± SD (N)	Mean± SD (N)	Mean± SD (N)
C_{max} (pg/mL)	43.1 ± 10.7	115 ± 53.9	223 ± 99.0	310 ± 54.3
	(7)	(8)	(8)	(8)
T_{max} (hr)[#]	0.566 (0.531, 1.00)	0.296 (0.250, 0.624)	0.494 (0.262, 0.579)	0.752 (0.251, 1.01)
	(7)	(8)	(8)	(8)
T_{last} (hr)[#]	2.01 (1.50, 4.00)	2.01 (1.00, 4.00)	4.00 (1.51, 6.01)	7.00 (4.00, 12.0)
	(7)	(8)	(8)	(8)
AUC_{0-t} (pg*hr/mL)	78.439 ± 45.472	160.52 ± 110.83	419.89 ± 275.15	949.89 ± 493.58
	(7)	(8)	(8)	(8)
$AUC_{0-\infty}$ (pg*hr/mL)	187.36 ± 54.536	257.17 ± 119.05	592.94 ± 281.40	1055.6 ± 513.61
	(4)	(5)	(6)	(8)
$AUC_{0-\tau}$ (pg*hr/mL)	186.92 ± 54.397	257.16 ± 119.02	592.90 ± 281.37	1053.2 ± 511.27
	(4)	(5)	(6)	(8)
$t_{1/2}$ (hr)	2.59 ± 0.690	1.05 ± 0.314	1.65 ± 0.254	2.30 ± 0.715
	(4)	(5)	(6)	(8)
k_{el} (1/hr)	0.282 ± 0.0722	0.713 ± 0.229	0.428 ± 0.0603	0.335 ± 0.127
	(4)	(5)	(6)	(8)
AUCR	0.521 ± 0.111	0.828 ±0.0449	0.838 ± 0.0703	0.892 ± 0.0369
	(4)	(5)	(6)	(8)
CL/F (L/hr)	28.56 ± 8.727	94.20 ± 46.04	84.15 ± 46.04	94.61 ± 51.09

= T_{max} and T_{last} are presented as Median (Minimum, Maximum)

Table 3: Summary of Plasma BA058 Pharmacokinetic Parameters Following 5 μg Through 80 μg BA058 Doses - Day 7

	Treatment A	Treatment B	Treatment C	Treatment D
Pharmacokinetic Parameters	Mean± SD (N)	Mean± SD (N)	Mean± SD (N)	Mean± SD (N)
C_{max} (pg/mL)	40.8 ± 7.63	109 ± 19.2	207 ± 77.7	436 ± 688
	(6)	(8)	(8)	(8)
T_{max} (hr)[#]	1.05 (0.514, 1.53)	0.512 (0.250, 3.05)	0.492 (0.349, 1.00)	0.507 (0.500, 1.00)
	(6)	(8)	(8)	(8)
T_{last} (hr)[#]	2.53 (1.50, 4.08)	3.00 (1.11, 4.00)	3.49 (2.00, 8.02)	6.00 (4.00, 8.02)
	(6)	(8)	(8)	(8)
AUC_{0-t} (pg*hr/mL)	80.704 ± 30.441	171.58 ± 82.031	407.98 ± 219.70	1003.0 ± 383.45
	(6)	(8)	(8)	(8)
$AUC_{0-\tau}$ (pg*hr/mL)	NC	228.20 ± 95.154	481.88 ± 226.19	1080.3 ± 408.57
	(0)	(6)	(8)	(8)
$t_{1/2}$ (hr)	NC	1.05 ± 0.244	1.43 ± 0.397	1.69 ± 0.425
	(0)	(6)	(8)	(8)
k_{el} (1/hr)	NC	0.694 ± 0.165	0.527 ± 0.192	0.437 ± 0.124
	(0)	(6)	(8)	(8)
CL/F (L/hr)	NC	103.9 ± 53.01	102.0 ± 53.34	82.74 ± 26.95
	(0)	(6)	(8)	(8)
AI	NC	1.10 ± 0.369	0.844 ± 0.0673	1.12± 0.353
	(0)	(5)	(6)	(8)

# = T_{max} and T_{last} are presented as Median (Minimum, Maximum)
NC= Not calculable

Table 4: Dose Proportionality Analysis of Plasma BA058 Following 5 μg Though 80 μg BA058 Doses

Day	Pharmacokinetic Parameters	Slope	Standard Error	95% CI
1	C_{max}	0.77861	0.1375	(0.4935, 1.0637)
	AUC_{0-t}	0.90714	0.1237	(0.6542, 1.1600)
	$AUC_{0-\infty}$	0.99565	0.2024	(0.5685, 1.4228)
7	C_{max}	0.99804	0.0985	(0.7938, 1.2023)
	$AUC_{0-\tau}$	1.14127	0.1649	(0.7974, 1.4852)

Figure 1: Mean Plasma BA058 Concentrations Following BA058 Doses

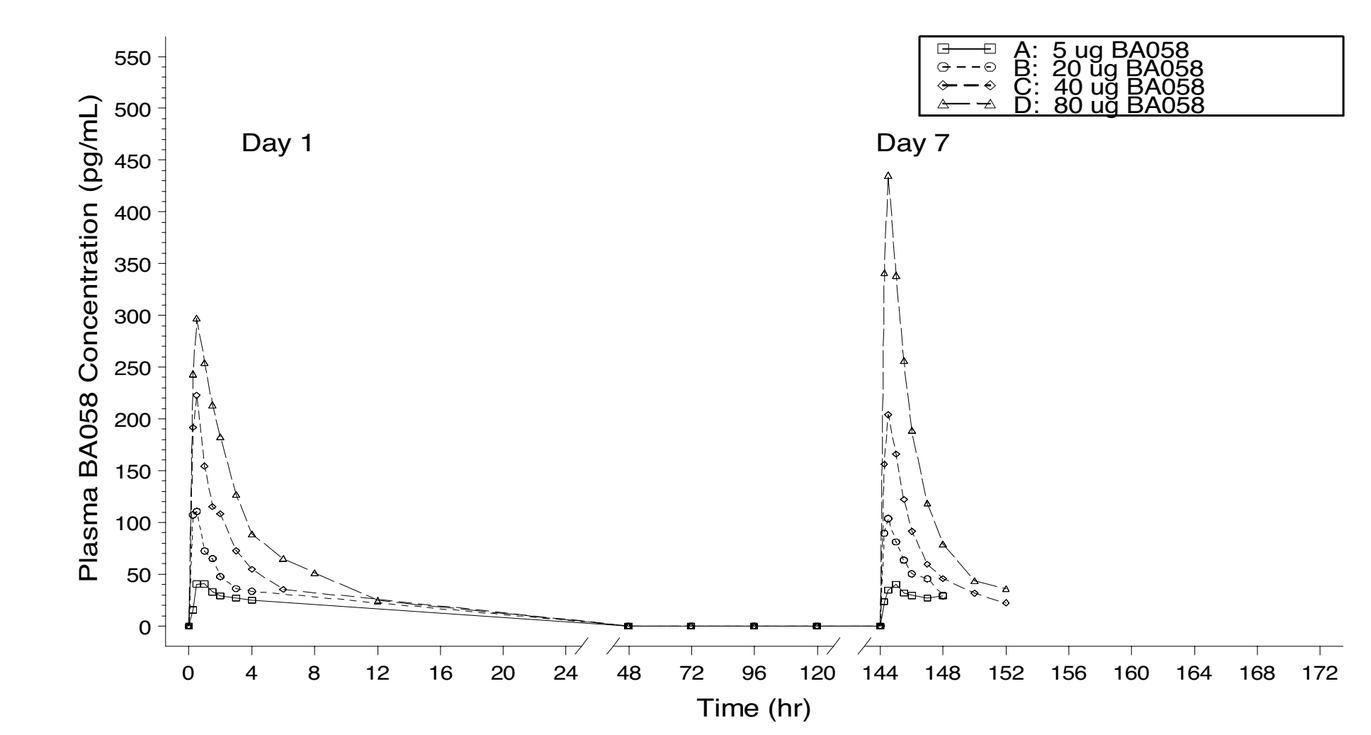


Figure 2: Dose Proportionality Assessments of BA058 Doses –Day 1

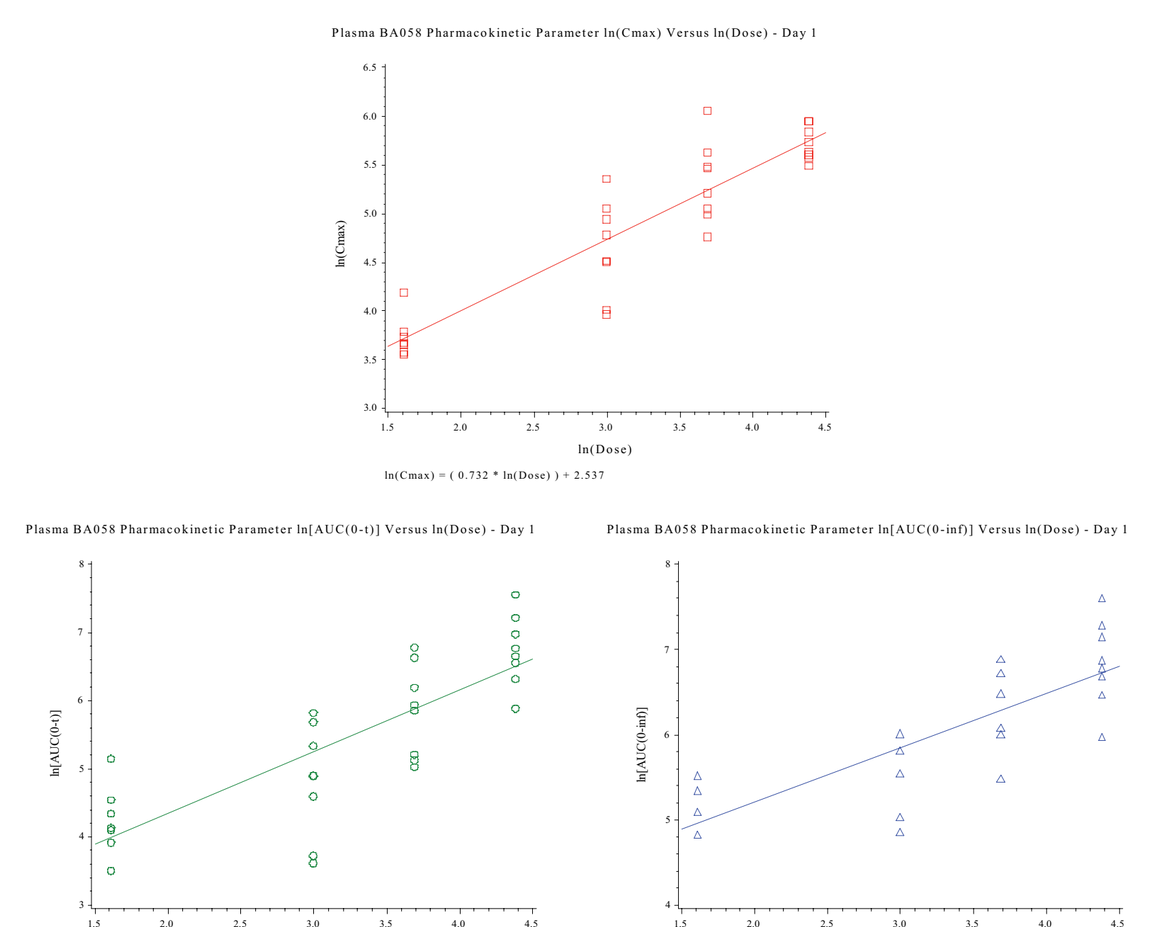


Figure 3: Dose Proportionality Assessments of BA058 Doses –Day 7

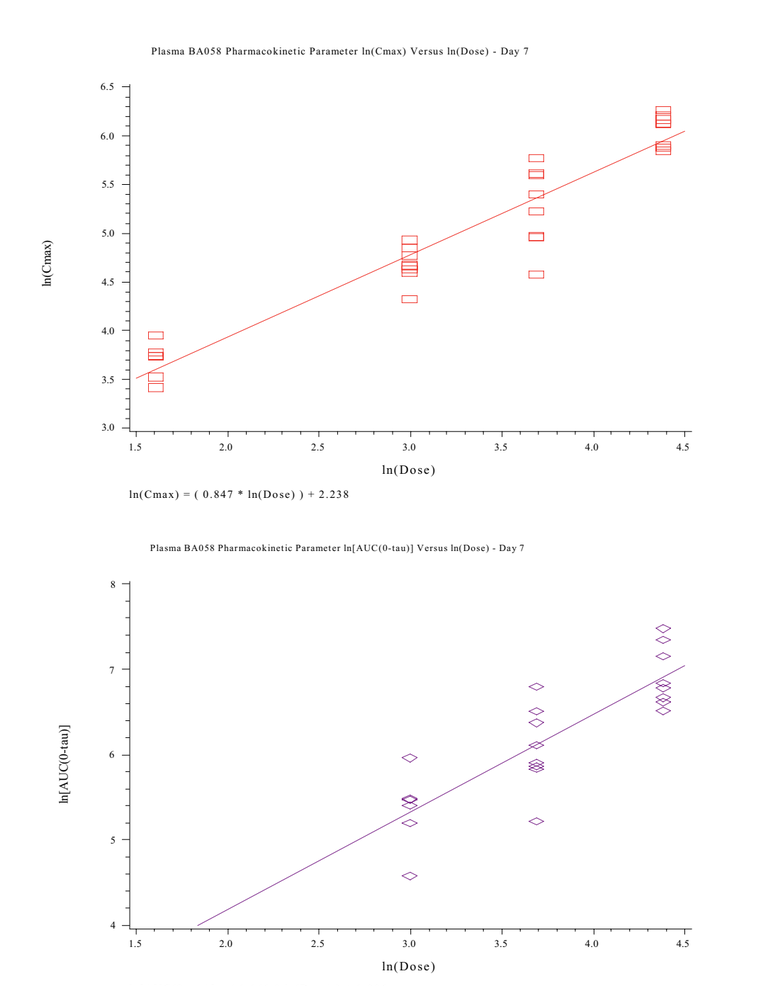


Figure 4: Mean Baseline-Adjusted Total and Ionized Calcium, Phosphorus and Vitamin D Following BA058 Doses and Placebo

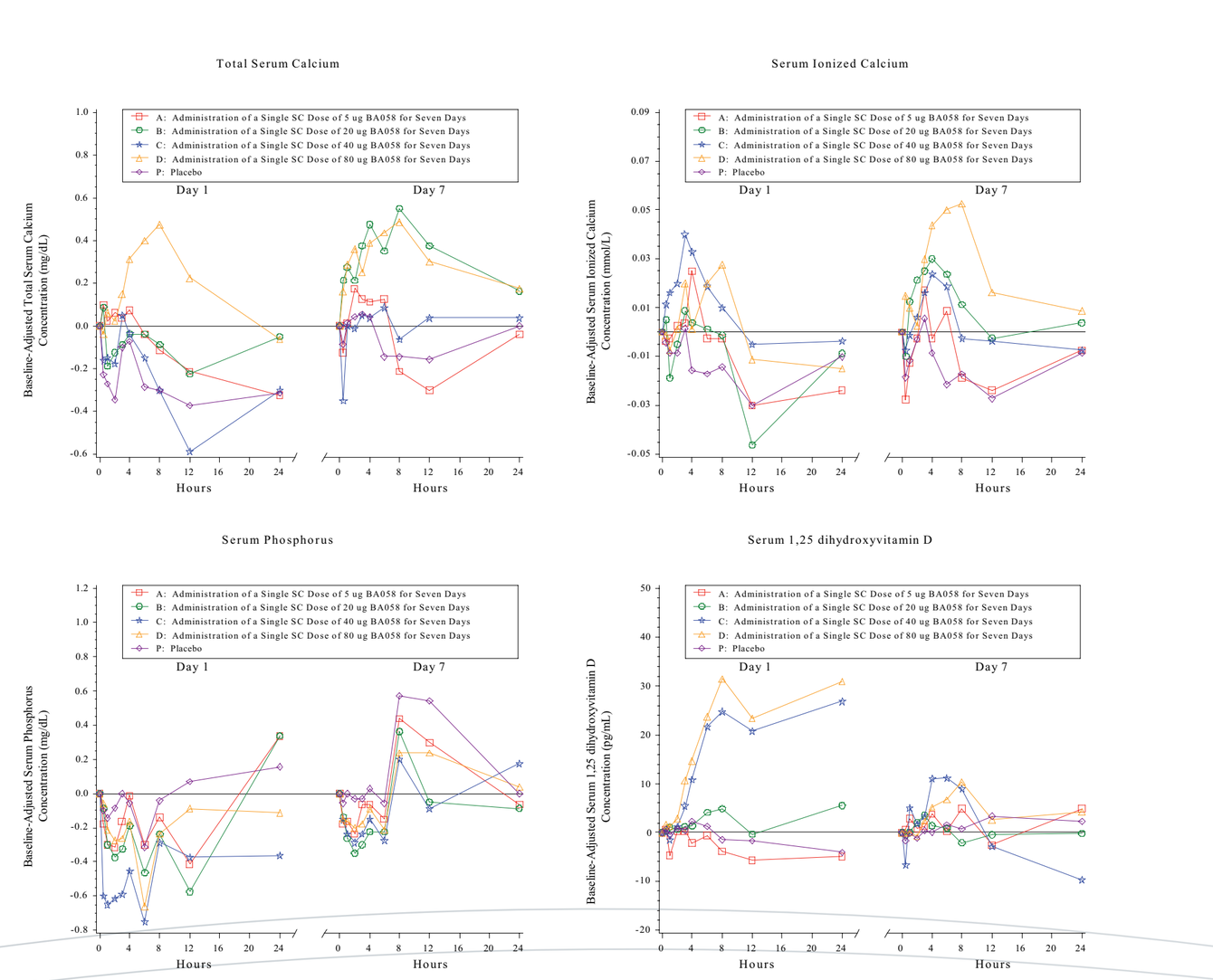


Figure 5: Mean Baseline-Adjusted PTH(1-84), P1NP, and CTX Following BA058 Doses and Placebo

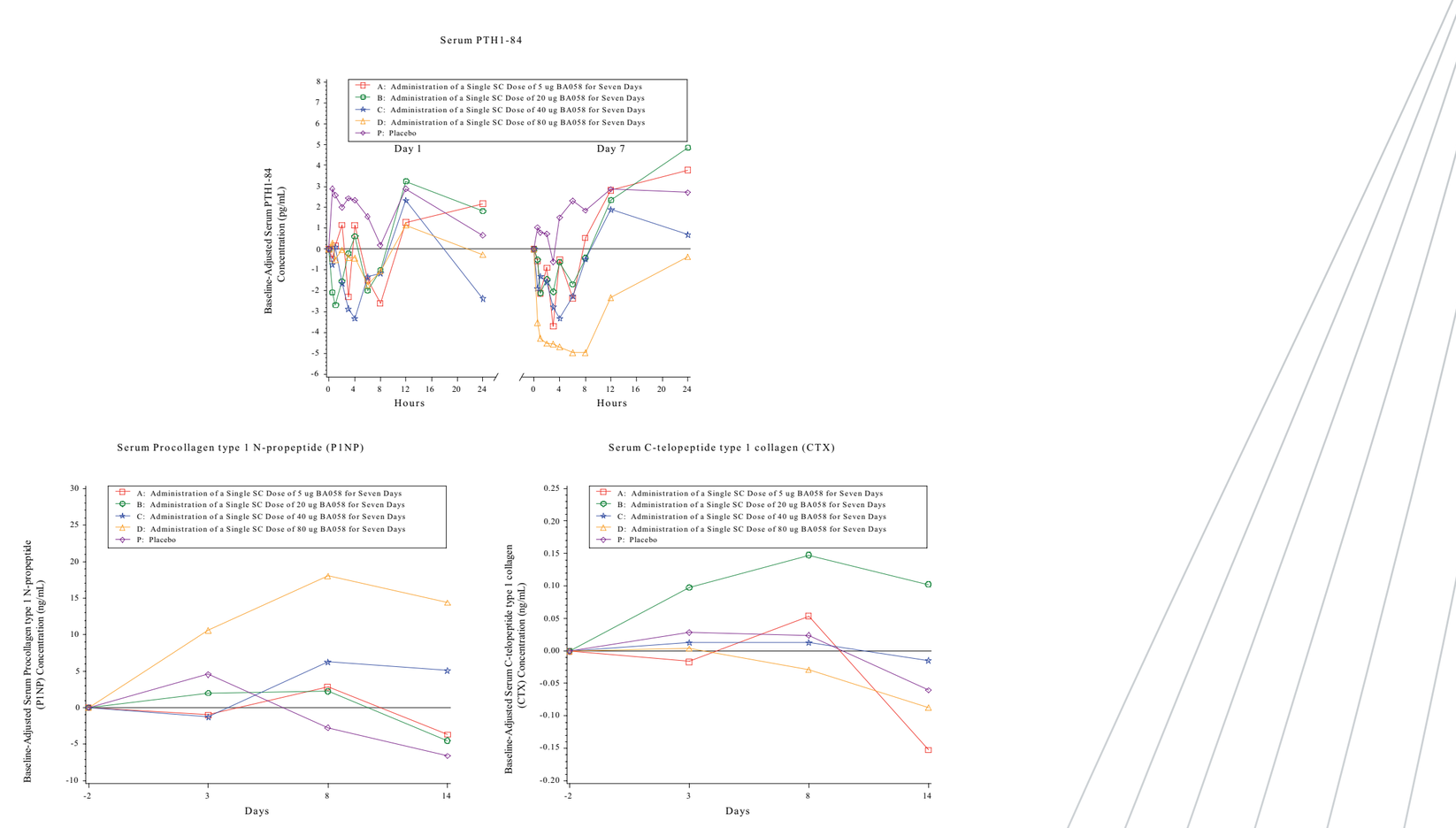
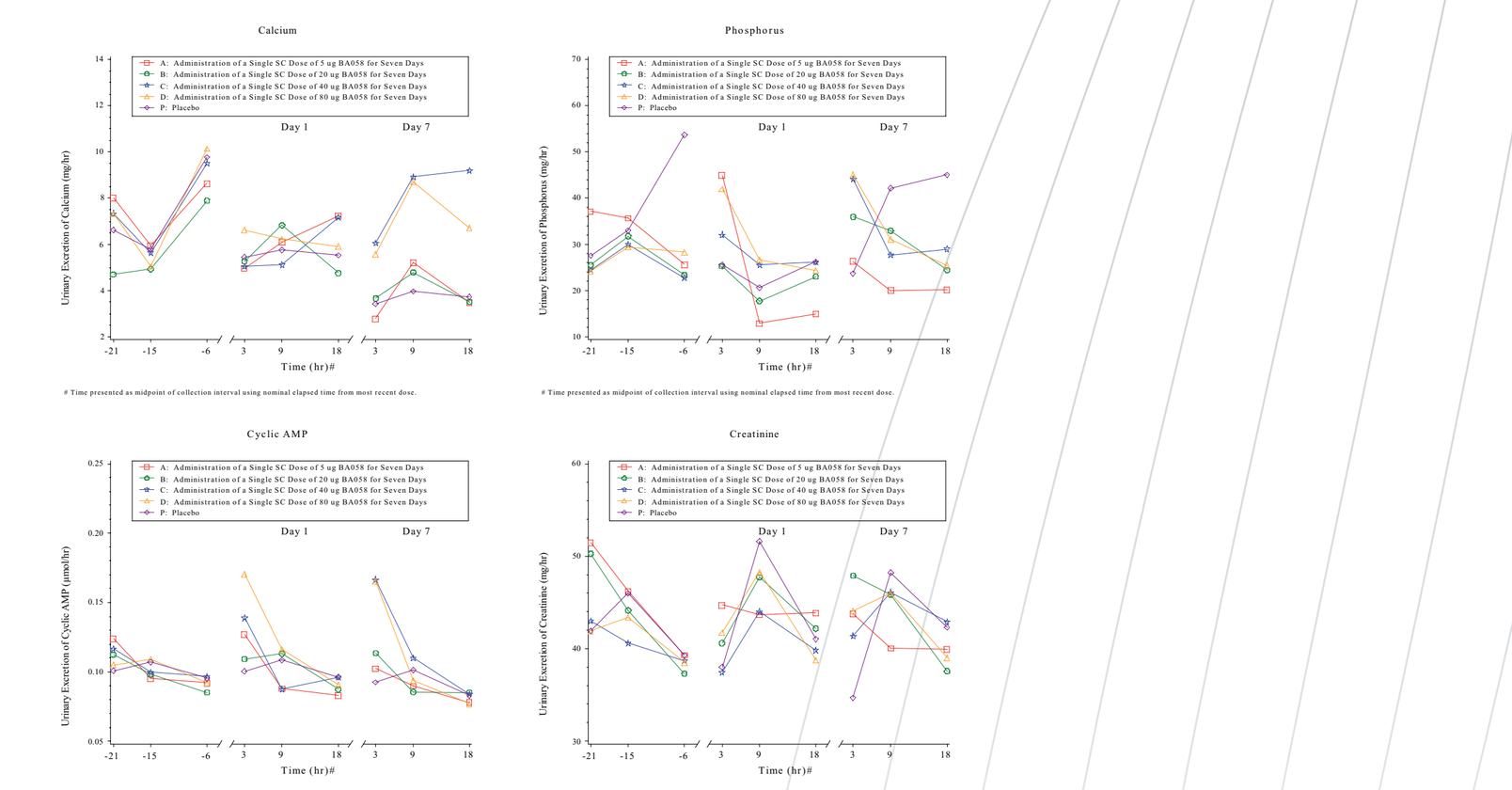


Figure 6: Mean Urinary Excretion Rate of Calcium, Phosphorus, c-AMP, and Creatinine Following BA058 and Placebo



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