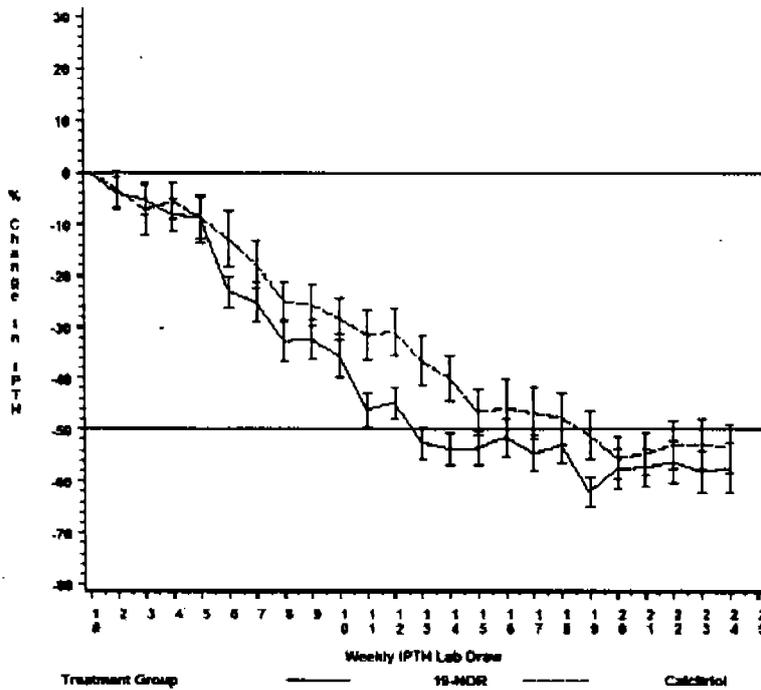


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Figure 4: Plot of Mean \pm SEM for Percent Change from Baseline in iPTH by Weekly iPTH Lab Draw for All Treated Patients (Cross Reference: Appendix 10.0, Figure 1a)



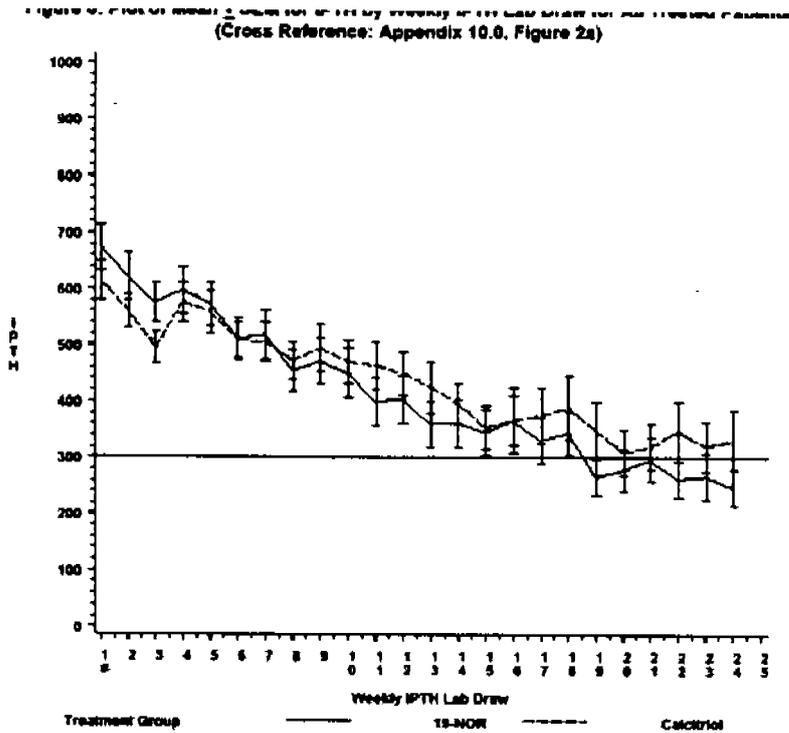
Lab Draw 1 is the Baseline laboratory determination
Note: Horizontal reference lines at 0 and -50

The mean percent change from last baseline in iPTH levels for all treated patient groups was greater than -50% by Week 13 for the [TRADE NAME] treatment group and Week 19 for the Calcijex treatment group. At Week 13, the mean percent change was -36.7% for the Calcijex treatment group. After achieving a mean 50 % iPTH reduction, both treatment group means stayed consistently below the -50 % iPTH reference line. At Treatment Week 24, the mean percent change from last baseline in iPTH levels for all treated patients was -57.4% for the [TRADE NAME] treatment group and -53.7% for the Calcijex treatment group.

A significantly greater reduction in percent change from baseline in iPTH occurred in the [TRADE NAME] treatment group at Treatment Weeks 11 through 14. The [TRADE NAME] treatment group had a mean percent change greater than -50% at Weeks 13 and 14. The maximum percent change for the Calcijex group during this period was -40 at Week 14.

APPENDIX 10.0
FIGURE 1a

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Lab Draw 1 is the Baseline laboratory determination
Note: Horizontal reference line at 300.

A minimum serum iPTH level of 300 pg/mL was required for entry into the Treatment Phase. In this graph for all treated patients, the baseline treatment group means for iPTH were approximately 670 pg/mL and 620 pg/mL for the [TRADE NAME] and Calcijex treatment groups respectively. At Treatment Week 19, the mean iPTH response for the [TRADE NAME] treatment group was below 300 and remained below 300 through Treatment Week 24. The mean iPTH response for the Calcijex group did not drop below 300.

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Table 15: Statistically Significant Change from Last Baseline in iPTH for All Treated Patients (Cross Reference 10.3.4.2.a)

Lab draw	Group	N	Baseline	Lab draw	Change from baseline	Between Group Comparisons for			
						change		baseline	
			mean (range)	mean (range)	mean (SE)	p-value	mean (SE)	p-value	
Week 11	Capthrol	75	704.71	399	-305.7	-115.4 (37.76)	0.003**	51.75 (61.65)	0.403
	Calcijex	74	662.98	482.62	-180.3				
Week 12	Capthrol	78	686.38	404	-282.4	-77.69 (35.85)	0.032*	32.40 (58.01)	0.584
	Calcijex	70	653.96	449.28	-204.7				
Week 13	Capthrol	72	692.31	358.72	-333.6	-104.3 (40.57)	0.011*	36.22 (62.70)	0.543
	Calcijex	67	654.09	424.78	-229.3				

*, **, *** indicate statistical significance (2-tailed) at the 0.05, 0.01, or 0.001 levels respectively.

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A significantly greater reduction in the [TRADE NAME] treatment group begins at Treatment Week 11 and continues through Week 13 ($p < 0.032$). A between group comparison of last baseline means was not statistically significant.

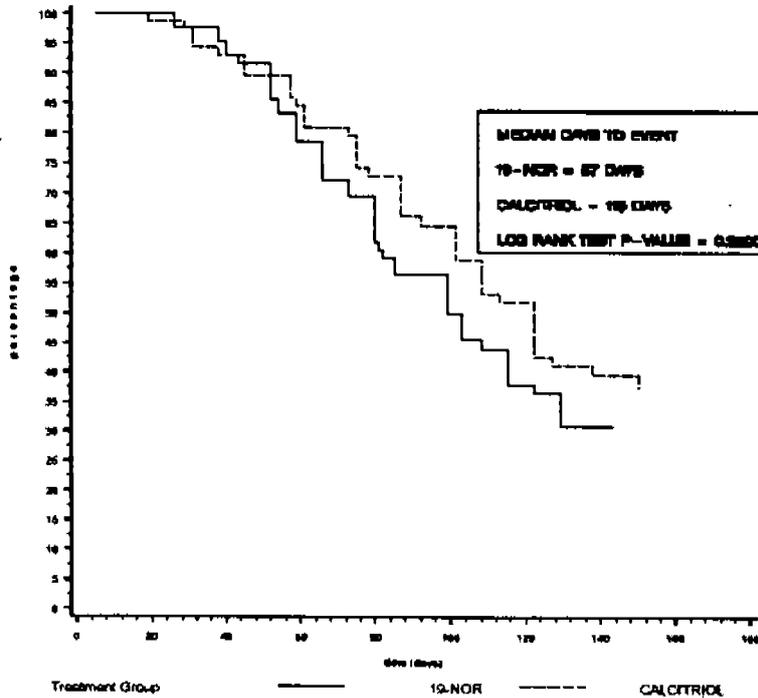
The previous Figures and Tables suggest that [TRADE NAME] was reducing iPTH levels more rapidly than Calcijex. To validate this observation, the number of days to the first period of four consecutive 50% decreases in iPTH was analyzed by the Kaplan-Meier method. As shown in the next Figure, the time to the first incidence of four consecutive 50% decreases in iPTH was not significant between treatment groups ($p = 0.2500$).

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Figure 6: Kaplan-Meier Curves for Time (Days) to First Period of Four Consecutive 60% Decreases in IPTH (Cross Reference Appendix 10.0, Figure 13a)



APPENDIX 10.0
FIGURE 13a

APPENDIX 10.0
FIGURE 13a

Primary Efficacy Variables, Serum Calcium and Calcium x Phosphorus Product

Serum Ca and Ca x P levels were evaluated to determine whether the incidence of hypercalcemia and/or elevated Ca x P was lower in patients receiving [TRADE NAME] than in patients receiving Calcijex. Testing was done prior to dialysis at the first and second dialysis sessions of the week, but the results were not available to the Investigator until at least the following dialysis session. Thus, the patient would have received at least two doses of drug and two calcium determinations prior to dose reduction for hypercalcemia, although per the protocol, a patient should have been dose reduced upon a single incidence of hypercalcemia for safety purposes. Therefore, two consecutive instances of hypercalcemia were chosen as an endpoint for analysis, to better approximate the clinical scenario of hypercalcemia upon which most dosing changes for drug were actually based. The same rationale led to choosing two measurements of Ca x P > 75 as evidence of clinically significant product elevation. The following Table is a summary of all treated patients meeting the protocol specified Ca and/or Ca x P elevation endpoints.

APPENDIX 10.0
TABLE 1

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Table 16: Summary of Calcium and Calcium x Phosphorus Elevation for All Treated Patients (Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Caphrol N = 99		Calcijex N = 99		p-value*
	number	percent	number	percent	
Patient became hypercalcemic and/or had a Ca x P > 75 at least once during treatment	77	78.6	64	64.6	0.040*
Patient became hypercalcemic for at least two consecutive lab draws and/or had a Ca x P > 75 for at least one period of four consecutive lab draws	31	31.6	32	32.3	1.000
Patient became hypercalcemic for at least one lab draw	27	27.8	17	17.2	0.069
Patient became hypercalcemic for at least one period of two consecutive lab draws	8	8.2	8	8.1	1.000
Patient was hypercalcemic at the final lab draw	4	4.1	6	6.1	0.747
Patient had a Ca x P > 75 for at least one lab draw	72	73.5	56	58.6	0.035*
Patient had a Ca x P > 75 for at least one period of four consecutive lab draws	26	26.5	26	26.3	1.000

* P-value derived from a Fisher's exact test.

* Indicates statistical significance (2-tailed) at the 0.05 level.

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For all treated patients, an analysis of serum Ca and P data indicated that the clinically relevant Ca and/or Ca x P elevation endpoints in the above tables were met without significant difference between treatment groups. Only the incidence of a single elevation of Ca and/or Ca x P was significantly higher in the [TRADE NAME] group (p < 0.040). This was not considered clinically relevant by the Sponsor. For all evaluable patients, the analysis of serum Ca and P data also showed a single incidence of an elevation of Ca and/or Ca x P was significantly higher in the [TRADE NAME] group (p < 0.025). This was not considered clinically relevant.

Table 17: Summary of Calcium and Calcium x Phosphorus Elevation in Relation to iPTH Endpoint for All Treated Patients* (Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Caphrol N = 83		Calcijex N = 75		p-value*
	number	percent†	number	percent†	
Patient had a 50% decrease in iPTH but became hypercalcemic prior	1	1.2	1	1.3	1.000
Patient had a 50% decrease in iPTH coincident with hypercalcemia	2	2.4	4	5.3	0.424 ✓
Patient had a 50% decrease in iPTH and became hypercalcemic after	22	26.5	12	16.0	0.124 ✓
Patient had a 50% decrease in iPTH but had elevated Ca x P values for four consecutive lab draws prior	1	1.2	4	5.3	0.191
Patient had a 50% decrease in iPTH coincident with elevated Ca x P values for four consecutive lab draws	1	1.2	0	0.0	1.000
Patient had a 50% decrease in iPTH but had elevated Ca x P values for four consecutive lab draws after	18	21.7	15	20.0	0.848

* P-value derived from a Fisher's exact test.

† Percentage of patients that achieved at least one 50 percent decrease in iPTH during treatment.

‡ The results were determined in relation to the first occurrence of each event.

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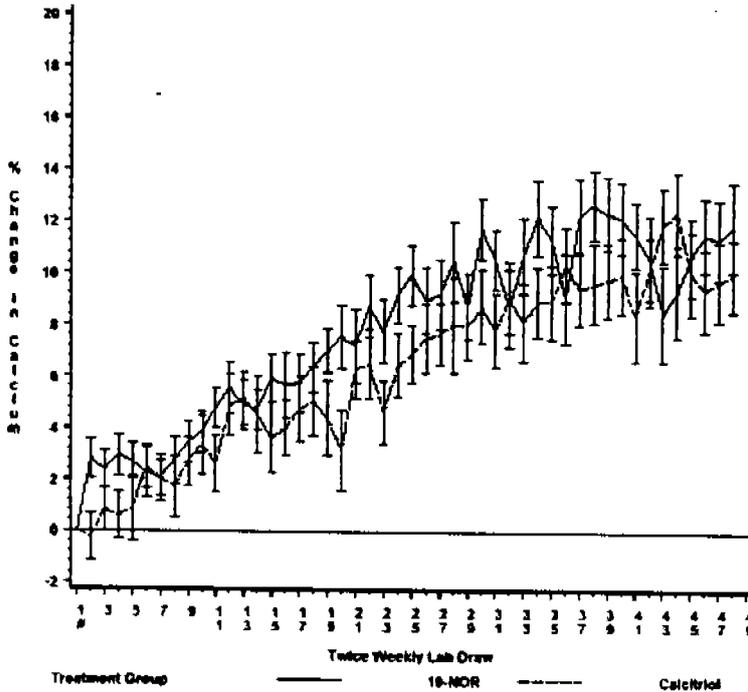
For all treated patients, the Ca and/or Ca x P endpoint criteria in relation to the iPTH endpoint were not significantly different in incidence between treatment groups.

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For all evaluable patients the analysis of serum Ca and P data also indicate that the Ca and/or Ca x P product endpoint criteria in relation to iPTH showed no significant differences

The following Figure presents the mean change from last baseline in Ca levels by twice weekly lab draw for all treated patients.

Figure 7: Plot of Mean \pm SEM for Percent Change from Last Baseline in Normalized Calcium by Twice Weekly Lab Draw for All Treated Patients (Cross Reference: Appendix 10.0, Figure 3a)



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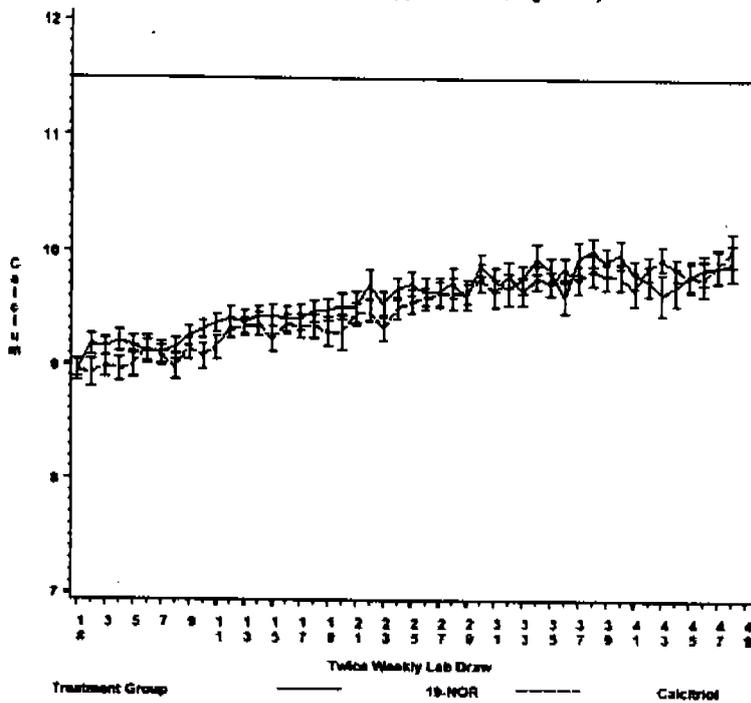
Lab draw 1 is the Baseline laboratory determination. Note: Horizontal reference line is at 0

For all treated patients, the maximum mean percent change from last baseline in serum Ca was approximately 12 percent at Lab Draw 38 (Week 19) for the [TRADE NAME] treatment group and also approximately 12 percent at Lab Draw 44 (Week 22) for the Calcijex treatment group.

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Figure 8: Plot of Mean \pm SEM for Normalized Calcium by Twice Weekly Lab Draw for All Treated Patients
(Cross Reference: Appendix 10.0, Figure 4a)



* Lab draw 1 is the Baseline and Follow-up laboratory determination.
Note: Horizontal reference line is at 11.5.

A serum Ca level of no more than 11.5 mg/dL was required for entry into the Treatment Phase. In this graph for all treated patients, the treatment group means for Ca were approximately 9.0 mg/dL for both treatment groups at last baseline. A horizontal reference line at 11.5 mg/dL is shown on the plot. The maximum [TRADE NAME] group mean for Ca was 10 mg/dL at Lab Draw 39 (Week 19) and was 10 mg/dL at Lab Draw 49 (Week 24) for the Calcijex treatment group

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Table 15: Statistically Significant Changes from Last Baseline in Calcium for All Treated Patients (Cross Reference 10.3.4.2.a)

Lab draw	Group	N	Baseline	Lab draw	Change from baseline	Between group comparisons for			
						change		baseline	
						mean (range)	mean (range)	mean (SE)	p-value
Week 1, draw 2	Capthrol	89	8.94	9.17	0.23** (0.074)	0.27 (0.106)	0.012*	-0.01 (0.134)	0.929
	Calcijex	86	8.96	8.92	-0.04 (0.076)				
Week 2, draw 2	Capthrol	91	8.98	9.21	0.24*** (0.071)	0.23 (0.101)	0.022*	0.02 (0.134)	0.894
	Calcijex	87	8.94	8.95	0.01 (0.072)				
Week 6, draw 1	Capthrol	92	8.98	9.37	0.41*** (0.074)	0.21 (0.105)	0.044*	0.00 (0.131)	0.995
	Calcijex	90	8.98	9.15	0.19* (0.075)				
Week 10, draw 2	Capthrol	72	8.87	9.52	0.65*** (0.117)	0.38 (0.162)	0.019*	-0.15 (0.138)	0.281
	Calcijex	79	9.02	9.28	0.26* (0.112)				
Week 12, draw 1	Capthrol	79	8.89	9.54	0.66*** (0.098)	0.30 (0.140)	0.035*	-0.08 (0.143)	0.396
	Calcijex	78	8.96	9.32	0.36*** (0.100)				
Week 12, draw 2	Capthrol	74	8.90	9.68	0.78*** (0.091)	0.27 (0.132)	0.045*	-0.09 (0.145)	0.339
	Calcijex	67	8.99	9.50	0.52*** (0.096)				
Week 13, draw 1	Capthrol	79	8.88	9.72	0.85*** (0.088)	0.28 (0.127)	0.028*	-0.13 (0.139)	0.355
	Calcijex	74	8.99	9.56	0.57*** (0.091)				

*, **, *** indicate statistical significance (2-tailed) at the 0.05, 0.01, or 0.001 levels respectively.

Table 18: Statistically Significant Changes from Last Baseline in Calcium for All Treated Patients (Cross Reference 10.3.4.2.a) (Continued)

Lab draw	Group	N	Baseline	Lab draw	Change from baseline	Between group comparisons for			
						change		baseline	
						mean (range)	mean (range)	mean (SE)	p-value
Week 17, draw 2	Capthrol	60	8.88	9.93	1.06*** (0.110)	0.31 (0.156)	0.046*	-0.15 (0.148)	0.312
	Calcijex	60	9.03	9.77	0.74*** (0.110)				

*, **, *** indicate statistical significance (2-tailed) at the 0.05, 0.01, or 0.001 levels respectively.

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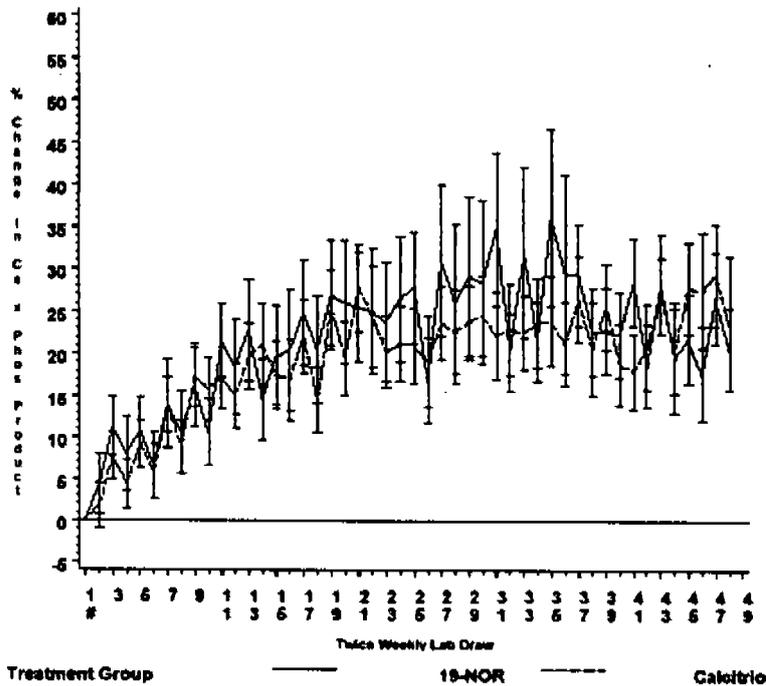
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A significant difference between treatment groups for the change from baseline in calcium occurs at Treatment Week 1, draw 2; and is also observed at Treatment Week 2, draw 2; Treatment Week 6, draw 1; Treatment Week 10, draw 2; Treatment Week 12, draws 1 and 2; Treatment Week 13, draw 1; ($p < 0.045$).

Figure 8: Plot of Mean \pm SEM for Percent Change from Baseline in Calcium x P by Twice Weekly Lab Draw for All Treated Patients (Cross Reference: Appendix 10.0, Figure 6a)

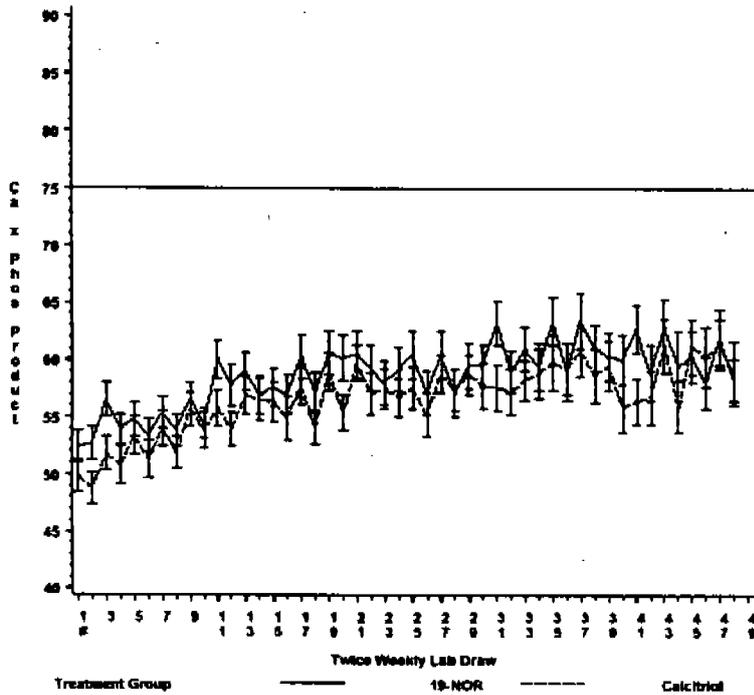


* Lab draw 1 is the Baseline laboratory determination.
Note: Horizontal reference line is at 0.

For all treated patients, the maximum mean for percent change from last baseline in serum Ca x P was approximately 35% at Lab Draw 35 (Week 17) for the [TRADE NAME] treatment group and 30% at Lab Draw 47 (Week 23) for the Calcijex treatment group.

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Figure 10: Plot of Mean \pm SEM for Calcium x P by Twice Weekly Lab Draw for All Treated Patients (Cross Reference: Appendix 10.0, Figure 6a)



* Lab draw 1 is the Baseline laboratory determination.
Note: Horizontal reference line is at 75.

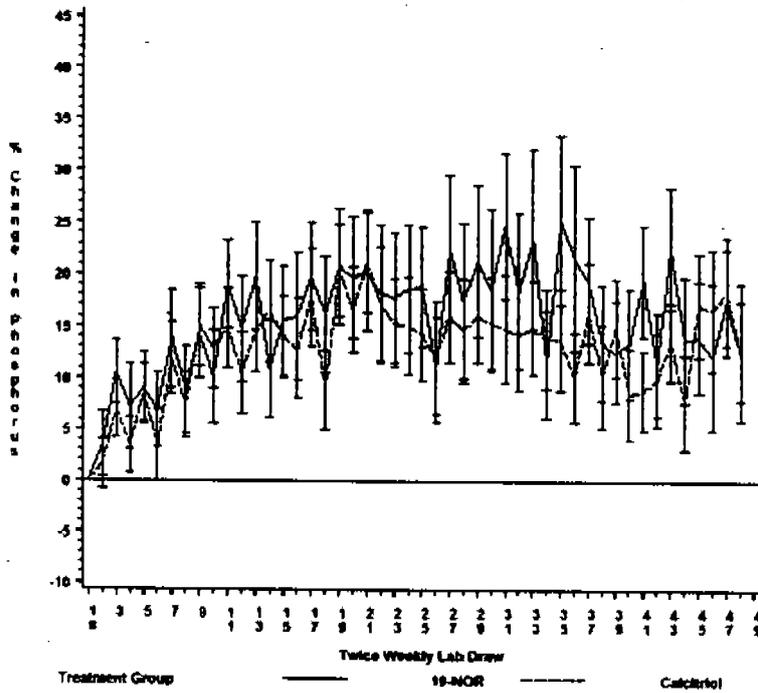
A serum Ca x P level of no more than 75 was required for entry into the Treatment Phase. In this graph for all treated patients, the treatment group means for Ca x P were approximately 50 and 52 at last baseline. The maximum [TRADE NAME] group mean for Ca x P was 64 at Lab Draw 36 (Week 18) and was 61 at Lab Draw 48 (Week 24) for the Calcijex treatment group. Similar results were obtained for all evaluable patients. There was no statistically significant difference between treatment groups in Ca x P product at any weekly visit.

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Figure 11: Plot of Mean \pm SEM for Percent Change from Baseline in Phosphorus by Twice Weekly Lab Draw for All Treated Patients (Cross Reference: Appendix 10.0 Figure 7a)



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Lab draw 1 is the Baseline laboratory determination.
Note: Horizontal reference line is at 0.

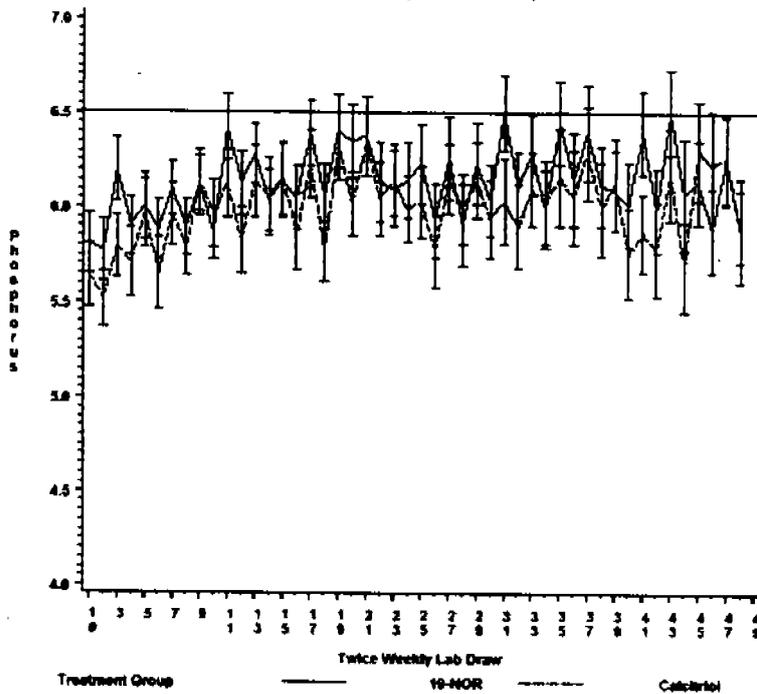
For all treated patients, the maximum mean for percent change from last baseline in serum P was approximately 25 percent at Lab Draw 35 (Week 17) for the [TRADE NAME] treatment group and approximately 25 percent at Lab Draw 21 (Week 10) for the Calcijex treatment group.

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Figure 12: Plot of Mean \pm SEM for Phosphorus by Twice Weekly Lab Draw for All Treated Patients



* Lab draw 1 is the Baseline laboratory determination.
Note: Horizontal reference line is at 6.5.

In this graph for all treated patients, the treatment group means for phosphorus were approximately 5.65 for the Calcijex treatment group and 5.8 for the [TRADE NAME] treatment group. The maximum [TRADE NAME] group mean for phosphorus was 6.53 mg/dL at lab draw 36 (Week 18) and 6.34 mg/dL at lab draw 22 (Week 11) for the Calcijex treatment group.

For each treatment group, an analysis of changes from last baseline to Treatment Week 12 and Follow-up evaluation in chemistry determinations was performed for all treated patients.

A complete laboratory profile was to be obtained at Treatment Week 12 and Follow-up (per protocol). For analysis, the Week 12 laboratory draw was obtained as the lab draw obtained closest to Week 12 for patients who had at least 10 weeks of treatment. The Follow-up lab draw was identified as such by the site and was not used for the Week 12 determination.

The next Table presents an analysis of the change from last baseline to Treatment Week 12 and Follow-up evaluation, for all treated patients, for Ca, Ca x P, P, and iPTH.

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Table 19: Changes from Baseline to Week 12[†] Lab Draw and Follow-up in Efficacy Related Chemistry Determinations for All Treated Patients (Cross Reference 10.3.A.3.a)

Group	Last Baseline		Lab Draw		Change from Baseline		Between Group Comparisons [‡] for:			
	Mean	Range	Mean	Range	Mean	SE	Change		Baseline	
							Mean SE	p-value	Mean SE	p-value
Treatment Week 12: Calcium (mg/dL)										
Capthrol N = 83	8.88		9.60		0.71	0.095 ^{***}	0.37 0.134	0.007 ^{***}	-0.07 0.136	0.621
Calcijex N = 83	8.95		9.3		0.35	0.095 ^{***}				
Follow-up: Calcium (mg/dL)										
Capthrol N = 88	8.93		9.67		0.94	0.162 ^{***}	0.25 0.143	0.084	-0.01 0.132	0.917
Calcijex N = 90	8.94		9.64		0.69	0.161 ^{***}				
Treatment Week 12: Calcium x Phosphorus										
Capthrol N = 83	50.948		58.745		7.799	1.928 ^{***}	-0.518 2.727	0.850	1.390 1.984	0.480
Calcijex N = 83	49.955		57.872		8.317	1.928 ^{***}				
Follow-up: Calcium x Phosphorus										
Capthrol N = 87	52.621		61.391		8.770	2.028 ^{***}	-0.672 2.844	0.813	2.342 2.032	0.251
Calcijex N = 90	50.279		59.721		8.442	1.984 ^{***}				

[†] The Week 12 Lab Draw was the lab draw obtained closest to the first dialysis session of Week 12 for patients with at least 10 weeks of treatment.

[‡] results based upon a one-way ANOVA.

*, **, and *** indicate statistical significance (2-tailed) at the 0.05, 0.01, and 0.001 levels, respectively

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Table 19: Changes from Baseline to Week 12^a Lab Draw and Follow-up in Efficacy Related Chemistry Determinations for All Treated Patients (Cross Reference 10.3.4.3.a) (Continued)

Group	Last Baseline		Lab Draw		Change from Baseline		Between Group Comparisons ^b for:			
	Mean	Range	Mean	Range	Mean	SE	Change		Baseline	
							Mean	p-value	Mean	p-value
Treatment Week 12: P (mg/dL)										
Capitrol N = 83	5.69		6.13		0.44	0.206*	-0.17	0.569	0.09	0.724
Calcijex N = 83	5.60		6.21		0.61	0.206**	0.269	0.242		
Follow-up: P (mg/dL)										
Capitrol N = 87	5.84		6.24		0.39	0.212	-0.13	0.673	0.14	0.552
Calcijex N = 90	5.70		6.22		0.52	0.208*	0.297	0.243		
Treatment Week 12: iPTH (pg/mL)										
Capitrol N = 83	686.57		400.11		-286.5	23.52***	-69.71	0.042*	30.30	0.601
Calcijex N = 80	656.26		436.51		-217.8	23.98***	33.58		57.90	
Follow-up: iPTH (pg/mL)										
Capitrol N=85	639.81		281.92		-357.9	33.58***	-80.87	0.069	-10.8	0.840
Calcijex N=87	629.01		351.99		-277.0	33.36***	47.31		53.386	

^a The Week 12 Lab Draw was the lab draw obtained closest to the first dialysis session of Week 12 for patients with at least 10 weeks of treatment.

^b results based upon a one-way ANOVA.

*, **, and *** indicate statistical significance (2-tailed) at the 0.05, 0.01, and 0.001 levels, respectively.

A between group comparison for mean changes from baseline to Week 12 and Follow-up evaluation showed that treatment groups demonstrated a statistically significant difference for Ca and iPTH at Week 12 only (p < 0.042). A between group comparison of baselines was not statistically significant.

Statistical/Analytical Issues

Adjustments for Covariates

There were no adjustments made for covariates.

Handling of Dropouts or Missing Data

The "All Treated Patients" analyses (intent to treat) used all available patient data in the efficacy analysis. Serum iPTH was collected weekly while Ca, P and albumin were collected twice weekly. A consecutive collection period excludes periods for which data are missing. Analyses were performed to examine the first occurrence of a 50 % decrease from baseline in iPTH (which was collected once a week) in relation to the first incidences of hypercalcemia and/or Ca x P greater than 75 (collected twice weekly). A patient may have realized their first incidence of hypercalcemia and/or a Ca x P greater than 75 while the iPTH result for this time point was not done, as specified in the protocol for laboratory procedures.

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Summary of Efficacy Results

Three-hundred-thirty patients were enrolled into the study, with 197 randomized (98 [TRADE NAME], 99 Calcijex). In the study, the only clinically relevant statistically significant differences were the [TRADE NAME] treatment group percent changes from baseline iPTH which were significantly greater than the Calcijex group beginning at Treatment Week 11; this significant reduction lasted through Week 14 ($p < 0.032$). The safety of [TRADE NAME] in all treated patients was characterized by the following parameters:

- adverse events throughout the study*
- chemistry and hematology results
- vital signs results

*All adverse events are included, such as transplantations, parathyroidectomies and their associated patient work-ups.

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Treatment Phase Discontinuations Due to an Adverse Event

Brief Summary of Adverse Events

The analysis of Pretreatment Phase adverse events indicated that the overall, Body System and COSTART term incidence rates were not significantly different between treatment groups. Forty five % (44/98) of [TRADE NAME] treatment group patients and 43 percent (43/99) of Calcijex treatment group patients were reported to have at least one adverse event during the Pretreatment Phase ($p = 0.886$).

For adverse events reported after the Treatment Phase began, there was no statistically significant difference ($p = 0.227$) between the number of patients reporting one or more adverse events between treatment groups. Eighty three % (81/98) of [TRADE NAME] treatment group patients and 89 % (88/99) of Calcijex treatment group patients were reported to have at least one adverse event after the Treatment Phase began. The analysis of Treatment Phase adverse events indicated that the overall, Body System and COSTART term incidences were not significantly different between treatment groups ($p = 0.227$). The analysis of Treatment Phase adverse events, excluding those not related to study drug, indicated that the overall and COSTART term incidence rates were not significantly different between treatment groups. However, the difference in the Body System incidence rate for "Body as a Whole" between the two treatment groups was statistically significant ($p = 0.048$), the Calcijex treatment group had a higher incidence in this category than the [TRADE NAME] treatment group. All of the individual COSTART term incidences within this Body System category were not significantly different between treatment groups. Nineteen percent (19/98) of [TRADE NAME] treatment group patients and 27 percent (27/99) of Calcijex treatment group patients were reported to have at least one adverse event after the Treatment Phase began ($p = 0.239$).

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**Table 23: Adverse Events Assessed "Probable" by the Investigator
(Cross Reference Appendix 12.2.24.b)**

Study drug	Patient number	Adverse Event
Capthrol	1102/104	injection site pain
Capthrol	1102/104	injection site pain
Capthrol	1107/105	hypercalcemia
Capthrol	1118/112	hypercalcemia
Capthrol	1118/112	hypercalcemia
Capthrol	1118/112	injection site pain
Calcijex	14118/1411	fatigue
Calcijex	17103/1701	rash
Calcijex	17103/1701	facial swelling
Calcijex	17103/1701	skin discoloration
Calcijex	22118/2209	chest pain

Table 24: Adverse Events Assessed "Definite" by the Investigator

Study drug	Patient number	Adverse Event
Capthrol	14107/1402	taste alteration
Capthrol	14111/1408	appetite loss
Capthrol	14111/1408	burning skin
Capthrol	14113/1409	taste perversion
Calcijex	5104/504	hypercalcemia
Calcijex	5115/501	hypercalcemia

Of these patients, only patient number 17103/1701 T-G (37 year old, female) discontinued the study due to a body rash with pruritus and facial swelling and discoloration during the fifth week of Calcijex treatment at dose level 2. The symptoms were considered probably related to the study drug and resolved upon withholding study drug.

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Listing and Narratives of Deaths

Table 25: Patient Deaths (Safety Update, 1997)

Treatment	Patient No.	Age (yrs.)	Sex (M/F)	Event	Cause of Death	Relation to Study Drug
Pre-treatment	6128	74	F	cardiac arrest	cardiac insufficiency due to acute myocardial infarction	NR
Capthrol	6123/608	60	M	cardiac arrest	cardiac arrest due to acute myocardial infarction	NR
Capthrol	8110/808	64	F	septic shock	septic shock	NR
Capthrol	10103/1101	74	F	peg tube site infection with bleeding	massive cerebrovascular accident	NR
Capthrol	13108/1308	89	M	asystole	asystole	NR
Calcijex	12121/1212	37	F	cardiac arrest	cardiac arrest	NR
Calcijex	22115/2208	57	F	intracranial bleed	intracranial bleed	NR
Calcijex	23102/2302	58	M	cardiorespiratory arrest	cardiorespiratory arrest secondary to hypertension	NR

NR = Not Related

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Table 29: Statistically Significant Changes from Last Baseline to Week 12 Lab Draw and Follow-up in Chemistry Determinations for All Treated Patients (Cross Reference 10.3.4.3.a)

Group	Baseline		Lab Draw		Change from Baseline		Between Group Comparisons for			
	Mean	Range	Mean	Range	Mean	SE	Change from Last Baseline		Last Baseline	
					Mean	SE	Mean	p-value	Mean	p-value
Treatment Week 12: Albumin (g/dL)										
Capthrol N = 83	3.80		3.58		-0.01	0.035	-0.11	0.031*	0.06	0.272
Calcijex N = 83	3.54		3.63		0.09	0.035**	0.050		0.052	
Follow-up: Albumin (g/dL)										
Capthrol N = 88	3.81		3.58		-0.04	0.035	-0.03	0.613	0.07	0.102
Calcijex N = 89	3.53		3.52		-0.01	0.035	0.050		0.052	
Treatment Week 12: Blood Urea Nitrogen (mg/dL)										
Capthrol N = 72	61.9		58.4		-3.6	2.16	-1.3	0.669	0.6	0.832
Calcijex N = 72	61.3		59.1		-2.2	2.16	3.05		2.88	
Follow-up: Blood Urea Nitrogen (mg/dL)										
Capthrol N = 85	64.2		58.9		-7.3	2.02**	-6.1	0.031*	2.9	0.185
Calcijex N = 89	60.9		59.7		-1.2	1.98	2.83		2.71	

The week 12 lab draws were the lab draws obtained closest to the first dialysis session of Week 12 for patients with at least 10 weeks of treatment.

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A between group comparison for changes from last baseline mean to Week 12 or Follow-up evaluation indicates that treatment groups demonstrated a statistically significant difference for albumin and blood urea nitrogen only.

Albumin: There was a statistically significant difference in albumin between the [TRADE NAME] and the Calcijex treatment groups at Treatment Week 12 (p = 0.031). A between group comparison at baseline indicated that both treatment groups were not significantly different.

BUN: There was a statistically significant difference in BUN between the [TRADE NAME] and the Calcijex treatment groups at Follow-up (p = 0.031). A between group comparison for baseline indicated that both treatment groups were not significantly different at baseline.

Table 30: Statistically Significant Normal Range Category Change From Last Baseline Compared to Follow-up: Uric Acid (mg/dL) (Cross Reference: 10.3.4.3.b)

	Not Assessable	Decreased	Unchanged	Increased	Total	P-value
Capthrol	12	14(15%)	68(80%)	3(3%)	88	
Calcijex	10	15(17%)	62(70%)	12(13%)	90	0.028*

The week 12 lab draws were the lab draws obtained closest to the first dialysis session of Week 12 for patients with at least 10 weeks of treatment.

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A frequency summary of changes from last baseline to Week 12 and to Follow-up evaluation indicates that both treatment groups were not significantly different after study drug administration for chemistry variables (excluding Ca, Ca x P, P, and iPTH levels), with the exception of uric acid at Follow-up (p= 0.028). The Calcijex treatment group showed more increases in uric acid than the [TRADE NAME] treatment group. For each treatment group, an analysis of changes from Enrollment to the last baseline evaluation in hematology determinations was performed for all treated patients. A between group

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comparison for changes from Enrollment mean to last baseline evaluation indicates that both treatment groups were not significantly different prior to study drug administration for all hematology variables. There were no significant between group differences.

Table 31: Statistically Significant Changes from Last Baseline to Week 12 Lab Draw and Follow-up in Hematology Determinations for All Treated Patients (Cross Reference 10.3.5.2.a)

Group	Baseline		Lab Draw		Change from Baseline		Between Group Comparisons for			
	Mean	Range	Mean	Range	Mean	SE	Change from Last Baseline		Last Baseline	
							Mean	p-value	Mean	p-value
							SE		SE	
Follow-up: Basophils ($\times 10^3$ /μL)										
Capitrol N = 68	0.058		0.051		-0.006	0.0037	-0.01	0.027*	0.01	0.071*
Calcijex N = 84	0.049		0.052		0.003	0.003	0.00		0.01	

The week 12 lab draws were the lab draws obtained closest to the first dialysis session of Week 12 for patients with at least 10 weeks of treatment.

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A between group comparison for changes from last baseline mean to Week 12 or Follow-up evaluation indicates that treatment groups demonstrated a statistically significant difference for basophil count only. Although abnormally elevated values are present in both treatment groups, a closer review of SGOT and SGPT level results is indicated as follows with focus on the [TRADE NAME] treatment group: Patients 24102/2404 and 4101/401 had mildly elevated SGOT and SGPT levels at Follow-up only. The Week 12 data does not support a study drug relationship.

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Summary of Safety Results

In the study, the only statistically significant differences were as follows:

- Adverse Events During Treatment Excluding Those Not Related to Study Drug: there was a statistical significance between treatment groups for Body System incidences for "Body as a Whole", $p = 0.048$; all of the individual COSTART term incidences within this Body System category were not significantly different between treatment groups
- in Change from Last Baseline to Treatment Week 12 and Follow-up (Chemistry): for all treated patients, chemistry determinations were not significantly different between treatment groups with the exception of albumin at Week 12 ([TRADE NAME] treatment group mean change -0.01 g/dL, Calcijex treatment group mean change $+0.09$ g/dL, $p = 0.031$) and BUN at Follow-up ([TRADE NAME] treatment group mean change -7.3 mg/dL, Calcijex treatment group mean change -1.2 mg/dL, $p = 0.031$)
- in Change from Last Baseline to Treatment Week 12 and Follow-up (Hematology): for all treated patients, hematology determinations were not significantly different between treatment groups with the exception of basophil count at Follow-up ([TRADE NAME] treatment group mean change -0.006×10^3 /mCL, Calcijex treatment group mean change $+0.003 \times 10^3$ /mCL, $p = 0.027$)
- in Vital Signs, Physical Findings, and Other Observations Related to Safety: for all treated patients, prestudy to Follow-up changes in vital signs and weight were not significantly different between treatment groups with the exception of mean systolic blood pressure ([TRADE NAME] treatment group mean change -9 mmHg, Calcijex treatment group mean change $+2$ mmHg, $p = 0.010$) and diastolic blood pressures ([TRADE NAME] treatment group mean change -6 mmHg, Calcijex treatment group mean change 0 mmHg, $p = 0.036$).

Efficacy

Previous studies had determined [TRADE NAME] to be safe and effective in reducing iPTH levels in ESRD patients undergoing hemodialysis. The objective of this study was to determine whether the incidence of hypercalcemia and/or elevated Ca x P level were lower in patients receiving [TRADE NAME] than in patients receiving Calcijex. In this study, the doses of [TRADE NAME] and Calcijex were to be escalated every four weeks for a maximum of five dose escalations or until one of the following conditions occurred:

- 50% decrease in serum iPTH level (from last baseline as determined on first day of Treatment Phase)
- hypercalcemia (serum Ca greater than 11.5 mg/dL)
- all serum Ca x P levels within a consecutive two-week period are greater than 75
- decrease in serum iPTH to below 100 pg/mL after two consecutive weeks of study drug administration on a given dose level

The dose of study drug could be reduced to the previous level if hypercalcemia, elevated Ca x P, or low iPTH levels occurred. If any of these events occurred at the first dose level, the patient was considered to have completed the study and was withdrawn.

The purpose of using an iPTH endpoint of 50% reduction from baseline in this study was to provide a reference point to gauge the potential hypercalcemic and hyperphosphatemic activity of Calcijex and [TRADE NAME]: a similar reduction in iPTH for all patients would suggest an equivalent treatment of the disease and any differences in serum Ca and P (P, a factor in Ca x P) would reflect the different effects of the drugs.

A 50% decrease in iPTH sustained over four consecutive lab draws observations was considered a clinically relevant improvement.

Labs were drawn prior to dialysis at the first and second dialysis sessions of the week and the results were not available to the Investigator until at least the following dialysis session. Thus, the patient would have received at least two doses of drug and two calcium determinations prior to dose reduction for hypercalcemia, although per the protocol, a patient was dose reduced upon a single incidence of hypercalcemia for safety purposes. Therefore, two consecutive instances of hypercalcemia were chosen as an endpoint for analysis, to better approximate the clinical scenario of hypercalcemia upon which most dosing changes for drug were actually based. The same rationale led to choosing two weeks of Ca x P > 75 as evidence of clinically significant product elevation.

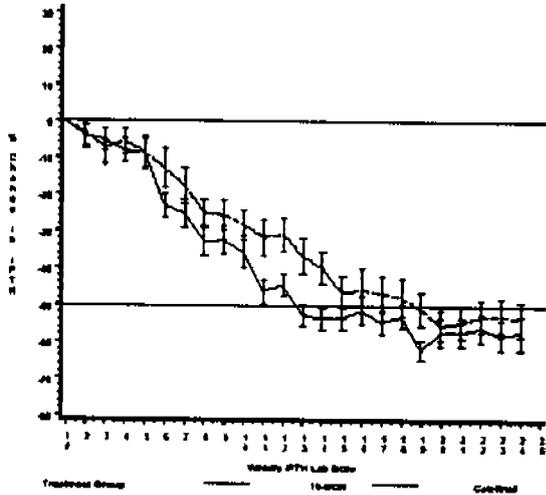
A between group comparison for last baseline means indicated that the treatment groups were not significantly different prior to study drug administration for Ca, Ca x P, P, and iPTH levels. The last baseline means for iPTH for both treatment groups were within _____, a range characteristic of patients with moderate secondary hyperparathyroidism.

For all treated patients, the analysis of serum iPTH data indicated that the iPTH endpoint criteria (a 50% decrease in iPTH at the final lab draw, at least one 50% decrease in iPTH during Treatment, and a 50% decrease in iPTH for at least one period of four consecutive iPTH lab draws) were met without significant difference between groups, providing a clinical reference point by which to judge Ca and P activity. At study's end, both treatment groups had a similar percent change in iPTH (-57.4 versus -53.7% for the [TRADE NAME] and Calcijex treatment groups, respectively).

For all treated patients, the analysis of serum Ca and P data indicated that the incidence of hypercalcemia and/or elevated Ca x P level was not statistically different between treatment groups for clinically relevant endpoints.

However, the treatment group mean for percent change from last baseline of -50% in iPTH, was met approximately six weeks earlier for the [TRADE NAME] treatment group than that for Calcijex (Week 13 vs. Week 19), as shown in the figure below. In addition, between group comparisons in change from last baseline mean were significant for iPTH at Weeks 11 through 13; the [TRADE NAME] group had a consistently greater decrease from baseline than the Calcijex group.

Figure 14: Plot of Mean \pm SEM for Percent Change from Last Baseline Draw for All Treated Patients



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As shown below in the Table, the percent of patients with hypercalcemia prior to or concomitant to the first 50% iPTH reduction is low in both treatment groups; hypercalcemia largely occurred after the first iPTH reduction endpoint had been met.

Table 44: Summary of Calcium and Calcium x Phosphorus Elevation from Last Baseline in Relation to iPTH Endpoint for All Treated Patients^a (Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Capthrol N = 83		Calcijex N = 75		p-value ^b
	number	percent ^c	number	percent ^c	
Patient had a 50% decrease in iPTH but became hypercalcemic prior	1	1.2	1	1.3	1.000
Patient had a 50% decrease in iPTH coincident with hypercalcemia	2	2.4	4	5.3	0.424
Patient had a 50% decrease in iPTH and became hypercalcemic after	22	26.5	12	16.0	0.124

^a P-value derived from a Fisher's exact test.

^b Percentage of patients that achieved at least one 50 percent decrease in iPTH during treatment.

^c The results were determined in relation to the first occurrence of each event.

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As seen below in the next Table, elevation in Ca x P also largely occurred after the first iPTH reduction endpoint had been met:

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Table 45: Summary of Calcium and Calcium x P Elevation from Last Baseline in Relation to IPTH Endpoint for All Treated Patients^a
(Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Capthrol N = 83		Calcijex N = 75		p-value ^b
	number	percent ^c	number	percent ^c	
Patient had a 50% decrease in IPTH but had elevated Ca x P values for four consecutive lab draws prior	1	1.2	4	5.3	0.191
Patient had a 50% decrease in IPTH coincident with elevated Ca x P values for four consecutive lab draws	1	1.2	0	0.0	1.000
Patient had a 50% decrease in IPTH but had elevated Ca x P values for four consecutive lab draws after	18	21.7	15	20.0	0.846

^a P-value derived from a Fisher's exact test.

^b Percentage of patients that achieved at least one 50 percent decrease in IPTH during treatment.

^c The results were determined in relation to the first occurrence of each event.

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Safety Endpoints

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Safety

In this comparative study, [TRADE NAME] displayed an excellent safety profile, consistent with previous placebo studies. Compared to the Calcijex treatment group, the [TRADE NAME] treatment group demonstrated no significant differences for overall, Body System and individual COSTART term incidence rates. No patient from the [TRADE NAME] treatment group was discontinued prematurely due to an adverse event. Patient deaths were reported in similar numbers, four for the [TRADE NAME] treatment group and three for the Calcijex treatment group; none of the deaths in either treatment group were assessed as related to study drug. Thirty-five serious adverse events excluding deaths were reported for the [TRADE NAME] treatment group and 55 for the Calcijex treatment group. Only one of the 35 serious adverse events in the [TRADE NAME] treatment group was assessed as possibly related to study drug by the Investigator as follows:

Patient number 20105/2007, a 70 year old male was hospitalized on 02 Oct 96 (Treatment Week Two, Dose Level One) for rectal bleeding during dialysis. Pertinent medical history includes diverticulosis (Jul 1995), anemia, alcohol abuse, colon cancer (1989) and sigmoidectomy. The patient's prestudy medical history notes blood per rectum last in Dec 1995. A colonoscopy revealed active gastrointestinal bleeding from approximately ten centimeters above the anal fissure. He was treated with vasopressin. [TRADE NAME] had been started on 27 Sep 96 and not interrupted by event, the patient having successfully received his last dose at Week 24 on 7 Mar 97. No other routine adverse events were reported during treatment. The Abbott Medical Safety Officer opinion of this serious adverse event was assessed as not related and remains so in light of the patient's history and absence of further similar events upon rechallenge. Another serious adverse event reported one day post-study for non-bloody diarrhea and dehydration occurring on 11 Mar 97 was considered by the Investigator to be not related to the study drug.

Changes in chemistry and hematology laboratory variables from Enrollment to last baseline were not significantly different between treatment groups indicating similar patient population values prior to study drug administration.

The statistically significant between group changes seen in chemistry and hematology determinations other than calcium and phosphorus from last baseline to Treatment Week 12 and Follow-up were of no clinical significance. In review of individual patient out-of-range laboratory data, all chemistry and

hematology values demonstrated no apparent trends that suggested a study drug relationship. Abnormal values were identified in both treatment groups as well as prior to study drug administration and were considered to be the result of non-study drug etiologies.

Changes in vital signs and weight during treatment were not significantly different between treatment groups with the exception of mean systolic and diastolic blood pressures: the [TRADE NAME] treatment group had a mean systolic change of -9 mmHg and the Calcijex treatment group, a mean change of +2 mmHg; the [TRADE NAME] treatment group had a mean diastolic change of -6 mmHg and the Calcijex treatment group, without mean change.

Changes in volume status are characteristic of this patient population; hypertension or hypotension are generally multifactorial, and often respond to intravenous fluid infusion, dialyzer blood flow, or ultrafiltration rate adjustment. Review of all hypotension and hypertension events during the Treatment Phase demonstrated no significant difference in incidence for these events in either treatment group. The mean changes in treatment group blood pressure parameters do not appear clinically significant.

Conclusion

[TRADE NAME] safely reduced intact parathyroid hormone levels in end-stage renal disease patients on hemodialysis without clinically significant differences in serum calcium and/or calcium x phosphorus product relative to Calcijex. The percent change from last baseline of a 50% decrease in intact parathyroid hormone was met six weeks earlier for the [TRADE NAME] group. A statistically significant greater decrease for the percent change in intact parathyroid hormone was observed at Weeks 11 through 14 in the [TRADE NAME] group.

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7.3.1.3 Other Studies

The only other completed study, not discussed in previous sections, is a controlled, Phase II study, 95022: Multidose Evaluation of 19-nor-1 alpha, 25-dihydroxyvitamin D₂ in End Stage Renal Disease Patients Undergoing Hemodialysis

Objective: The objective of this study was to evaluate the safety of Paracalcin Injection, and the dose required to achieve one or more the following effects within a dosage group of 10 patients with chronic renal failure (CRF) undergoing hemodialysis:

Decrease serum intact PTH (iPTH) by at least 30% in 75% of patients

Increase the serum Ca to greater than 11.5 mg/dL in 50% of patients

Increase the Ca x P product to greater than 70 in 50% of patients

Methodology: This was a double-blind, placebo-concurrent controlled, randomized (three active drug: two placebo), multi-Investigator study evaluating escalating dose levels of Paracalcin Injection in CRF patients undergoing hemodialysis.

The study was conducted by 5 Investigators, with one group per Investigator, and a maximum of 10 patients randomized per group. Each group received different dosages: Group 1, 0.04 mcg/kg; Group 2, 0.08 mcg/kg; Group 3, 0.16 mcg/kg; Group 4 0.24 mcg/kg; Group 5, 0.32 mcg/kg.

The study was performed in two phases: a pretreatment phase and a treatment phase. The first two weeks of pretreatment served as a washout phase for any patient previously receiving calcitriol or any other vitamin D therapy prior to enrollment in the study. The last two weeks of the pretreatment phase served as a baseline period during which time baseline values for Ca, P, and iPTH were determined. Any patient not previously receiving calcitriol or vitamin D therapy may have entered the study at the baseline period.