

**Table 18 (Continued): Summary of Study Drug Administration for All Treated Patients
(Cross Reference 10.1.9)**

End of Fifth Four Week Interval						
Capthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	12	10.91	0.42	0.09	131.0	8.29
0.08	13	11.82	0.82	0.27	136.3	5.84
0.12	19	17.27	0.98	0.24	135.1	7.33
0.16	7	6.36	1.35	0.34	134.7	7.85
0.20	8	7.27	1.65	0.43	138.0	0.00
Dropped Pt	51	46.37				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	10	8.77	0.41	0.10	132.7	10.16
0.02	12	10.63	0.72	0.11	136.8	5.05
0.03	15	13.16	1.20	0.23	138.3	6.47
0.04	12	10.63	1.44	0.31	136.2	4.69
0.05	21	18.42	1.64	0.40	138.5	5.49
Dropped Pt	44	38.59				
End of Sixth Four Week Interval						
Capthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	8	7.27	0.45	0.11	157.0	9.75
0.08	17	15.45	0.73	0.25	163.9	6.08
0.12	7	6.36	1.09	0.16	165.9	0.90
0.16	8	7.27	1.36	0.39	163.1	8.13
0.20	3	2.73	1.60	0.47	166.0	0.00
0.24	3	2.73	1.83	0.18	166.0	0.00
Dropped Pt	64	58.19				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	9	7.69	0.36	0.07	154.2	10.87
0.02	11	9.65	0.76	0.14	165.8	0.80
0.03	13	11.40	1.17	0.21	164.8	4.75
0.04	6	7.02	1.40	0.36	165.3	1.17
0.05	5	4.39	1.93	0.27	166.0	0.00
0.06	12	10.53	2.05	0.56	163.7	6.32
Dropped Pt	56	49.12				

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**Table 18 (Continued): Summary of Study Drug Administration for All Treated Patients
(Cross Reference 10.1.9)**

End of Seventh Four Week Interval						
Capthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	6	5.45	0.31	0.06	191.3	6.53
0.08	17	15.45	0.76	0.19	193.7	1.11
0.12	9	8.18	0.97	0.24	192.0	6.76
0.16	1	0.91	1.61	-	194.0	-
0.20	3	2.73	1.91	0.42	194.0	0.00
0.24	2	1.82	1.56	0.23	186.5	6.36
Dropped Pt	72	65.46				
End of Eighth Four Week Interval						
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	10	8.77	0.36	0.07	191.6	5.64
0.02	7	6.14	0.62	0.17	194.3	0.49
0.03	11	9.65	0.96	0.19	189.0	10.17
0.04	6	5.26	1.67	0.26	189.7	7.45
0.05	3	2.63	2.12	0.11	193.3	1.16
0.06	8	7.02	2.02	0.30	194.0	0.00
Dropped Pt	69	60.53				
End of Eighth Four Week Interval						
Capthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	6	5.45	0.36	0.06	222.2	0.41
0.08	5	4.55	0.76	0.16	214.4	11.85
0.12	5	4.55	1.06	0.19	218.6	8.17
0.16	4	3.64	1.35	0.36	216.5	7.00
0.24	1	0.91	2.71	-	222.0	-
Dropped Pt	69	60.90				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	6	5.26	0.36	0.06	216.5	5.01
0.02	5	4.36	0.65	0.17	220.4	1.67
0.03	2	1.75	1.31	0.02	221.0	1.41
0.04	2	1.75	1.54	0.27	212.5	13.44
0.05	1	0.88	2.00	-	201.0	-
0.06	9	7.89	2.09	0.51	221.6	0.68
Dropped Pt	69	78.08				

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Doses of [TRADE NAME] and Calcijex were adjusted for each patient to achieve at least a 50% reduction in serum iPTH levels from last baseline. At each dose level, Calcijex treatment group patients received doses equal in volume to that for [TRADE NAME] group patients (calculated by individual patient weight).

By the end of the sixth four week interval (Week 24), patients from both treatment groups had been exposed to each of the six doses levels of study drug.

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Major Factor Affecting Efficacy, Serum iPTH

The purpose of using an iPTH reduction endpoint of 50% in this study was to provide a reference point to gauge the potential hypercalcemic and hyperphosphatemic activity of [TRADE NAME] and Calcijex: 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 product) would reflect the different effects of the drugs.

Table 19: All Treated Patients With a 50 Percent or Greater Decrease from Last Baseline in iPTH Levels (Cross Reference 10.2.1.a)

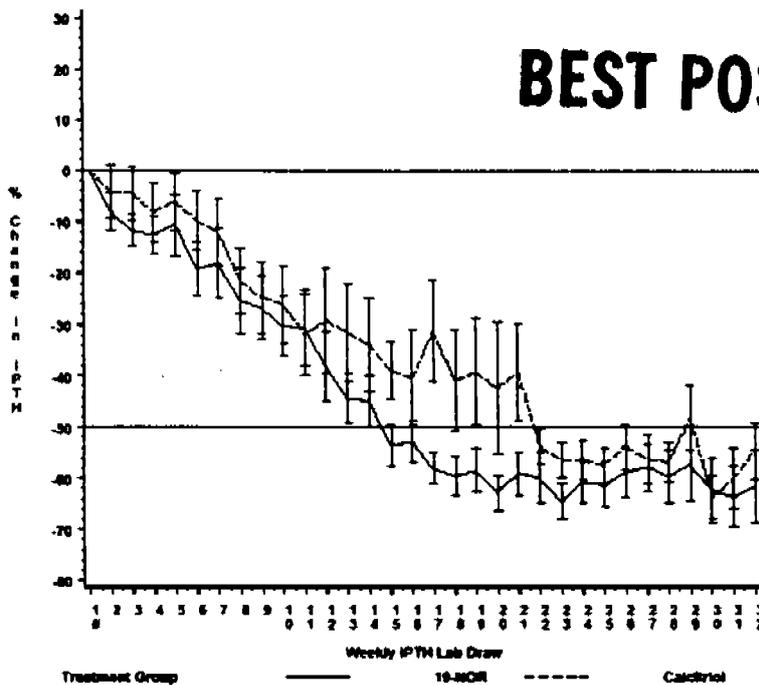
Criteria Achieved by Patient:	Capthrol N=116		Calcijex N=14		p-value
	number	percent	number	percent	
At least one 50 percent decrease in iPTH during Treatment	89	80.9	94	82.5	0.863
A 50 percent decrease in iPTH for at least one period of four consecutive iPTH lab draws	65	58.1	58	51.4	0.285
A 50 percent decrease in iPTH at the final lab draw	67	60.0	63	55.3	0.419

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For all treated patients, the analysis of serum iPTH data indicates that the iPTH endpoint criteria between treatment groups were not statistically different.

For all evaluable patients, the analysis of serum iPTH data also indicates that the iPTH endpoint criteria were not statistically significant between treatment groups.

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)



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* Lab Draw 1 is the Baseline laboratory determination.

The mean percent change from last baseline in iPTH levels for all treated patient groups was greater than -50% by Week 15 for the [TRADE NAME] treatment group and Week 22 for the Calcijex treatment group. At Week 15, the mean percent change remained approximately -35% of last baseline for the Calcijex treatment group.

After achieving a mean 50% reduction in iPTH, both treatment group means stayed consistently below the -50% reference line except at Week 29 when the reduction in iPTH was slightly less than -50% for the Calcijex treatment group.

The mean percent change from last baseline in iPTH levels for all treated patients was approximately -60% at study end for the [TRADE NAME] treatment group and approximately -55% for the Calcijex treatment group.

Table 20: Statistically Significant Percent Change from Last Baseline in iPTH for All Treated Patients (Cross Reference 10.3.4.2.b)

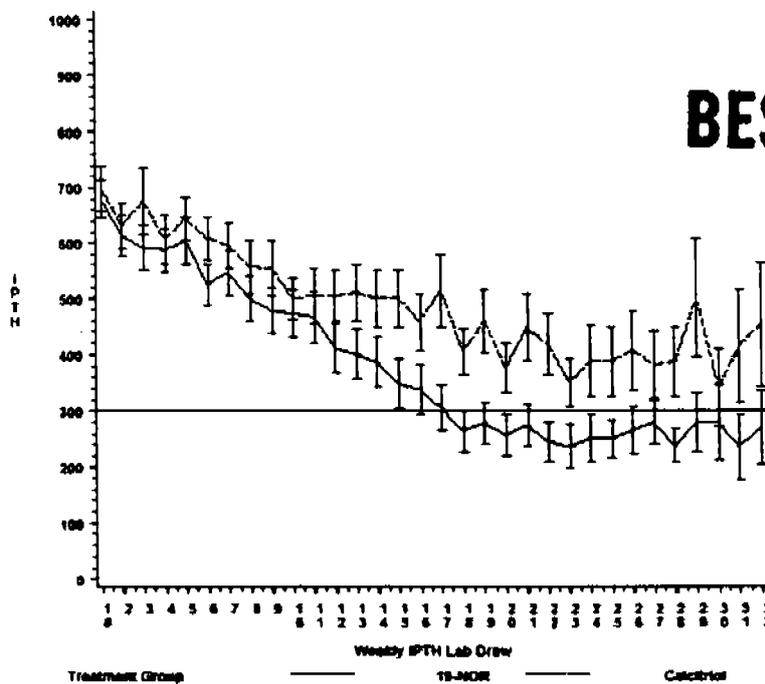
Lab draw	Group	N	Percent Change in iPTH			Between Group Comparison		
			mean	SE	range	mean	SE	p-value
Week 15	Capthral	65	-53.53	5.07		-14.65	7.00	0.038*
	Calcijex	72	-38.66	4.82				
Week 17	Capthral	58	-58.17	8.04		-20.84	10.86	0.016*
	Calcijex	65	-31.33	7.46				

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

Significantly greater percent reduction in iPTH occurred in the [TRADE NAME] treatment group at Treatment Weeks 15 ([TRADE NAME] mean percent change -53, Calcijex mean percent change -39, p = 0.038) and 17 ([TRADE NAME] mean percent change -58, Calcijex mean percent change -31, p = 0.016).

Figure 6: Plot of Mean ± SEM for iPTH by Weekly iPTH Lab Draw for All Treated Patients (Cross Reference Appendix 10.6, Figure 2a)



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

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Table 21: 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			
			mean (range)	mean (range)			change	baseline		
			mean (range)	mean (range)	mean (SE)	mean (SE)	p-value	mean (SE)	p-value	
Week 17	Captritol	56	708.98 -----	304.54 -----	-405.4*** (42.32)	-135.0 (57.745)	0.021*	-75.42 (81.351)	0.358	
	Calcijex	85	785.40 -----	514.84 -----	-270.5*** (39.28)					

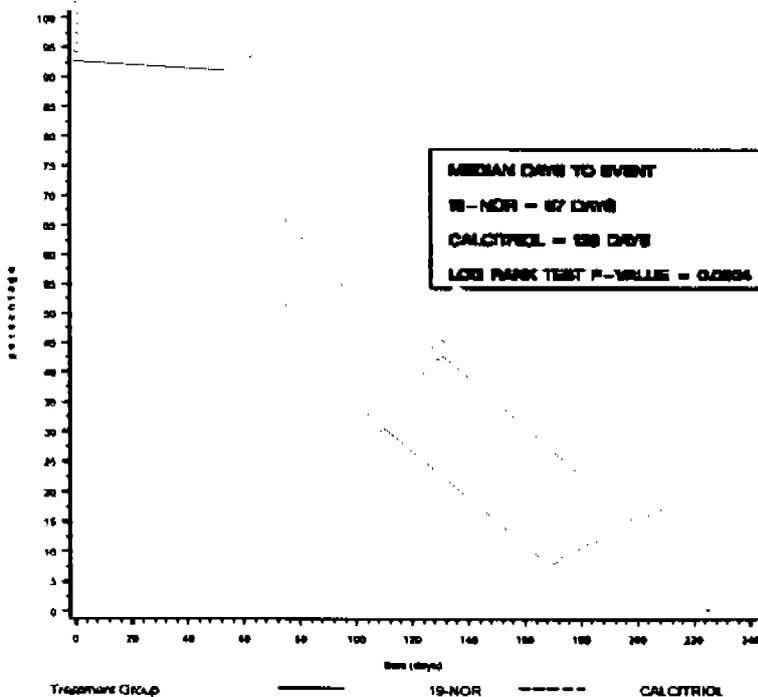
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*, **, *** indicate statistical significance (2-tailed) at the 0.05, 0.01, or 0.001 levels respectively.

Significantly greater absolute reduction in iPTH occurred in the [TRADE NAME] treatment group at Treatment Week 17 ([TRADE NAME] mean change -405.4, Calcijex mean change -270.5, $p = 0.021$). A between group comparison for last baseline mean indicates that both treatment groups were similar for iPTH levels

The Figures and Tables above suggest that [TRADE NAME] reduced 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 below, there was a significantly ($p=0.0204$) more rapid decrease in the patients who received [TRADE NAME].

Figure 6: Kaplan-Meier Curves for Time (Days) to First Period of Four Consecutive 50% Decreases in iPTH (Cross Reference Appendix 10.0, Figure 13a)



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Primary Efficacy Variables: Serum Ca and Ca x P Product

Serum Ca and Ca x P levels were evaluated to determine whether the incidence of hypercalcemia and/or elevated Ca x P product was lower in patients receiving [TRADE NAME] than in patients receiving Calcijex.

Although dose was reduced upon a single incidence of hypercalcemia for safety purposes, two consecutive instances of hypercalcemia were chosen as an endpoint for analysis, to approximate the clinical scenario of hypercalcemia upon which most dosing changes for Calcijex are actually based. The same rationale led to choosing two weeks of Ca x P > 75 as a clinically significant end point.

The incidence of consecutively elevated serum calcium and/or calcium x phosphorus product was lower in patients receiving [TRADE NAME] (18/110) than in patients receiving Calcijex (35/114), p = 0.012). For all evaluable patients, the same criteria showed significant difference (p = 0.040) with the [TRADE NAME] group showing a lesser incidence of consecutively elevated calcium and/or calcium x phosphorus product.

Table 22: Summary of Calcium and Calcium x Phosphorus Product Elevation for All Treated Patients (Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Capthral N = 110		Calcijex N = 114		p-value*
	number	percent	number	percent	
Patient became hypercalcemic for at least two consecutive lab draws and/or had a Ca x P product > 75 for at least one period of four consecutive lab draws	18	16.4	35	30.7	0.012*
Patient became hypercalcemic for at least one lab draw	25	22.7	28	22.8	1.000
Patient became hypercalcemic for at least one period of two consecutive lab draws	9	8.2	14	12.3	0.381
Patient was hypercalcemic at the final lab draw	0	0.0	5	4.4	0.060
Patient had a Ca x P product > 75 for at least one lab draw	63	57.3	67	58.8	0.892
Patient had a Ca x P product > 75 for at least one period of four consecutive lab draws	14	12.7	25	21.9	0.079

* P-value derived from a Fisher's exact test.
 * Indicates statistical significance (2-tailed) at the 0.05 level.

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Table 23: Summary of Calcium and Calcium x Phosphorus Product Elevation in Relation to iPTH Endpoint for All Treated Patients (Cross Reference 10.2.1.a)

Criteria Achieved by Patient:	Capthrel N = 88		Calcijex N = 84		p-value ¹
	number	percent ²	number	percent ²	
Patient had a 50% decrease in iPTH but became hypercalcemic prior	2	2.2	1	1.1	0.613
Patient had a 50% decrease in iPTH coincident with hypercalcemia	3	3.4	2	2.1	0.676
Patient had a 50% decrease in iPTH and became hypercalcemic after	18	20.2	20	21.3	1.000
Patient had a 50% decrease in iPTH but had elevated Ca x P product values for four consecutive lab draws prior	2	2.2	1	1.1	0.613
Patient had a 50% decrease in iPTH coincident with elevated Ca x P product values for four consecutive lab draws	0	0.0	0	0.0	M
Patient had a 50% decrease in iPTH but had elevated Ca x P product values for four consecutive lab draws after	9	10.1	19	20.2	0.066

- ¹ P-value derived from a Fisher's exact test.
- ² Percentage of patients that achieved at least one 50 percent decrease in iPTH during treatment.
- ³ The results were determined in relation to the first occurrence of each event.
- M P-value was not generated since a Fisher's exact test could not be performed.

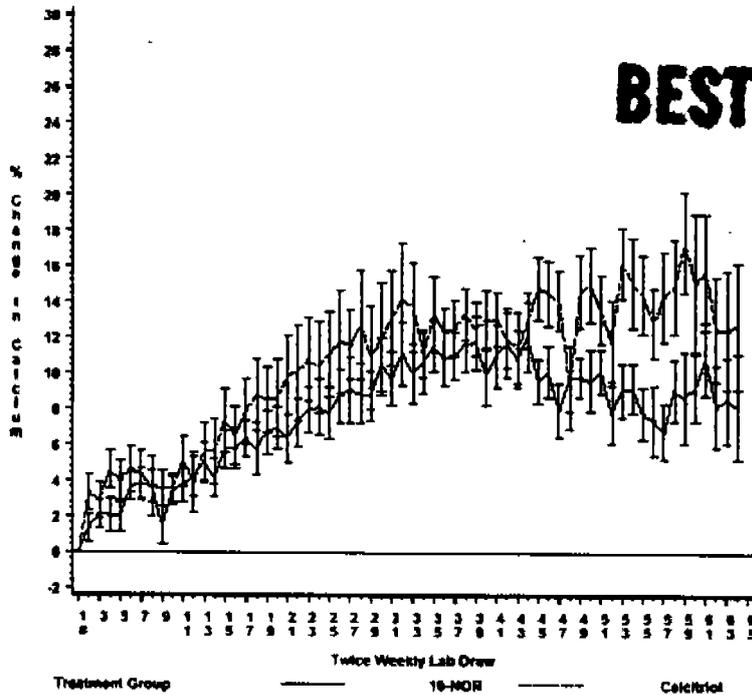
For all treated patients, the calcium and/or calcium x phosphorus product endpoint criteria in relation to the iPTH endpoint were not significantly different in incidence between treatment groups.

For all evaluable patients, the analysis of serum Ca and P data also indicates that the Ca and/or Ca x P product endpoint criteria in relation to iPTH between treatment groups showed no significant difference

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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 44 (Week 22) for the [TRADE NAME] treatment group and approximately 17 percent at Lab Draw 59 (Week 29) for the Calcijex treatment group

A serum Ca level of no more than 11.5 mg/dL was required for entry into the Treatment Phase. A horizontal reference line at 11.5 mg/dL is shown on the plot. In this graph for all treated patients, the treatment group means for Ca were approximately 9.0 mg/dL for [TRADE NAME] and 8.9 mg/dL for Calcijex at last baseline. The maximum [TRADE NAME] group mean for Ca was 10.01 mg/dL at Lab Draw 46 (Week 23).

For the Calcijex treatment group, the maximum mean for Ca was 9.98 mg/dL at Lab Draw 59 (Week 30)

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Table 24: 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			
			mean (range)	mean (range)	mean (SE)	mean (SE)	p-value	mean (SE)	p-value
Week 23, draw 1	Capthrol	40	9.02	9.85	0.83***	-0.36 (0.174)	0.041*	0.43 (0.198)	0.032*
	Calcijex	51	8.59	9.78	1.19***				
Week 24, draw 1	Capthrol	37	9.10	9.78	0.68***	-0.45 (0.176)	0.015*	0.49 (0.201)	0.017*
	Calcijex	50	8.61	9.74	1.13***				
Week 27, draw 1	Capthrol	36	9.04	9.61	0.76***	-0.54 (0.181)	0.008**	0.46 (0.219)	0.039*
	Calcijex	41	8.58	9.69	1.30***				
Week 28, draw 1	Capthrol	31	9.05	9.72	0.67***	-0.46 (0.201)	0.027*	0.46 (0.238)	0.056
	Calcijex	36	8.58	9.71	1.12***				
Week 29, draw 1	Capthrol	22	8.95	9.52	0.57**	-0.56 (0.238)	0.023*	0.31 (0.267)	0.278
	Calcijex	25	8.64	9.77	1.13***				
Week 30, draw 1	Capthrol	20	8.88	9.57	0.70**	-0.69 (0.307)	0.030*	0.28 (0.297)	0.352
	Calcijex	24	8.60	9.68	1.38***				

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

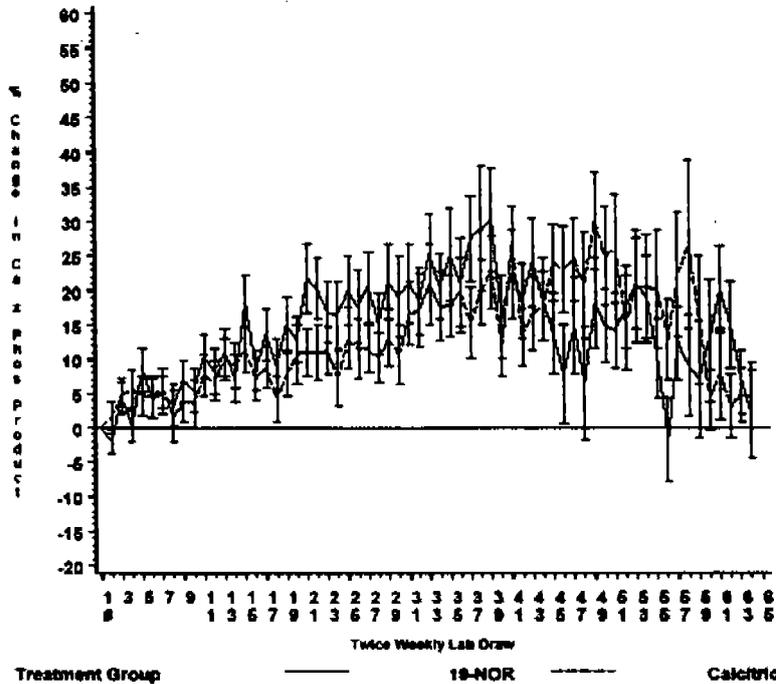
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A significant difference between treatment groups for the change from baseline in serum calcium begin at Treatment Week 23 (p = 0.041) and is also observed at Treatment Weeks 24, 27, 28, 29, and 30 (maximum p-value = 0.030). The [TRADE NAME] group had smaller changes from baseline than Calcijex.

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Figure 3: Plot of Mean \pm SEM for Percent Change from Baseline in Calcium x Phosphorus Product 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.

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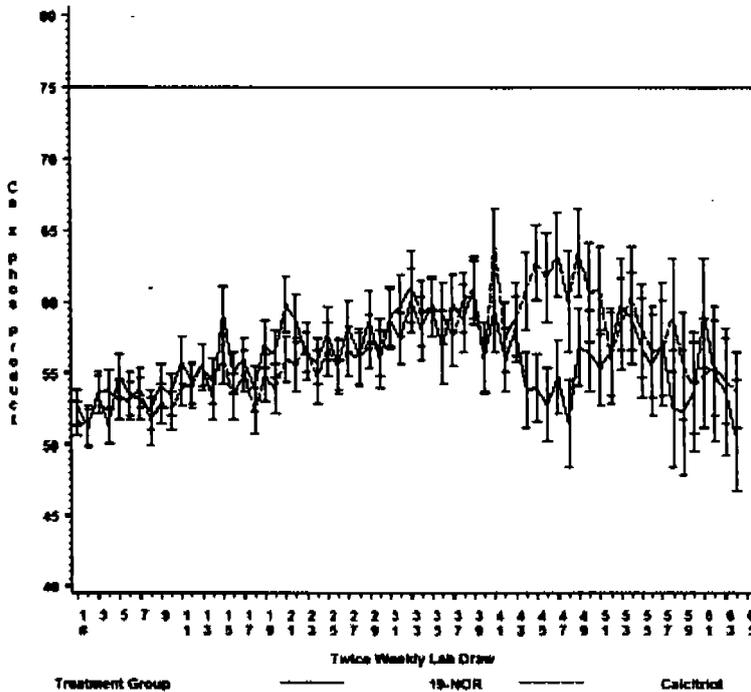
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For all treated patients, the maximum mean percent change from last baseline in serum Ca x P product was approximately 30 percent at Lab Draw 39 (Week 20) for the [TRADE NAME] treatment group and approximately 30 percent at Lab Draw 49 (Week 25) for the Calcijex treatment group.

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Figure 10: Plot of Mean \pm SEM for Calcium x Phosphorus Product by Twice Weekly Lab Draw for A Treated Patients (Cross Reference Appendix 10.0, Figure 9a)



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

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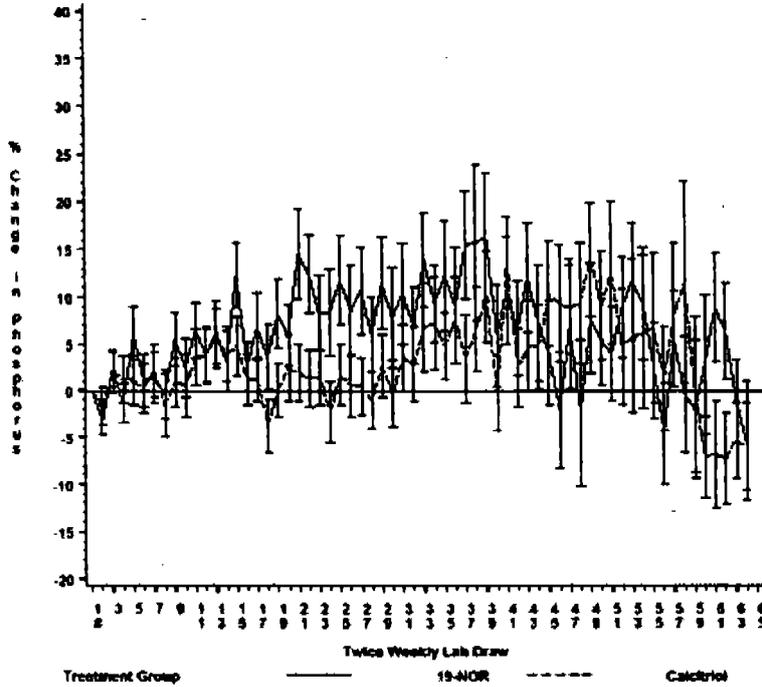
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A serum Ca x P product level of no more than 75 was required for entry into the Treatment Phase. In the graph for all treated patients, the treatment group means for Ca x P product were approximately 53 ([TRADE NAME]) and 52 (Calcijex) at last baseline. The maximum [TRADE NAME] group mean for Ca x P product was 61 at Lab Draw 39 (Week 20) and was 64 at Lab Draw 41 (Week 21) for the Calcijex treatment group. There was no 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 7e)



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 P was approximately 15% at Lab Draw 39 (Week 20) for the [TRADE NAME] treatment group and approximately 13 % at Lab Draw 49 (Week 25) for the Calcijex treatment group.

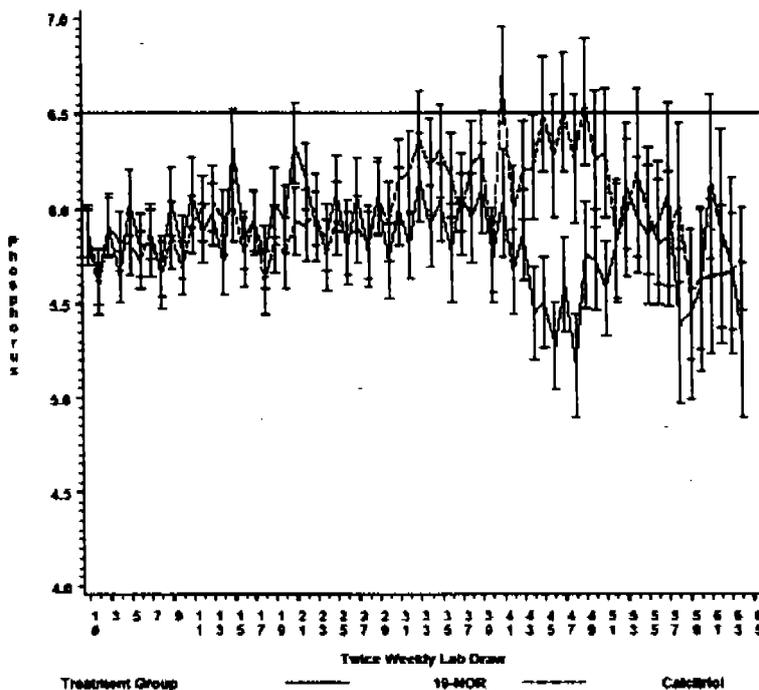
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Figure 12: Plot of Mean \pm SEM for Phosphorus by Twice Weekly Lab Draw for All Treated Patients (Cross Reference Appendix 10.0 Figure 8a)



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

In the graph above for all treated patients, the treatment group means for P were approximately 5.8 mg/dL for both treatment groups at last baseline. The maximum [TRADE NAME] group mean for P was approximately 6.35 mg/dL at Week 11 (Lab Draw 21) and 6.70 mg/dL at Week 21 (Lab Draw 41) for the Calcijex treatment group.

Table 25: Statistically Significant Changes from Last Baseline in Phosphorus 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			
						mean (range)	mean (range)	mean (SE)	p-value
Week 11, draw 1	Capitol	84	5.62	6.35	0.53** (0.190)	0.62 (0.267)	0.021*	-0.17 (0.236)	0.460
	Calcijex	86	5.88	5.90	-0.09 (0.188)				

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

A significant difference between treatment groups in the change from baseline in P occurred at Treatment Week 11 (p = 0.021).

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Change From Baseline in iPTH, Calcium, Calcium x Phosphorus Product, and Phosphorus Values
For each treatment group, an analysis of changes from last baseline to Treatment Week 16 and Follow-up evaluation in chemistry determinations was performed for all treated patients.

A complete laboratory profile was to be obtained at Treatment Week 96 and Follow-up (per protocol). For analysis, the Week 16 laboratory draw was defined as the lab draw obtained closest to Week 16 for patients who had at least 14 weeks of treatment. The Follow-up lab draw was identified as such by the site and was not used for the Week 16 determination.

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Table 26: Changes from Baseline to Week 16 Lab Draw and Follow-up in Efficacy Related Chemistry Determinations for All Treated Patients (Cross Reference 10.3.4.3.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 16: Ca (mg/dL)										
Capthrol N = 68	8.95		9.78		0.82***	0.129	-0.11 (0.176)	0.528	0.25 (0.173)	0.154
Calcijex N = 78	8.71		9.64		0.93***	0.120				
Follow-up: Ca (mg/dL)										
Capthrol N = 102	9.02		9.74		0.71***	0.092	-0.07 (0.129)	0.612	0.02 (0.133)	0.905
Calcijex N = 105	9.01		9.78		0.78***	0.090				
Treatment Week 16: Ca x P										
Capthrol N = 68	51.311		58.585		7.274***	2.224	0.665 (3.039)	0.853	-1.31 (2.232)	0.509
Calcijex N = 78	52.618		59.328		6.709**	2.072				
Follow-up: Ca x P										
Capthrol N = 102	52.743		58.076		5.333**	1.674	-0.797 (2.367)	0.737	1.321 (1.812)	0.467
Calcijex N = 102	51.423		57.553		6.130***	1.674				
Treatment Week 16: P (mg/dL)										
Capthrol N = 68	5.75		5.99		0.24	0.218	0.18 (0.298)	0.545	-0.36 (0.255)	0.160
Calcijex N = 78	6.11		6.17		0.06	0.203				
Follow-up: P (mg/dL)										
Capthrol N = 102	5.85		5.97		0.11	0.178	-0.07 (0.251)	0.793	0.08 (0.201)	0.844
Calcijex N = 103	5.77		5.94		0.17	0.177				

The Week 16 Lab Draw was the lab draw obtained closest to the first dialysis session of Week 16 for patients with at least 14 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 26 (Continued): Changes from Baseline to Week 16 Lab Draw and Follow-up in Efficacy Related Chemistry Determinations for All Treated Patients (Cross Reference 10.3.4.3.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 16: iPTH (pg/mL)										
Capitol N = 68	708.94		336.35		-372.6***	36.55	-47.53 (48.956)	0.343	-73.61 (72.616)	0.311
Calcijex N = 76	782.75		467.58		-325.1***	34.06				
Follow-up: iPTH (pg/mL)										
Capitol N=103	675.11		325.03		-350.1***	34.32	11.70 (48.417)	0.808	-34.61 (54.584)	0.527
Calcijex N=104	709.72		347.04		-361.8***	34.15				

§ The Week 16 Lab Draw was the lab draw obtained closest to the first dialysis session of Week 16 for patients with at least 14 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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A between group comparison for changes from last baseline mean to Week 16 and Follow-up evaluation demonstrated no statistically significant differences between treatment groups. Summary of Efficacy Results: Four-hundred-and-twenty-five patients were enrolled into the study, with 224 randomized (110 [TRADE NAME], 114 Calcijex). Patients receiving [TRADE NAME] (18/110) had a significantly (p = 0.012) reduced incidence of hypercalcemia and/or elevated Ca x P product relative to Calcijex (35/114) in all treated patients. [TRADE NAME] significantly (p = 0.0204) reduced iPTH levels more rapidly than Calcijex, but to the same degree.

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Brief Summary of Adverse Events

For adverse events reported after the Treatment Phase began, there was no statistically significant difference (p = 0.807) between the number of patients reporting one or more adverse events between treatment groups. 93% (102/110) of [TRADE NAME] treatment group patients and 91% (104/114) of Calcijex treatment group patients were reported to have at least one adverse event after the Treatment Phase began. (104/114) of Calcijex treatment group patients were reported to have at least one adverse event after the Treatment Phase began (p = 0.807). [TRADE NAME] treated patients had a greater incidence of adverse events within the Body System *Digestive System* than the patients receiving Calcijex (p = 0.029). Also, within the Body System *Hemic and Lymphatic*, there was a greater incidence of the COSTART term *Ecchymosis* (p = 0.027) in the [TRADE NAME] group. There were no statistically significant differences in incidence between treatment groups for any other Body System or COSTART terms. The [TRADE NAME] treatment group had a statistically higher incidence of events in Body Systems *Cardiovascular System* (p = 0.027) and *Nervous System* (p = 0.027) than the Calcijex treatment group. There were no statistically significant differences in incidence between treatment groups for the remaining Body System or COSTART terms.

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Safety

In this comparative study, [TRADE NAME] displays a safety profile consistent with previous placebo studies.

The only COSTART term that was statistically significant ($p=0.027$) was Ecchymosis. This was reported only in five patients who received [TRADE NAME] (patient numbers 3113/314, 11124/1119, 16107/1603, 21139/2124, and 23101/2302). None of these patients was thrombocytopenic. Two instances occurred at dose level 1 after two doses and the other three at dose level 3 after 30 to 33 injections. In the latter group, the medical complaint ranged from severe ecchymosis to slight ecchymosis, discoloration of the thigh. The patient with severe ecchymosis was a 77 year old female who terminated the study one month later because of possible metastatic adenocarcinoma and still had the ecchymosis. It was considered not related to study drug by both the investigator and the Abbott medical monitor. In the other patients the events cleared up and were also considered not related to study drug.

One death, patient 21141/2129, was considered possibly related to study drug by the investigator. The admitting event was mild elevation of liver enzymes, possible myocarditis of unclear etiology, pulmonary edema, and cardiac arrest. The patient expired from adult respiratory distress syndrome secondary to intra-abdominal sepsis after three doses of [TRADE NAME].

Another patient (11128/1123), who was hospitalized for a seizure and subsequently died of a cardiac arrest was considered possibly related by the Abbott medical monitor but not by the Investigator. The patient had received Calcijex.

Patient 8108/803, a 57 year old female was diagnosed with breast cancer on 11 Dec 96. Biopsy revealed poorly differentiated ductal cancer. The investigator considered there was a possible relationship to study drug and drug was discontinued. The patient had been placed on [TRADE NAME] therapy on 02 Jul 96 and discontinued therapy on 14 Dec 96 on dose level 5 although she had previously received nine doses at dose level 6 and a total of 71 doses.

Except for patients experiencing hypercalcemia, the only other patient prematurely discontinued due to an adverse event had received [TRADE NAME] for two months and was at dose level 2. This was a 42 year old female (5103/506) who developed myoclonic jerks, unsteady gait and veering to the left. None of these events suggested a safety concern.

Other adverse events, including changes in chemistry and hematology values, were not clinically significantly different in occurrence between treatment groups nor were there any apparent trends suggesting a study drug relationship.

Conclusion

There were statistically ($p = 0.012$) fewer instances of elevated serum calcium and/or calcium x phosphorus product in patients receiving [TRADE NAME], while [TRADE NAME] safely reduced iPTH levels significantly ($p = 0.0204$) more rapidly than Calcijex in end-stage renal disease patients on hemodialysis.

Study 95034

Title: Phase III Study: A 24-Week Comparison Between 19-Nor and Intravenous Calcitriol

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Study Objectives

The objective of this study was to determine the safety of [TRADE NAME] in ESRD patients undergoing hemodialysis, and to determine whether the incidence of hypercalcemia and/or elevated calcium x phosphorus product (Ca x P) level was lower in patients receiving [TRADE NAME] than in patients receiving Calcijex®. Efficacy was to be based on the incidence of hypercalcemia and/or elevated Ca x P. The evaluation of safety included changes from last baseline in laboratory tests and physical examinations, and the incidence of adverse events.

Protocol, Inclusion and Exclusion Criteria, and Treatment for this study were the same as in Study 95028 (Section 7.3.1.2.5 above) except for the duration of the study. Study 95034 was conducted as a comparative, double blind, randomized, multicenter study to determine whether there was a lower incidence of hypercalcemia (normalized serum Ca greater than 11.5 mg/dL) and/or elevated Ca x P (greater than 75) in ESRD patients receiving [TRADE NAME] than in patients receiving Calcijex. After randomization, patients were administered [TRADE NAME] or Calcijex three times a week, at 48- to 72-hour intervals (at the end of each of the patient's regular hemodialysis sessions), for 24 weeks. The doses of [TRADE NAME] and Calcijex were to be escalated every four weeks for a maximum of 5 dose escalations or until one of the following conditions occurred:

- 50 percent 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

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Disposition of Patients

Prior to breaking the blind, an efficacy or "evaluable" subset of patients was determined. After all data was entered and patients were classified, the blind was broken.

Use of an Efficacy or "Evaluable" Subset of Patients

The following guidelines were used to classify patients as being evaluable for the statistical analysis prior to the breaking of the blind.

1. A patient was to have achieved a Ca level of >11.5 mg/dL, or a Ca x P of > 75 or a decrease in iPTH of > or = to 50 percent from last baseline during Treatment to be considered evaluable.
2. If a patient inadvertently received a dose of calcitriol (or other Vitamin D therapy) during Treatment, the patient data was analyzed up to the point of receiving the Vitamin D therapy. All data after that point were not analyzed.
3. A patient must have had an iPTH level of at least 300 pg/mL at randomization in order to be considered evaluable.
4. Patients were to be considered evaluable if Ca x P < 75 and/or Ca < 11.5 mg/dL at randomization.
5. If a patient was supposed to be either dose increased or dose decreased and was not, the patient was still considered evaluable.
6. If a patient was supposed to be dose reduced because they had met an endpoint, but was discontinued from the study instead, the patient's data was still considered evaluable up until the point of discontinuation.

7. If a patient had received IV/oral prednisone during Treatment, the patient was still considered evaluable. A distinction was not made between long and short-term use.

8. If a patient's dialysate Ca concentration was not 2.5 mEq/L for greater than 3 consecutive dialysis sessions, all data from that point forward were excluded.

Complete efficacy analyses were performed on all evaluable patients.

Patients unevaluable for not meeting a protocol-specified endpoint for Ca, Ca x P, or iPTH were:

[TRADE NAME]: Treatment patients numbers 405, 608, 812, 816 and 1306

Calcijex: Treatment patients numbers 607, 801, 811, 1203, 1701, 2002, 2006 and 2302.

Patients unevaluable for not meeting Enrollment iPTH criteria were:

[TRADE NAME]: Treatment patient number 508

Calcijex: Treatment patients numbers 604, 2006, 2105 and 2305.

Patients with data excluded as unevaluable after receiving inadvertent doses of Calcijex after the Treatment Phase began were:

[TRADE NAME]: Treatment patient number 603 (July 18, 1996).

Calcijex: Treatment patients numbers 506 (August 21, 1996), 601 (June 6, 1996), 1406 (July 31, 1996), 1702 (October 9, 1996), and 1809 (May 23, 1996).

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Protocol Deviations

In reviewing the data for all patients, deviations from the protocol were identified. The deviations noted did not compromise safety analyses. Deviations were divided into the following categories:

1. *Admission Criteria* Exceptions made against protocol-specified criteria.
2. *Study Drug Administration* Exceptions made against protocol-specified criteria for dosing due to miscalculation or timing.
3. *Concurrent Medications* Exceptions made against protocol-specified restrictions.
4. *Clinical Laboratory* Laboratory values not obtained, missing due to sampling or laboratory error, or values not obtained at protocol-specified times.
5. *Premature Termination* Terminations that occurred due to circumstances other than the successful completion of a study criteria.
99. *Other* Study procedures or parameters not recorded or measured at the protocol-specified times.

Deviations by Category

Category	Number of Deviations
1. Admission Criteria	79
2. Study Drug Administration	723
3. Concurrent Medications	28
4. Clinical Laboratory	650
5. Premature Termination	14
99. Other	287

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Three hundred of the 330 total enrolled patients had a deviation.

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Efficacy Evaluation

The efficacy of [TRADE NAME] in all treated patients was characterized by the following parameters:

- the incidence of hypercalcemia
- and/or
- the incidence of elevated Ca x P level

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Data Sets Analyzed

The primary data set analyzed for efficacy and safety was all treated patients. There were 197 patients in the all treated patients data analysis (98 [TRADE NAME], 99 Calcijex) and 180 patients in the all evaluable patients data set (92 [TRADE NAME], 88 Calcijex). Analysis for all enrolled patients was also performed (excluding efficacy analysis) and was presented in the Appendices.

Demographic and Other Baseline Characteristics

Descriptive statistics were used to summarize gender, race, age, height, weight and vital signs by treatment group. Statistical tests were performed to compare the two treatment groups with respect to these variables. A one-way ANOVA was used to compare treatment groups for continuous variables (age, weight, height, temperature, blood pressure and pulse) while a Fisher's exact test was used for categorical variables

Table 6 presents a summary and comparison of demographics for all treated patients.

Table 6: Demographics for All Treated Patients (Cross Reference: 10.1.1.a)							
	Total N=197		Capthrol N=98		Calcijex N=99		p-value ¹
	number	percent	number	percent	number	percent	
Gender							
Male	101	51	48	49	53	54	0.570
Female	96	49	50	51	46	46	
Race							
Caucasian	24	12	9	9	15	15	0.276
Black	155	79	78	80	77	78	
Hispanic	17	9	11	11	6	6	
Other	1	1	0	0	1	1	
Age (years)							
18 - < 35	22	11	10	10	12	12	
35 - < 65	120	61	58	59	62	63	
65 - < 80	51	26	28	29	23	23	
> 80	4	2	2	2	2	2	
Mean ± s.d.	53.80 ± 15.00		55.80 ± 14.00		51.80 ± 15.73		0.057
Range							
Height (cm)							
Mean ± s.d.	169.8 ± 12.36		170.6 ± 10.95		169.0 ± 13.63		0.351
Range							
Weight (kg)							
Mean ± s.d.	81.10 ± 21.17		82.50 ± 20.41		79.60 ± 21.90		0.336
Range							

¹P-value comparing treatment groups is from a 2 x 2 Fisher's Exact test for gender and race (Caucasian versus non-Caucasian) or a one-way ANOVA for age, height, and weight.

The analysis of demographic data indicated that the gender, race, and mean age, height, and weight values were not significantly different between treatment groups.

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**Table 7: Prestudy Vital Signs for All Treated Patients
(Cross Reference 10.1.1.a)**

	Total N = 197 number	Capthrol N = 98 number	Calcijex N = 99 number	p-value
Temperature (°C)				
Mean ± s.d.	36.30 ± 0.58	36.40 ± 0.56	36.30 ± 0.60	0.466
Range				
Systolic BP (mm Hg)				
Mean ± s.d.	152.9 ± 28.88	158.4 ± 30.94	147.4 ± 25.69	0.007**
Range				
Diastolic BP (mm Hg)				
Mean ± s.d.	82.90 ± 16.90	84.30 ± 18.42	81.50 ± 15.21	0.247
Range				
Pulse (bpm)				
Mean ± s.d.	84.00 ± 13.10	84.90 ± 12.13	83.10 ± 13.99	0.342
Range				

*p-value comparing treatment groups is from a one-way ANOVA.

The analysis of prestudy vital sign data indicated that the mean body temperature, mean diastolic blood pressure, and mean pulse values were not significantly different between treatment groups. The difference in the mean systolic blood pressure between the two treatment groups was statistically significant (p=0.007). For each treatment group, patient medical history was summarized by the count and percentage of normal and abnormal findings for each medical history variable.

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**Table 8: Summary of Patient Medical History for All Treated Patients
(Cross Reference 10.1.2.a)**

Body System	Caphrol N = 98		Calcijex N = 99	
	number of patients with abnormal medical history	percent of patients with abnormal medical history	number of patients with abnormal medical history	percent of patients with abnormal medical history
Respiratory	36	37	44	44
Ear/Eyes/Throat	30	31	46	46
Gastrointestinal	34	35	37	37
Hepatic/Renal	61	62	56	56
Genito-Urinary/Reproductive	50	51	47	47
Nervous System	55	56	59	60
Endocrine/Metabolic	25	26	42	42
Hematopoietic/Lymphatic	39	40	36	36
Dermatologic	62	63	61	62
Musculoskeletal	31	32	25	25
Surgical	21	21	14	14
Psychiatric	78	80	76	77
Allergies	60	61	60	61
Dialysis Access	12	12	12	12

Table 9: Summary of Patient Cardiovascular/Cerebrovascular History for All Treated Patients (Cross Reference 10.1.4.a)

	Caphrol N = 96		Calcijex N = 99	
	number of patients with positive history	percent of patients with positive history	number of patients with positive history	percent of patients with positive history
Hypertension	95	97	90	91
Congestive Heart Failure	23	23	30	30
Myocardial Infarction	16	16	13	13
Valvular Dysfunction	21	21	20	20
Arrhythmias/Conduction	31	32	32	32
Cardiomyopathy	10	10	11	11
Stroke	14	14	11	11
Vascular Disease	26	27	24	24

The following Table presents a summary of renal disease and dialysis information for all treated patients.

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Table 10: Summary of renal disease and dialysis information for All Treated Patients (Cross Reference 10.1.3.a)

	Caphrol N=98		Calcjex N=99	
	number	percent	number	percent
Treatments Patient has Received¹				
Oral Calcitrol	8	8	9	9
Oral Dihydroxycholesterol	1	1	0	0
Calcjex	87	81	83	79
No Vitamin D Analogs	10	9	13	12
Length of Time Patient has been on Dialysis				
Less than one year	18	18	24	24
One year but less than five years	48	48	50	51
Five years but less than ten years	28	29	14	14
Ten years or longer	4	4	10	10
Major Cause of Chronic Renal Failure²				
Focal Glomerulosclerosis	5	3	9	6
Membranoproliferative glomerulonephritis	0	0	3	2
Idiopathic Crescentic Glomerulonephritis	0	0	1	1
Diabetes	54	38	30	21
Post-infectious Glomerulonephritis	1	1	1	1
Systemic Lupus Erythematosus	2	1	2	1
Analgesic Nephropathy	1	1	0	0
Reflux Nephropathy with Pyelonephritis	0	0	1	1
Polycystic Kidney Disease	5	3	3	2
Medullary Cystic Disease	0	0	1	1
Hypertension	66	44	66	46
Renal Vascular Disease	0	0	2	1
Obstructive Uropathy	0	0	1	1
Unknown	6	4	0	0
Other ³	11	7	22	15

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¹A patient may have received one, more than one, or no previous Vitamin D treatment.

²A patient may have more than one cause of chronic renal failure.

³The specification for Other is given in Appendix 10.1.3.c.

The analysis of the length of time a patient had been on dialysis was not significant.

The analysis of the length of time a patient had been on dialysis was not significantly different between treatment groups ($p = 0.494$).

The next Table presents an analysis of these changes from Enrollment to the last baseline evaluation, for all treated patients, for those chemistry variables used either directly (Ca, Ca x P, and P) or indirectly (iPTH), in the efficacy evaluation. Statistically significant values are indicated with asterisks.

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Table 11: Analysis of Changes from Enrollment to the Last Baseline Evaluation in Chemistry Determinations Related to Efficacy for All Treated Patients (Cross Reference 10.3.4.1.a)

Treatment group	Enrollment mean (range)	Final baseline mean (range)	Change from Enrollment mean (SE)	Between group comparison for	
				Change mean (SE) p-value	Enrollment mean (SE) p-value
Calcium (mg/dL)^a					
Capthrol n=85	9.31	8.97	-0.34 (0.07)***	-0.12 (0.1) 0.24	0.15 (0.13) 0.24
Calcijex n=96	9.16	8.93	-0.23 (0.07)***		
Calcium x Phosphorus^b					
Capthrol n=93	53.44	52.11	-3.33(1.7)	0.03 (2.36) 0.99	2.6 (2.01) 0.20
Calcijex n=95	52.84	49.48	-3.36(1.65)		
Phosphorus (mg/dL)					
Capthrol n=93	5.90	5.76	-0.22(0.19)	0.01 (0.27) 0.97	0.12 (0.23) 0.59
Calcijex n=95	5.65	5.62	-0.23 (0.19)		
iPTH (pg/mL)					
Capthrol n=95	577.6	686.3	88.69 (22.25)***	0.07 (31.31) 0.90	46.44 (52.17) 0.39
Calcijex n=97	531.2	611.8	80.63 (22.02)***		

^a P-value based upon a one-way ANOVA.
^b Ca values normalized to an albumin of 4.0 g/dL.
 *, **, *** indicate statistical significance (2-tailed) at the 0.05, 0.01, or 0.001 levels respectively.

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A between group 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 Ca, Ca x P, P, and iPTH levels.

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Efficacy Results and Tabulations of Individual Patient Data

Per the protocol, laboratory draws were to be obtained twice a week during Treatment for Ca, P, and albumin (Ca x P was subsequently reported) and once a week for iPTH levels.

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Analysis of Efficacy

For statistical analyses, the baseline evaluation was defined as the last laboratory evaluation obtained prior to the first dose of study drug administration. The study was designed such that the laboratory value obtained prior to dialysis on Treatment Day One would serve as baseline. However, in such cases where the Treatment Day One results were not available (e.g. the iPTH sample was severely hemolyzed and could not be analyzed by the central laboratory) or did not satisfy the prior to first dose of study drug administration criterion, the last laboratory result obtained prior to Treatment served as baseline. The laboratory evaluations at Enrollment were excluded from the baseline assessment. The Follow-up laboratory determinations (defined in the protocol) were from the final or last lab draw for all patients unless this Follow-up procedure was not performed. For patients in which the Follow-up procedure was not performed, the final lab draw is the last lab draw the patient underwent.

The efficacy of treatment groups was assessed by determining the incidence of hypercalcemia and/or incidence of a Ca x P product > 75. A 2x2 Fisher's Exact test was used to test for a difference between treatment groups in the number of patients who became hypercalcemic and/or had a Ca x P product > 75. In addition, the number of patients who became hypercalcemic for two consecutive lab draws and/or had a Ca x P product > 75 for 4 consecutive lab draws, the number of patients who became hypercalcemic at least once during treatment, the number of patients who became hypercalcemic for a period of two consecutive lab draws, the number of patients who became hypercalcemic at the final lab draw, the number of patients who had a Ca x P product > 75 and the number of patients who had a Ca x P product > 75 for 4 consecutive lab draws were compared with a 2x2 Fisher's Exact Test.

Although a patient was dose reduced upon a single incidence of hypercalcemia for safety purposes, two consecutive instances of hypercalcemia were chosen as an elevation endpoint for analysis, to approximate the clinical scenario of hypercalcemia upon which most dosing changes for Calcijex are actually based. The same rationale led to choosing 2 weeks of Ca x P > 75 as evidence of clinically significant product elevation.

The time (in days) to the first occurrence of 4 consecutive 50% decreases from last baseline in iPTH was modeled using the Kaplan-Meier method of generating survival curves. The log-rank test was used to test for the equality of survival curves between treatment groups.

Major Factor Affecting Efficacy and Primary Efficacy Variables

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Major Factor Affecting Efficacy, Serum iPTH

The purpose of using an iPTH reduction endpoint of 50% 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. The following Table is a summary of all treated patients meeting the iPTH reduction endpoint.

Table 13: All Treated Patients With a 50 Percent or Greater Decrease from Last Baseline in iPTH Levels (Cross Reference: 10.2.1.a)

Criteria Achieved by Patient:	Capthol N=98		Calcijex N=99		p-value*
	number	percent	number	percent	
All least one 50 percent decrease in iPTH during Treatment	83	84.7	75	75.8	0.152
A 50 percent decrease in iPTH for at least one period of four consecutive iPTH lab draws	39	57.1	52	52.5	0.988
A 50 percent decrease in iPTH at the final lab draw	60	61.2	51	51.5	0.187

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

For all treated patients, the analysis of serum iPTH data shows no statistically significant difference between treatment groups.

For all evaluable patients (not shown), serum iPTH data show a similar result.

The next Figure presents the mean percent change from last baseline in iPTH levels by weekly lab draw for all treated patients.

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