

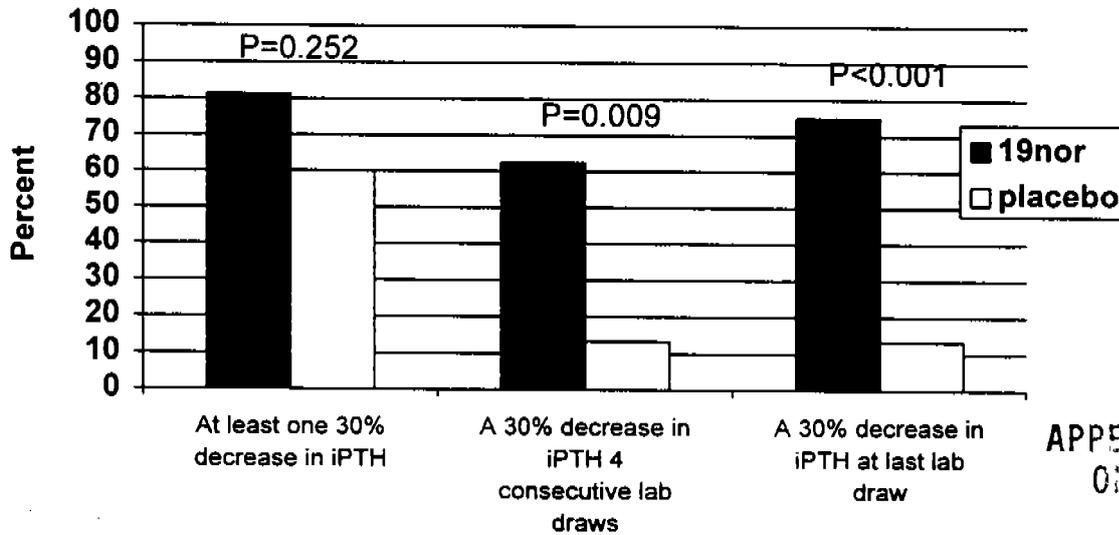
Three variables were evaluated for a comparison of efficacy between active and placebo patients.

- Those patients experiencing one incidence of at least a 30 % decrease in iPTH at any time during the study.
- Those patients experiencing at least a 30 % decrease in iPTH for four consecutive laboratory measurements.
- Those patients experiencing at least a 30 % decrease in iPTH at the final visit.

The next Figure and Table present the number and percentage of all treated patients who met the above conditions based on the last available baseline determination prior to study drug administration.

All Treated Patients With a 30 Percent or Greater Decrease from Baseline in iPTH Levels, Study 95036

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All Treated Patients With a 30 Percent or Greater Decrease from Baseline in iPTH Levels, Study 95036

	Active		Placebo		p-Value [†]
	number	percent	number	percent	
At least one 30 % decrease in iPTH	13/16	81.3	9/15	60.0	0.252
A 30% decrease in iPTH for at least 4 consecutive lab draws	10/16	62.5	2/15	13.3	0.009**
A 30 % decrease in iPTH at final visit	12/16	75.0	2/15	13.3	<0.001***

[†] P-value based upon a 2 x 2 Fisher's exact test.

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

For the three variables evaluated for all treated patients, active patients demonstrated a statistically significant difference in iPTH reduction for at least four consecutive lab draws and at final visit in comparison to placebo patients.

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Change From Baseline in iPTH Values

The next Table presents a comparison between treatment groups in changes from baseline to final evaluation for iPTH with statistically significant values underlined.

Changes from Baseline in iPTH Values, Study 95036						
Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between-group Comparisons		
				Change Mean (SE) P-value [†]	Baseline Mean (SE) P-value [†]	
iPTH (pg/ml)	Active	736.3	435.4	<u>-30]</u> <u>[70.01]*</u> **	<u>-264 (101)</u>	49.65 (161)
	Placebo	686.7	650.1	-36.6 [72.30]	<u>0.014*</u>	0.761

[†] P-value based upon a one-way ANOVA.

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

A between-group analysis of changes from baseline to final evaluation for all treated patients indicates that active patients demonstrated a statistically significant reduction in iPTH in comparison to placebo patients.

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Other Variables

The following Table presents a comparison of changes from baseline to final evaluation for alkaline phosphatase with statistically significant values underlined.

Changes from Baseline in Alkaline Phosphatase Values, Study 95036						
Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between-group Comparisons		
				Change Mean (SE) P-value [†]	Baseline Mean (SE) P-value [†]	
Alk. Phos. (U/L)	Active	148.0	97.58	<u>-50.4 [16.82]**</u>	<u>-54.1 (23.8)</u>	24.25 (45.5)
	Placebo	123.8	127.4	3.667 [16.82]	<u>0.033*</u>	0.599

[†] P-value based upon a one-way ANOVA.

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

As a marker for bone remodeling activity, alkaline phosphatase provided an additional efficacy variable. A between-group analysis of changes from baseline to final evaluation for all treated patients shows that

active patients demonstrated a statistically significant reduction in alkaline phosphatase in comparison to placebo patients.

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Study 95036 Conclusions

Efficacy: A double-blind, placebo-concurrent controlled, randomized, multi-investigator study and an intent to treat primary analysis of the percentage of patients to have a 30% iPTH reduction were selected to determine efficacy. This study determined that Paracalcin Injection significantly reduces elevated iPTH levels in patients with CRF. An analysis of all treated patients showed that 63% (10/16) of the patients receiving Paracalcin Injection achieved at least a 30% decrease in iPTH values for at least four consecutive lab draws compared to 13% (2/15) of the patients who received placebo ($p = 0.009$). Patients receiving active drug had a mean iPTH reduction of 301 pg/ml compared to a reduction of 36.6 pg/ml following treatment with placebo ($p < 0.014$). Serum alkaline phosphatase decreased by 50.4 U/L in active patients while there was an increase of 3.7 U/L in the placebo group ($p = 0.033$). This change is consistent with decreased bone osteoblast activity in patients after they receive Paracalcin Injection.

Safety: It was concluded following review and analysis of adverse events, including signs, symptoms, and laboratory tests, that Paracalcin Injection significantly reduced the elevated iPTH levels safely. There were two deaths in the study: one pretreatment patient and one active patient. Neither death was considered by the Investigator or the Abbott Medical Monitor to be drug related and neither was unanticipated in this patient population. Similar numbers of Serious Adverse Events occurred in the Pretreatment Phase as after randomization; all were considered to have no relationship to study drug administration.

The incidence and type of other, non-serious adverse events observed during Pretreatment and during Treatment were similar and were considered by the Investigators to be either not related or only possibly related to treatment, with no probable and one definite relationship reported (placebo, 3105/302, mild taste perversion). A review of vital signs and physical examinations following Treatment revealed no clinically significant changes.

Because of the known occurrence of hypercalcemia and/or elevated Ca x P product with calcitriol therapy, these parameters were closely monitored during Treatment. A comparison of the change in Ca values between active and placebo patients from baseline to Follow-up did not indicate a statistically significant difference ($p = 0.081$) between the two groups. Paracalcin patients experienced an increase in mean Ca values of 0.34 mg/dL compared to a decrease of 0.23 mg/dL in placebo patients. A single occurrence of hypercalcemia required dose adjustment. No patient from either treatment group became hypercalcemic during the Treatment Phase of the study. No patient from either treatment group was hypercalcemic at the final lab draw.

A comparison of the change in Ca x P values between active and placebo patients from baseline to Follow-up indicated a statistically significant difference ($p < 0.001$) between the two groups. Paracalcin patients experienced an increase in mean Ca x P values of 14.11 compared to a decrease of 1.66 in placebo patients. However, the difference in the incidence of patients with a Ca x P greater than 75 for two consecutive determinations, the clinical parameter requiring dose adjustment, was not statistically significant. Thirteen % (2/16) of active patients and no placebo patients had such occurrences. Three active patients discontinued the study during treatment; one patient upon request of the attending physician, one patient was randomized below the iPTH inclusion criteria, and one patient relocated. Although the effects of the test drug on serum Ca x P and serum Ca values were not statistically

significant from those of placebo, there was indication of a possible safety issue in the drug group which should be noted in the labeling.

Other chemistry and hematology variables showed random variation with no trends in active patients when compared with Pretreatment values for those patients or when compared with the results in placebo patients except for the eosinophil count which showed a marginal ($p = 0.031$) increase in eosinophil count ($0.07 \text{ cells} \times 10^3/\text{microliter}$) compared to a marginal decrease in placebo ($-0.07 \text{ cells} \times 10^3/\text{microliter}$). None of the individual out-of-range chemistry or hematology values recorded during Treatment were considered to be study drug related.

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Conclusion

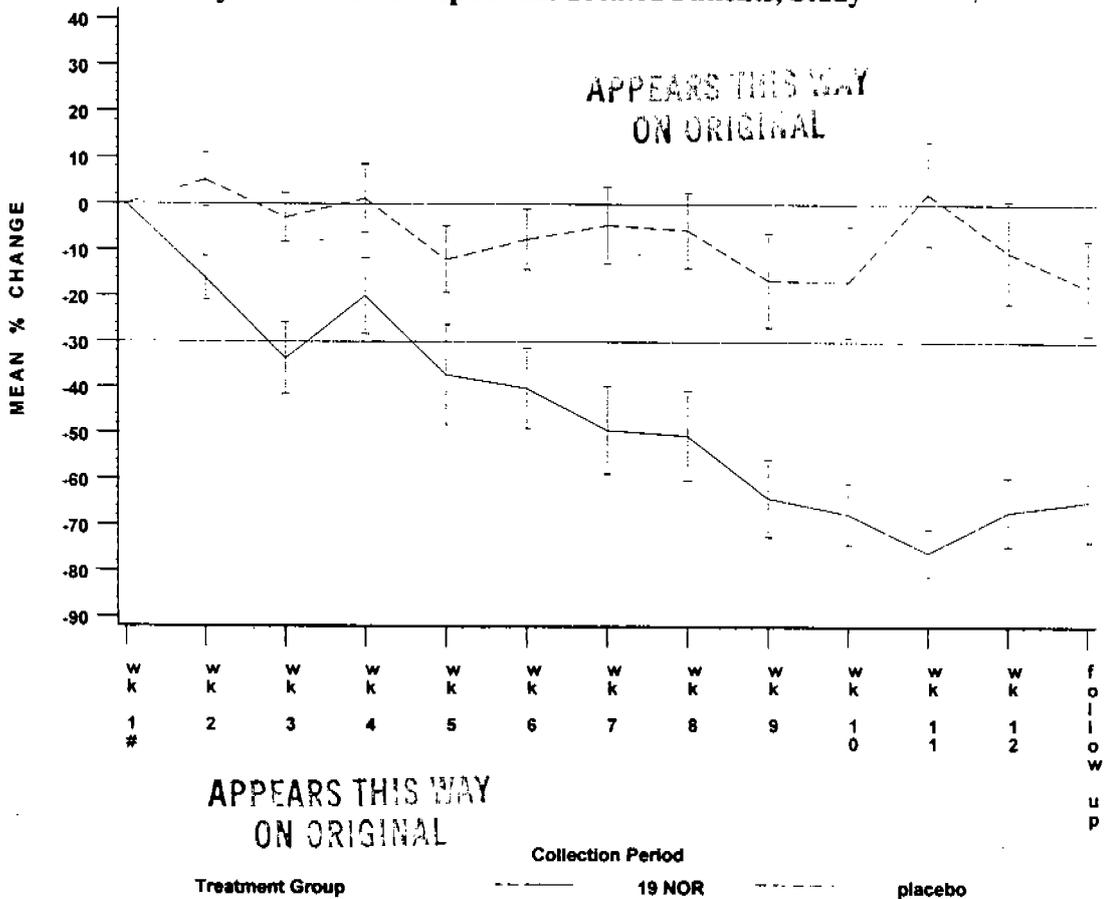
Compared to placebo, Paracalcin Injection effectively and safely reduced iPTH levels in CRF patients on hemodialysis

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7.3.1.2.3 Study 95037

Primary Efficacy Variable—iPTH Level

Weekly Mean \pm 1 SEM for Percent Change from Baseline for iPTH Levels by Treatment Group for All Treated Patients, Study



95037

Week 1 is the baseline iPTH determination.
 Note: Horizontal reference lines at 0 and -30. Standard error bars included at each mean.

The mean % change from baseline in iPTH levels for all treated patients was greater than -30% by Week 5 for active patients while the mean percent change remained within -20% of baseline for placebo patients. The mean % change from baseline in iPTH levels for all treated patients was greater than -60% from baseline at the Follow-up visit for active patients while the mean for % change for placebo patients again was within -20% of baseline.

Three variables were evaluated for a comparison of efficacy between active and placebo patients.

- At least a 30% decrease in iPTH at any time during the study.
- At least a 30% decrease in iPTH for four consecutive laboratory draws.
- At least a 30% decrease in iPTH at the final visit.

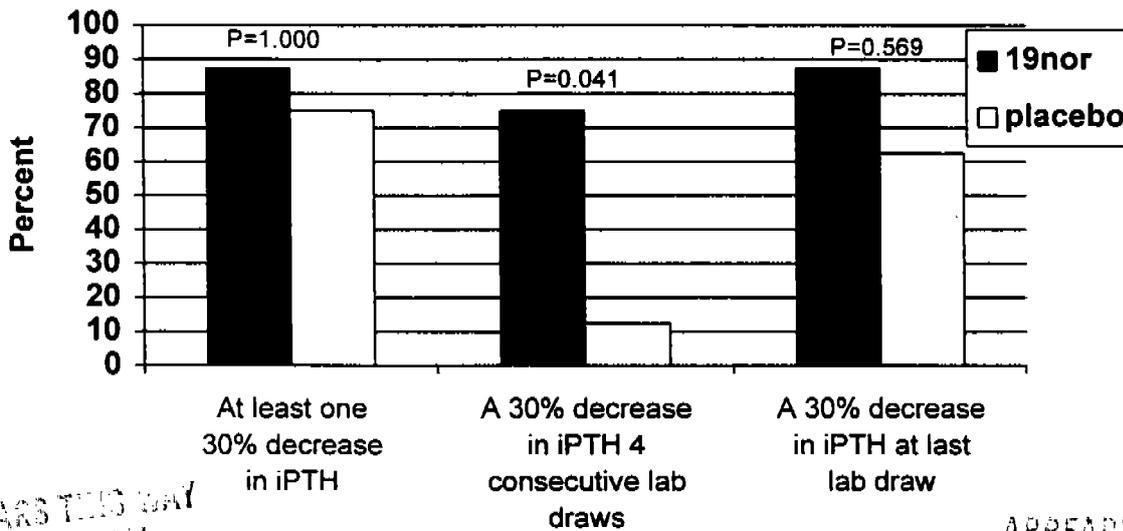
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The next Figure and Table show the number and percentage of all treated patients who met the above conditions based on the last available baseline determination prior to study drug administration.

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**All Treated Patients With a 30 Percent or Greater Decrease
from Baseline in iPTH Levels, Study 95037**

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**All Treated Patients With a 30 Percent or Greater Decrease
from Baseline in iPTH Levels, Study 95037**

	Active		Placebo		p-value [†]
	number	percent	number	percent	
At least one 30 percent decrease in iPTH	7/8	87.5	6/8	75.0	1.000
A 30 percent decrease in iPTH for at least 4 consecutive lab draws	6/8	75.0	1/8	12.5	0.041*
A 30 percent decrease in iPTH at the final lab draw	7/8	87.5	5/8	62.5	0.569

[†] P-value based upon a 2 x 2 Fisher's Exact test.

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

Active patients demonstrated a statistically significant difference in iPTH reduction for at least four consecutive lab draws in comparison to placebo patients.

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Change from Baseline in iPTH Values

The next Table presents a comparison between treatment groups in changes from baseline to final evaluation for iPTH with statistically significant values underlined.

Change from Baseline in iPTH Values, Study 95037						
Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between Group Comparisons		
				Change Mean (SE) p-value [†]	Baseline Mean (SE) p-value [†]	
iPTH (pg/ml)	Active	870.9	365.5	<u>-505</u> <u>[90.36]</u> ***	<u>-372</u> (128)	-154 (181)
	Placebo	1025	892.0	-133 [90.36]	<u>0.011</u> *	0.409

[†] P-value based upon a one-way ANOVA.

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

A between-group analysis of changes from baseline to final evaluation for all treated patients indicates that active patients demonstrated a statistically significant reduction in iPTH in comparison to placebo patients.

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Study 95037 Conclusions

Efficacy: In a double-blind, placebo-concurrent controlled, randomized, multi-investigator study, an intent to treat primary analysis of the percentage of patients to have a 30% iPTH reduction demonstrated efficacy. This study showed that Paracalcin Injection significantly reduces elevated iPTH levels in patients with CRF. An analysis of all treated patients showed that approximately 75% (6/8) of the active patients achieved at least a 30% decrease in iPTH values for at least four consecutive lab draws compared to approximately 13% (1/8) of the patients who received placebo ($p = 0.041$). Active patients had a mean iPTH reduction of 505 pg/ml compared to a reduction of 133 pg/ml following treatment with placebo ($p = 0.011$).

Safety: It was concluded following review and analysis of adverse events, including signs, symptoms, and laboratory tests, that Paracalcin Injection significantly reduced the elevated iPTH levels safely. There were no deaths. Similar numbers of Serious Adverse Events occurred in the Pretreatment Phase as after randomization; all considered to have no relationship to study drug administration.

The incidence and type of other, non-serious adverse events observed during Pretreatment and during Treatment were similar and were considered by the Investigators to be either not related or only possibly related to treatment, with the exception of one probable (active, patient 1110/102, mild impotence) and one definite (placebo, patient 4105/402, mild increased vertigo) relationship reported. A review of vital signs and physical examinations following Treatment revealed no clinically significant changes.

Because of the known occurrence of hypercalcemia and/or an elevated Ca x P product with calcitriol therapy, these parameters were closely monitored during Treatment.

A comparison of the change in Ca values between active and placebo patients from baseline to Follow-up did not indicate a statistically significant difference ($p = 0.650$) between the two groups. Paracalcin patients experienced an increase in mean Ca values of 0.44 mg/dL compared to a increase of 0.29 mg/dL in placebo patients.

A single occurrence of hypercalcemia required dose adjustment. No patients in either treatment group became hypercalcemic at any time during Treatment. No patient from either treatment group was hypercalcemic at their final laboratory draw.

A comparison of the change in Ca x P values between active and placebo patients from baseline to Follow-up did not indicate a statistically significant difference ($p = 0.702$) between the two groups. Paracalcin patients experienced a decrease in mean Ca x P values of 2.79 compared to a decrease of 5.84 in placebo patients. Moreover, the difference in the incidence of patients with a Ca x P greater than 75 for two consecutive lab draws, the clinical parameter requiring dose adjustment, was not statistically significant. Twenty-five % (2/8) of active patients and approximately 13% (1/8) of placebo patients had such occurrences. One active patient (2109/203) was discontinued from the study due to elevated Ca x P products. No patient discontinued from the study due to elevated Ca.

As found in the two previous studies, the increased serum Ca and serum Ca x P, while not statistically significant, suggest possible safety issues associated with Paracalcin.

Other chemistry and hematology variables showed random variation with no trends observed in active patients during treatment that were discernible when compared with Pretreatment values in active patients or when compared with the results observed in placebo patients. None of the individual out-of-range chemistry or hematology values recorded during Treatment were considered by the Investigator or the Abbott Medical Monitor to be study drug related.

Patients at the University of Michigan Medical Center (Site 4, Patients 401 – 408) probably had a discrepancy in their dosage schedule. Of the patients that were to receive placebo, all four (Patients 403, 404, 405, and 406) had measurable paracalcin concentrations consistent with having received paracalcin rather than placebo. The other four patients at this site who were to receive paracalcin (Patients 401, 402, 407, and 408) had no measurable paracalcin concentrations for all samples collected, suggesting that these patients received placebo rather than paracalcin. All other patients at Sites 1 - 3 in this study for which blood samples were collected had paracalcin concentrations that were consistent with their assigned dosage randomization. In addition, an audit of Paracalcin Injection clinical supplies showed that labeling of clinical supplies for 95035, all sites; 95036, all sites; and 95037, Sites 1 – 3 was accomplished appropriately and on the same date. However, clinical supplies for Study 95037, Site 4 were labeled at a later date, without proper documentation, and apparently according to a reversed randomization schedule. Because of the apparent incorrect labeling of clinical supplies and substantial pharmacokinetic evidence, all tables and data listings have been generated based on the corrected dosage regimen for patients in Site 4 of Study 95037. No significant safety issues occurred with any of the patients enrolled at this site.

Conclusion: Compared to placebo, Paracalcin Injection effectively and safely reduced iPTH levels in CRF patients on hemodialysis.

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7.3.1.2.4 Analysis of All Three Phase III Placebo-Concurrent Controlled Studies

Summary of Patient Demographics: All Phase III Placebo-Concurrent Controlled Trials							
	Total (n = 78)		Paracalcin (n = 40)		Placebo (n = 38)		p- value†
	number	percent	number	percent	number	percent	
Gender							1.000
Male	40	51	21	53	19	50	
Female	38	49	19	48	19	50	
Race							0.512
Caucasian	10	13	4	10	6	16	
Black	62	79	35	88	27	71	
Hispanic	6	8	1	3	5	13	
Age (years)							
18 - < 35	7	9	2	5	5	13	
35 - < 65	53	68	28	70	25	66	
65 - < 80	16	21	8	20	8	21	
80 and >	2	3	2	5	0	0	
Mean ± s.d.	54.00 ± 14.88		54.40 ± 14.43		53.50 ± 15.52		0.775
Range							
Height (cm)							
Mean ± s.d.	168.9 ± 12.31		169.5 ± 11.37		168.3 ± 13.36		0.676
Range							
Weight (kg)							
Mean ± s.d.	78.80 ± 18.57		81.0 ± 17.79		76.50 ± 19.33		0.294
Range							

Gender frequencies, race, and mean age, height, and weight were comparable between groups, as were mean values for iPTH, Ca, P, and Ca x P product.

**Last Baseline Values for Selected Chemistry Determinations: All Phase III
Placebo-Concurrent Controlled Trials**

	Treatment Group	Baseline		Comparisons	
		Mean	[range]	Mean (SE)	p-value†
iPTH (pg/ml)	active	783.4		38.14 (84.9)	0.655
	placebo	745.3			
Ca* (mg/dL)	active	9.26		0.20 (0.15)	0.188
	placebo	9.06			
Phosphorus (mg/dL)	active	5.803		-0.200 (0.351)	0.570
	placebo	6.003			
Ca x P product*	active	53.75		-0.276 (3.30)	0.933
	placebo	54.03			

* Ca values normalized to an albumin of 4.0 g/dL.

† P-value based upon a one-way ANOVA.

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Weekly Patient Count During Treatment: All Phase III Placebo-Concurrent Controlled Trials

Week(s)	≥ 1*	≥ 1	≥ 2	≥ 3	≥ 4	≥ 5	≥ 6	≥ 7	≥ 8	≥ 9	≥ 10	≥ 11	≥ 12
No. of Pts.	40	39	38	37	36	35	35	34	33	32	31	31	27

* ≥ 1 dose

The average dose during treatment was 0.09 mcg/kg/dose and at the end of treatment the average dose was 0.11 mcg/kg/dose. Only 2/40 patients required the highest dose studies, 0.24 mcg/kg.

**Summary of Dose Level During Treatment:
All Phase III Placebo-Concurrent Controlled Trials**

Count and Percentage of Patients at Each Dose Level

0.04 mcg/kg		0.08 mcg/kg		0.12 mcg/kg		0.16 mcg/kg		0.20 mcg/kg		0.24 mcg/kg	
n	%	n	%	n	%	n	%	n	%	n	%
40	100.0	36	90.00	24	60.00	13	32.50	6	15.00	2	5.00

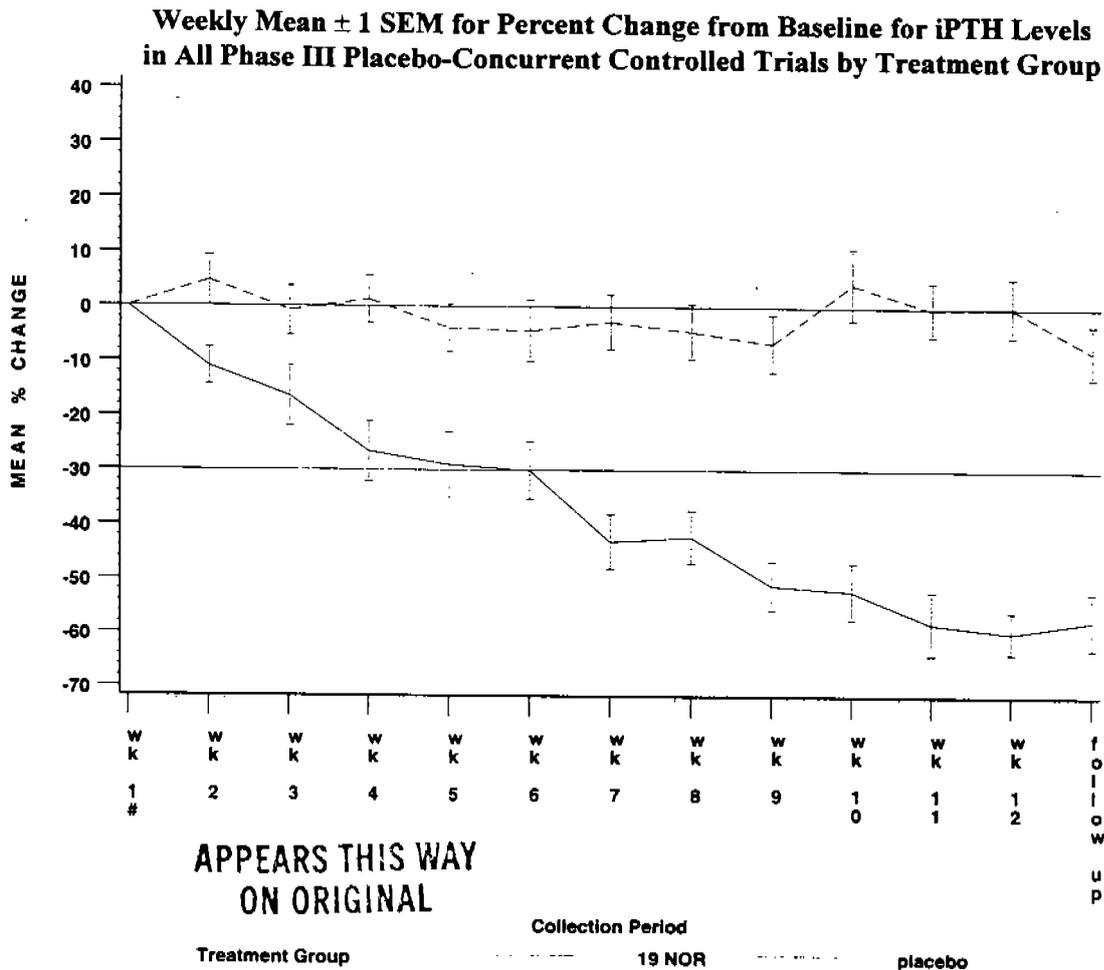
Summary of Days of Study Drug Administration: All Phase III Placebo-Concurrent Controlled Trials

N	Mean Days	Median Days	Maximum Days	Minimum Days	Std. Deviation
40	70.80	82			23.224

The mean number of days of active drug administration was approximately 71 and the maximum number of days was 85.

The total days of drug administration for the 40 patients in the active group was 2832 days which equals 7.8 patient years of experience with Paracalcin Injection. The patient years were determined by adding the number of days that each patient received Paracalcin Injection and dividing the total by 365 days to determine the number of years.

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Week 1 is the baseline iPTH determination.

Note: Horizontal reference lines at 0 and -30. Standard error bars included at each mean.

The mean percent change from baseline in iPTH levels was more than -30% at Week 6 for active patients while the mean percent change remained within -10% of baseline for placebo patients. The mean % change from baseline in iPTH levels was more than -50 % from baseline at the Follow-up visit for active patients while the mean % change for placebo patients was within -10% of baseline.

Three variables were evaluated for a comparison of efficacy between active and placebo patients.

One incidence of at least a 30% decrease in iPTH at any time during the study.

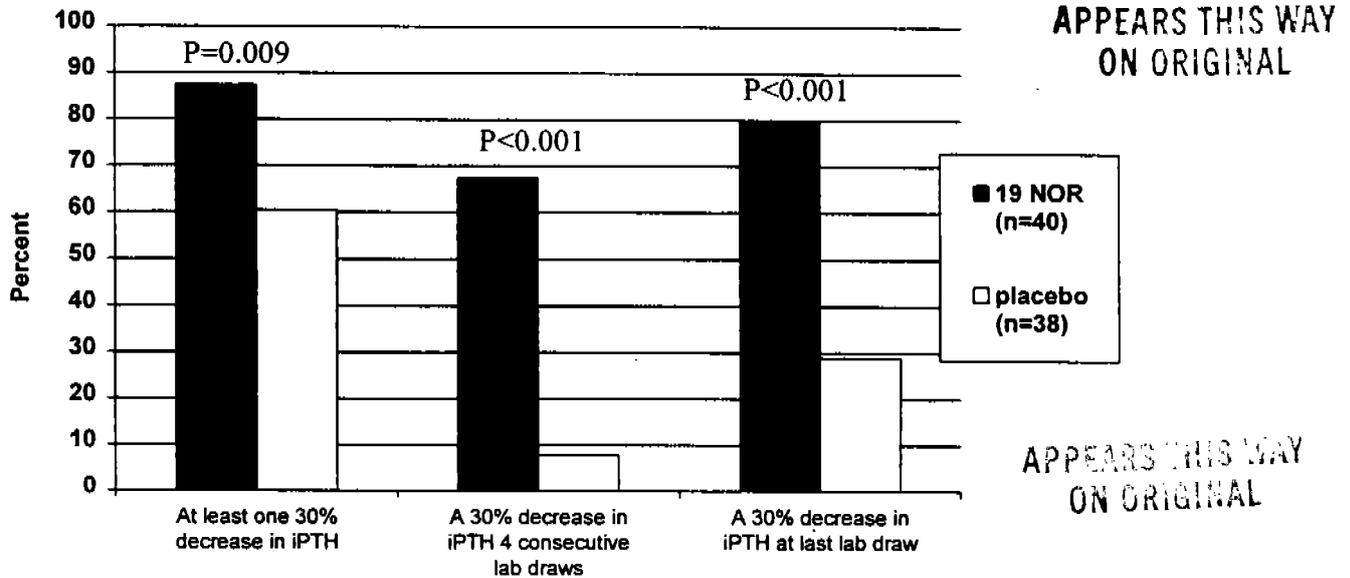
At least a 30% decrease in iPTH for four consecutive laboratory draws.

At least a 30% decrease in iPTH at their final visit.

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Study Endpoint Results for All Phase III Placebo-Concurrent Controlled Trials Based Upon a 30 Percent or Greater Decrease from Baseline in iPTH



Patients in All Phase III Placebo-Concurrent Controlled Trials With a 30 Percent or Greater Decrease from Baseline in iPTH Levels

	Active		Placebo		p-value [†]
	number	percent	number	percent	
At least one 30 percent decrease in iPTH	35/40	87.5	23/38	60.5	0.009**
A 30 percent decrease in iPTH for at least one consecutive period of four lab draws	27/40	67.5	3/38	7.9	<0.001***
A 30 percent decrease in iPTH at the final lab draw	32/40	80.0	11/38	28.9	<0.001***

[†] P-value based upon a 2 x 2 Fisher's Exact test.

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

For the three variables evaluated, active patients demonstrated a statistically significant difference in iPTH reduction in comparison to placebo patients.

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Change from Baseline in iPTH Values for Patients in All Phase III Placebo-Concurrent Controlled Trials						
Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between Group Comparisons		
				Change Mean (SE) p-value [†]	Baseline Mean (SE) p-value [†]	
iPTH (pg/ml)	Active	783.4	404.0	-379 [43.66]***	-310 (62.5)	38.14 (84.9)
	Placebo	745.3	675.7	-69.6 [44.79]	<0.001***	0.655

[†] P-value based upon a one-way ANOVA.

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

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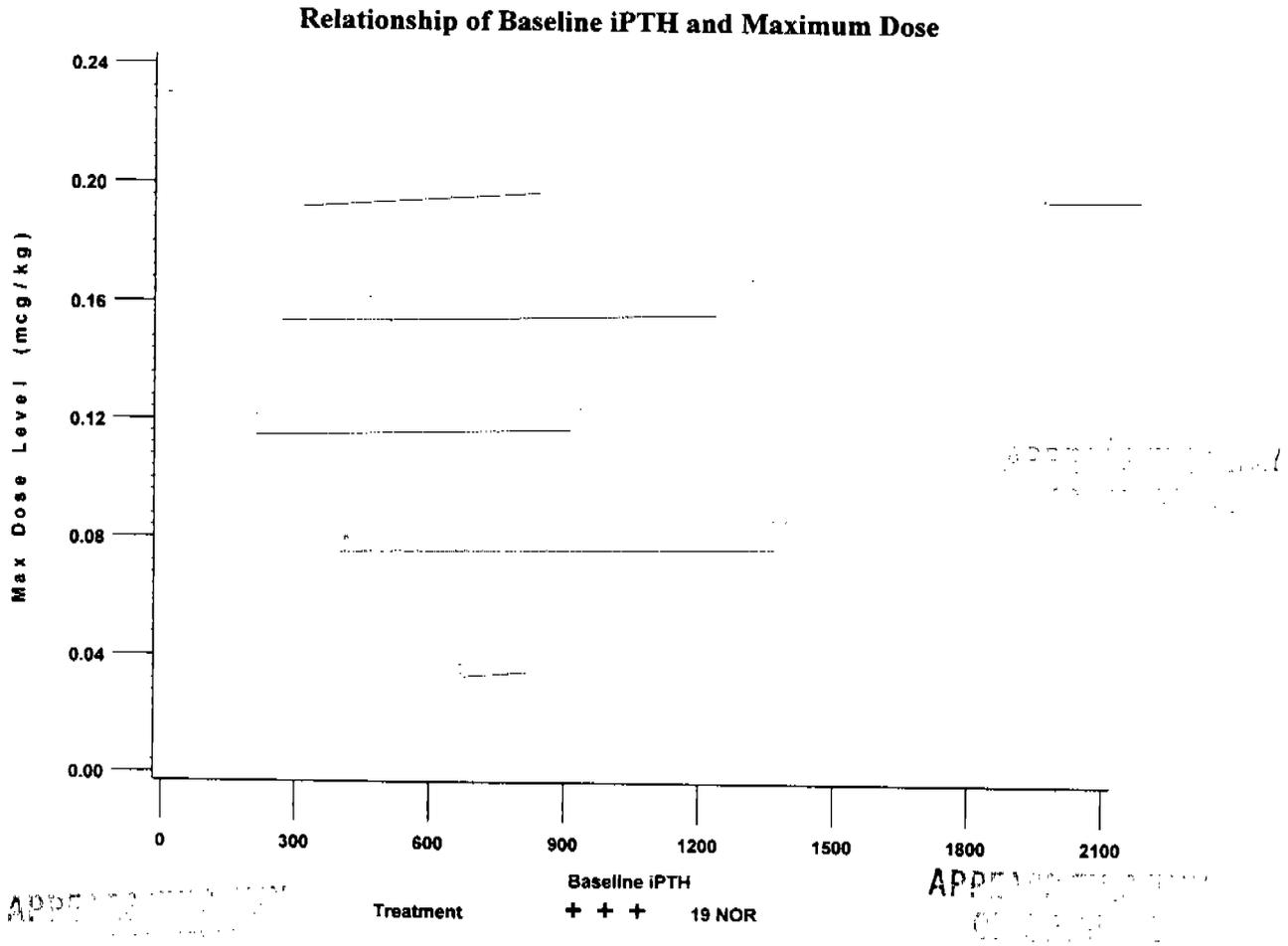
A between-group analysis of changes from baseline to final evaluation for patients in all Phase III placebo-concurrent controlled trials indicates that active patients demonstrated a statistically significant reduction in iPTH in comparison to placebo patients.

Changes from Baseline in Alkaline Phosphatase Values for Patients in All Phase III Placebo-Concurrent Controlled Trials						
Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between Group Comparisons		
				Change Mean (SE) p-value [†]	Baseline Mean (SE) p-value [†]	
Alk. Phos. (U/L)	Active	149.7	108.3	-41.5 [10.59]***	-44.1 (14.6)	-18.8 (36.6)
	Placebo	168.6	171.1	2.588 [10.11]	0.004**	0.609

[†] P-value based upon a one-way ANOVA.

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

As a marker for bone remodeling activity, alkaline phosphatase provides an additional efficacy variable. A between-group analysis of changes from baseline to final evaluation for all treated patients indicates that active patients demonstrated a statistically significant reduction in alkaline phosphatase in comparison to placebo patients. The reduction in alkaline phosphatase is the desired response. The maximum dose a patient would require for at least a 30% decrease in iPTH level could not be predicted based on the baseline iPTH value. This is represented graphically in the next Figure.



The Phase III placebo-concurrent controlled studies determined that Paracalcin Injection significantly reduces elevated iPTH levels in patients with CRF. A 30% decrease sustained over more than one observation (we chose four consecutive values) was considered a clinically relevant improvement. A double-blind, placebo-concurrent controlled, randomized study and an intent-to-treat primary analysis of the percentage of patients to have a 30% iPTH reduction were selected to determine efficacy. Sixty-eight% (27/40) of the patients receiving active drug achieved at least one 30% decrease in iPTH levels for at least four consecutive laboratory draws compared to eight% (3/38) of the patients who received placebo ($p < 0.001$). Analyses of the single incidences of at least a 30% reduction ($p = 0.009$) and occurrences at the final visit ($p < 0.001$) resulted in the same conclusion. Patients receiving active drug had a mean iPTH reduction of 379 pg/ml compared to a reduction of 69.6 pg/ml following placebo ($p < 0.001$). Finally, alkaline phosphatase decreased by 41.5 U/L in paracalcin patients while an increase of 2.6 U/L ($p < 0.004$) was noted for the same variable in the placebo group. This change in alkaline phosphatase is consistent with decreased bone osteoblast activity in patients after receiving Paracalcin Injection.

Subgroup analyses for age, gender, and race did not detect statistically significant differences. The sponsor recognizes that the number of patients in the subgroup analyses is not equally balanced for race

and to a lesser extent by age. The trials were not designed to randomize patients equally by subgroups; hence, analyses were performed with the data that were available.

Of the 27 paracalcin treated patients in the Phase III placebo-concurrent controlled trials who had at least a 30% decrease in iPTH for at least one consecutive period of four laboratory determinations, one patient's maximum dose was 0.04 mcg/kg, nine patients' maximum dose was 0.08 mcg/kg, eight patients required 0.12 mcg/kg, six patients 0.16 mcg/kg, and three patients' maximum dose was 0.20 mcg/kg. The average dose during treatment was 0.09 mcg/kg/dose and 0.1 mcg/kg/dose at the end of treatment.

Compared to placebo, Paracalcin Injection effectively reduced iPTH levels in patients with chronic renal failure.

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7.3.1.2.5 Study 95028

Title: Phase III Study: A 12-32 Week Comparison Between 19-Nor and Intravenous Calcitriol (Calcijex)

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 Ca x P was different from that seen with the use of Calcijex (R). Efficacy was 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

Study 95028 was conducted as a comparative, double blind, randomized, multicenter study at investigational sites throughout the U.S. and Europe; this summary reflects only the U.S. portion of the study. (Just prior to completion of this review, the Sponsor informed us that the European studies have not been completed at this time.) At each site, 50% of patients were randomized to receive [TRADE NAME] and 50% were randomized to receive Calcijex. A maximum of 300 patients were to be randomized for the entire study with further patients added if anticipated that fewer than 200 statistically evaluable patients would complete the study. The study was designed to detect a 15% difference between the two treatment groups in the number of patients experiencing at least one incidence of hypercalcemia and/or elevated Ca x P during the study, with an alpha level of five percent and a power of 80%. This assumes a ten % incidence rate of hypercalcemia in the [TRADE NAME] treatment group and a 25% incidence rate in the Calcijex treatment group.

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The study consisted of two phases: a Pretreatment Phase (Washout/Baseline) and Treatment Phase. During the Pretreatment Phase, any patient receiving calcitriol, dihydrotachysterol, alfacalcidol, or calcitonin prior to enrollment underwent a two-week washout period. This was followed by a 2 to 6 week baseline period for the purpose of measuring Ca, P, albumin, and iPTH levels. Any patient not receiving calcitriol, dihydrotachysterol, alfacalcidol, or calcitonin prior to enrollment could have entered the study at the start of the baseline period. The 2 week washout period was not mandatory for these patients.

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Following the baseline period, patients meeting inclusion/exclusion criteria were randomized to receive either IV [TRADE NAME] or IV Calcijex. Each patient received 3 injections of [TRADE NAME] or Calcijex at 48- to 72-hour intervals (at the end of their regular dialysis session) every week for 12 to 32

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weeks. The study drug dose was escalated every 4 weeks for a maximum of 5 dose escalations (from 0.04 to 0.24 mcg/kg, as in the previously discussed studies) or until a 50 % decrease in serum iPTH level (from last baseline as determined on first day of Treatment Phase) was detected. A patient was maintained at the dose which decreased serum iPTH levels by at least 50% from last baseline for an additional eight weeks, for a total of 12 weeks maximum. However, if the iPTH decreased to less than 100 pg/mL after 2 weeks at a given dose level, the dose was reduced to the previous level. If any of these conditions occurred at the first dose level the patient was considered to have completed the study and follow-up procedures were performed. Patients developing a serum Ca value greater than 11.5 mg/dL at any time were considered to have completed the study. Patients who had all Ca x P products greater than 75 within a consecutive 2 week period at a given dose level were also considered to have completed the study. Treatment was discontinued for these patients and follow-up procedures were initiated.

At the time of enrollment into the Pretreatment Phase, patients previously receiving vitamin D therapy were required to have an iPTH value greater than or equal to 250 pg/mL, a Ca value of less than 11.5 mg/dL, and a Ca x P product of less than 70 as determined from the initial screening laboratory values. Patients not previously receiving vitamin D therapy were required to have an iPTH value greater than or equal to 300 pg/mL, a Ca value of less than 11.5 mg/dL, and a Ca x P product of less than 70 as determined from the initial screening laboratory values.

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Inclusion Criteria for Entry into Pretreatment Phase of the Study

Patients must have met the following criteria to be eligible for inclusion in the Pretreatment Phase:

- sign an Informed Consent form
- be 18 years of age or older
- have ESRD, be undergoing maintenance HD three times a week, and be expected to remain on HD for the duration of the study

In addition to the above criteria, female candidates of child-bearing potential could not be nursing and had to be using one of the following forms of birth control (to prevent pregnancy) upon enrollment into the study, and had to continue using that contraceptive method throughout the study:

- surgical sterilization (bilateral tubal ligation or hysterectomy)
- oral contraceptive
- barrier method
- intrauterine device
- total abstinence
- maintain a monogamous relationship with a vasectomized partner

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Postmenopausal female patients had to be so for a minimum of one year prior to the start of the study. Female patients of child-bearing potential had to undergo a serum pregnancy test with negative results, during the Pretreatment Phase.

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Exclusion Criteria for the Pretreatment Phase of the Study

The following conditions were cause for exclusion from entry into the study:

- An iPTH value of less than 300 pg/mL based on the results from initial screening laboratory values for any patient not previously receiving vitamin D therapy.

- An iPTH value of less than 250 pg/mL based on the results from initial screening laboratory values for any patient previously receiving vitamin D therapy.
- Serum Ca x P product of greater than 70, at enrollment
- History of clinically significant allergic reaction to calcitriol or other vitamin D compounds
- Current malignancy or clinically significant liver disease (e.g., SGOT, SGPT, or bilirubin twice the upper limit of normal) at enrollment
- History of drug or alcohol abuse within the last six months
- Participation in another investigational study within 30 days prior to enrollment in this study

The following types of patients were excluded from the study:

- patients who, in the Investigator's opinion, are at risk for aluminum-related bone disease
- patients who, during the course of the study, required calcitonin, maintenance oral or IV glucocorticoids, or other drugs that may effect Ca or bone metabolism throughout the entire study, other than females on stable estrogen and/or progestin therapy
- patients considered unreliable and/or non-compliant
- patients who were anticipated not to be able to complete the entire study (e.g., scheduled for transplant, concurrent disease, etc.)
- patients who, in the Investigator's opinion, were at increased risk by the study procedures
- patients who were randomized in a previous [TRADE NAME] study
- patients who, within one month prior to enrollment, were receiving pharmacologic doses of vitamin D, other than calcitriol, or dihydrotachysterol, or alfacalcidol
- patients who, for the duration of the study, required chronic use of phosphate binders containing aluminum
- patients with evidence of known blood-born infectivity (e.g., HIV, antigen positive hepatitis); however, patients with antibody positive Hepatitis C were excluded only if they also had clinical evidence of liver disease

Inclusion Criteria for Entry into the Treatment Phase of the Study

Patients were entered into the Treatment Phase of the study only if, at the end of the Pretreatment Phase, they satisfied the following inclusion and exclusion criteria:

- Patients with total normalized serum Ca concentration less than or equal to 11.5 mg/dL, serum Ca x P product less than or equal to 75 and serum iPTH levels of at least 300 pg/mL at the last available result taken during the baseline period

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Exclusion Criteria for the Treatment Phase of the Study

The following patients were excluded from the Treatment Phase of the study:

- Patients receiving calcitriol, other vitamin D therapy, calcitonin, oral or I.V. maintenance glucocorticoids or other drugs that could effect Ca or bone metabolism (other than females on stable estrogen and/or progestin therapy) during the washout/baseline period.
- females with a positive pregnancy test during the Pretreatment Phase

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Removal of Patients from Therapy or Assessment

The occurrence of a severe or unexpected patient adverse event could have resulted in a withdrawal from the study. In this event, all documentation required by the protocol, from the time of initial incident occurrence through complete recovery or satisfactory resolution, were included in the Symptoms and

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Abbreviated Physical Examination During Pretreatment Phase case report form for events occurring during Pretreatment and in the Adverse Event case report form for events occurring during Treatment. A complete description of the event relevant to the adverse event was included on the report. Reasons for patient withdrawal or discontinuation from the study were noted on the Reason for Termination case report form. Patients were withdrawn from the study if a request was made by the patient, guardian, or Investigator. Patients not completing the study would not be replaced.

A patient would be withdrawn from the study and follow-up procedures were conducted if three consecutive doses (one week of treatment) were missed.

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Treatments Administered

A single, bolus dose of [TRADE NAME] or Calcijex was administered intravenously at the end of each regular HD session, 3 times a week, at 48- to 72- hour intervals, once the patient was enrolled in the Treatment Phase of the study. The dose was given after dialysis. The dose was calculated using the post-dialysis weight from the first Treatment Day or the last dialysis session before Treatment, regardless of weight fluctuation subsequently.

Patients could have been escalated five times through six dose levels. At the first dose level, all patients randomized to [TRADE NAME] received 0.04 mcg/kg and were escalated by 0.04 mcg/kg increments (after specified criteria were met) until the sixth dose level, 0.24 mcg/kg, which was the maximum [TRADE NAME] dose level. All patients randomized to Calcijex received 0.01 mcg/kg at the first dose level and were escalated by 0.01 mcg/kg increments (after specified criteria were met) until the sixth dose level, 0.06 mcg/kg, which was the maximum Calcijex dose level.

All patients entered into the study began Treatment at the first dose level, 0.04 mcg/kg/dose of [TRADE NAME] or 0.01 mcg/kg of Calcijex. Dose adjustment criteria were monitored on a weekly basis. Dose escalation could occur at 4 week intervals and dose reduction could occur at weekly intervals. Dose escalation or reduction occurred with the first dose of a Treatment Week after evaluation of the prior Week's lab results.

A patient was maintained on a given dose level if all the following occurred:

- the iPTH level was greater than or equal to 100 pg/mL
- the serum iPTH level was reduced by greater than or equal to 50% from last baseline (as determined on Treatment Day One), and remained reduced at the given dose level
- the serum Ca level was less than or equal to 11.5 mg/dL
- at least one serum Ca x P value within the preceding consecutive 2 week period at a given level was less than or equal to 75

Once a patient was receiving a maintenance dose of study drug, the patient was kept on that maintenance dose for a total of 12 weeks, provided all the maintenance criteria continued to be met during this time. If any of the maintenance dose criteria were no longer met at any time, the dose would then be adjusted on the escalation, reduction, or completion criteria.

A patient was increased to the next dose level if all the following occurred at the first, second, third, fourth, or fifth dose level:

- a minimum of four weeks of Treatment on the given dose level had been completed

- the iPTH level did not decrease by at least 50% from last baseline (as determined on Treatment Day One) after the preceding consecutive four weeks of study drug dosing;
 - OR the iPTH level, previously reduced by greater than or equal to 50 % from last baseline (as determined on Treatment Day One), had increased and was no longer reduced by greater than or equal to 50% from last baseline.
 - the serum Ca level was less than or equal to 11.5 mg/dL.
 - at least one serum Ca x P value was less than or equal to 75 within the preceding consecutive two-week period at a given dose level.
- If all the above criteria were met the dose was increased to the next dose level.

A patient was reduced to the previous dose level if the iPTH level was less than 100 pg/mL after 2 consecutive weeks of treatment on a given dose level

A patient was considered to have completed the study if any of the following occurred:

- the serum Ca level was greater than 11.5 mg/dL at any single occurrence (*Note: Prior to Amendment 9, patients that had a single instance of hypercalcemia would be dose-reduced. This did not effect the analysis of any patients.*)
- all serum Ca x P levels within the preceding consecutive two-week period at a given dose level were greater than 75

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Efficacy and Safety Variables

Efficacy was based on the incidence of hypercalcemia or incidence of elevated Ca x P and incidence of a 50% iPTH reduction. Statistically tested variables included total Ca concentration, Ca x P level, iPTH, incidence of hypercalcemia, and/or incidence of elevated Ca x P. Safety variables included changes in physical examination, medical history, adverse events, and general chemistry and hematology profiles.

Efficacy Assessments

Serum Ca, P, iPTH, and albumin levels (for the purpose of normalized serum total Ca concentration) were measured to assess efficacy.

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Safety Measurements

Chemistry and hematology profiles were measured as an assessment of safety, at enrollment, on Treatment Day 1, prior to dialysis on Treatment Week 16, and at Follow-up.

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Primary Efficacy Variables

Efficacy was determined by comparing the between group incidence of hypercalcemia and/or an elevated Ca x P > than 75 during the Treatment Phase of the study Serum Ca and Ca x P levels were the primary efficacy variables.

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Statistical and Analytical Plans

Descriptive statistics calculated for all treated patients and by time for all primary variables of interest. Statistically tested variables include demographic variables, total calcium concentration, Ca x P, iPTH,

incidence of hypercalcemia and/or elevated Ca x P. Adverse events tabulated by patient and treatment group and the frequency and types of side effects reported.

All analyses were performed with SAS (version 6.12) procedures GLM, FREQ, LIFETEST, MEANS, and UNIVARIATE. All statistical tests were two-tailed and p-values < 0.05 were considered statistically significant. Safety analyses were performed on all treated patients. Efficacy analyses were performed on all treated patients and on all evaluable patients.

The serum iPTH (last baseline result) on treatment day-1 for patient 2122 was 340 pg/mL as reported by the central laboratory). This value was excluded from all analyses since the other iPTH results for this patient ranged _____ The baseline iPTH value used in subsequent calculations for this patient was 2775 pg/mL, the value obtained on the last day of the baseline period, prior to the first day of treatment.

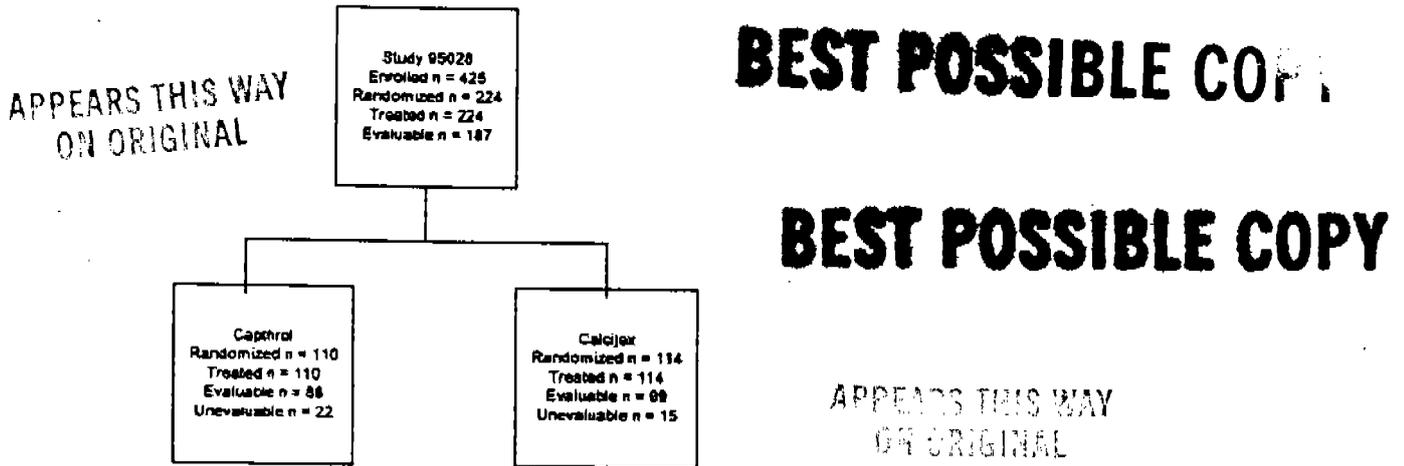
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Disposition of Patients

In addition to those patients for which the protocol guidelines were followed, the following guidelines were used to classify patients as being evaluable for the 95028 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 product of > 75 or a decrease in iPTH of > or = to 50% 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 an endpoint had been met, but was discontinued from the study instead, the patient's data were 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 three consecutive dialysis sessions, all data from that point forward were excluded.
9. If a patient's iPTH level was <100 after two weeks on a given dose level and the patient's dose was not reduced (or the patient was not discontinued from the study if the occurrence was at Dose Level 1), data from that point forward were excluded.

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Protocol Deviations

In reviewing the data for all patients, deviations from the protocol were identified by the Sponsor. 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	175
2. Study Drug Administration	1300
3. Concurrent Medications	66
4. Clinical Laboratory	678
5. Premature Termination	48
99. Other	470

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Three hundred and forty four of the 425 total enrolled patients had a deviation.

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 product level

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Data Sets Analyzed

The primary data set analyzed for efficacy and safety was all treated patients.

There were 224 patients in the all treated patients data analysis (110 [TRADE NAME], 114 Calcijex) and 187 patients in the all evaluable patients data set (88 [TRADE NAME], 99 Calcijex). Analysis for all enrolled patients was also performed (excluding efficacy analysis) and was presented in the Appendices along with the all treated and all evaluable patients.

**Table 12: Demographics for All Treated Patients
(Cross Reference 10.1.1.a)**

	Total N=224		Caphrol N=110		Calcijex N=114		p-value ¹
	number	percent	number	percent	number	percent	
Gender							
Male	129	58	62	56	67	59	0.787
Female	95	42	48	44	47	41	
Race							
Caucasian	35	16	14	13	21	18	0.273
Black	157	70	81	74	78	67	
Hispanic	19	8	9	8	10	9	
Oriental	6	3	3	3	3	3	
Other	7	3	3	3	4	4	
Age (years)							
18 - < 35	13	6	8	7	5	4	
35 - < 65	143	64	65	59	78	68	
65 - < 80	61	27	32	29	29	25	
> 80	7	3	5	5	2	2	
Mean ± s.d.	55.80 ± 14.72		58.10 ± 15.50		55.50 ± 13.98		0.771
Range							
Height (cm)							
Mean ± s.d.	169.3 ± 11.07		169.5 ± 11.09		169.2 ± 11.09		0.835
Range							
Weight (kg)							
Mean ± s.d.	76.20 ± 21.18		76.80 ± 22.19		75.60 ± 20.25		0.873
Range							

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

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

The analysis of prestudy vital sign data showed that the mean body temperature, mean diastolic blood pressure, mean systolic blood, and mean pulse values were not significantly different between treatment groups. The analysis of dialysis data indicated that the length of time a patient had been on dialysis was not significantly different ($p = 0.824$) between treatment groups.

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Table 17: 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*
Ca (mg/dL)^a					
Capthrol n=110	9.05	8.98	-0.07	0.08 (0.098)	-0.03 (0.138)
Calcelex n=111	9.09	8.93	-0.16*	0.396	0.824
Ca x P^b					
Capthrol n=109	52.853	52.599	-0.274 (1.329)	1.098 (1.875) 0.659	-0.135 (1.858) 0.842
Calcelex n=110	52.998	51.628	-1.372 (1.325)		
P (mg/dL)					
Capthrol n=109	5.89	5.89	0.00 (0.147)	0.07 (0.207) 0.729	-0.03 (0.210) 0.893
Calcelex n=110	5.91	5.84	-0.07 (0.146)		
iPTH (pg/mL)					
Capthrol n=108	654.78	660.63	25.85 (25.64)	-3.27 (37.506) 0.931	-10.39 (61.452) 0.868
Calcelex n=110	665.16	664.28	29.12 (25.40)		

* P-value based upon a one-way ANOVA.
^a Ca values normalized to an albumin of 4.0 g/dL.
^b indicates statistical significance (2-tailed) at the 0.05 level.

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A between group comparison for changes from Enrollment mean to last baseline evaluation indicates that the treatment groups were not significantly different from each other prior to study drug administration for Ca, Ca x P, P, and iPTH levels.

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

End of First Four Week Interval						
Ceptrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	110	100.0	0.39	0.12	24.13	4.95
Dropped Pt	0					
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	113	99.12	0.38	0.10	24.53	4.70
0.02	1	0.88	0.55	-	26.00	-
Dropped Pt	0					
End of Second Four Week Interval						
Ceptrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	15	13.64	0.38	0.08	51.33	6.69
0.08	81	73.64	0.79	0.25	53.38	2.47
0.12	1	0.91	0.75	-	54.00	-
Dropped Pt	13	11.81				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	11	9.85	0.37	0.08	50.73	6.70
0.02	88	77.19	0.75	0.20	52.74	4.02
0.03	1	0.88	0.67	-	54.00	-
Dropped Pt	14	12.28				

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

End of Third Four Week Interval						
Cepthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	20	18.18	0.42	0.13	77.66	6.32
0.08	19	17.27	0.76	0.18	80.74	4.21
0.12	50	45.45	1.14	0.41	80.82	3.77
0.16	1	0.91	1.77	-	82.00	-
Dropped Pt	20	18.19				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	11	9.65	0.42	0.13	78.00	7.38
0.02	20	17.54	0.70	0.16	79.20	7.65
0.03	60	52.63	1.07	0.25	81.22	3.23
Dropped Pt	23	20.18				
End of Fourth Four Week Interval						
Cepthrol						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.04	13	11.82	0.41	0.16	105.7	7.41
0.08	17	15.45	0.84	0.21	106.5	7.10
0.12	18	16.36	1.07	0.40	106.5	4.20
0.16	24	21.82	1.37	0.37	108.9	0.68
Dropped Pt	38	34.55				
Calcijex						
	N	Percent	Mean Total mL	SD Total mL	Mean days	SD days
0.01	9	7.69	0.43	0.16	108.8	5.24
0.02	21	18.42	0.76	0.15	108.4	3.68
0.03	17	14.91	1.07	0.21	108.6	0.53
0.04	35	30.70	1.39	0.33	108.1	5.95
Dropped Pt	32	28.08				

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