CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020819

MEDICAL REVIEW(S)

H+D-SIC Hedin
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1.1 MEDICAL OFFICER'S REVIEW
NDA No. 20-819
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APPEARS THIS WAY
ON ORIGINAL

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1.2 DRUG

1.2.1 GENERIC NAME: Paracalcitol injection (formerly, Paracalcin injection): 19-nor 1α,25 Dihydroxyvitamin D_2

1.2.2 PROPOSED TRADE NAME: [TRADE NAME]

1.2.3 CHEMICAL NAME: 19-nor 1α,3β,25-trihydroxy-9,10-secoergosta-5,7[E]-triene

1.3 SPONSOR: Abbott Laboratories

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1.4 PHARMACOLOGIC CATEGORY: Hormone

1.5 PROPOSED INDICATION(S): Prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism associated with chronic renal failure by reduction of parathyroid hormone levels.

1.6 DOSAGE FORMS AND ROUTE(S) OF ADMINISTRATION: Single patient use ampuls containing 1 ml, 2 ml, and 5 ml containing 5 mcg drug/ml.

1.7 NDA DRUG CLASSIFICATION: 1S

APPEARS THIS WAY
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1.8 RELATED DRUGS: Calcijex (calcitriol)

1.9 RELATED REVIEWS:

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ON ORIGINAL

SUMMARY:

Three double-blind, placebo-controlled, multi-center studies (Studies 35, 36, and 37) were submitted to support the efficacy of 19-nor Vitamin D to control secondary hyperparathyroidism in patients with chronic renal failure on hemodialysis. The studies were conducted under identical protocols and data were therefore analyzed separately, as well as combined into a single study. After a 4-week pre-treatment phase (washout and baseline), the patients received the drug intravenously, three times weekly, for 12 weeks. The starting dose was 0.04mcg/kg, increasing every two weeks until the clinical end-point was achieved (or a maximum of five escalations) to a maximum dose of 0.24 mcg/kg. Efficacy was defined as a 30% decrease from baseline in the level of iPTH. Success was defined as one of the following: 1) at least one visit with a 30% decrease; 2) a 30% decrease for 4 consecutive visits; a 30% decrease at the follow-up visit 44 hours after the final dose. All three definitions, it should be noted, were established post-hoc. All three definitions were met in Study 35; Study 36 met definitions 2 and 3; Study 37 met only definition 3. When the definition was modified to 30% decrease at 3 consecutive visits plus the follow-up visit, the proportion of patients who met this was significantly greater in the subjects treated with 19-nor in all groups. When the data from all three studies were pooled, all proposed endpoints were statistically achieved. Subsequently, two additional studies were submitted, Numbers 28 and 34, in which 19-Nor was compared with the active control substance, Calcijex (intravenous calcitriol) with similar dose escalation protocols as in the placebo-controlled studies. Study 28, consisting of 224 patients at 21 U.S. sites and an unknown number of European sites, lasted 32 weeks. However, patients were considered to have "completed" the study if iPTH levels dropped below 100 pg/ml or if the serum calcium levels increased to above 11.5 mg/dL. Only data from the U.S. studies were submitted. Study 34 was conducted at 23 sites in the U.S. with 197 patients followed for up to 24 weeks. The Sponsor's analysis of the results of these studies suggested that there were fewer incidence of hypercalcemia or of elevated serum Ca X P product with 19-Nor than with calcitriol, but our analysis showed no differences in Study 28 and a slightly higher incidence in the 19-Nor group.

RECOMMENDATION: APPROVABLE. See Recommendations for Label Change, particularly INDICATIONS Section.

2 TABLE OF CONTENTS

3 MATERIALREVIEWED

NDA submission: 74 volumes, particularly Volumes 1, 17-30 (Pharmacology and Toxicology), 31-32 (Pharmacokinetics and Metabolism), 33-34 (Human Pharmacokinetics), 36-72 (Clinical Data).

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4 CHEMISTRY/MANUFACTURING CONTROLS: Reviewed by Chemistry Reviewer

5 ANIMAL PHARMACOLOGY & TOXICOLOGY: Reviewed in detail by Pharmacologist

5.1 Pharmacology Studies in Relation to Proposed Therapeutic Indication

5.1.1 American Journal of Kidney Diseases, Vol. 26, No 5 (November), 1995: pp 852-860 by Eduardo Slatopolsky, MD, Jane Finch, Cindy Ritter, Masashi Denda, MD, Jeremiah Morrissey, PhD, Alex Brown, PhD, and Hector DeLuca, PhD from the Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, and the Department of Biochemistry, University of Wisconsin, Madison, WI: A New Analog of Calcitriol, 19-Nor-1,25-(OH)2D2, Suppresses Parathyroid Hormone Secretion in Uremic Rats in the Absence of Hypercalcemia.

Maximum suppression of PTH secretion by cultured bovine parathyroid cells was obtained with either calcitriol or paracalcin at a concentration of 10^{-7} mol/L.

Renal insufficiency was induced in female Sprague-Dawley rats by 5/6 nephrectomy. Daily injections of 10 ng/rat of paracalcin did not significantly increase the serum calcium. When the dose of paracalcin was increased to 100 ng/rat, the increment in serum calcium was the same as that induced by calcitriol at 10 ng/rat. A further increase in the dose of paracalcin to 1.0 µg/rat produced significant hypercalcemia.

Neither calcitriol nor paracalcin modified the serum creatinine in the uremic animals. Serum ionized calcium increased significantly in uremic rats receiving 8 ng of calcitriol every other day compared to uremic control animal, $P < 0.02$. Paracalcin did not increase the serum ionized calcium even at a dose of 75 ng/rat.

The only dose of calcitriol that suppressed PTH to a statistically significant degree ($P<0.01$) was 8.0 ng/rat. PTH decreased from 201.8 pg/ml pre-treatment to 90 pg/ml post-treatment. All doses of paracalcin were effective in suppressing PTH. The maximum effect was achieved with the 75 ng/rat dose, which decreased PTH from 193 ± 48 to 53 ± 16 pg/ml, a decrease of 73 percent. Calcitriol, at 8 ng/rat, increased serum phosphorus to 8.64 ± 1.1.5 mg/dL compared to 5.57 ± 0.50 mg/dL in the uremic controls. The largest dose of paracalcin (75 ng/rat) increased serum phosphorous to only 6.17 ± 0.68 mg/dL, not a significant change from the vehicle control levels.

5.1.2 Fumiaki Takahashi, Jane L. Finch, Masashi Denda, Adriana S. Dusso, Alex J. Brown and Eduardo Slatopolsky: "A New Analog of 1,25-$(0H)_2D_3$, 19-nor-1,25-$(OH)_2D_3$, Suppresses Serum PTH and Parathyroid Gland Growth in Uremic Rats Without Elevation of Intestinal Vitamin D Receptor Content".

Renal insufficiency was induced in female Sprague-Dawley rats by 5/6 nephrectomy. Immediately after nephrectomy the groups of rats were administered by intraperitoneal injection 3 times a week for 8 weeks one of the following: (a) 100 µl of propylene glycol (normal and uremic); (b) 2 ng of 1,25-$(OH)_2D_3$ (uremic); (c) 6 ng of 1,25-$(OH)_2D_3$ (uremic); (d) 25 ng of 19-nor-1,25-$(OH)_2D_2$ (uremic);(e) 100 ng of 19-nor-1,25-$(OH)_2D_2$ (uremic)

The rats were killed 24 hours after the last injection. Serum creatinine and BUN levels increased in the nephrectomized rats compared to the normal control animals but the various groups of nephrectomized rats did not differ from one another. Uremia produced a slight increase in the serum ionized calcium but only treatment with 6 ng of 1,25-$(OH)_2D_3$ statistically increased ($p<0.05$) the ionized calcium above the uremic control group. Uremia also caused a mild increase in the serum phosphorus and treatment with 6 ng of 1,25-$(OH)_2D_3$ caused a marked statistically significant ($p<0.01$) increase in the serum phosphorus (6.67±0.63 mg/dL vs. 4.34±0.03 mg/dL in uremic controls and 3.37±0.18 mg/dL in normal controls). Neither dose of 19-nor-1,25-$(OH)_2D_2$ produced a change in the ionized calcium or serum phosphorus above the uremic control value. Uremia itself did not reduce serum 1,25-$(OH)_2D_3$ levels over the 8 weeks of this study. Although treatment with 2 ng of 1,12-$(0H)_2D_3$ did not significantly raise serum 1,25-$(OH)_2D_3$ levels, the 6 ng dose of 1,25-$(OH)_2D_3$ increased serum 1,25-$(OH)_2D_3$ levels to 68.1±7.2 pg/ml ($p<0.01$ compared to normal or uremic controls). In contrast, both doses of 19-nor-1,25-$(OH)_2D_2$ decreased serum 1,25-$(OH)_2D_3$ levels to 30.4±2.0 pg/ml ($p<0.05$) and 27.9±3.2 pg/ml ($p<0.01$) respectively. Serum PTH increased from 13.3±0.9 pg/ml to 52.7±10.2 pg/ml ($p<0.01$). Serum PTH was not affected by the 2 ng dose of 1,25-$(OH)_2D_3$; 6 ng suppressed the serum PTH secretion

to 25.7±6.7 pg/ml ($p<0.01$), accompanied by an increase in both serum ionized calcium and phosphorus. Both doses of 19-nor-1,25-$(OH)_2D_3$, 25 ng and 100 ng, significantly reduced serum PTH to 28.7±6.5 ($p<0.05$) and 20.7±3.1 pg/ml ($p<0.01$) respectively, without changes in serum ionized calcium.

Parathyroid gland (PTG) weight normalized for body weight (BW) increased nearly 2-fold, from 0.87±0.05 µg/g of body weight in normal rats to 1.49±0.10 µg/g of body weight in the uremic control group ($p<0.01$) Although parathyroid gland weight increased in all uremic groups as compared to normal animals, only the parathyroid gland weight of animals receiving 100 ng of 19-nor-1,25-$(OH)_2D_2$ was lower that that of the uremic control animals (1.16±0.05 µg/g of body weight, $p<0.05$). A positive correlation was observed between serum PTH and parathyroid gland weight ($r = 0.889$, $p = 0.044$ in uremic rats).

Intestinal vitamin D receptor content, assessed by maximal specific binding of ^{3}H-1,25-$(OH)_2D_3$ to the intestinal VDR, was not changed by renal insufficiency alone. Rats treated with 6 ng of 1,25-$(OH)_2D_3$ had a significantly higher intestinal VDR content (138.5±20.0 fmol/mg protein) compared to rats receiving either dose of 19-nor-$(OH)_2D_2$ (25 ng:84.0±11.9, p,0.05: and 100 ng: 78.4±10.9 fmol/mg protein, $p<0.01$).

5.1.3 Summary: These two studies demonstrated in 5/6 nephrectomized rats that paracalcin (19-nor-1,25-$(OH)_2D_2$) has the following advantages over calcitriol (1,25-$(OH)_2D_3$) at doses that give equivalent or greater reduction of serum PTH.

- No increase in serum ionized calcium
- No increase in serum phosphorus
- Reduction of endogenous serum calcitriol levels
- Reduction in intestinal vitamin D receptor content
- Decreased parathyroid gland growth

5.2 Toxicology Summary

The systemic toxicity of paracalcin (19-nor-1α, 25-dihydroxyvitamin D_2) was assessed in mice, rats and dogs in studies ranging in duration from a single dose in mice and rats to twelve months of intravenous administration in dogs. The compound also was evaluated in rats and rabbits for adverse effects in all phases of the reproductive process; a battery of *in vitro* and *in vivo* mutagenicity studies was conducted. Reductions in serum PTH, the primary pharmacologic effect, were observed at most dosages in rats and dogs. Effects directly or indirectly related to calcemic activity included extraskeletal calcification, renal pathology with increases in serum BUN and creatinine, anorexia with decreased body weight gain, increased adrenal weight, alkalosis, and hyperostosis. The occurrence of the calcemic effects in the subchronic and chronic toxicity studies, particularly in dogs, precluded evaluation of dosages that were large multiples of the clinical dosages. Effects resulting from prolonged elevations in serum calcium (and/or phosphorus) would not be expected to occur in the intended patient population since serum calcium and phosphorus levels are monitored during vitamin D therapy, and treatment is interrupted in the event of hypercalcemia or hyperphosphatemia. Effects not clearly related to hypercalcemia included decreased white blood cell counts in dogs, thymic atrophy in dogs, altered APTT values (increased in dogs, decreased in rats), and hepatocellular hydropic degeneration in a small number of dogs. Except for reductions in WBCs, more profound effects were seen in rats and dogs treated with the same dosages of calcitriol (the naturally-occurring, active form of vitamin D_3). WBC changes have not been observed in subjects or patients treated with paracalcin. Paracalcin was found to be non-genotoxic and was not a developmental toxin.

No significant differences were noted in the concentration of radioactivity in eyes between pigmented rats and albino rats. In addition, there were only minimal differences in the concentration of total radioactivity between pigmented and nonpigmented skin from the Lister Hooded rats. These findings indicate that retention or preferential binding to melanin-containing tissues was minimal.

6 Human Pharmacokinetics Summary (to be reviewed in detail by Biopharmaceutics)

6.1 Paracalcin Pharmacokinetics

6.1.1 Absorption/Bioavailability

Because paracalcin currently is administered only intravenously and no oral dosage form is available, no bioavailability/bioequivalency studies have been conducted.

6.1.2 Pharmacokinetics in Normal Subjects

A study was conducted to determine the pharmacokinetics of paracalcin in normal subjects (13 males and 5 females) after single and multiple doses of 0.04, 0.08, and 0.16 μg/kg. For each of the three dose levels, the mean ± SD (n=4) paracalcin pharmacokinetic parameters after the first and last doses are given as follows:

	Dose (μg/kg)		
Parameter	**0.04**	**0.08**	**0.16**
	First Dose (Study Day 1)		
C_{max} (pg/ml)	256 ± 44	664 ± 146	1242 ± 226
$AUC_{0-\_}$ (pg•hr/ml)	683 ±165	2221 ± 401	5247 ± 893
CL (L/hr)	4.2 ± 2.1	2.7 ± 0.6	2.4 ± 0.4
$t_{1/2}$ (hr)[H*]	2.7 ± 0.4	5.3 ± 1.3	7.3 ± 1.0
V_{ss} (L)	17 ± 10	20 ± 6	23 ± 2

	Third Dose (Study Day 5)		
C_{max} (pg/ml)	232 ± 51	553 ± 137	1061 ± 117
$AUC_{0-\_}$ (pg•hr/ml)	1077 ± 343	2104 ± 726	5331 ± 939
CL (L/hr)	2.5 ± 0.1	3.0 ± 1.2	2.4 ± 0.3
$t_{1/2}$ (hr)[H]	5.6 ± 4.9	4.8 ± 1.7	6.8 ± 1.2
V_{ss} (L)	25 ± 17	20 ± 2	22 ± 3

[H] Harmonic means and pseudo standard deviations; the arithmetic means ± SD after doses of 0.04, 0.08, and 0.16 µg/kg were 2.7 ± 0.4, 5.7 ± 1.9, and 7.4 ± 0.9 hr after the first dose and 7.1 ± 4.5, 5.4 ± 2.3, and 7.0 ± 1.0 hr after the last dose, respectively.

* Statistically significant difference between dose groups (based on statistical analysis of b, p = 0.0007).
Note: For the 0.04 µg/kg dose group, n = 2 for all parameters except for C_{max}, where n = 4.

Elimination of paracalcin was biphasic; many of the samples collected during the terminal phase following the lowest dose had concentrations below the lower limit of quantification (LLQ, 40 pg/ml). Little or no accumulation of paracalcin was observed with the dosage regimen of every other day (QOD, 3/week) in healthy volunteers; no differences in parameters from Study Day 1 to Study Day 5 were statistically significant. The paracalcin dose-adjusted mean C_{max} and $AUC_{0-\_}$, and mean values of CL, $t_{1/2}$, and V_{ss} were independent of dose size. There was a statistically significant difference in $t_{1/2}$ for the different dose sizes after the first dose. The Sponsor suggests that this may have been due to: 1) high variability at the lower concentrations, and/or 2) concentrations were below the LLQ for many of the samples obtained after the distribution phase following the lowest dose. There were no statistically significant differences in CL, $t_{½}$, or V_{ss} compared across doses administered on Study Day 5.

It is noteworthy that these data are derived from observations from very few subjects, with many missing data points.

6.1.3 Pharmacokinetics in Patients With ESRD

6.1.3.1 Phase II

Pharmacokinetics of paracalcin was studied in 8 male and 8 female patients with ESRD. For 4 weeks, a bolus dose was given intravenously three times weekly after the regularly scheduled hemodialysis session for a total of 12 doses. Doses for patients randomized to receive paracalcin were 0.04, 0.08, 0.16, and 0.24 µg/kg for Groups 1-4, respectively. The pharmacokinetics of paracalcin were determined after the first and last dose for each patient.

For most patients, samples obtained immediately prior to the last dose of the study had paracalcin concentrations below the LLQ; thus, little or no accumulation of paracalcin was observed with the QOD dosage regimen in patients. Mean parameter values could be calculated from values obtained after the first and last doses combined. For the four dose levels, mean ± SD paracalcin pharmacokinetic parameters are tabulated below for the data of the first and last dose administrations combined:

	Dose (µg/kg)

Parameter	0.04[a]	0.08[b]	0.16[c]	0.24[d]
C_{max} (pg/ml)	253 ± 93	1656 ± 1615	4566	1850 ± 664
$AUC_{0-\infty}$ (pg•hr/ml)	6094 ± 2735	14399 ± 11340	18232	27382 ± 8230
CL (L/hr)	0.69 ± 0.27	0.58 ± 0.29	0.91	0.72 ± 0.24
$t_{1/2}$ (hr)[H]	32.0 ± 18.3	11.3 ± 16.2	25.0	13.6 ± 1.9
V_{SS} (L)	34 ± 9	9 ± 5	31	6 ± 2

a N = 6 patients, 12 observations for C_{max}; n = 3 patients, 4 observations for all other parameters.

b N = 3 patients, 3 observations for C_{max}; n = 2 patients, 2 observations for all other parameters.

c N = 1 patient, 1 observation for all parameters.

d N = 6 patients, 11 observations for C_{max}; n = 5 patients, 7 observations for all other parameters.

H Harmonic means and pseudo standard deviations; the arithmetic means ± SD after doses of 0.04, 0.08, and 0.24 µg/kg were 40.6 ± 24.9, 17.0 ± 14.0, and 13.9 ± 2.2 hr, respectively.

Elimination of paracalcin appeared to be biphasic in patients requiring hemodialysis (as in those with normal renal function), with the distribution phase essentially complete by 2 hr after the dose. Although the data are limited, mean $AUC_{0-\infty}$ values were consistent with linear kinetics. The overall (all doses, n=14) harmonic mean (± pseudo standard deviation) half-life was 16.4 ± 8.9 hr. There was no evidence of accumulation in these patients; concentrations immediately prior to the last dose were typically below the LLQ for all doses. For patients receiving the highest dose, mean C_{max} and $AUC_{0-\infty}$ values were lower after the last dose than after the first dose (1728 *vs.* 1951 pg/ml and 25662 *vs.* 28671 pg•hr/ml, respectively). Since protein binding of paracalcin is high, ranging from _____ extraction of paracalcin by hemodialysis is unlikely.

Statistical tests (t-test) of the dose-adjusted $AUC_{0-\infty}$ values from all doses (5 males and 9 females) and of the dose-adjusted $AUC_{0-\infty}$ values of the 0.24 µg/kg dose group (3 males and 4 females) showed no differences due to gender ($p>0.47$). It should be noted that data were not available for many of the 16 patients entered into the study.

6.1.3.2 Phase III

Three Phase III studies were conducted in which up to 4 blood samples were collected after a dose in Week 12 (3 doses each week). The concentrations in two of the studies, 95035 and 95036, were consistent with those of the previous Phase II study. In addition, the mean $t_{1/2}$ values for Studies 95035 and 95036 were consistent with those of the Phase II study (15 hr, and 12 hr, respectively).

The third Phase III study (Study 95037) which had samples collected for pharmacokinetic analysis had the randomization scheme reversed for one of the four sites. Patients at one site that were to receive placebo (n=4) had measurable paracalcin concentrations consistent with a dose of paracalcin, and patients that were to receive paracalcin (n=4) had no measurable paracalcin concentrations. The mean $t_{1/2}$ of about 15 hr for Study 95037 was consistent with those of other studies in patients. The paracalcin harmonic mean half-life of all values from patients in Studies 95022, 95035, 95036, and 95037 was about 14 hr.

6.2 *In Vitro* Studies

6.2.1 Plasma Protein Binding and Erythrocyte Distribution

Plasma protein binding of radiolabeled paracalcin in mouse, rat, dog, monkey, and human plasma, was determined using an equilibrium dialysis technique at four different concentrations: 1, 5, 20, and 100 ng/ml, demonstrating binding of paracalcin in plasma of >99.9%, independent of concentration in all five species The distribution of paracalcin into erythrocytes was negligible. The ratio of the concentration of [^{3}H]paracalcin in red blood cells to that in plasma averaged 0.04, indicating that [^{3}H]paracalcin does not associate to an appreciable extent with the formed elements of whole blood.

6.3 Metabolism and Excretion

In healthy subjects (n=4), all detectable plasma radioactivity after a single 0.16 µg/kg intravenous bolus dose of [^{3}H]paracalcin was attributed to unchanged paracalcin Paracalcin was eliminated primarily by hepatobiliary excretion; 74% of the radiolabeled dose was recovered in feces and 16% in urine. Several unidentified metabolites were detected in both the urine (M3, M4, and M8) and feces (M3, M4, M5, and M7), with no detectable unchanged paracalcin in the urine. None of these metabolites were identified nor was biological activity determined.

6.4 Analytical Procedures for Paracalcin Human Studies

To be reviewed by Chemistry Reviewer.

7 Clinical Data Summary and Results of Statistical Analysis

7.1 Clinical Pharmacology (Phase I Studies 95003, 95018, and 95016)

Table 1: All Phase I Studies

Protocol	Investigator	Study Design	Number of Subjects/ Gender	Age Range	Dose (mcg/kg)	Duration of Dosing
95003	Cavanaugh	placebo-concurrent controlled, double-blind, randomized	11 male 2 female			every 7 days x 3
95018	Cavanaugh	placebo-concurrent controlled, double-blind, randomized	13 male 5 female			every 2 days x 3
96016		open-label	4 male		0.16	single

8.1.2

7.1.1 Phase I, Study 95003

Study Design

This was a double blind, placebo-concurrent controlled, randomized, dose-escalating study evaluating the safety, pharmacodynamic, and pharmacokinetic profiles of single intravenous injections of Paracalcin Injection, at six different dosages, in healthy subjects. There was a seven-day washout period between each dose. Twelve participants were randomly divided into two groups. Four subjects within each group received active drug, and two subjects received an equal volume of placebo. Subjects in Group 1 received a 0.005 mcg/kg IV injection of the active drug or placebo at 0800 on the morning of the first dosing day. Subjects were then monitored for the next 48 hours. If prior to the next scheduled dosing period, subject Ca levels were below 11.0 mg/dL, subject Ca x P products were below 70, and no clinically significant, drug-related adverse events occurred, the next dose could be administered in Group 2. Administration of active drug or placebo continued in this alternating manner for all dose escalations in each group.

Safety Results

Nine subjects received active drug and four subjects received placebo. One subject was withdrawn due to elevated liver enzymes after receiving the lowest dose (0.005 mg/kg) of study drug (possibly due to Epstein-Barr virus). No other study drug-related, clinically-significant adverse events were reported for this study. The other slightly abnormal laboratory values noted suggest either laboratory or biological variation as evident by lack of a dose response pattern, occurrence of these values in both treated groups (active and placebo), or presence of the abnormal values prior to the administration of study drug.
No subject or study group was withdrawn from the study because of elevated Ca level (11.0 mg/dL or greater). No subject or study group was withdrawn from the study due to a Ca x P product of 70 or greater.

Pharmacodynamic Results

Pharmacodynamic profiles indicated no significant difference between active-treated subjects and placebo-treated subjects.

Pharmacokinetic Results

Pharmacokinetic analyses could not be performed since the concentrations for most of the samples were estimated to be below the limits of quantitation.

Conclusion

This study supports the safety of Paracalcin Injection.

Correlation with animal data

In animal acute toxicity studies, the intravenous no-effect dose was 24 mcg/kg in male and female mice, and 16 mcg/kg in male and female rats. This was the largest dose that could be administered to either species.

7.1.2 Phase I, Study 95018

Study Design

This was a double blind, placebo-concurrent controlled, randomized, dose-escalating study to evaluate the safety, pharmacodynamic, and pharmacokinetic profiles of a single IV injection of Paracalcin Injection administered at 48-hour intervals in healthy subjects, in escalating dosing groups (0.04, 0.08, 0.16 mcg/kg). A total of 18 subjects were randomly assigned to one of three groups (Group 1, Group 2, and Group 3), with six subjects (four active, two placebo) in each group. Subjects in Group 1 received three separate IV injections of 0.04 mcg/kg of the active drug or placebo with a 48-hour observation period between each injection. If during the observation period after each injection a subject's total serum Ca level remained below 11.0 mg/dL, the Ca x P product remained below 70, and no serious adverse events occurred, the next dose could be administered. If these criteria were met after three doses, dosing for Group 2 (0.08 mcg/kg) was administered. If these criteria were met for Group 2, dosing for Group 3 (0.16 mcg/kg) was initiated.

Group 1 subjects received three separate injections of 0.04 mcg/kg. Group 2 subjects received injections of 0.08 mcg/kg and subjects in Group 3 received injections of 0.16 mcg/kg. If no serious adverse experiences occurred, serum Ca levels remained below 11.0 mg/dL, and Ca x P products remained below 70, the first dose (0.08 mcg/kg) for Group 2 could be administered. Following the same criteria, when the same dosing regimen had been completed for Group 2, the first dose (0.16 mcg/kg) for Group 3 could then be administered. The same dosing criteria were applied at all dose administrations for Group 3.

Safety Results

Twelve subjects received active drug and six subjects received placebo. For the COSTART term "edema" there was a greater incidence ($p = 0.025$) of adverse experiences reported for placebo-treated subjects (50%, 3/6 edema) compared to active-treated subjects (0 percent, 0/12). Of the total number of episodes of adverse experiences, 49/51 were rated as mild in intensity. Two adverse experiences for one subject in the placebo-treated group were rated as moderate in intensity. There were no severe or serious adverse experiences. The majority of adverse experiences (35/51) were resolved within 24 hours.

No subject or study group was withdrawn from the study because of an elevated Ca level (11.0 mg/dL or greater). No subject or study group was withdrawn from the study due to a Ca x P product of 70 or greater.

Pharmacodynamic Results

Measurement of serum total Ca, P, Ca x P product and iPTH did not demonstrate any differences between the active and placebo-treated subjects.

Pharmacokinetic Results

In general, the pharmacokinetics were linear for the dose range of _____ with little or no accumulation of paracalcin observed in blood with the dosing regimen in healthy subjects. After the first dose of 0.16 mcg/kg, paracalcin mean (± SD) values of C_{max} and $AUC_{0-\infty}$ were 1242 ± 226 pg/ml and 5247 ± 893 pg•hr/ml respectively. The terminal $t_{1/2}$ in healthy subjects was approximately five to seven hours. Due to the extremely low levels of paracalcin in urine, the pharmacokinetic profile for those samples was not evaluated.

Conclusion

This study supports the safety of Paracalcin Injection in healthy subjects.

Correlation with Animal Data

In animal studies with repeat dosing, with intravenous administration three times per week, two or three days apart, to mimic how Paracalcin Injection would be administered in the dialysis units, the non toxic effect dose was 0.3, 3.0 and 0.5 mcg/kg/dose in male and female Crl:CD®(SD)BR rats at one, three, and six months, respectively. The non toxic effect dose was 0.1, 0.02, 0.06 and 0.02 mcg/kg/dose in male and female beagle dogs at one, three, six and 12 months, respectively.

7.1.3 Phase I, Study 96016

Study Design

This was an open-label study to determine the metabolism and excretion of Paracalcin Injection in healthy volunteers. The subjects were administered a single 0.16 mcg/kg IV dose of the drug labeled with tritium in the 9 and 11 positions of the molecule. A _____ assay employing radioactivity _____ was used to obtain the metabolic profiles of [^{3}H] Paracalcin Injection in select plasma, urine, and fecal samples.

Table 4: Demographic and Dosage Information for Subjects in Study 96016

Subject	Sex	Age (yr)	Weight (kg)	Height (cm)	µg	µCi	µg/kg
1	male	30	83.8	182			
2	male	31	71.9	168			
3	male	30	81.9	173			
4	male	40	77.1	175			

Results

The major route of elimination of [^{3}H] Paracalcin Injection appeared to be biliary excretion; 73.7 percent of the dose of radioactivity was recovered in the feces over ten days with approximately 68 percent of the mean tritium dose in the feces between Days 2 – 6. An average of 15.8% of the tritium dose appeared in urine over seven days following dosing. Most of the radioactivity (14.5% of the radioactive dose) excreted in urine appeared in the first 72 hours following dosing. Less than 1% of the total radioactivity of the tritium label equilibrated with body water as shown by measurements of volatile radioactivity in urine and plasma.

The metabolic patterns in 24 – 168 hour fecal samples showed the presence of several unknown metabolites, denoted M-3, M-4, M-5, and M-7, as well as numerous minor radioactive _____ The contribution of parent compound and M-3, M-4, M-5, and M-7 to fecal radioactivity amounted to 58.8 percent. In urine, three unknown products, as well as M-3, M-4, and M-8, accounted for 51.3 percent of the 0 – 48 hour urinary radioactivity, with the remainder represented by a number of minor unknown peaks. Treatment of urine with β-glucuronidase resulted in the reduction of these unknown peaks at 13 – 22 minutes and of M-4, with the subsequent appearance of Paracalcin Injection and a group of peaks eluting between 34 – 42 minutes. These results suggest that the peaks in urine at 13 – 22 minutes and M-4 are glucuronide conjugates of Paracalcin Injection and its metabolites. In 0 – 48 hour urine and 24 – 168 hour feces, Paracalcin Injection accounted for only 5.7 percent of the total dose radioactivity

excreted, whereas M-3, M-4, M-5, M-7, and M-8 accounted for 10.9%, 9.1%, 16.4%, 4.3%, and 2.1% of the total radioactivity.

Upon intravenous administration of [^{3}H] Paracalcin Injection, total plasma radioactivity declined rapidly

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The decline was slower thereafter, with a mean plasma concentration of 0.39 ng equivalents/ml measured at three hours and 0.02 ng equivalents/ml observed at 168 hours post-dose. Parent drug was the only significant radioactive component detected in plasma out to 24 hours with a mean terminal elimination half-life of 21.0 hours and a mean AUC $_{0\text{-}24h}$ of 7.2 ng•hr/ml. Thereafter, the low levels of radioactivity present in the plasma samples did not permit accurate quantitation.

Correlation with Animal Data

The metabolism and excretion of [^{3}H] Paracalcin Injection in humans was similar to that observed in dogs. Excretion of [^{3}H] paracalcin-related radioactivity in dog feces and urine were 84.5% and 10.6% of the total tritium dose, respectively. The metabolite profile in the 0 – 120 hour dog feces contained M-3 and M-5, contributing 39.6% and 18%, respectively, of the fecal radioactivity. In the rat fecal extracts, M-3 and M-5 accounted for 50.4% and 10.1% of the fecal radioactivity, while those unknown products eluting between 34 – 42 minutes were not detected. However, the metabolite profiles in both rat and dog urine were similar to that of human urine, with M-3 being the major metabolite detected. Only [^{3}H] paracalcin was detected in rat and dog plasma, similar to what was observed in humans.

7.2 Overview of Phase II Clinical Studies

The development of the study design for the Phase III trials was based on the safety and efficacy data collected in the preclinical and Phase I and II studies.

Dosing in the Phase III placebo-concurrent controlled studies was selected from analysis of data from the Phase II study. In the four week Phase II study with chronic renal failure (CRF) patients, doses ranged from 0.04 mcg/kg up to 0.24 mcg/kg. No statistical differences in adverse events were noted between the active and placebo groups. Fifteen of the 22 patients (68%) achieved the 30% iPTH reduction endpoint compared with 2/13 (15%) of the placebo patients. Sixty seven % of patients in the 0.04 mcg/kg dose group reached this endpoint; 83% of patients in the 0.24 mcg/kg dose group reached this endpoint.

7.3 Phase III Studies

Three of the eight Phase III studies were placebo-concurrent controlled and were complete at the time of submission of the NDA. These three completed placebo-concurrent controlled studies were detailed as proof of efficacy. All studies, completed and interim reports on four additional studies, were presented for safety. The eighth study (95027) did not have treated patients at the time of data collection (16 August 1996) for this submission.

Three placebo-concurrent controlled studies, 95035, 95036, and 95037, determined the safety and efficacy of Paracalcin Injection in decreasing iPTH levels in patients with CRF. Efficacy would be established if there was at least a 30% decrease from baseline in a patient's iPTH level. The duration of the studies was 12 weeks.

Three active comparator studies, 95027, 95028, and 95034, were included in the safety analysis of Paracalcin Injection in CRF patients undergoing hemodialysis, and evaluated for comparison of the incidence of hypercalcemia and/or elevated Ca x P product in patients receiving Paracalcin Injection with patients receiving IV (95028, 95034) or oral (95027) calcitriol. Efficacy was based on the incidence of

hypercalcemia and/or elevated calcium x phosphorus product upon the reduction of iPTH level by at least 50% from final baseline.

Two ongoing open-label studies, 95029 and 96004, will determine the long-term safety and efficacy of Paracalcin Injection in CRF patients undergoing hemodialysis when used at dosages sufficient to maintain serum iPTH levels at clinically appropriate levels (approximately one and a half to three times the non-uremic upper limit of normal), as determined by the Investigator. Interim reports for 95029 and 96004 as of 16 August 1996 were included in this NDA submission.

7.3.1 Controlled Clinical Studies

Efficacy was demonstrated by a statistically significant ($p \leq 0.05$) difference between the two treatment groups [Paracalcin Injection (active) vs. placebo] in the number of patients experiencing at least a 30% decrease from baseline in their iPTH values. A patient's iPTH level was the primary efficacy variable. Alkaline phosphatase provided additional information as a marker for bone remodeling activity and was analyzed as a secondary efficacy variable of interest.

Three adequate and well controlled Phase III placebo-concurrent controlled clinical studies demonstrated efficacy. The study design for the three studies was identical; therefore the data were pooled for analysis.

Table 5: Phase III Placebo-Concurrent Controlled Studies Summary
Protocol numbers: 95035, 95036, 95037 **Population**: CRF patients on hemodialysis **Paracalcin Injection**: 5 mcg/ml ( ) alcohol, and ( ) propylene glycol vs. Placebo: 20% (v/v) alcohol, and 30% (v/v) propylene glycol **Dose**: 0.04 to 0.24 mcg/kg/dose or equivalent volume of Placebo, IV, 3 times per week for 12 weeks

Study	Design		Treatment Group
95035	Initiation Date:	7 March 1996	Total analyzed: n = 31
	Completion Date:	10 September 1996	Active group: n = 16
	Design:	A double-blind, placebo-concurrent controlled, randomized, multi-investigator study.	Placebo group: n = 15
	No. of Centers:	4	
	Study Length:	Four-week Pretreatment Phase (washout/baseline) and a 12-week Treatment Phase.	
	Dose Selection:	During the Treatment Phase, potential dose increases occurred every two weeks. 0.04 mcg/kg/dose to 0.24 mcg/kg/dose (depending on iPTH response), administered intravenously three times weekly.	
95036	Initiation Date:	14 March 1996	Total analyzed: n = 31
	Completion Date:	18 September 1996	Active group: n = 16
	Design:	A double-blind, placebo-concurrent controlled, randomized, multi-investigator study.	Placebo group: n = 15
	No. of Centers:	3	
	Study Length:	Four-week Pretreatment Phase (washout/baseline) and a 12-week Treatment Phase.	
	Dose Selection:	During the Treatment Phase, potential dose increases occurred every two weeks. 0.04 mcg/kg/dose to 0.24 mcg/kg/dose (depending on iPTH response), administered intravenously three times weekly.	
95037	Initiation Date:	14 March 1996	Total analyzed: n = 16
	Completion Date:	18 September 1996	Active group: n = 8
	Design:	A double-blind, placebo-concurrent controlled, randomized, multi-investigator study.	Placebo group: n = 8
	No. of Centers:	4	
	Study Length:	Four-week Pretreatment Phase (washout/baseline) and a 12-week Treatment Phase.	
	Dose Selection:	During the Treatment Phase, potential dose increases occurred every two weeks. 0.04 mcg/kg/dose to 0.24 mcg/kg/dose (depending on iPTH response), administered three times weekly intravenously.	
		Total analyzed:	Active group: n = 40 Placebo group: n = 38

7.3.1.1 All Phase III Placebo-Concurrent Controlled Studies, 95035, 95036, and 95037

Phase III Study: Multidose Evaluation of 19-nor-1 alpha, 25-dihydroxyvitamin D_2 in End Stage Renal Disease Patients Undergoing Hemodialysis

Objective: to determine the safety and efficacy of Paracalcin Injection in decreasing iPTH levels in patients with CRF.

Methodology: These were double-blind, placebo-concurrent controlled, randomized, multi-investigator studies evaluating the safety and efficacy of IV administration of Paracalcin Injection. Drug was administered 3 times a week, at 48 to 72-hour intervals (at the end of the patient's regular hemodialysis

session), for 12 weeks, with potential dose increases every 2 weeks until the clinical objective was met or for a maximum of 5 dose escalations.
The study was performed in two phases: a Pretreatment Phase (washout/baseline) and a Treatment Phase. During Pretreatment, any patient receiving calcitriol, dihydrotachysterol, or calcitonin prior to enrollment underwent a 4-week washout period. The last 2 weeks of this washout period served as a baseline period for measurement of serum calcium, phosphorous, and iPTH levels. Any patient not receiving calcitriol, dihydrotachysterol, or calcitonin prior to enrollment entered into the study at the start of the baseline period.
Following the baseline period, all patients who met the Treatment Phase inclusion/ exclusion criteria were randomized to receive active drug or placebo. The study drug dose was escalated until a patient's iPTH level was decreased from baseline by at least 30 percent or for a maximum of 5 dose escalations, starting at a dose of 0.04 mcg/kg and increasing according to protocol to 0.08, 0.12, 0.16, 0.20, and 0.24 mcg/kg. A patient was maintained at the dose which decreased the iPTH level by at least 30% from baseline. However, if the iPTH level decreased to less then 100 pg/ml, or all Ca x P products were greater than 75 within any consecutive two-week period at a given dose level, or serum calcium became greater than 11.5 mg/dL at any single occurrence, 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.

Diagnosis and Main Criteria for Inclusion

Pretreatment Phase (washout, baseline):

- Undergoing maintenance hemodialysis three times a week
- Expected to remain on hemodialysis for the duration of the study
- Sign an informed-consent form
- 18 years or older
- End stage renal disease
- Female candidates of child-bearing potential could not be nursing; had to be using birth control upon enrollment and had to continue using the contraceptive method throughout the study. Post-menopausal female patients had to have been 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, within four weeks prior to study drug administration.
- Serum Ca x P product of less than or equal to 70, at enrollment.
- Cannot have a history of clinically significant allergic reaction to calcitriol or other vitamin D compounds.
- Cannot have a current malignancy or clinically significant liver disease (e.g., SGOT, SGPT, or bilirubin 2x the upper limit of normal) at enrollment.
- Cannot have a history of drug or alcohol abuse within the last six months.
- Cannot be participating in another investigational study within 30 days prior to enrollment.
- Cannot, in the Investigator's opinion, be at risk for aluminum-related bone disease

- Cannot, during the course of the study, receive calcitonin, maintenance glucocorticoids, or other drugs that may effect Ca or bone metabolism, other than females on stable estrogen and/or progestin therapy
- Cannot be considered unreliable and/or non-compliant
- Cannot be anticipated to be unable to complete the entire study (e.g., scheduled for transplant, concurrent disease, etc.)
- Cannot, in the Investigator's opinion, be at increased risk by the study procedures
- Could not have been randomized in a previous Paracalcin Injection study
- Cannot, within one month prior to enrollment, be receiving pharmacologic doses of vitamin D, other than calcitriol, or dihydrotachysterol
- Cannot require chronic use of phosphate binders containing aluminum
- Cannot have evidence of known blood-born infectivity (e.g., HIV, antigen positive hepatitis)

Treatment Phase (randomized eligibility)

- Must have normalized total serum calcium concentration from _____, serum Ca x P product less than 75, and elevated iPTH levels of at least 400 pg/ml at the last measurement during the baseline period.
- Must not have received calcitriol, other vitamin D therapy, calcitonin, glucocorticoids or other drugs that could have affected calcium or bone metabolism (other than females on stable estrogen and/or progestin therapy) during the Pretreatment Phase.
- No positive pregnancy test within four weeks prior to initiation of the Treatment Phase.

Criteria for Evaluation

Efficacy: At least 30 percent decrease from baseline in a patient's iPTH level.

Safety: The safety of Paracalcin Injection in treating secondary hyperparathyroidism was determined by evaluating the adverse events occurring during study and the chemistry and hematology results throughout the study; in particular, the effect on serum calcium and Ca x P levels.

Statistical Methods

All analyses were performed with SAS® (version 6.11) procedures GLM, FREQ, 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. Graphs were constructed using procedure GPLOT in SAS and MICROSOFT® POWERPOINT® to present important findings of this study and as a visual aid for interpreting the data.

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 iPTH laboratory result obtained prior to Treatment served as baseline. The laboratory evaluations at enrollment were excluded from the baseline assessment.
The incidence of at least one 30% decrease from baseline in iPTH within each treatment group was compared with a 2 x 2 Fisher's Exact test. The incidence of a 30 percent decrease from baseline, maintained for at least four consecutive laboratory draws within each treatment group was compared with a 2 x 2 Fisher's Exact test. Similarly, the incidence of a 30% decrease at the final laboratory draw was also compared with a 2 x 2 Fisher's Exact test.
Per the protocol, laboratory draws were to be obtained once a week during Treatment.
The primary data set analyzed for efficacy were all treated patients which included any patient that received at least one dose of study drug. The all treated patients data set is presented though an analysis of evaluable patients (per protocol) and is available in the individual study reports. A total of 78 all treated patients were analyzed in the combined Phase III placebo-concurrent controlled studies; 40 active and 38 placebo.

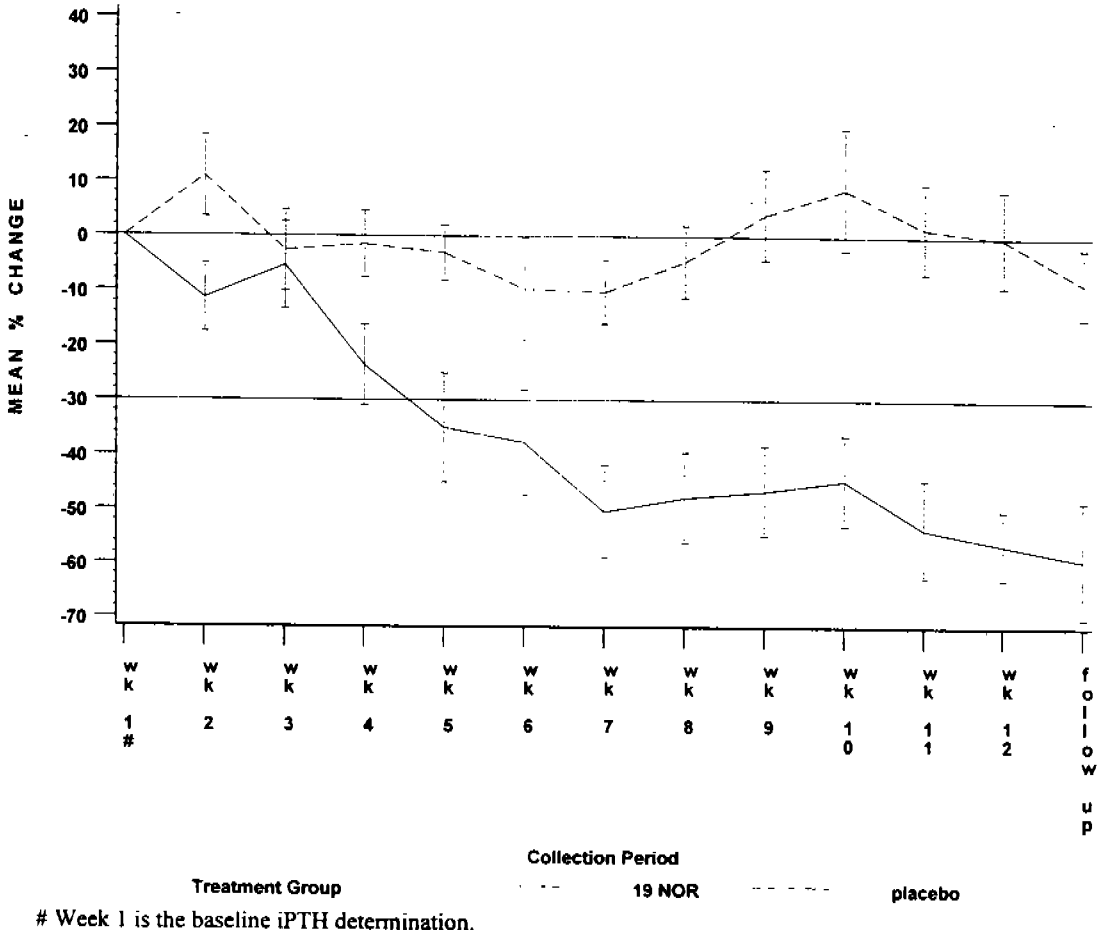
7.3.1.2 Results and Analysis for Individual Studies

7.3.1.2.1 Study 95035

Primary Efficacy Variable—iPTH Level

The following Figure presents the weekly mean ± 1 SEM for percent change from baseline for iPTH levels by treatment group.

Weekly Mean ± 1 SEM For Percent Change From Baseline For iPTH Levels By Treatment Group, Study 95035



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

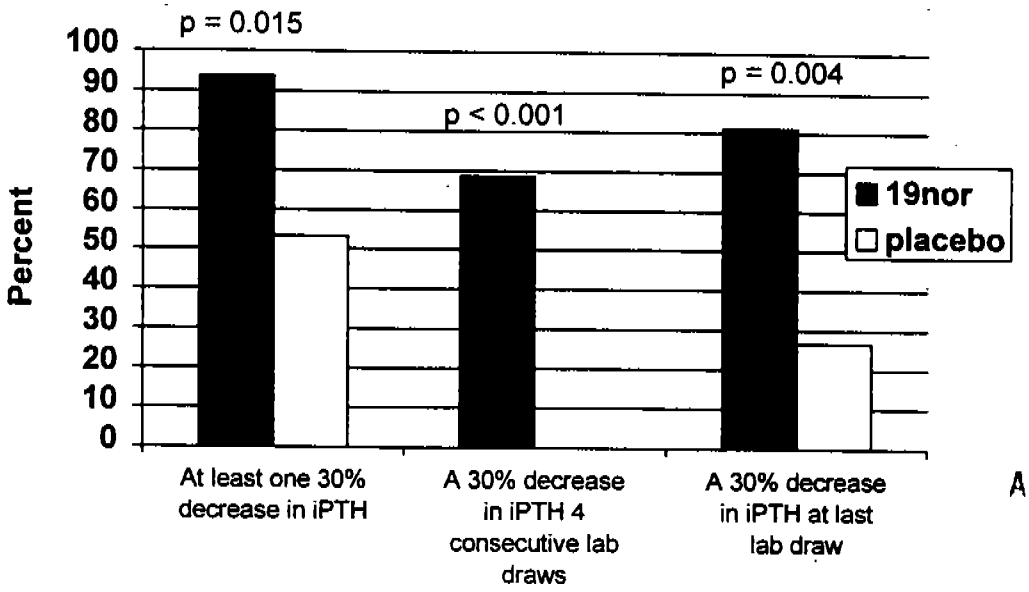
The mean percent change from baseline in iPTH levels for all drug-treated patients was greater than -30 % after Week 4, while the mean percent change remained within -10% of baseline for placebo patients. The mean percent change from baseline in iPTH levels for all treated patients was greater than -50% from baseline at the follow up visit while the mean percent 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 final visit.

The next Figure and Table show the number and percentage of all treated patients who met the above criteria 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 95035



All Treated Patients With a 30 Percent or Greater Decrease from Baseline in iPTH, Study 95035

	Active		Placebo		
	number	percent	number	percent	p-value†
At least one 30 percent decrease in iPTH	15/16	93.8	8/15	53.3	0.015*
A 30 percent decrease in iPTH for at least 4 consecutive lab draws	11/16	68.8	0/15	0.0	<0.001***
A 30 percent decrease in iPTH at the final lab draw	13/16	81.3	4/15	26.7	0.004**

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

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

For the three variables evaluated for all treated patients, patients on drug demonstrated a statistically significant difference in iPTH reduction in comparison to placebo patients.

Change from Baseline in iPTH Values

The following 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 95035

	Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between Group Comparisons: Change Mean (SE) p-value†	Between Group Comparisons: Baseline Mean (SE) p-value†
iPTH (pg/ml)	Active	786.8	391.8	-395 [70.83]***	-326 (102)	132.2 (96.2)
	Placebo	654.6	585.9	-68.7 [73.15]	0.003**	0.180

† P-value based upon a one-way ANOVA.

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

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

Other Variables

Changes from Baseline in Alkaline Phosphatase Values, Study 95035

	Treatment Group	Baseline Mean [Range]	Final Mean [Range]	Change from Baseline Mean [SE]	Between Group Comparisons: Change Mean (SE) p-value†	Between Group Comparisons: Baseline Mean (SE) p-value†
Alk. Phos. (U/L)	Active	141.7	105.3	-36.4 [9.141]***	-57.2 (12.7)	27.8 (28.5)
	Placebo	113.9	134.7	20.8 [8.831]*	<0.001***	0.338

† P-value based upon a one-way ANOVA.

* and *** indicate statistical significance (2-tailed) at the 0.05 and 0.001 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 showed that active patients demonstrated a statistically significant reduction in alkaline phosphatase in comparison to placebo patients which is the desired response.

Study 95035 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 found that Paracalcin Injection significantly reduces elevated iPTH levels in patients with CRF. Approximately 69% (11/16) of the active patients achieved at least a 30% decrease in iPTH values for at least four consecutive lab draws compared to none of the 15 patients who received placebo ($p < 0.001$). Analyses of the single incidences of at least a 30% reduction and occurrences at the final visit led to the same conclusion. Active patients had a mean iPTH reduction of 395 pg/ml compared to a reduction of 68.7 pg/ml following treatment with placebo ($p = 0.003$). Serum alkaline phosphatase decreased by 36.4 U/L in active patients while there was an increase of 20.8 U/L ($p < 0.001$) in the placebo group. This change is consistent with decreased bone osteoblast activity in patients on drug.

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; one active patient and one placebo 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 or definite relationships 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. Patients receiving active drug had a statistically significant increase ($p = 0.026$) in mean Ca values of 0.62 mg/dL from baseline to follow-up compared to a mean increase of 0.05 mg/dL in the placebo group. A single occurrence of hypercalcemia required dose adjustment. Thirteen percent (2/16) of active patients became hypercalcemic at least once during treatment while no placebo patients became hypercalcemic. This was not a statistically significant difference, but suggests a potential safety issue under clinical use. No patient from either treatment group was hypercalcemic at the final laboratory testing.

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 ($p = 0.027$) between the two groups. Paracalcin patients experienced an increase in mean Ca x P values of 7.05 compared to a decrease of 5.51 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. Thirty eight % (6/16) of active patients and seven % (1/15) of placebo patients had such occurrences. One active patient and one placebo patient discontinued from the study due to elevated Ca x P products; one active patient discontinued from the study due to elevated Ca; one active patient discontinued from the study due to an iPTH level of less than 100 pg/ml. Although these differences may not be statistically significant in this small population, they suggest potential safety concerns in general clinical use.

Other chemistry and hematology variables showed random variation with no trends in active patients that were discernible when compared with pretreatment values in active patients or when compared with the results observed in placebo patients except for LDH values. Active patients had a decrease in mean LDH levels of 22.3 U/L while the placebo group had a mean increase of 7.2 U/L ($p = 0.019$). The clinical

significance of this is unknown. 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.

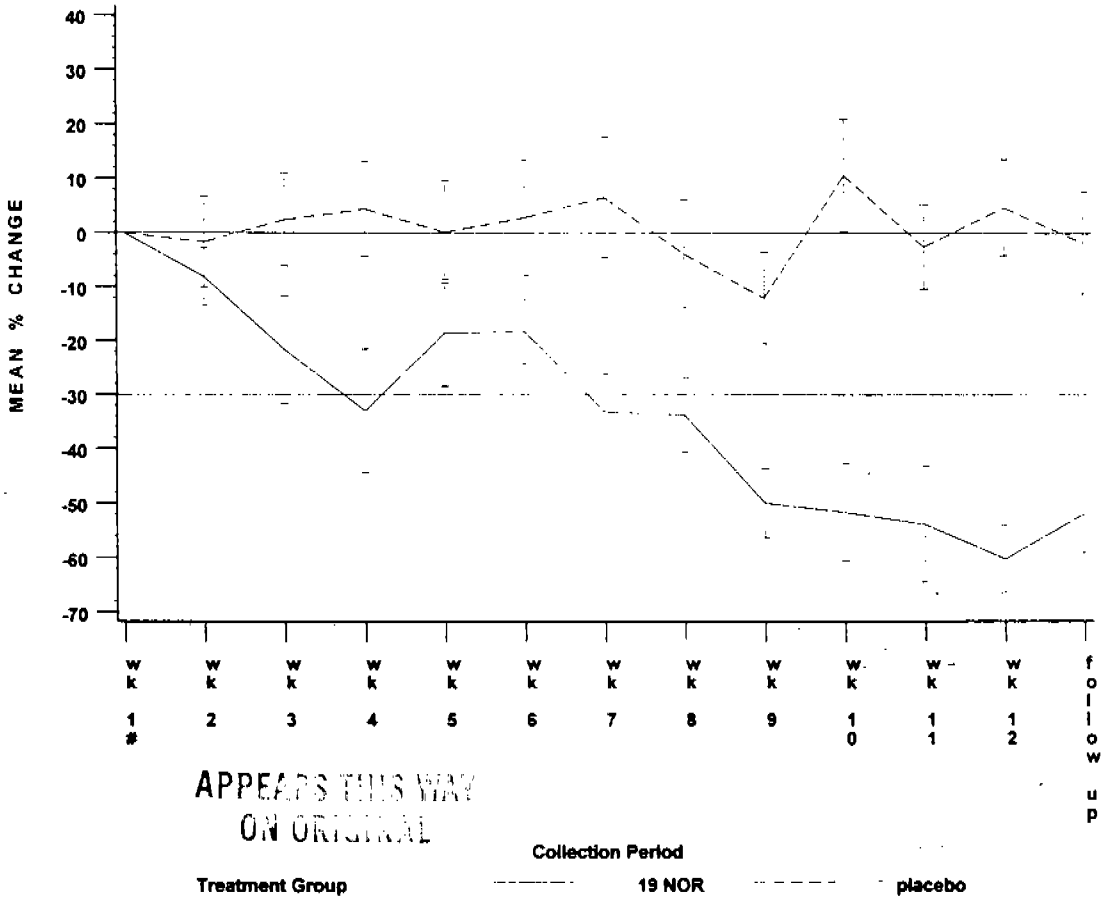
Conclusion: Compared to placebo, Paracalcin Injection effectively and safely reduced iPTH levels in CRF patients on hemodialysis.

7.3.1.2.2 Study 95036

Primary Efficacy Variable—iPTH Level

The following Figure presents the weekly mean ± 1 SEM for percent change from baseline for iPTH levels by treatment group for all treated patients.

Weekly Mean ± 1 SEM for Percent Change from Baseline for iPTH Levels By Treatment Group, Study 95036



The mean % change from baseline in iPTH levels for all drug patients was greater than -30 % at Week 7 while the mean % change remained within 10 % of baseline for placebo patients. The mean % change from baseline in iPTH levels for all drug patients was approximately -50% from baseline at the Follow-up visit while the mean for placebo patients was within -10 % of baseline.