CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020819

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

MAR 20 1998

Date:

NDA#:	20-819
Applicant:	Abbott Labs
Name of Drug:	Capthrol [tradename] Paracalcin Injection / Paricalcitol Injection [generic name] (1α, 3β, 7E, 22E) -19-nor-9,10,-secoergosta-5,7,22-triene-1,3,25-triol abbreviated as 19-NOR
Indication:	Prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism encountered with chronic renal failure
Documents Reviewed:	10-22-97 Vol.1; 10-31-97 electronic data; 11-6-97 Vol.1-30 & Vol 1-41; 12-15-97
Statistical Reviewer:	Barbara Elashoff, M.S. (HFD-715)
Medical Input:	Leo Lutwak, M.D. (HFD-510)

APPEARS THIS WAY
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Summary

The sponsor submitted three double-blind, placebo-controlled, randomized, multi-center studies (Studies 35, 36, and 37) to support the efficacy of 19-NOR in chronic renal failure patients on hemodialysis and two studies (28 and 34) to support the claim that 19-NOR maintains a lower calcemic and phosphatemic profile than Calcijex (intravenous calcitriol). This review summarizes the active-controlled clinical trials; it is an addendum to the review dated 2-23-98.

The results of Study 34 demonstrate that the incidence of elevated Ca and/or Ca x P levels, as defined in the protocol, was statistically significantly greater in the 19-NOR group (the study was expected to show the opposite). ***Study 28 was not completed at the time of this review. The sponsor unblinded and analyzed the data before all the patients had completed the study.*** *The results of the preliminary analysis found no statistically significant difference between the two groups for the primary variable, as defined in the protocol. The sponsor presented results of a different analysis as evidence that the preliminary data demonstrated statistical significance in favor of 19-NOR; however, this was a post-hoc analysis of a subset of the entire dataset and should be viewed as descriptive, not confirmatory.*

1 Introduction

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1.1 Design

Studies 28 and 34 were active-controlled clinical trials comparing the incidence of hypercalcemia and elevated Ca x P product level between 19-NOR and Calcijex (intravenous calcitriol), another drug used to treat renal osteodystrophy.

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Table 1: Active-Controlled Safety Studies

Study	Dates Conducted	Study Arms	# of sites	Duration of treatment phase	Number Randomized (in the U.S.)
28	5/96 - 6/97[1]	Calcijex (intravenous calcitriol) 19-NOR	21 U.S. sites and an unknown number of European sites[2]	32 weeks[3]	224
34	3/96 - 4/97	Calcijex (intravenous calcitriol) 19-NOR	23 U.S. sites	24 weeks[4]	197

1 The study report states that the last patient completed the study on June 7, 1997. However, in a telecon with the sponsor (2-25-98), the sponsor stated that the study was still ongoing in Europe. The sponsor did not have the case report forms or the data for the European sites as of the date of the telecon.

2 The study report states that the study was conducted at sites in U.S. and Europe, however only the U.S. sites were listed in the appendix. The sponsor did not state in the NDA how many European sites there were.

3 The study report stated that the treatment phase was 12-32 weeks, however if iPTH levels dropped below 100 pg/mL at the lowest dose level, or if the Ca levels increased to above 11.5 mg/dL (after Amendment 9 was approved), treatment was discontinued and the patient was considered to have completed the study.

4 The study report stated that the treatment phase was 24 weeks, however, if iPTH levels dropped below 100 pg/mL at the lowest dose level, if the Ca levels increased to above 11.5 mg/dL at the lowest dose level, or if all Ca x P values were greater than 75 within any consecutive two-week period at the lowest dose level, treatment was discontinued and the patient was considered to have completed the study.

Study 28

Study 28 consisted of two phases: a pretreatment phase (2 washout plus a 2-6 week baseline period) and treatment phase (32 weeks). The patients who met the baseline criteria after the pretreatment phase were randomized to receive either 19-NOR or Calcijex, both intravenously. Each patient was to receive three injections of 19-NOR or Calcijex at 48-72 hour intervals (at the end of their regular hemodialysis session) every week for 32 weeks. The study drug was to be escalated every four weeks for a maximum of five dose escalations 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% for an additional eight weeks, for a total of 12 weeks maximum. However, if the iPTH decreased to less than 100 pg/mL after two weeks at a given dose level, the dose was reduced to the previous level. If this occurred at the first dose level the patient was considered to have completed the study and follow-up procedures were performed.

The protocol originally stated that a patient would be dose reduced upon a single incidence of hypercalcemia and if the patient were already at the lowest dose, treatment was discontinued (and the patient was considered to have completed the study). A protocol amendment in Study 28 (approved February 24, 1997, mid-way through the trial) stated that a patient was considered to have completed the study upon a single incidence of hypercalcemia, <u>at any dose level</u>. Therefore, patients in Study 28 developing a Ca value greater than 11.5 mg/dL at any time *after the amendment was approved at the individual sites* were considered to have completed the study.

Reviewer Comment

The study report stated that the treatment phase was 12-32 weeks. It is unclear what this means. The patients were considered to have completed the study if iPTH levels dropped below 100 pg/mL at the lowest dose level, or if the Ca levels increased to above 11.5 mg/dL. There was no minimum number of weeks a patient was required to receive treatment.

Study 34

Study 34 was conducted at twenty-three investigational sites in the United States. Similar to Study 28, the study consisted of two phases: a pretreatment phase (2 washout plus a 2-6 week baseline period) and treatment phase (24 weeks). The treatment phase in this study was 8 weeks shorter than that of Study 28. The dosing regimen was similar to that of Study 28. If iPTH levels dropped to below 100 pg/mL, if the Ca levels increased to above 11.5 mg/dL, or if all Ca x P values were greater than 75 within any conseeutive two-week period, the dose of the study drug was to be reduced to the previous level. If any of these conditions occurred at the first dose level, treatment was discontinued and the patient was considered to have completed the study. (Unlike Study 28, the protocol of this study was not amended to change this procedure.)

1.2 Foreign Sites Not Included

Study 28 was conducted at multiple investigational sites throughout the United States and Europe, however, the company only submitted the data from the U.S. sites in the submissions of 10-22-97, 10-31-97 and 11-6-97. The study report of Study 28 stated the following:

> "The study was conducted at multiple investigational sites throughout the U.S. and Europe; this summary reflects only the U.S. portion of the study. At each site, 50 percent of patients were randomized to receive Capthrol and 50 percent 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."

In a teleconference with the sponsor (3/2/98), the agency learned that the study is ongoing in Europe as of the date of this review. The European patients constitute 14.8% of the treated patients in the study. The sponsor stated in the telecon that it was their intention to use the European arm to support approval in Europe. This was not stated in the protocol.

Reviewer Comment

The sponsor stated on the cover page and page i of the study report that the last patient completed the study on June 7, 1997. However, in the telecon on 2-25-98, the sponsor stated that the last patient (recruited in Europe) had not yet completed the study.

It is good clinical practice in clinical trials to unblind the data only after all patients have completed the study, unless otherwise specified in the protocol. There was no planned interim analysis stated in the protocol. The sponsor unblinded and analyzed the data after only 85.2% of the patients had completed the study. It is assumed that the sponsor did not make any decisions whether to stop the study early or accrue more patients than originally planned based on the results of the interim analyses.

Interim looks at the data do not necessarily accurately represent the final results of the studies. Therefore the results of the preliminary data of Study 28 presented in this review should be viewed as descriptive.

2 Adverse Events

2.1 Summary

There was no obvious relationship between treatment groups and number of patients reporting at least one adverse event.

Table 2: Incidence of Patients Reporting At Least One Adverse Event After Treatment Began

Study	19-NOR	Calcijex (active-control)
28	84/110 (76%)	84/114 (74%)
34	44/98 (45%)	43/99 (43%)

2.2 Hypercalcemia (Primary Variable)

Studies 28 and 34 were designed to detect a difference in incidence of hypercalcemia between 19-NOR and the comparator. The protocols stated that the objectives were,

1. to demonstrate the safety of 19-NOR in end stage renal disease patients undergoing hemodialysis, and
2. to determine whether the incidence of hypercalcemia (normalized serum calcium greater than 11.5 mg/dL [2.88 mmol/L]) and/or elevated calcium x phosphorous product (greater than 75 [6.1]) is lower in patients receiving 19-NOR than in patients receiving intravenous calcitriol.

2.2.1 Descriptive Statistics

The values of Calcium and Ca x P product level increased slightly between the baseline visit and the follow-up visit (the last visit the patient was seen). The means and standard deviations are presented in Table 3. Figures 1-4 show the means plotted for various visit intervals. One observation per patient is plotted for each visit interval. The means and 95% confidence intervals around the means are shown as horizontal lines. The visits were grouped into categories and the maximum value of the variable for each patient was plotted in the graph and used in the calculation of the mean. No patient was counted twice. The numbers at the bottom of the graphs are the total numbers of patients left in each treatment group. The plot on the far right of each graph is a plot of the data at the follow-up visit. The data from the follow-up visit does not necessarily represent a point in time after the data from the visits 56-65 for Study 28 or visits 45-49 for Study 34. It represents different times for each patient. Some patients completed the study after visit 20, some after visit 30, etc. The follow-up visit was conducted within a few days of the patient's last dose.

Table 3: Means and Standard Deviations of Baseline, Final Visit (Follow-Up Visit) and Change From Baseline

			19-NOR N=102		Calcijex N=105		Difference	95% CI	p-value
Study	Variable		Mean	Std Dev	Mean	Std Dev			
28	Calcium (mg/dL)	Baseline	9.0	0.9	9.0	1.1			
		Final	9.7	0.8	9.8	1.1			
		Change	0.7	0.8	0.8	1.0	-0.1	(-0.3,0.2)	0.62
	Ca x P units	Baseline	52.6	13.1	51.7	13.3			
		Final	58.2	17.1	58.1	18.8			
		Change	5.5	17.1	6.7	16.9	-1.3	(-6.0, 3.4)	0.60
			19-NOR N=88		Calcijex N=90				
			Mean	Std Dev	Mean	Std Dev			
34	Calcium (mg/dL)	Baseline	8.9	0.8	8.9	1.0			
		Final	9.9	0.9	9.6	1.3			
		Change	1.0	0.9	0.7	1.0	0.3	(-0.1, 0.6)	0.06
	Ca x P units	Baseline	52.1	14.1	49.9	14.1			
		Final	61.4	16.2	59.7	19.2			
		Change	9.2	18.2	9.4	19.7	-0.2	(-5.8, 5.4)	0.94

Reviewer Comment

The changes from baseline of Calcium appeared to be fairly consistent across treatment groups and across studies, with the exception of the 19-NOR group in Study 34. This treatment group had a slightly greater mean change from baseline (1.0 mg/dL) than the Calcijex group in Study 34 (0.7 mg/dL) and also greater than the changes in Study 28 (19-NOR: 0.7 mg/dL; Calcijex: 0.8 mg/dL). The mean changes from baseline of the Ca x P level, while consistent across treatment groups within the studies, varied greatly between the studies. The mean changes in Study 28 were 5.5 and 6.7 for the 19-NOR and Calcijex treatment groups, respectively; and in Study 34 they were notably higher at 9.2 and 9.4 for the 19-NOR and Calcijex groups, respectively. None of the differences were statistically significant.

The mean values increased over time, (Figures 1-4), but appeared to decrease in the last category of visits (55-65 in Study 28 and 46-49 in Study 34). The decrease in means may have been due to the fact that most of the patients had already completed at this point in time (79% in Study 28 and 71% in Study 34) and the remaining patients had and continued to have lower Ca and Ca x P levels. The patients whose Ca and Ca x P levels increased over time had already completed the study.

Figures 1-4 demonstrate the similarities between the results of the two studies. The distribution, range and mean values of the variables were similar over time across studies.

The fact that the studies look similar with respect to the means over time and the mean changes from baseline is important because the analyses the sponsor presented (proportions of patients with elevated Ca and Ca x P levels, page 9) are not consistent across studies. Therefore, the data may be best analyzed as continuous variables (using means and variances) rather than as proportions. This is discussed more fully in the reviewer comment on page 10).

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2.2.2 Primary Analysis

The primary analysis, while not specifically stated, was implied in the explanation of the sample size calculation as well as by objective #2 stated above. Both protocols based the sample size on, "a 15% difference between the two treatment groups in the number of patients experiencing at least one incidence of hypercalcemia and/or an elevated calcium x phosphorous product greater than 75 during the study..." Therefore, it is inferred that the primary endpoint was the proportion of patients manifesting at least one elevation of *either* calcium or calcium x phosphorous product. There was no difference between the two groups for this endpoint in Study 28 (using the preliminary subset of patients who completed the study) and a statistically significant difference between the two groups favoring the comparator in Study 34 (see Table 4). However, after breaking the blind, the company decided that this variable was not considered clinically relevant and changed "at least one incidence" to "two consecutive lab draws". The following explanation was presented in the study report of both studies for the change in the primary variable:

> "Although a patient was dose reduced upon a single incidence of hypercalcemia for safety purposes, two consecutive instances of hypercalcemia were chosen as an elevation endpoint for analysis, to better approximate the clinical scenario of hypercalcemia upon which most dosing changes for Calcijex [active control] are actually based. The same rationale led to choosing two weeks of Ca x P > 75 as evidence of clinically significant product elevation."
>
> Submission received Oct. 22, 1997, Volume 1, p. 48

Recall that the protocols of both studies stated that the patients would be dose reduced upon a single incidence of hypercalcemia. Protocol amendment #9 in Study 28 (approved February 24, 1997, mid-way through the trial) stated that a patient was considered to have completed the study upon a single incidence of hypercalcemia.[1] Several patients in both trials had two consecutive instances of hypercalcemia even though the dose was reduced after one incidence of hypercalcemia and after February 24, 1997 patients in Study 28 completed the study after a single incidence. Two reasons account for this phenomenon:

1) the blood levels of a patient at a certain visit were seen by the physician at the next visit; and
2) blood was drawn before the patient was dosed.

[1] Protocol Amendment #9 in Study 28 changed the action taken when a patient had one instance of hypercalcemia from a dose reduction to treatment discontinuation. It would appear that this amendment would interfere with the results of the analysis of the endpoint "hypercalcemic for at least 2 consecutive lab draws" because if a patient is discontinued after one instance of hypercalcemia, the probability of the patient achieving two instances is greatly reduced. (The probability is not zero because of the explanation in footnote 2 on page 9.) However, this amendment did not affect the results of the trial because only 1 patient (#2303) became hypercalcemic after the amendment was implemented. Patient #2303 was hypercalcemic on April 8th and at the follow-up visit on April 10th. This patient had *two consecutive instances* of hypercalcemia and was terminated on April 15th due to hypercalcemia. Since there were no other patients whose completion of the study was due to one instance of hypercalcemia (preventing them from having two consecutive instances later on in the trial), the amendment did not affect the results of the analyses presented in this review.

Therefore, blood was drawn *twice* before any action regarding dose reduction or completion of the study occurred.[2]

The primary variable was changed from that defined in the protocol based on the fact that the physician in the clinical setting would not have knowledge of the patient's hypercalcemia and/or elevated Ca x P level until after two instances had occurred.

The new definition upon which safety was based was, "patient became hypercalcemic for at least two consecutive lab draws and/or had a Ca x P product > 75 for at least one period of four consecutive lab draws." The company also presented the results of five more definitions, *post-hoc*. The results of all seven analyses are presented in Table 4.

Table 4: Supplemental Safety Studies 28 and 34

Definition	Study 28 19-NOR n=110	Study 28 Calcijex (Comparator) n=114	Study 28 p-value	Study 34 19-NOR n=98	Study 34 Calcijex (Comparator) n=99	Study 34 p-value
PROTOCOL-CORRECT						
1	67 (60.9%)	74 (64.9%)	0.581*	77 (78.6%)	64 (64.6%)	0.040
POST-HOC						
2	[illegible]	[illegible]	[illegible]	31 (31.6%)	32 (32.3%)	>0.999
3	25 (22.7%)	26 (22.8%)	>0.999	27 (27.6%)	17 (17.2%)	0.089
4	9 (8.2%)	14 (12.3%)	0.381	8 (8.2%)	8 (8.1%)	>0.999
5	0 (0.0%)	5 (4.4%)	0.060	4 (4.1%)	6 (6.1%)	0.747
6	63 (57.3%)	67 (58.8%)	0.892	72 (73.5%)	58 (58.6%)	0.035
7	14 (12.7%)	25 (21.9%)	0.079	26 (26.5%)	26 (26.3%)	>0.999

* Reviewer Analysis. The sponsor did not present the results of this analysis.
All p-values are from a Fisher's Exact test.

Definitions, where hypercalcemic is defined as having a normalized serum calcium > 11.5 mg/dL:

1. Hypercalcemic and/or had a Ca x P > 75 at least once during treatment **(protocol-correct).**
2. Hypercalcemic for at least 2 consecutive lab draws and/or had a Ca x P > 75 for at least one period of four consecutive lab draws **(analysis sponsor emphasized in NDA).**
3. Hypercalcemic for at least one lab draw.
4. Hypercalcemic for at least one period of two consecutive lab draws.
5. Hypercalcemic at the final lab draw.
6. Ca x P > 75 for at least one lab draw.
7. Ca x P > 75 for at least one period of four consecutive lab draws.

[2] For example, blood drawn on visit 1 would be seen at visit 2. Blood drawn on visit 2 would be seen at visit 3. Suppose a patient was hypercalcemic at visits 1 and 2. The lab results from visit 1 (seen at visit 2) showed hypercalcemia. The doctor would draw blood at visit 2, then dose the patient with a reduced dose. Laboratory results of the blood drawn at visit 2, (before the dose was reduced) was seen by the physician at visit 3 and showed hypercalcemia for the second time. Therefore, the patient was hypercalcemic at visits 1 and 2, and dose reduced at visit 2 - altering the results of visit 3 (not visit 2). Patients who completed the study after a single instance of hypercalcemia also had the opportunity to exhibit two consecutive instances of hypercalcemia. For example, suppose a patient was hypercalcemic at visit 7 and 8. The blood sample from visit 7 (seen by the physician at visit 8) showed hypercalcemia. The patient would discontinue medication immediately and the blood sample from visit 8 (seen later in the week after the patient discontinued) showed hypercalcemia also. Therefore, the patient was discontinued after one instance of hypercalcemia, but actually experienced two instances of hypercalcemia (and was on the same dose for both episodes).

Reviewer Comment

If one considers all seven definitions of elevated calcium and calcium x phosphorous product, 19-NOR appears to be superior in Study 28, and the comparator appears to be superior in Study 34. As was the case with the efficacy variable in Studies 35, 36, and 37 (see statistical review, February 23, 1998), there are numerous ways to alter the definition stated in the protocol. However, unlike the efficacy variable in Studies 35, 36, and 37, ***the primary variable in Studies 28 and 34 was explicitly stated in the objectives of the protocols, and it remained unchanged until after the blind was broken.*** *Also, unlike the results of Studies 35, 36 and 37, the various post-hoc analyses did not, in general, reach similar conclusions. Furthermore, the sponsor argued to change the primary analysis because dosing changes are made after two instances of hypercalcemia have already occurred (due to a delay of information). It is true that dose reductions are not made until the physician has results of two visits, however, the relationship between the sponsor's argument and the objective of the study has not been made. The objective of the study was to determine if hypercalcemia (and/or Ca x P product level) is lower in patients receiving 19-NOR than in patients receiving Calcijex. Dosing changes may occur after two instances of elevated Ca and/or Ca x P level, but hypercalcemia (and/or elevated Ca x P level) occurs after just one instance. The physician's knowledge of the patient's hypercalcemia is delayed by one visit, therefore the dose reduction is also delayed, but the hypercalcemia is nevertheless present after only one instance. The delay of information does not negate the facts. In Study 34, the percentage of patients with hypercalcemia (and/or elevated Ca x P level) was statistically significantly greater in the 19-NOR group.*

Since the definitions of success of analyses #2-7 were defined after breaking the blind of both studies, (and in the absence of a plausible argument for changing the primary analysis), the results of the protocol-specified definition (analysis #1 in Table 4), should be used as the basis for assessing safety. Thus, the results of Study 28 (using the preliminary subset of patients who completed the study) demonstrate that there was no statistically significant difference found between the two groups; the results of Study 34 demonstrate that the incidence of elevated Ca and/or Ca x P levels was statistically significantly greater in the 19-NOR group.

It is noteworthy to mention that the sponsor's analyses yield very different results across the two studies. The results of analyses #2, 5 and 7 in Study 28 appear to favor 19-NOR. However, these same analyses in Study 34 do not detect any difference between the two treatment groups. The results of analyses #1, 3, and 6 favor Calcijex in Study 34, whereas in Study 28 the same analyses show either a slight advantage for 19-NOR or no difference between the treatment groups. The disparate results of the analyses may demonstrate the weakness of analyzing continuous variables using categorical methods (Fisher's Exact Test). The variables, Ca and Ca x P product level, are continuous and perhaps they should be analyzed as continuous variables. Testing differences between means of variables is one such way to analyze continuous data. The differences in mean changes from baseline of the variables, (presented and graphed on pages 5-7), were not statistically significantly different in either of the two studies.

3 Conclusions and Labeling Recommendations

3.1 Conclusions of Active-Controlled Studies 28 and 34

The results of Study 34 demonstrate that the incidence of elevated Ca and/or Ca x P levels, as defined in the protocol, was statistically significantly *greater* in the 19-NOR group (the study was expected to show the opposite). The results of the preliminary analysis of Study 28 found no statistically significant difference between the two groups for the primary variable, as defined in the protocol. The sponsor presented results of a different analysis as evidence that Study 28 (using the subset of patients that completed) demonstrated statistical significance in favor of 19-NOR; however, this was a *post-hoc* analysis and should be viewed as descriptive, not confirmatory. In the context of the descriptive statistics, the primary, protocol-correct analyses, and the *post-hoc* analyses of both the preliminary data of Study 28 and the completed data of Study 34, the sponsor has not demonstrated that the incidence of hypercalcemia in patients receiving 19-NOR is lower than that in patients receiving Calcijex.

3.2 Labeling Recommendations

The label states that "Studies in patients with chronic renal failure show that Trade Name suppresses PTH levels while maintaining a lower calcemic and phosphatemic profile than calcitriol." The studies that the sponsor submitted to support this claim (28 and 34) do not demonstrate that 19-NOR maintains a lower calcemic and phosphatemic profile than Calcijex (intravenous calcitriol). In fact, the only completed study comparing the two drugs (Study 34), shows that calcitriol is statistically significantly superior to 19-NOR in maintaining a lower incidence of elevated calcium and/or elevated Ca x P product level. Therefore, the label should not state that 19-NOR maintains a lower calcemic and phosphatemic profile than Calcijex.

/S/ 3/20/98

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cc:
Orig. NDA 20-819
HFD-510 / Division File
HFD-510 / SSobel, GTroendle, LLutwak, DHedin
HFD-715 / Chron, division file
HFD-715/ BElashoff, JMele

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

FEB 23 1998

Date:

NDA#:	20-819
Applicant:	Abbott Labs
Name of Drug:	Capthrol [tradename] Paracalcin Injection / Paricalcitol Injection [generic name] (1α, 3β, 7E, 22E) -19-nor-9,10,-secoergosta-5,7,22-triene-1,3,25-triol abbreviated as 19-NOR
Indication:	Prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism encountered with chronic renal failure
Documents Reviewed:	2-10-97 Vol. 1-74; 6-16-97 electronic data
Statistical Reviewer:	Barbara Elashoff, M.S. (HFD-715)
Medical Input:	Leo Lutwak, M.D. (HFD-510)

Summary

The sponsor submitted three double-blind, placebo-controlled, randomized, multi-center studies (Studies 35, 36, and 37) to support the efficacy of 19-NOR in chronic renal failure patients on hemodialysis and two studies (28 and 34) to support safety. The three efficacy studies had identical protocols and were carried out at the same time (March to September, 1996). In each study, there was a four-week pre-treatment phase (washout/baseline) and a twelve-week treatment phase. The study drug was administered intravenously, three times weekly. The starting dose was 0.04 mcg/kg and increased every two weeks, until the clinical objective was met or after a maximum of five dose escalations, (potentially increasing to a maximum of 0.24 mcg/kg). The intact parathyroid hormone molecule (iPTH) levels were measured weekly for twelve weeks. A follow-up examination was performed 44 hours after the final dose (for both completers and dropouts). The protocols defined efficacy as, "a 30% decrease from baseline in a patient's iPTH level," but did not specify a statistical analysis. Each study report analyzed three different definitions of success on a patient by patient basis as follows:

1. *at least one visit with a 30% decrease in iPTH;*
2. *a 30% decrease in iPTH for four "consecutive" visits; and*
3. *a 30% decrease in iPTH at the final visit (follow-up visit).*

A Fisher's Exact test was used to analyze the differences in success rates between treatments. The results were consistently statistically significant across definitions for Study 35, but analysis 1 did not show statistically significant results for Studies 36 and 37, and analysis 2 did not show statistically significant results for Study 37. The protocol definition could be interpreted many different ways, however several of these ways ignore the iPTH levels at the end of the trial. Each definition has advantages and disadvantages, but because the protocol was not specific, all are post-hoc. Of the three definitions the sponsor proposed, the reviewing medical officer prefers the one that provides information of duration of effect over more than one visit (#2). The reviewing medical officer suggested a slight modification of this analysis, "a 30% decrease at 3 consecutive visits and at the final visit", to insure that the iPTH levels at the end of the study were incorporated also. The proportions of patients who achieved success using this modified variable was statistically significantly greater in the 19-NOR group in all three studies.

The medical officer for this drug requested an analysis that combined the three studies. The results of the combined analysis demonstrate a statistical difference between the two treatment groups for the

sponsor's three post-hoc endpoints and the post-hoc endpoint requested by the reviewing medical officer.

The sponsor submitted two additional studies (28 and 34) to support the claim that 19-NOR has a better safety profile than intravenous calcitriol, specifically, that the incidence rate of hypercalcemia is lower. Studies 28 and 34 are summarized and reviewed in another document.

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Reviewer Note

The placebo-controlled studies (35, 36 and 37) were submitted in February 1997. The drug (1α, 3β, 7E, 22E) -19-nor-9,10,-secoergosta-5,7,22-triene-1,3,25-triol was abbreviated and identified as 19-NOR and sometimes as Paracalcin Injection. The United States Adopted Name (USAN) council rejected the name Paracalcin Injection. The active-controlled studies, (28 and 34) were submitted in October 1997. 19-NOR was identified as Paricalcitol Injection in these two studies, rather than Paracalcin Injection. According to the October 1997 submission, 19-NOR, is "now known as "paricalcitol" when referring to bulk drug, "Paricalcitol Injection" when referring to the generic name of the finished product and "Capthrol" when referring to the tradename of the finished product." This review refers to the drug as either "active drug" or "19-NOR".

Review of Placebo-Controlled Clinical Trials

1 Introduction

Table 1 below summarizes the three placebo-controlled studies completed by the sponsor. The studies were double-blind, randomized, parallel designs in patients with Renal Osteodystrophy. All of the studies had 2 arms (placebo injection and 19-NOR injection). After a four-week pre-treatment baseline/washout phase, patients were randomized to receive treatment for 12 weeks. The studies assessed iPTH[1] levels in the blood. The iPTH levels were measured weekly (before dosing) for the 12-week treatment period. The dose of the 19-NOR or placebo injection was variable, depending on the

[1] IPTH: Intact parathyroid hormone is the measurable biologically active PTH in the blood or serum.

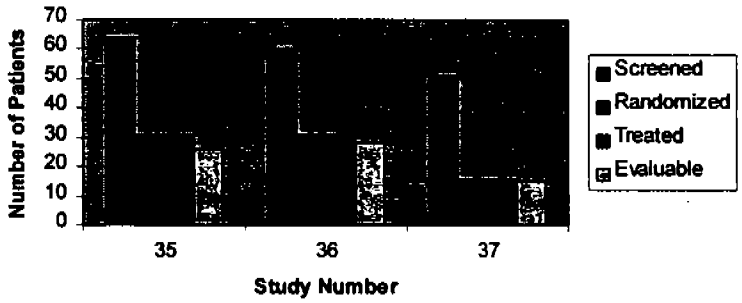
iPTH response from the previous two weeks. During the treatment phase, potential dose increases occurred every two weeks until the clinical objective was met or for a maximum of five dose escalations. The starting dose was 0.04 mcg/kg and potentially increased to a maximum of 0.24 mcg/kg, depending on the iPTH response. It was administered intravenously, three times weekly, at the end of each regular hemodialysis (HD) session through the patient's HD access site. The proposed labeling reflects this dose escalation strategy. After the last dose, the patient returned within 44 hours for a follow-up visit. The follow-up visit was used as the "final visit" for the third primary efficacy variable. If a patient did not return, the value of iPTH at the last visit the patient was seen was used for the final visit. A total of six patients in the three studies combined (all on active treatment) did not return for the follow-up visit. These patients are discussed in more detail in Section 1.3, page 5.

Table 1: Primary Efficacy Studies

Study	Dates Conducted	Study Arms (dosing)	# of sites	Duration of treatment	Number Randomized
35	3/96-9/96	placebo 19-NOR	4 (San Antonio, TX; Galveston, TX; 2 in New Orleans, LA)	12 wks	31
36	3/96-9/96	placebo 19-NOR	3 (Tampa, FL; New Orleans, LA; St. Louis, MO)	12 wks	31
37	3/96-9/96	placebo 19-NOR	4 (Baltimore, MD; Washington, D.C.; Lawrenceville, GA; Ann Arbor, MI)	12 wks	16

Figure 1 below is a barchart of the number of patients screened, randomized, treated and "evaluable" (protocol-correct) in each study. All randomized patients were treated.

Figure 1: Summary Chart of Patient Activity



1.1 Incorrect Treatments Given

Study 37 had a problem with randomization and/or careless conduct.

"Of the 4 sites where Study 95037 was conducted, patients at the University of Michigan Medical Center (Site 4, Patients 401-408) appeared to have had a discrepancy in their dosage schedule. Of the patients that were to receive placebo, all 4 (Patients 403, 404, 405, and 406) had measurable paracalcin concentrations consistent with having received paracalcin rather than placebo. Of the other 4 patients at this site that were to receive paracalcin (Patients 401, 402, 407, and 408), all 4 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 [19-NOR] 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 Site 4, Study 95037."

2-10-97 submission; Volume 53, p. 21

There is no mention in the study report as to when the mistake was discovered. The sponsor theorized that the incorrect treatments had been given and analyzed all eight patients as though they had received the opposite treatment to which they had been assigned. Therefore the intent-to-treat population throughout the study report referred to the patients with the treatment they supposedly received, rather than the treatment to which they had been *assigned.* This reviewer conducted analyses on the patients using the treatment to which they were assigned (not presented here). The conclusions were different than the sponsor's conclusions. The results were not statistically significantly different between treatment groups. The analyses presented in this review are the sponsor's analyses using the treatment actually received by the patient, not the treatment to which the patient was assigned.

Reviewer Comment

There were only sixteen patients in Study 37, therefore changing the treatment assignments of eight of those patients was a significant modification. However, as will be seen in Section 2.2 page 9, the results from Study 37 using the opposite treatments (the sponsor's analyses) are merely supportive evidence of efficacy. The randomization process in Studies 35 and 36 (studies with strong results) did not have the same problem. Thus, while the carelessness of the trial conduct in Study 37 detracts from the confidence of the conclusions drawn, the problem was not found in Studies 35 and 36, the larger and more conclusive studies.

1.2 Baseline Demographics

The sponsor's analyses of demographic data indicated that the treatment groups within each study were balanced with respect to gender frequencies, race and mean age, height, and weight. A summary of patient demographics for all treated patients is presented in Table 2 below. Study participants were primarily black. End-stage renal disease occurs as a consequence of uncontrolled hypertension and/or uncontrolled diabetes, conditions more common in African-Americans than in Caucasians.

Table 2: Demographics for All Treated Patients

Study Number Treatment Total N	35 Active n=16	Placebo n=15	36 Active n=16	Placebo n=15	37 Active n=8	Placebo n=8
Gender						
-Male	8 (50)	8 (53)	9 (56)	7 (47)	4 (50)	4 (50)
-Female	8 (50)	7 (47)	7 (44)	8 (53)	4 (50)	4 (50)
Race						
-Caucasian	3 (19)	0 (0)	1 (6)	3 (20)	0 (0)	3 (38)
-Black	12 (75)	10 (67)	15 (94)	12 (80)	8 (100)	5 (63)
-Hispanic	1 (6)	5 (33)	0 (0)	0 (0)	0 (0)	0 (0)
Age (years)						
-mean ± s.d.	54.8 ± 15.5	55.0 ± 13.3	54.6 ± 14.2	54.5 ± 16.3	53.3 ± 14.5	48.7 ± 18.9
-range						
Height (cm)						
-mean ± s.d.	169.4 ± 11.7	169.3 ± 15.2	169.7 ± 12.3	169.9 ± 10.9	169.2 ± 9.9	163.5 ± 14.2
-range						
Weight (kg)						
-mean ± s.d.	85.5 ± 16.6	80.3 ± 15.8	79.4 ± 20.9	76.0 ± 23.2	75.1 ± 11.9	70.4 ± 18.0
-range						

Reviewer Comment

The sponsor did not perform any subgroup analyses. The responses to treatment and placebo were tabulated for gender and age subgroups in Sections 2.4 and 2.5. The study was not diverse enough racially to perform a subgroup analysis on race.

1.3 Dropouts

The individual patient profiles of the entire 12-week treatment period are presented graphically in Appendix A. The graphs show the iPTH levels plotted over time. The iPTH level measured at Visit 1 was the baseline value (denoted as "B" below the patient's graph). The patient was dosed for the last time at Visit 12 and measured within 44 hours for the "final" or "follow-up" visit (denoted as "F" below the patient's graph). The gray area on each graph is the area which is at least 30% below the patients baseline iPTH value; therefore the gray area is different for each patient. The graphs show numbers of missed visits for each patient (denoted as "M" below the patient's graph) and number of instances the patients' iPTH levels fell to 30% below their baseline value (denoted as bold squares inside the gray area). The graphs with squares drawn around them identify the patients who had at least one instance of a 30% decrease in iPTH level.

The analyses did not account for missed visits. All patients (whether they completed the study or not) were used in all the analyses. In the "final visit" analysis for patients without follow-up visits, data from the last visit were used for the "final visit". Only five patients did not have a follow-up visit (3 in Study 35 and 2 in Study 36). All five were on active treatment. Two of these five patients without the follow-up visit completed twelve weeks of the study.

The percent of patients who did not complete Visit 12 was balanced across treatment groups in Studies 35 and 37 (See Table 3 below).

Table 3: Dropout Rates

Dropouts: Patients who did not complete Visit 12

Study		Active	Placebo
35	Randomized	16	15
	6 week completers	15	14
	12 week completers	12	11
	# (%) of dropouts	4 (25.0)	4 (26.7)
36	Randomized	16	15
	6 week completers	14	15
	12 week completers	13	14
	# (%) of dropouts	3 (18.8)	1 (6.7)
37	Randomized	8	8
	6 week completers	6	8
	12 week completers	5	5
	# (%) of dropouts	3 (37.5)	3 (37.5)

The sponsor identified 13 patients as premature discontinuations. It appears as though the sponsor considered any patient who completed either the twelfth visit *or* the tenth visit plus the follow-up visit as a completer. Table 4 lists all patients who did not complete the 12th visit or did not have a follow-up visit.

Table 4: Patients who did not complete the 12th visit or did not have a follow-up visit

Study	Treatment	Patient	Last Visit	Reason	Follow Up Visit?
35	active	108	3	Death	
		109	12	Not considered a dropout by sponsor, thus no reason given	
		303	12	Not considered a dropout by sponsor, thus no reason given	
		306	6	Elevated Ca x P Product	√
		403	9	iPTH value < 100	√
		406	8	Elevated Ca	√
	placebo	304	8	Elevated Ca x P Product	√
		305	11	Not considered a dropout by sponsor, thus no reason given	√
		409	9	Failing health	√
		410	2	Missed 3 consecutive doses	√
36	active	108	2	Sickle cell nephropathy	
		301	1	Randomized with iPTH level below inclusion criteria	√
		313	9	Moved	
37	active	101	11	Not considered a dropout by sponsor, thus no reason given	√
		102	5	Adverse Event: Impotence	√
		203	2	Missed 3 consecutive doses	√
	placebo	204	8	Elevated Ca x P Product	√
		205	10	Not considered a dropout by sponsor, thus no reason given	√
		301	10	Not considered a dropout by sponsor, thus no reason given	√

Reviewer Comment

Defining dropouts as patients without visit 12 data, the dropout rate was balanced across treatment groups in Studies 35 and 37. Study 36, however, only had four dropouts, three of which were in the 19-NOR group. Two of these three patients dropped out early in the study (visits 1 and 2). The impact the differential dropout rate had on the efficacy results was to possibly reduce the treatment effect because the three 19-NOR patients were counted as "failures" and the one placebo dropout was a success.

2 Efficacy Results

2.1 Descriptive Statistics

The values of iPTH and Percent Change From Baseline were skewed to the right, thus the median and 25th and 75th percentiles are more appropriate measures of the middle and the spread of the data than the mean and standard deviation. These descriptive statistics are presented in Table 5. Boxplots with 95% confidence intervals around the medians are presented in Figures 2-8. Additionally, the sponsor provided graphs of the weekly mean percent changes in iPTH levels for each treatment group (see Appendix B).

Table 5: Medians, Means, 25th and 75th Percentiles of Baseline iPTH, Final Visit iPTH, and Percent Change from Baseline iPTH

				19-NOR				Placebo	
Study		Median	Mean	25th Percentile	75th Percentile	Median	Mean	25th Percentile	75th Percentile
35	Baseline	775.0	786.8	497.5	1016.5	1003.0	1025.3	739.5	1275.0
	Final	163.5	391.8	118.5	504.0	683.5	892.0	485.0	1337.5
	% Change	-67.2	-59.4	-82.1	-48.6	-31.7	-18.1	-34.6	-7.8
36	Baseline	576.5	741.5	358.5	877.5	671.0	654.6	475.0	705.0
	Final	226.5	435.4	135.5	638.0	507.0	585.9	441.0	689.0
	% Change	-58.2	-48.1	-64.8	-29.9	-11.4	-8.4	-32.2	-2.0
37	Baseline	804.5	870.9	604.0	1030.5	614.0	686.7	468.0	728.0
	Final	189.0	365.5	113.0	504.5	524.0	650.1	434.0	841.0
	% Change	-73.9	-64.8	-80.9	-49.2	-12.7	0.7	-22.2	35.7

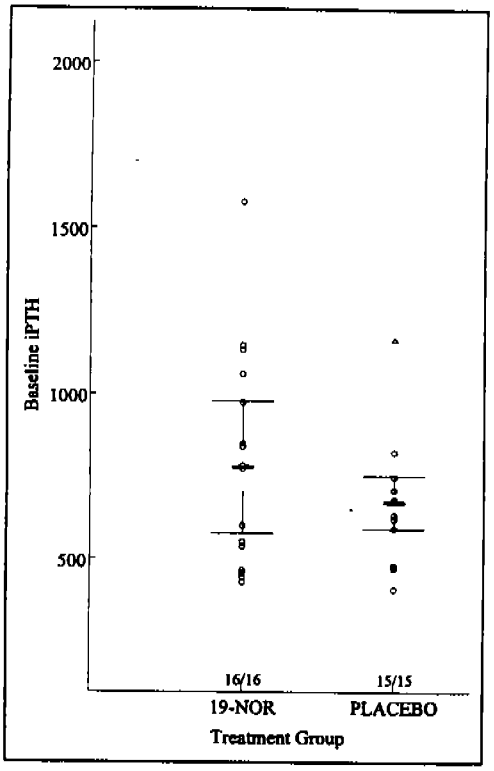
Reviewer Comment

In all three studies, the final visit data (Table 5 and Figures 2-8) and the sponsor's graphs (Appendix B) all illustrate a larger reduction in iPTH for the 19-NOR treatment group compared to placebo.

Figures 2-8: Boxplots and 95% Confidence Intervals Around Medians

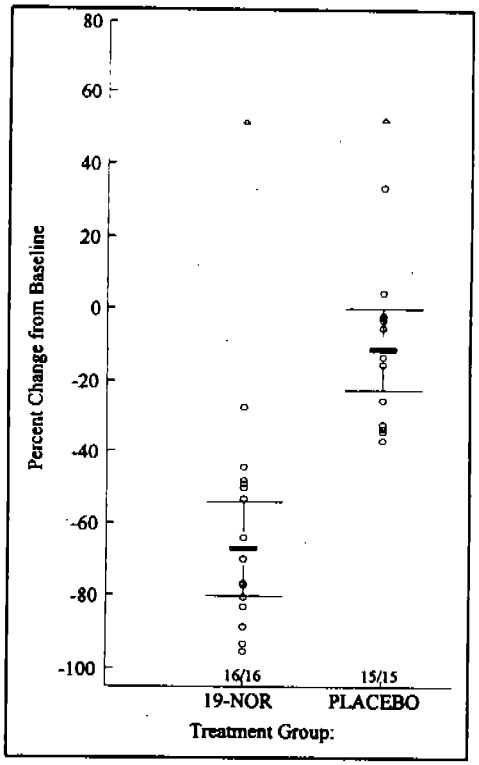
STUDY 35

Baseline iPTH by Treatment Group



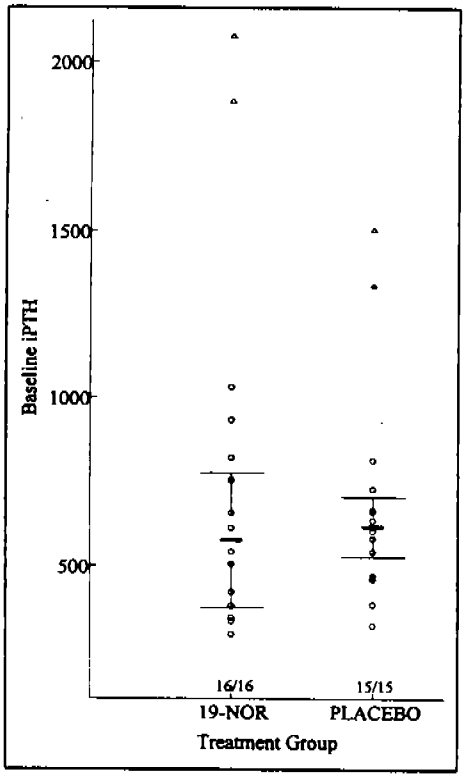
STUDY 35

Percent Change From Baseline of iPTH at Final Visit by Treatment Group



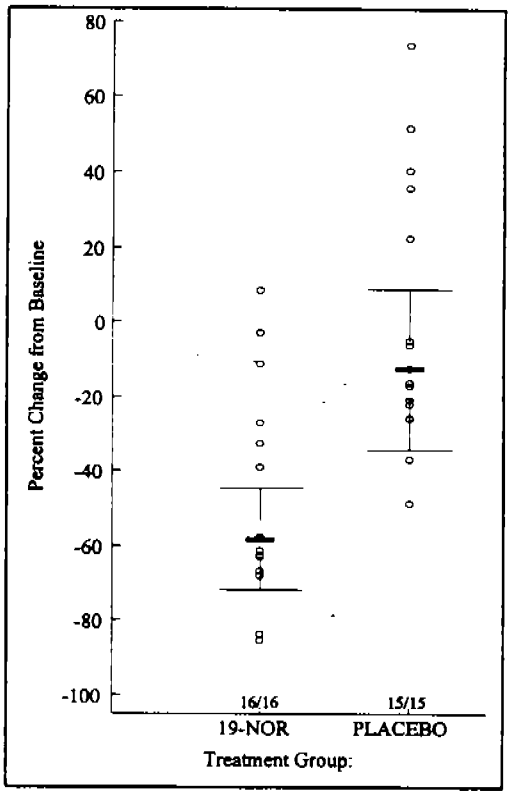
STUDY 36

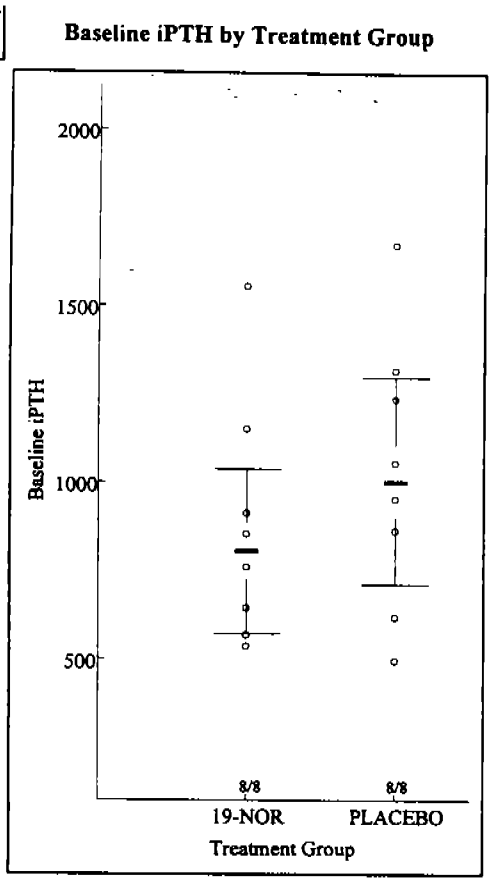
Baseline iPTH by Treatment Group

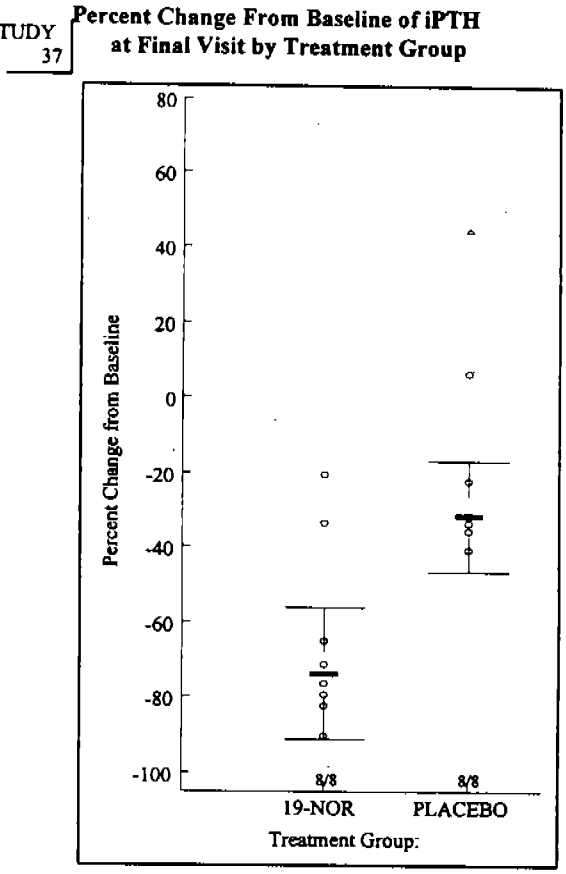


STUDY 36

Percent Change From Baseline of iPTH at Final Visit by Treatment Group







2.2 Primary Efficacy Variable

Recall that in the study reports the sponsor identified *post-hoc* three definitions of success as being relevant for a comparison of efficacy between active and placebo patients,:

1. at least one visit with a 30% decrease in iPTH;
2. a 30% decrease in iPTH for four "consecutive" visits[2]; and
3. a 30% decrease in iPTH at the final visit[3].

A Fisher's Exact Test was performed on these three definitions. Study 35 showed a statistically significant difference between the two treatment groups for all three analyses, Study 36 for the latter two, and Study 37 for the decrease sustained over four consecutive visits (see Table 6 below). The sponsor's overall conclusions emphasized the analysis of "four consecutive decreases", to be the most relevant:

> "A 30 percent decrease sustained over more than one observation (we chose four consecutive values) was considered a clinically relevant improvement that avoided random variation and potential errors in the handling of samples that could lead to isolated reductions in iPTH (e.g., samples not centrifuged, not separated, and/or frozen incorrectly can result in iPTH degradation *ex vivo*.)"
>
> 2-10-97 submission; Volume 48 p.100

[2] Four consecutive visits with measurements. This sometimes encompassed more than four visits if some visits had missing values.

[3] Final visit was defined as the follow-up visit. If the patient did not return for the follow-up visit, the last visit the patient was seen was used instead.

Of the three definitions of success that the sponsor proposed, the reviewing medical officer preferred the one that provides information of duration of effect over more than one visit (#2). The reviewing medical officer suggested a slight modification of this definition to insure that the iPTH levels at the end of the study are incorporated also. The proportions of patients achieving success using this modified definition, "a 30% decrease at 3 consecutive visits and at the final visit", was statistically significantly different between the two treatment groups in all three studies.

Table 6: Results of All treated Patients

	35					36				
	Active n=16	Placebo n=15	Trt Effect (Diff in %)	Estimated RR	p-value	Active n=16	Placebo n=15	Trt Effect (Diff in %)	Estimated RR	p-value
At least one 30% Decrease	15/16 (93.8)	8/15 (53.3)	40.5	1.8	[redacted]	13/16 (81.3)	9/15 (60.0)	21.3	1.4	0.252
4 consecutive	11/16 (68.8)	0/15 (0.0)	68.8	Not app*	[redacted]	10/16 (62.5)	2/15 (13.3)	49.2	4.7	[redacted]
30% Decrease at Final Visit	14/16 (87.5)	4/15 (26.7)	60.8	3.3	[redacted]	12/16 (75.0)	2/15 (13.3)	61.7	5.6	[redacted]
3 consecutive AND a 30% Decrease at Final Visit	11/16 (68.8)	0/15 (0.0)	68.8	Not app*	[redacted]	11/16 (68.8)	2/15 (13.3)	55.5	5.2	[redacted]

	37				
	Active n=8	Placebo n=8	Trt Effect (Diff in %)	Estimated RR	p-value
At least one 30% Decrease	7/8 (87.5)	6/8 (75.0)	12.5	1.2	>0.999
4 consecutive	6/8 (75.0)	1/8 (12.5)	62.5	6.0	[redacted]
30% Decrease at Final Visit	7/8 (87.5)	5/8 (62.5)	25.0	1.4	0.569
3 consecutive AND a 30% Decrease at Final Visit	6/8 (75.0)	1/8 (12.5)	62.5	6.0	[redacted]

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* An relative risk ratio cannot be calculated when one or more cells of the table are equal to zero.
The relative risk (RR) indicates the likelihood of achieving success in the active group relative to those in the placebo group. For example, in Study 35, using the first definition of success (at least one 30% decrease), the estimated RR equals 1.8, indicating that the patients in the active group are 1.8 times as likely to achieve success as the placebo patients.

Reviewer Comment

The primary efficacy endpoint was not explicitly defined in the protocol, therefore all analyses performed on these data are post-hoc. *All the definitions of success that the sponsor proposed have advantages and disadvantages. A difference in proportions of the patients achieving success on the first two definitions is inconclusive in determining how the drug performs over twelve weeks because the iPTH levels could drop and then rise again. The third interpretation of the protocol definition of success relies on only one measurement. Since measurement error is high for iPTH levels, inferences drawn from analyses dependent on one measurement are inconclusive as well. Of the three analyses the sponsor proposed, the reviewing medical officer prefers the one that provides information of duration of effect over more than one visit (#2), with a slight modification: "3 consecutive decreases*

and a decrease at the final visit".[4] *In view of the fact that any analysis performed on these data is* post-hoc, *this review will base efficacy on the reviewing medical officer's preferred definition. The difference in the proportions of success (of this definition) between active and placebo treatments was statistically significant at the 0.05 α-level in all three studies (Table 6).*

Since the sponsor provided no rationale for performing the three post-hoc analyses, it seemed reasonable to this reviewer to perform additional analyses varying the number of timepoints showing a 30% decrease and varying the number of consecutive decreases (Table 7). In general, the results of these analyses consistently favor 19-NOR over placebo and illustrate the robustness of the primary analyses.

Table 7: Results of All treated Patients

	35			36			37		
	Active n=16	Placebo n=15	p-value	Active n=16	Placebo n=15	p-value	Active n=8	Placebo n=8	p-value
At least one 30% Decrease*	15/16 (93.8)	8/15 (53.3)	[illegible]	13/16 (81.3)	9/15 (60.0)	0.252	7/8 (87.5)	6/8 (75.0)	>0.999
At least 2	12/16 (75.0)	4/15 (26.7)	[illegible]	13/16 (81.3)	7/15 (46.7)	0.0660	7/8 (87.5)	4/8 (50.0)	0.2820
At least 3	12/16 (75.0)	3/15 (20.0)	[illegible]	13/16 (81.3)	4/15 (26.7)	[illegible]	6/8 (75.0)	2/8 (25.0)	0.1320
At least 4	11/16 (68.8)	3/15 (20.0)	[illegible]	12/16 (75.0)	2/15 (13.3)	[illegible]	6/8 (75.0)	2/8 (25.0)	0.1320
At least 5	11/16 (68.8)	2/15 (13.3)	[illegible]	12/16 (75.0)	2/15 (13.3)	[illegible]	6/8 (75.0)	1/8 (12.5)	[illegible]
At least 6	10/16 (62.5)	0/15 (0.0)	[illegible]	10/16 (62.5)	1/15 (6.7)	[illegible]	5/8 (62.5)	1/8 (12.5)	0.1190
At least 7	8/16 (50.0)	0/15 (0.0)	[illegible]	7/16 (43.8)	1/15 (6.7)	[illegible]	5/8 (62.5)	1/8 (12.5)	0.1190
;ast 8	7/16 (43.8)	0/15 (0.0)	[illegible]	6/16 (37.5)	1/15 (6.7)	0.0830	5/8 (62.5)	0/8 (0.0)	[illegible]
At least 9	7/16 (43.8)	0/15 (0.0)	[illegible]	6/16 (37.5)	1/15 (6.7)	0.0830	3/8 (37.5)	0/8 (0.0)	0.2000
2 consecutive	11/16 (68.8)	3/15 (20.0)	[illegible]	13/16 (81.3)	4/15 (26.7)	[illegible]	7/8 (87.5)	1/8 (12.5)	[illegible]
3 consecutive	11/16 (68.8)	0/15 (0.0)	[illegible]	11/16 (68.8)	2/15 (13.3)	[illegible]	6/8 (75.0)	1/8 (12.5)	[illegible]
4 consecutive*	11/16 (68.8)	0/15 (0.0)	[illegible]	10/16 (62.5)	2/15 (13.3)	[illegible]	6/8 (75.0)	1/8 (12.5)	[illegible]
5 consecutive	8/16 (50.0)	0/15 (0.0)	[illegible]	10/16 (62.5)	2/15 (13.3)	[illegible]	6/8 (75.0)	1/8 (12.5)	[illegible]
6 consecutive	6/16 (37.5)	0/15 (0.0)	[illegible]	8/16 (50.0)	1/15 (6.7)	[illegible]	4/8 (50.0)	1/8 (12.5)	0.2821
7 consecutive	4/16 (25.0)	0/15 (0.0)	0.101	4/16 (25.0)	1/15 (6.7)	0.3326	4/8 (50.0)	0/8 (0.0)	0.0769
8 consecutive	4/16 (25.0)	0/15 (0.0)	0.101	2/16 (12.5)	0/15 (13.3)	[illegible]	4/8 (50.0)	0/8 (0.0)	0.0769
30% Decrease at Final Visit*	13/16 (81.3)	4/15 (26.7)	[illegible]	12/16 (75.0)	2/15 (13.3)	[illegible]	7/8 (87.5	5/8 (62.5)	0.569

* "Primary Efficacy Analyses" as specified in the study reports.

2.3 Secondary Efficacy Variables

The protocols did not identify any secondary efficacy variables. The only mention of variables other than the variable "30% decrease in iPTH" was as follows.

[4] Final visit was defined as the follow-up visit. If the patient did not return for the follow-up visit, the last visit the patient was seen was used instead. This is consistent with what the sponsor used for the variable, "30% decrease at the final visit".

"Statistically tested variables include demographic variables, total calcium concentration, Ca*P product, PTH, and incidence of hypercalcemia."

Protocol, p.27 (Volume 44, p.58)

Total Calcium Concentration, Ca x P and incidence of hypercalcemia are safety parameters. The sponsored provided results of the calcium, Ca x P product levels and incidence of hypercalcemia; these are presented in Section 2.7, Adverse Events. (The sponsor used the acronym "PTH" interchangeably with "iPTH".)

The study reports identified alkaline phosphatase (*post-hoc*) as, "an additional efficacy variable". (2-10-97 submission; Volume 43, p.68.) The reviewing medical officer confirmed that this was a useful measure of efficacy. Alkaline phosphatase was used as a marker for bone remodeling activity. 19-NOR patients in Studies 35 and 36 experienced a statistically significant reduction in alkaline phosphatase in comparison to placebo patients (Table 8 below). The change from baseline values were analyzed using a one-way ANOVA with treatment group as the only classification variable. In Studies 35 and 36, the placebo patients' levels increased on average, (20.8 units/liter in Study 35; 3.7 units/liter in Study 36), whereas the 19-NOR patients' levels decreased on average, (36.4 units/liter in Study 35; 50.4 units/liter in Study 36). In Study 37, the placebo treatment group average reduction was numerically superior to the 19-NOR treatment group average reduction, but the difference was not statistically significant.

Table 8: Results of Sponsor's Analyses on Secondary Efficacy Variable Alkaline Phosphatase

Study	Mean ± SE			p-value
	19-NOR	Placebo	Treatment Difference	
35	**n=14**	**n=15**		
Baseline	141.7 ± 106.3	113.9 ± 28.6		
Final	105.3 ± 69.6	134.7 ± 48.9		
Δ from Baseline	-36.4 ± 42.1	20.8 ± 24.8	-57.2 ± 12.7	<0.001
36	**n=12**	**n=12**		
Baseline	148.0 ± 145.9	123.8 ± 59.5		
Final	97.6 ± 82.4	127.4 ± 66.1		
Δ from Baseline	-50.4 ± 68.3	3.7 ± 46.1	-54.1 ± 23.8	0.033
37	**n=5**	**n=7**		
Baseline	176.4 ± 94.2	362.4 ± 307.7		
Final	142.2 ± 115.2	324.1 ± 256.9		
Δ from Baseline	-34.2 ± 30.3	-38.3 ± 122.9	4.1 ± 56.9	0.944

Some patients did not have both baseline and final values for this endpoint, thus the sample sizes are smaller than those in the tables of the primary endpoints.

2.4 Analyses of All Studies Combined

The reviewing medical officer, Dr. Lutwak, requested an analysis that combined all the studies. Since the designs of all three studies were identical, this reviewer performed a test of homogeneity (see Appendix C), combined the data and performed an exact analysis of the two-by-two tables for each of the three variables, stratified by study. The proportions of patients achieving a "success" was statistically significantly different between the two treatment groups for all four definitions of success.

Table 9: Results of All Studies Combined

	Active n=16	Placebo n=15	Trt Effect (Diff in %)	Estimated RR	p-value
At least one 30% Decrease	35/40 (87.5)	23/38 (82.1)	5.4	1.1	[redacted]
4 consecutive	27/40 (67.5)	3/38 (7.9)	59.6	8.5	[redacted]
30% Decrease at Final Visit	33/40 (82.5)	11/38 (28.9)	53.6	2.9	[redacted]
3 consecutive AND a 30% Decrease at Final Visit	28/40 (70.0)	3/38 (7.9)	62.1	8.9	[redacted]

The relative risk (RR) indicates the likelihood of achieving success in the active group relative to those in the placebo group. For example, in Study 35, using the first definition of success (at least one 30% decrease), the estimated RR equals 1.1, indicating that the patients in the active group are 1.1 times as likely to achieve success as the placebo patients.

2.5 Gender Analysis

A subgroup analysis on gender was performed to identify any differences in treatment effect between the genders. With the exception of the first variable (at least one 30% decrease), the results were consistent across genders.

Table 10: Results of the Studies Combined, for Males and Females

	Males				Females			
	Active n=21	Placebo n=19	Trt Effect (Diff in %)	Estimated RR	Active n=19	Placebo n=19	Trt Effect (Diff in %)	Estimated RR
At least one 30% Decrease	18/21 (85.7)	7/19 (36.8)	48.9	2.32	17/19 (89.5)	16/19 (84.2)	5.3	1.1
4 consecutive	13/21 (61.9)	1/19 (5.3)	56.6	11.7	13/19 (68.4)	2/19 (10.5)	57.9	6.5
30% Decrease at Final Visit	16/21 (76.2)	4/19 (21.1)	55.1	3.6	16/19 (84.2)	7/19 (36.8)	47.4	2.3
3 consecutive AND a 30% Decrease at Final Visit	12/21 (57.1)	1/19 (5.3)	51.8	10.8	16/19 (84.2)	2/19 (10.5)	73.7	8.0

The percentages of males with at least one 30% decrease were notably different between the two treatment groups (85.7% of active, 36.8% of placebo). However, among females, the percentages of success between the treatment groups were similar (89.5% of active, 84.2% of placebo). The differences in response were between the placebo groups, not the active groups. The active treatment groups responded similarly between males and females; however, the females on placebo had a greater response rate compared to the males on placebo.

Reviewer Comment

There were no notable differences in treatment effect across genders for three of the four endpoints.. The differences between the genders in response rates of the endpoint, "At least one 30% Decrease", do not appear to be due to differences in how the patients respond to the active treatment.

2.6 Age Analysis

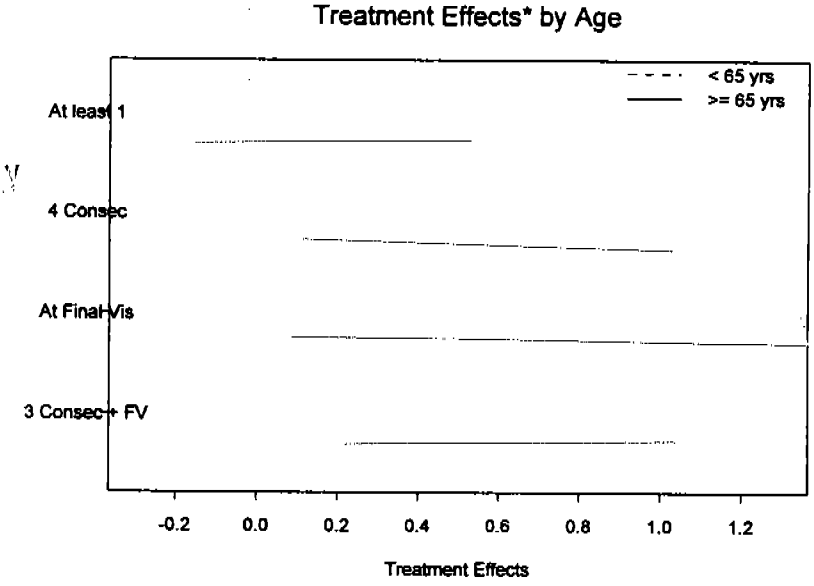
A subgroup analysis on age was performed to identify any differences in treatment effect between the genders. With the exception of the first analysis (at least one 30% decrease), the results were consistent across age groups. For the first analysis, it appeared that the older age

group had a greater chance of achieving the endpoint, regardless of treatment. However, the treatment effect of the older age group was similar to that of the younger patients for the other three endpoints (see Table 11 and Figure 11).

Table 11: Results of the Studies Combined, for Younger and Older Age Groups

	Age < 65				Age ≥ 65			
	Active n=30	Placebo n=30	Trt Effect (Diff in %)	Estimated RR	Active n=10	Placebo n=8	Trt Effect (Diff in %)	Estimated RR
At least one 30% Decrease	25/30 (83.3)	16/30 (53.3)	30.0	1.6	10/10 (100.0)	7/8 (87.5)	12.5	Not App*
4 consecutive	18/30 (60.0)	1/30 (3.3)	56.7	18.2	8/10 (80.0)	2/8 (25.0)	55.0	3.2
30% Decrease at Final Visit	23/30 (76.7)	7/30 (23.3)	53.4	3.3	10/10 (100.0)	4/8 (50.0)	50.0	Not App*
3 consecutive AND a 30% Decrease at Final Visit	19/30 (63.3)	1/30 (3.3)	60.0	19.2	9/10 (90.0)	2/8 (25.0)	65.0	3.6

Figure 11



* The treatment effects plotted in this figure are the treatment differences measured as *proportions*, not percentages, as reported in Table 11.

Reviewer Comment

There were no notable differences in treatment effect across age groups for three of the four endpoints.. The differences between the age groups in response rates of the endpoint, "At least one 30% Decrease", do not appear to be due to differences in how the patients respond to the active treatment.