2.7 Adverse Events

2.7.1 Summary

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

Table12: Incidence of Patients Reporting At Least One Adverse Event After Treatment Began

Study	Placebo	Active
35	14/15 (93%)	13/16 (81%)
36	10/15 (67%)	8/16 (50%)
37	6/8 (75%)	6/8 (75%)

2.7.2 Hypercalcemia

The effects of 19-NOR on calcium and a related laboratory parameter, calcium-phosphorous product levels (Ca x P), were examined for all patients. Hypercalcemia was defined as a calcium level of greater than 11.5 mg/dL. Values of Ca x P product level greater than 75 units were considered "elevated". The incidence of hypercalcemia was numerically, (but not statistically significantly), greater in the 19-NOR group in Study 35 (p=0.484). There was no incidence of hypercalcemia in Studies 36 or 37, in either treatment group. The incidence of elevated Ca x P product level was numerically, (but not statistically significantly), greater in the 19-NOR group in all three studies, (35: p= 0.083; 36: p=0.484; 37: p>0.999).

Table 13: Hypercalcemia and Elevated Ca x P Product Level

Variable	Study	Active	Placebo	p-values
Hypercalcemic at least once	35	2/16 (13%)	0/15 (0%)	0.484
	36	0/16 (0%)	0/15 (0%)	Not applicable
	37	0/8 (0%)	0/8 (0%)	Not applicable
Ca x P > 75 for 2 consec. lab draws	35	6/16 (38%)	1/15 (7%)	0.083
	36	2/16 (13%)	0/15 (0%)	0.484
	37	2/8 (25%)	1/8 (13%)	>0.999

3 Summary and Labeling Recommendations

3.1 Summary of Placebo-Controlled Studies 35, 36 and 37

The primary efficacy variable was not explicitly defined in any of the protocols, thus many different efficacy variables were available to the sponsor from which to choose (i.e., at least one 30% decrease, at least two 30% decreases, at least three 30% decreases, etc.) The sponsor presented the results of three variables in the study reports. Of the three variables the sponsor proposed, the reviewing medical officer preferred the one that provided 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". In view of the fact that any analysis performed on these data is *post-hoc*, efficacy was based on the reviewing medical officer's preferred definition of success. 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. In addition, the results of analyses of several other reasonable definitions of success favor 19-

NOR over placebo and illustrate the robustness of the primary analyses. Therefore, results of all three studies are evidence of efficacy of 19-NOR.

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3.2 Labeling Recommendations

The sponsor did not define a primary efficacy variable in the protocol, leaving open the prospect of choosing one after the blind was broken. This review has identified one variable as a reasonable interpretation of the broadly defined objective, "30% decrease in iPTH", upon which the evaluation of efficacy was made. The labeling should report the results of the studies using one endpoint. The endpoint should not be reported as showing statistical significance because statistical significance is not possible without a pre-specified endpoint. P-values should not be reported in the label either.

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/S/ 2-23-98

Barbara Elashoff VD
Mathematical Statistician

concur: Ms. Mele /S/ 2/23/98
Dr. Nevius /S/ 2/22/98

cc:
Orig. NDA 20-819
HFD-510 / Division File
HFD-510 / SSobel, GTroendle, LLutwak, DHedin
HFD-715 / Chron
HFD-715/ BElashoff, JMele, Biometrics Division 2

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Appendix A

The graphs below show the iPTH levels plotted over time. The individual patient profiles of the entire 12-week treatment period are presented for each treatment group in each study. 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 denote the patients who had at least one instance of a 30% decrease in iPTH level.

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pages of trade

secret and/or

confidential

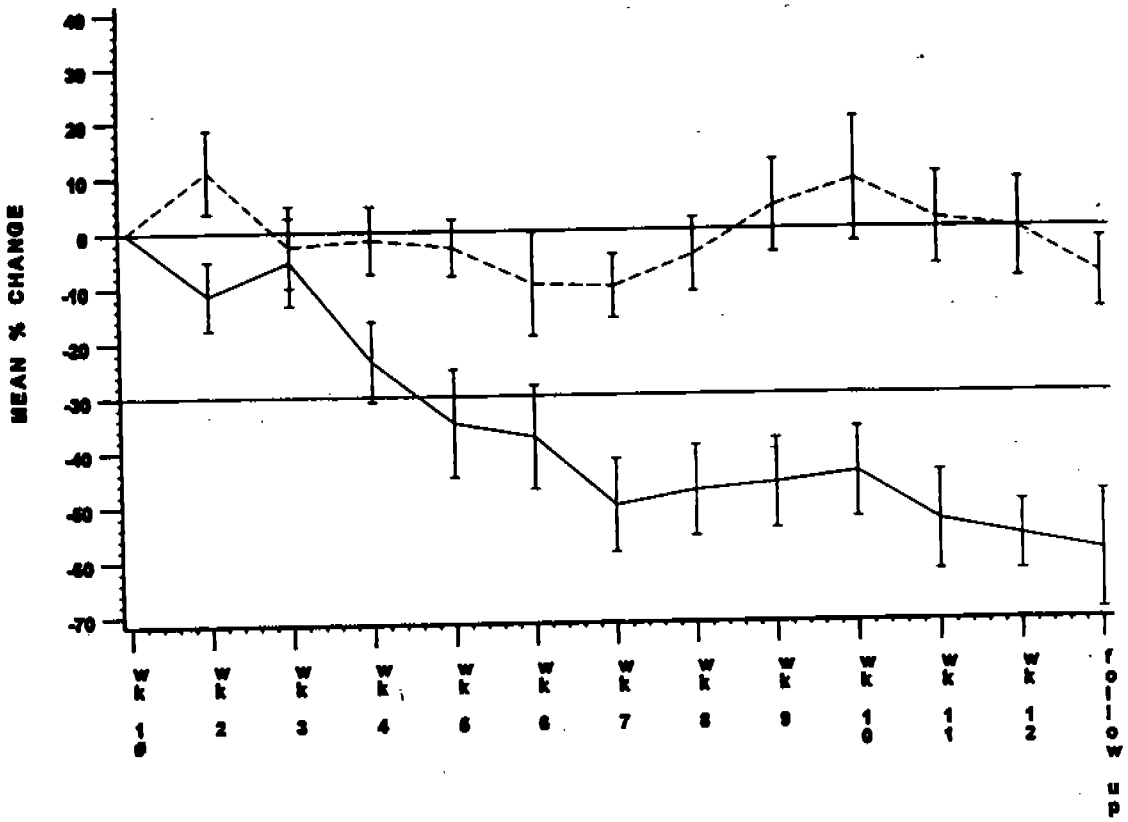
commercial

information

Appendix B

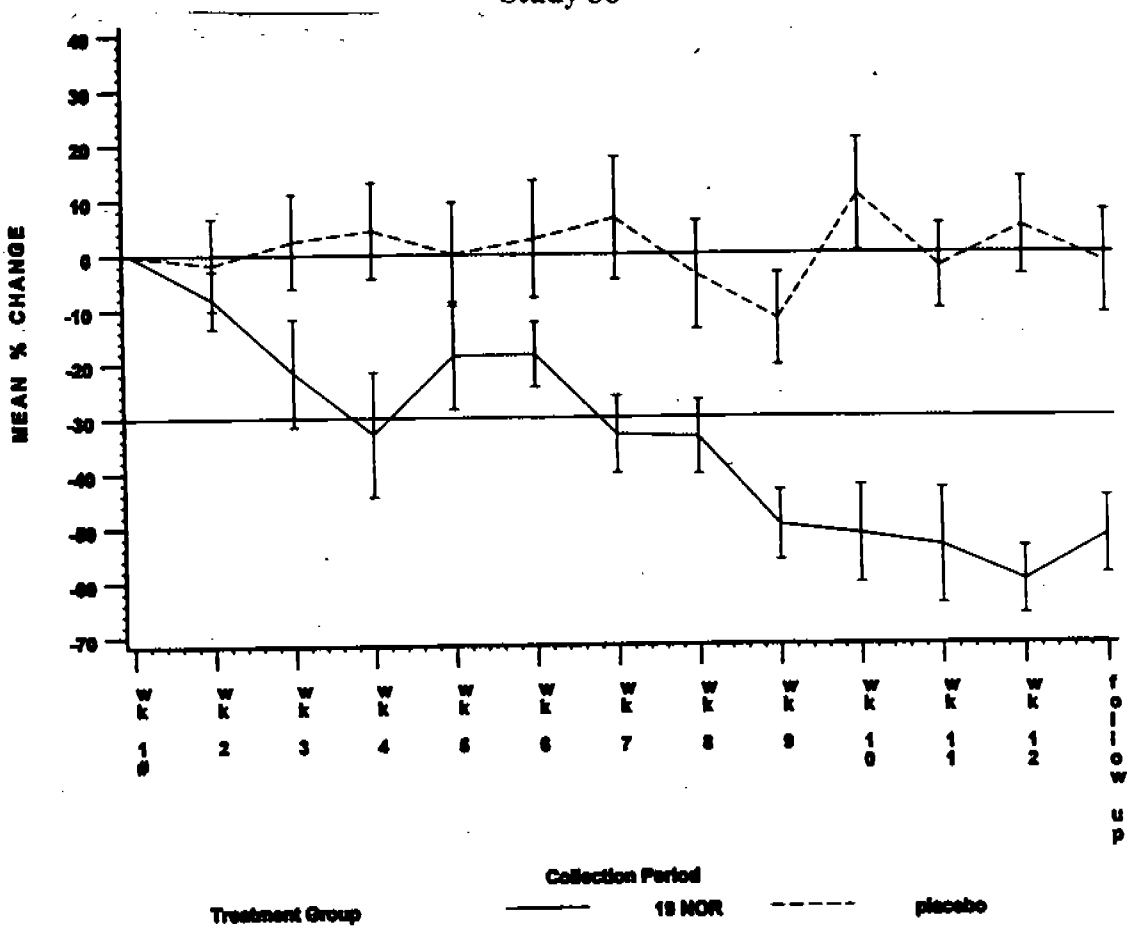
The following three graphs were scanned in from the sponsor's study reports. They show the weekly mean percent changes in iPTH levels for each treatment group.

Study 35



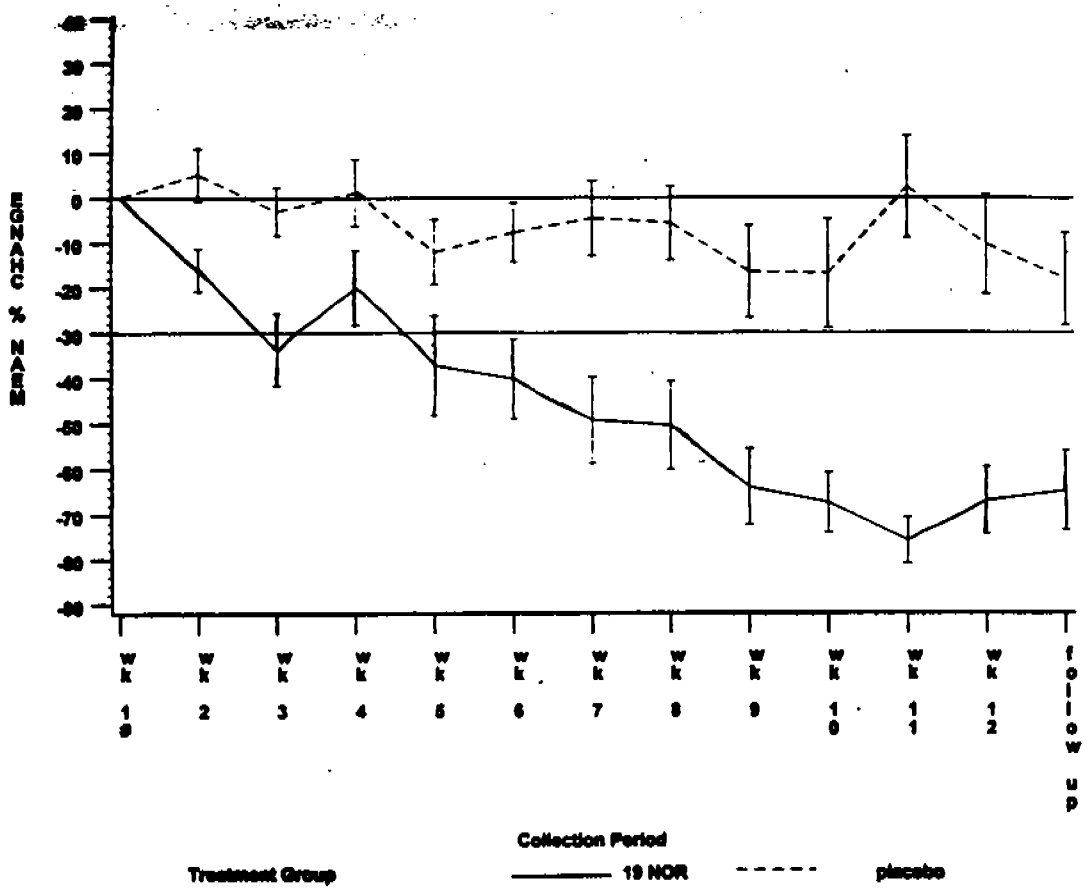
Week 1 is the baseline IPTH determination.
Note: Horizontal reference lines at 0 and -30. Standard error bars included at each mean.

Study 36



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

Study 37



Week 1 is the baseline iPTH determination.

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

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Appendix C

Test of Homogeneity

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.

Before a combined analysis can be performed, a test of homogeneity (to determine whether the odds ratios of the levels of the stratification factor differ significantly), must be done. If the odds ratios of the three studies are statistically significantly different, then a combined analysis should not be performed. The tests of homogeneity were not significant (i.e., the odds ratios were not found to be statistically significantly different), thus the combined analyses, stratified by study, were performed for all four variables. The results are in Table 9, page 13. The proportions of patients achieving a "success" was statistically significantly different between the two treatment groups for all four analyses.

Tests of Homogeneity, Stratified by Study

Variable	p-value for Test of Homogeneity*
At least 1 30% Decrease	0.4263
4 consecutive	0.6853
30% Decrease at Final Visit	0.4799
3 consecutive AND a 30% Decrease at Final Visit	0.6853

* Insignificant p-values indicate that the test of homogeneity did not find the odds ratios to be different across studies, therefore it is appropriate to pool the data from the three studies.