CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020862

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Date: APR 2 5 1999

NDA: 20-862
Drug Class: Class 3S
Drug name: 1-alpha-hydroxyvitamin D_2 (1α-OH-D_2, Hectorol)
Applicant: Bone Care International, Inc.
Indication: Treatment of secondary hyperparathyroidism in end stage renal disease (ESRD) patients.
Documents Reviewed: Vol 1.1, 1.30-1.34, 1.36-1.42, 1.45 dated March 8, 1998, Vol. 4.1 dated April 28, 1998, 1 volume (no number) dated October 26, 1998, Vol. 9.1 dated November 25, 1998, Vol. 10.1 dated December 4, 1998, Vol. 11.1 dated December 8, 1998, Vol. 12.1 - 12.3 dated December 14, 1998, Vol. 13.1-13.2 dated December 17, 1998, Vol. 14.1 dated December 27, 1998, Vol. 17.1 dated January 14, 1999, Vol. 20.1 dated February 1, 1999, Vol. 21.1 dated February 12, 1999 and Vol. 2.1 dated March 2, 1999.
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Key Words and Phrases:
Repeated Measurements Analysis, End-Stage Renal Disease (ESRD), Hemodialysis.

I. Introduction/ Background

The sponsor in this submission is requesting approval for pulse dose oral 1-Alpha-hydroxy-vitamin D_2 (1α-OH-D_2), hectorol, for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on hemodialysis. The sponsor claims that hectorol, a synthetic vitamin D prohormone, has an improved therapeutic index relative to vitamin D hormones and analogs currently approved for this indication and for related metabolic bone disease including osteoporosis and renal osteodystrophy. Accordingly, the sponsor indicated that 1α-OH-D_2 can be given at higher doses for greater therapeutic benefit. The proposed drug product is formulated as a soft gelatin capsule containing 2.5 μg of 1α-OH-D_2. The sponsor claims that hectorol significantly reduces elevated blood parathyroid hormone (PTH) levels, which was taken as the primary efficacy endpoint. The safety endpoints were serum calcium and serum phosphorus.

To support their claims of safety and efficacy of hectorol the sponsor submitted the results of 2 Phase III studies conducted under the same protocol, Protocol # H-108, in two different locations, the greater Los Angeles, CA, area and the greater Memphis, TN, area. The sponsor also presented the results of two Phase II studies, Study H-106 and Study H-110. Study H-110 was a follow-up study on the patients of Study H-106.

This review mainly addresses the Phase III studies (H-108-LA and H-108-Memphis). Section II describes the design of these studies; in addition, it summarizes the main findings of Phase II studies, which their results were used for planning the Phase III studies. Section III presents the sponsor's statistical analysis plan. Section IV summarizes the sponsor's efficacy and safety results along with this reviewer's comments on them. Section V presents this reviewer's overall comments about the efficacy analysis and the results of his re-analysis of the efficacy data. Section VI summarizes the sponsor's safety results. Finally, Section VI gives an overall summary and conclusion of the clinical trials findings.

II. Overview of the Clinical Studies:

Section II.A presents a brief summary of Phase II studies and Section II.B describes study procedures and conducts of Phase III studies.

II.A. Design of Phase II Studies (Study # H-106 and H-110)

Study # H-106 was an open label multicenter (4 investigators) study. The study consisted of an 8 weeks washout (or control) period and 12 weeks treatment period. The objective of the study was to determine the effective oral dose range and the response time for reduction of serum PTH levels. The starting dose of 1α-OH-D_2 was 4.0 μg administered either daily or three times weekly (after each hemodialysis) for a total of 28.0 or 12.0 μg/ week. Doses were titrated downward as necessary to prevent oversupression of PTH, to maintain PTH within a target range of 130-250 pg/mL, and to manage incidents of hypercalcemia or hyperphosphatemia. Twenty seven patients enrolled in the study, and of these 24 patients completed the study. The sponsor reported that by the last week of treatment (Week 12) the mean serum PTH was 293 pg/mL (with s.e.= 37) compared with the mean at baseline of 643 pg/mL (with s.e.= 67). The serum PTH level fell by 51% (range: 48% to 96%) by the end of the study compared with the pre-treatment levels.

Study # H-110 was an open label multicenter (3 investigators, Vol. 1.1, page 158) follow-up study conducted in patients who completed Study # H-106 with a duration of up to 12 weeks and enrollment of 10 patients. The study was conducted to refine the pulse dosing regimen for effective PTH reduction in ESRD patients. The starting dose was 10.0 μg administered three times weekly (after each hemodialysis) for a total of 30.0 μg/ week. Doses were titrated downward as necessary to manage incidents of hypercalcemia or hyperphosphatemia. Patients were considered to complete the study when their plasma PTH level fell below 100 pg/mL. The sponsor indicated that no attempt was made to maintain PTH within a target range of 130-250 pg/mL. The safety parameters for Phase II studies were serum calcium and phosphorus.

II.B. Design of Phase III Studies (Study # H-108 LA and H-108 Memphis)

These two studies were multicenter studies conducted under the same protocol (No. H-108) in two different locations (the greater Los Angeles, CA, area and the greater Memphis, TN, area). ESRD patients undergoing chronic hemodialysis were eligible to participate in the study. The entry criteria were: a patient between ages 20 and 75 years; has maintained an average serum phosphorus in the range of 2.5 to ≤ 6.9 mg/dL during the previous two months; has a history of elevated plasma (PTH) values (> 400 pg/mL) when not receiving 1α, 25-$(OH)_2$ -D_3 therapy; and has a normal or minimally reduced serum albumin during the previous two months (not lower than 0.5 g/dL below the normal range).

Each of the two studies consisted of 3 periods: The first is an 8-week washout period during which any prior treatment with D-hormones had been suspended. The second is an open label, 16-weeks period of therapy with 1α-OH-D_2. This is followed by an 8-week, (randomized), double-blind, placebo-controlled period, in which approximately 1/2 of the patients will continue on the 1α-OH-D_2 therapy, and the other group will be on placebo. The randomization was carried out in a block of size 10, upon patient's enrollment into the study, that is at the start of the washout period. We will comment on the randomization later.

During the study period, patients were to undergo routine hemodialysis (3 times per week) using a 2.5 mEq (1.25mM) calcium dialysate, and were to be monitored each week for predialysis levels of serum calcium, serum phosphorous and plasma intact parathyroid hormone (PTH) at the mid-week hemodialysis.

The studies were conducted using pulse dosing (3 times weekly) at starting dose of 10.0 μg of 1α-OH-D_2 after each hemodialysis (30.0 μg/ week). The protocol stated that the dose might be adjusted as necessary to control PTH within the target range of 150 - 300 pg/mL, as well as to manage incidents of hypercalcemia or hyperphosphatemia. The maximum dose was limited to 30.0 μg/ week in the original protocol dated 1/29/96. However, this maximum dose was changed from 30.0 μg/ week to 60 μg/week in the first revision of the protocol, dated 7/24/96. Also, this revision of the protocol included changes in disqualification criteria for entering the first treatment period. The revised protocol indicated that patients were to be prematurely terminated from the study if they failed to exhibit an average serum calcium of ≤ 10.5 mg/dL during the washout period or if they failed to exhibit an average serum calcium(mg/dL) x serum phosphorous (mg./ dL) product of < 70.0 during the washout period. There are two additional revisions for the protocol; the second revision was dated 10/4/96 and the third revision was dated 12/4/96.

Other differences between the original protocol and the three revisions include changes in the number of patients. The original protocol required enrollment of up to 160 ESRD patients (up to 80 patients in each geographical region) in the two studies. This number of patients was changed to 200 patients in the first revision of the protocol. In addition, the last revision of the protocol called for the enrollment of up to 250 patients (up to 125 patients from each geographical region). The successive revisions of the protocol, however, did not specify the reason for the changes in the number of patients, or the changes in the qualification criteria for entering the first treatment period of the trial.

It was not clear from the sponsor's submission how the number of patients was determined. In one case, the sponsor referred to a meeting with the agency held on November 12,1996 and stated that ' the proposed number of 40 completing patients/site was thought to be adequate' (Vol 1.1, p.156). In another explanation, the protocol stated (page 6) that: ' 40 patients are needed per region to provide an 80% chance (β) of detecting a difference in plasma PTH of at least a significance level (α) of 0.05 ' . As it is not clear from the last statement the type or magnitude of difference used in the sample size calculations, this reviewer requested further explanation form the sponsor (see Attachment I). The sponsor's response of October 26, 1998 was that the results of Phase II were used. However, the results of Study 106 (Phase II) trial were expressed in terms of the mean reduction in plasma PTH as well as the percentage of reduction

from the baseline. In addition, no criteria was set for treatment success (in terms of the amount or percentage of reduction in PTH) to be used in the sample size calculations. Furthermore, for estimating the size of the trial in order to have a 40 completing patients, some assumption had to be made about the dropout rate during the trial. No such assumption was given in the protocol. The sponsor, however, justified the need for increasing the sample size to their underestimating the drop-out rate, since this rate was based on the observed dropout rate of Study 106 (Phase II trial) which was of a shorter duration (12 weeks) than the current Phase III Trials (24 weeks).

Among other issues raised in this reviewer's request of October 20, 1998 which were also discussed with the sponsor during the meeting of October 26, 1998, is having the randomization done at the time of enrollment the trial, which preceded the actual treatment allocation by 24 weeks (8 weeks of washout period and 16 weeks of first treatment period). During this time interval a total of 73 patients out of a total of 211 patients enrolled (34.6%) dropped out after being randomized to treatments. As it is not clear, and it is difficult to test, whether this dropout occurred at random or not, one can not ensure whether the integrity of the randomization was maintained after the dropout. The importance of maintaining a random allocation throughout the course of the trial should not be underestimated since the validity of the statistical inference (calculated p-values for efficacy) is based on the integrity of this randomization.

In addition to carrying out the randomization upon enrollment the sponsor used a block of size 10 for the treatment assignment. This is an unusually large block for the size of these trials, and makes it difficult to test for bias in treatment allocation. The sponsor's justification for selecting a large block size is to reduce the chance that an investigator could guess the next treatment allocation, and consequently reduce the bias.

Also, comparison of the sequential treatment allocation and the patients' date of enrollment show some inconsistencies between the enrollment date and the sequential treatment allocation (see Attachment II). The sponsor, in their response to this reviewer's request for an explanation about this as shown in Attachment I, indicated that some clinics prefer to have the lab tests done in one day of the week (or month) instead of having them done upon the enrollment of each patients. In this reviewer's opinion, however, still patients who enroll at a later date should be assigned a later treatment sequence than another patient who enrolled at an earlier date.

Study H-108-LA started on 5/29/96 and was carried out in 11 centres (10 investigators as reported in Vol, 1.1, p. 158, and 11 sites as reported in Vol 1.45 p. 006). One hundred and four patients enrolled in the washout period and were randomized to the treatment groups. However, only 62 subjects (30 on active treatment and 32 on placebo) began the first treatment period with 1α-OH-D_2 . Out of these, 38 patients completed the study and were evaluable for statistical purposes (see criteria for evaluable patients below).

Study H-108-Memphis started on 6/20/96 and was carried out in 10 centers (4 investigators according to Vol, 1.1 p.158, and 10 sites according to Vol 1.45, p. 007). One hundred and seven patients enrolled in the washout period and 76 subjects (41 active / 35 placebo) began treatment with 1α-OH-D_2 during the first treatment period. Of these, 61 patients completed the study and were evaluable for statistical purposes.

III. Sponsor's Statistical Analysis Plan:

This section describes the efficacy and safety endpoints, population analyzed and statistical methods planned for the analysis.

III. A. Efficacy and Safety endpoints:

The protocol specified the efficacy and safety parameters by the following:
- The primary endpoint for drug efficacy is plasma PTH, and
- The primary evidence of test drug's safety were serum calcium and phosphorus.

The above description of the primary endpoints does not specify the magnitude of change in the plasma PTH, or in the serum calcium and phosphorus for treatment efficacy and safety. The sponsor in reporting the results of Study 106 (Phase II), used in different locations the reduction in mean plasma PTH and the percentage reduction. In addition, the above definition does not specify a primary period or week as a primary period for efficacy and safety assessment.

III. B. Population Analyzed:

The protocol indicated that the planned statistical analysis is to be carried out for the 'Evaluable Patients' and also indicated for 'Intent-to-Treat Analysis'.

According to the protocol (Vol 1.45 p.18) a patient who received a test drug is considered ' evaluable' provided that:

i-The patient has maintained an average serum phosphorus in the range of 2.5 to ≤ 6.9 mg/dL during the treatment period.

ii-The patient has consumed at least 80% of the prescribed test dosage.

iii-The patient has not undergone renal transplant surgery or partial or complete parathyroidectomy during treatment period.

iv-The patients has not received 1α-OH-D_3 therapy or received aluminum-containing products as phosphate binders during treatment period.

v- Analysis of the patient's plasma confirms a circulating level of 1α- $(OH)_2$ D_2 which is consistent with the prescribed dosage of test drug .

The protocol also defined (vol 1.45 p.18) that an intent-to-treat analysis (ITT) were to 'include all patients randomized to receive drug '.

Taking into account that the randomization was carried out at the time of enrollment in the study and that some of the randomized patients were disqualified for enrollment in the first treatment period, it is not clear how the above definition of the ITT population would be applied. The sponsor's results show that the ITT analysis included those patients who were qualified for the first treatment period.

Also, the efficacy results were presented for the 'per-protocol' patients which was not defined, instead the 'evaluable patient' was defined. The sponsor in the meeting with the review team on October 26, 1998 indicated that they used the 'per-protocol' patients to refer to the 'evaluable patient'.

III. C. Statistical Methods:

The protocol indicated (Vol 1.45, page 017) that efficacy and safety parameters of treatment groups were to be compared with their baseline values. The baseline values for all evaluable parameters were defined as the average of the data collected during the last three visits during the washout period (weeks -3,-2,-1). At each post-baseline visit, the treatment groups were to be compared with respect to change from the baseline, using the t-test or the Wilcoxon two-sample test. Additionally, the significance of the change from the baseline for each of the evaluable

parameters at each of the time points was to determined using either a paired t-test or a Wilcoxon one-sample test. The protocol indicated also that the analysis was to be performed on data from both geographical regions, and separately to data from each region. However, no efficacy results for data for the combined geographical regions was presented. In a response to this reviewer's request for explanation, the sponsor indicated at the meeting of 10/26/1998 that such analysis was intended for efficacy in case the findings from individual studies did not reach the required significance level. The sponsor reasoned that as the results of individual studies show efficacy, consequently there is no need for the combined analysis.

Concerning the statistical analysis for the safety data, the protocol indicated that the CBC and chemistry profile parameters for the treatment groups were to be compared in two ways: 1) the proportion of patients for whom the parameters was normal at baseline and then abnormal, post-baseline, using Fisher's exact test; and 2) the mean change from baseline using a t-test or Wilcoxon two-sample test. The protocol indicated that these analyses were to be performed at each sampling time as well as at the end point.

This reviewer has several comments about the statistical methods proposed in the protocol. These comments were conveyed to the sponsor in the request of October 20, 1998 (Attachment I) and are summarized below:

i) It is not clear from the definition of the primary endpoints what was the magnitude of change, and whether this change is expressed in terms of absolute number or as percentage of reduction, required for treatment efficacy. In addition, no primary period for analysis was specified. Furthermore, for the second treatment period it is not clear whether comparison of PTH levels for patients on active drug against that of placebo treatment, or comparison of PTH levels during the treatment period with their baseline (Week 16) values is the primary analysis.

ii) As each of the two treatment periods extended over several weeks (16 weeks for the first treatment period and 8 weeks for the second treatment period) the description of the statistical methods did not make reference for a specific weekly readings as the primary measurement for efficacy assessment, nor did it address the issues of multiplicity otherwise.

iii) It is not clear how the proposed Wilcoxon two-sample test would be applied to data from the first treatment period when one has only one treatment arm. If one assumes that such a

comparison was intended for the second treatment period of the trial, then it is not clear whether the analysis would be applied to the actual reading of the PTH levels or to the change from their baseline at the end of the first treatment period.

iv) As the collected data involves repeated measurements over time, which are expected to be correlated, the proposed statistical methodology does not address the correlation among the repeated measurements in order to provide a more accurate efficacy assessment.

This reviewer's re-analysis in Section V will address some of these issues.

IV. Sponsor's Efficacy and Safety Results:

The sponsor's efficacy results are organized in this section as follows: Section IV.A.I. presents the results of comparing the mean change of plasma PTH for the first and second treatment periods from that of the baseline, as well as that of the second treatment period from that at the end of first treatment period, for the ITT population. Section IV.A.II. presents the results of similar comparisons to those of Section IV.A.I. for the per-protocol population. Section IV.A.III. compares the mean change in plasma PTH for active and placebo treatments during the second treatment period. Section IV.A.III. summarizes the sponsor's results for analyzing the waiting time for response data. Finally, Section IV.B. briefly summarizes the sponsor's safety results for the serum calcium and phosphorus as well as the serious adverse events. Reviewer's comments about specific results are presented when the results are presented. Overall reviewer's comments about the statistical methodology and population analyzed, along with results of his re-analysis are given Section V.

In presenting their efficacy results, the sponsor did not specify the statistical methods (t-test or Wilcoxon test) they used to derive the reported p-values. Instead, the sponsor stated (Vol 1.45, p.210) 'the significance of changes was determined ...using either a paired t-test or Wilcoxon one-sample test, as appropriate'. This reviewer's re-analysis of the sponsor's data of their submission dated January 14, 1999 shows the results from the two proposed methods are similar. However, as the sponsor's analysis did not account for all ITT patients, as will be seen, this reviewer preferred to report the sponsor's results as they are, and later (in Section V) presents the results of his re-analysis after taking into account all ITT patients and using a repeated measurements approach.

IV.A.I. Analysis of Change From Baseline For Plasma PTH During The First Treatment Period.

Table 1 summarizes the sponsor's efficacy results for analyzing the significance of change from baseline for plasma PTH during the first treatment period for the ITT population in the two pivotal studies.

Table 1/ Reviewer's Table

Results of Analysis of Change From Baseline For Plasma PTH For Selected Weeks of The First Treatment Period, ITT Population, In the Two Pivotal Studies

	Study # H-108 LA				Study # H-108 Memphis			
Week	N	Mean (S.E)	Change from Baseline		N	Mean (S.E)	Change from Baseline	
			Mean	p-values			Mean	p-values
-8	61	550.61 (51.26)			75	794.62 (59.01)		
0	62	904.62 (95.73)			76	993.05 (61.94)		
Baseline	62	829.35 (79.81)			76	981.50 (60.66)		
1	61	667.63 (92.51)	-162.93	<.001	73	858.08 (73.41)	-129.49	.004
4	56	500.24 (85.07)	-340.67	<.001	69	695.70 (70.27)	-286.62	<.001
8	55	428.37 (66.68)	-395.57	<.001	69	613.82 (70.40)	-344.14	<.001
12	50	511.58 (163.43)	-274.77	.004	71	482.72 (56.58)	-500.11	<.001
16	53	462.11 (95.63)	-373.62	<.001	68	459.20 (49.25)	-519.97	<.001

Source: Extracted from the sponsor's results in Section II.A.3.a. Vol. 1.45, p. 211 and Section II.B.3.a, Vol 1.45, p .234.

The sponsor's results, as summarized in Table 1, shows that a significant decrease in mean plasma PTH occurred during the first treatment period in comparison to the mean plasma PTH at the baseline (the average plasma PTH during the last 3 weeks of the preceding this treatment period). The results of Table 1 show that: (i) there is large number of variations in the number of patients analyzed in the 'claimed' ITT analysis. For Study H-108 LA the number of patients changed from a maximum of 62 patients at the baseline to a minimum of 50 patients for Week 12, and (ii) Week 12 plasma PTH readings for LA did not follow the observed pattern of decline of other weeks. Also, the standard error for this week's readings was about twice as large as those of other weeks. With these comments, our interest is in checking the robustness of the efficacy results findings when all patients are included in the analysis.

For Study H-108 Memphis, the results of Table 1 show also that a significant decrease in mean plasma PTH occurred during the first treatment period in comparison to the mean plasma PTH at the baseline. Here also the number of patients analyzed was not fixed for the ITT analysis, but it ranged from 76 patients at the baseline to 68 patients at Week 16 of the first treatment period.

Table 2 summarizes the sponsor's efficacy results for analyzing the significance of change from baseline, as well as from Week 16 (the last week of the first treatment period) levels, for plasma PTH during the second treatment period for the ITT population in the two pivotal studies.

Table 2/ Reviewer's Table

Results of Analysis of Change From Baseline and From Week 16 For Plasma PTH For Selected Weeks of The Second Treatment Period, ITT Population, In the Two Pivotal Studies

	Study # H-108 LA						Study # H-108 Memphis					
Week	N	Mean (S.E)	Change from Baseline		Change from Week 16		N	Mean (S.E)	Change from Baseline		Change from Week 16	
			Mean	p - value	Mean	p - value			Mean	p - value	Mean	p - value
Active												
Baseline(W16)	30	797.18 (81.02)					41	973.87 (88.56)				
20	24	323.70 (65.42)	-480.22	<.001	-60.60	.224	35	451.38 (70.32)	-503.90	<.001	-12.39	.676
24	21	404.39 (57.38)	-445.35	<.001	16.65	.769	35	459.78 (74.88)	-520.88	<.001	-5.04	.886
Placebo												
Baseline(W16)	32	859.51 (135.90)					35	991.02 (82.58)				
20	26	916.42 (212.03)	40.78	.589	414.98	<.001	30	855.07 (133.49)	-141.97	.148	354.6	<.001
24	24	672.57 (72.86)	-35.56	.577	338.08	<.001	30	871.88 (113.85)	-137.54	.080	417.8	<.001

Source: Extracted from the sponsor's results in Section II.A.3.a. Vol. 1.45, p. 212 and Section II.B.3.a, Vol 1.45, p.235.

The results of Table 2 show that for both studies the mean plasma PTH for patients on active treatment during the second treatment period was significantly lower than its value at the baseline (i.e., before the start of treatment). Also, the mean plasma PTH for the active treatment does not differ significantly from their levels at the end of the first treatment period, where all patients were on active treatment. That is to say, the decrease in the mean plasma PTH experienced for the active drug during the first treatment period continued for the second period for the active treatment patient. This in contrast to the results of placebo treatment patients, where the mean plasma PTH did not differ significantly from those at the baseline (i.e. before the start of the

treatment). Also, a significant increase in the mean PTH occurred after changing their treatment from hectorol treatment during the first period to placebo during the second period.

In summary, disregarding the changes in the number of patients analyzed, the results of Table 2 indicate that the mean PTH for the first treatment period was significantly lower than that at the baseline (end of the washout period). For patients continuing on hectorol for the second treatment their PTH levels during this period were comparable to that at the end of the first treatment period. In contrast the mean plasma PTH for patients switched to placebo treatment, during the second treatment period, increased significantly from their levels at the start of this period. As can be seen from Table 2, the results of this analysis, as in Table 1, were based on a varying number of patients. In the following section we will investigate the effect of the change in the number of patients on the efficacy results.

Table 3 summarizes the sponsor's efficacy results for analyzing the significance of change from baseline for plasma PTH for the first treatment period for the per protocol population.

Table 3 Reviewer's Table

Comparison of Plasma PTH for Selected Weeks, First Treatment Period,

Phase III Studies, Per Protocol Analysis

	Study # H-108 LA				H-108 Memphis			
Week	N	Mean (S.E)	Change from Baseline		N	Mean (S.E)	Change from Baseline	
			Mean	p-values			Mean	p-values
-8	38	541.60 (63.73)			60	777.41 (68.40)		
0	38	785.01 (71.76)			61	1012.08 (73.75)		
Baseline	38	757.37 (66.41)			61	984.69 (72.73)		
1	38	552.49 (55.96)	-204.88	<.001	60	847.97 (83.91)	-141.53	.008
4	38	390.78 (54.92)	-366.59	<.001	55	712.77 (81.84)	-281.14	<.001
8	37	346.31 (60.56)	-393.50	<.001	58	568.11 (72.42)	-391.98	<.001
12	36	300.81 (32.14)	-395.67	<.001	61	423.63 (55.27)	-561.06	<.001
16	38	348.61 (57.23)	-408.76	<.001	60	402.63 (44.31)	-574.43	<.001

Source: Extracted from the sponsor's results in Section II.A.3.a. Vol. 1.45, p. 213 and Section II.B.3.a, Vol 1.45 p.236.

The conclusion from Table 3 is similar to that of Table 1; that is, there is a significant decrease in mean plasma PTH during the first treatment period in comparison to that the baseline. Here however, the standard error for mean plasma PTH for Week 12 is about half of those of the other

weeks. Thus, in conjunction with the results of the ITT analysis in Table 1, one concludes that the large variations in the ITT data for this week can be attributed to PTH readings of patients who were excluded from the per protocol analysis (50-36 = 14 patients).
Table 4 presents the sponsor's efficacy results for comparing the mean plasma PTH for the second treatment period for the per protocol population.

Table 4/ Reviewer's Table

Comparison of Plasma PTH for Selected Weeks, Second Treatment Period, Active and Placebo Treatments, Phase III Studies, Per Protocol Analysis

	Study # H-108 LA						H-108 Memphis					
Week	N	Mean (S.E)	Change from Baseline		Change from Week 16		N	Mean (S.E)	Change from Baseline		Change from Week 16	
			Mean	p-value	Mean	p-value			Mean	p-value	Mean	p-value
Active												
Baseline (W16)	17	832.47 (123.36)					31	961.42 (111.91				
20	17	326.51 (85.81)	-505.97	<.001	-60.15	.329	30	384.99 (67.15)	-554.06	<.001	-	.908
24	17	394.33 (70.24)	-438.14	<.001	7.67	.911	31	373.09 (68.35)	-588.34	<.001	3.90	.779
Placebo											-10.0	
Baseline(W16)	21	696.58 (67.06)					30	1009.43 (94.00)				
20	21	700.35 (77.21)	3.77	.954	382.54	<.001	28	838.59 (136.25)	-168.88	.088		<.001
24	21	662.29 (77.76)	-34.29	.627	344.48	<.001	30	871.88 (113.85)	-137.54	.080	371.24	<.001
											17.8	

Source: Extracted from the sponsor's results in Section II.A.3.a. Vol. 1.45, p. 214 and Section II.B.3.a, Vol 1.45 p.237.

The results of Table 4, as those of Table 2, show for both studies that active treatment patients experienced a significant reduction in their plasma PTH counts compared to the baseline values. For these patients the change in the mean plasma PTH during the second treatment period from that experienced at the end of the first treatment period was not significant. For placebo patients, however, the plasma PTH increased significantly after they switched from hectorol to placebo treatment.

The sponsor's per-protocol results were based, as in the ITT analysis, on a varying number of patients. For the Los Angeles study the number of patients changed from 17 initially to a minimum of 14 patients at Week 18 (not shown above) and for the Memphis study the number changed from 21 patients initially to 19 patients at Week 17 (not shown above).

IV.A.II. Comparison of Mean PTH for the Active and Placebo Treatments During the Second Treatment Period:

Table 5 summarizes the sponsor's results for comparing the plasma PTH for the active and placebo treatment groups.

Table 5/ Reviewer's Table

Comparison of Plasma PTH for Active and Placebo Treatments for Selected Weeks During the Second Treatment period, ITT Analysis

	Study # H-108 LA					Study # H-108 Memphis				
Week	Active		Placebo		Difference in	Active		Placebo		Difference
	N*	Mean	N*	Mean	Mean (p-value)	N	Mean	N	Mean	Mean (p-value)
16	24	384.31	29	526.50	-142.20 (.465)	36	435.47	32	485.91	-50.44 (.613)
20	24	323.70	26	916.42	-592.72 (.013)	35	451.38	30	855.07	-403.68 (.007)
24	21	404.39	24	672.57	-268.18 (.007)	35	459.78	30	871.88	-412.11 (.003)

Source: Extracted from the sponsor's results in Section II.A.3.a. Vol. 1.45, p. 215 and Section II.B.3.a, Vol 1.45 p.238.

* The sponsor results show inconsistency in the placebo and treatment arms of the above table with those of other tables which this reviewer attributed to interchanging the number of patients in the two treatment arms.

The sponsor's results, as summarized in Table 5, show for each study no significant difference between the mean plasma PTH for placebo and active treatment at Week 16 (baseline), but there are significant differences at Week 20 and Week 24, thus indicating a significant treatment effect for hectorol against placebo. Aside from the change in the number of patients analyzed as discussed for the previous tables, the magnitude of change in the plasma PTH and the reported p-values are not consistent; that is, a larger change in the PTH did not necessarily lead to smaller p-values. For example, a mean change in plasma PTH of magnitude 592.72 at Week 12 led to a p-value of .013, whereas a mean change of magnitude 268.18 at Week 24 led to a p-value of .007. This implies, assuming the calculations were done correctly, that there are large variations in the data over the course of this treatment period, which caused the standard errors to be of different magnitude, and thus effecting the denominator of the test statistics.

IV.A.III. Analysis of The Waiting Time to Response:

In addition to the previous efficacy results, the sponsor presented also the results of an analysis for the waiting time until response, which are summarized in Table 6, below .

The results of Table 6 show that the plasma PTH levels fell by ≥ 30% in 100% of the 38 evaluable patients in Study H-108-LA during the first treatment period of hectorol, and that this response occurred after 15.5±2.0 (SE) days of treatment. Similarly, for this study reductions in plasma PTH of ≥ 50% and ≥ 70% were observed in 97.4% and 89.5% of these subjects, respectively. The mean number of days for patients to achieve these response rates were 29.8 ± 4.3 (SE) and 45.3 ±5.9 (SE) days of treatment, respectively. Similar interpretation can be placed on Study H-108-Memphis findings.

Table 6 /Sponsor's Table

PTH Suppression by Degree and Days to Response,

Per-Protocol Analysis For the First Treatment Period in Phase II and III Studies

Study ID	Control	Total no. of subjects	Initial dose (dose range) per week)	degrees of and days to PTH suppression					
				≥ 30%		≥ 50%		≥70%	
				% of subjects	Days to response Mean ±SE	% of subjects	Days to response Mean ±SE	% of subjects	Days to response Mean ±SE
H-108-LA	Placebo	38	30 µg (0-60 µg)	100%	15.5 ± 2.0	97.4%	29.8 ± 4.3	89.5%	45.3 ±5.9
H-108-Memph.	Placebo	61	30 µg (0-60 µg)	96.7%	22.4 ±3.3	91.8%	32.1 ± 3.8	86.9%	48.4 ±4.4
H-106	Historical	24	12-28µg (0-60 µg)	100%	27.3 ±4.3	95.8%	39.6 ± 5.0	NA	NA
H-110	Historical	10	30 µg (24-30µg)	100%	7.2 ±1.6	100%	22.0 ± 5.9	NA	NA

The dose frequency was 10µg/3x per week except for study H-106 in which was 4µg daily or/3x per week week

Source : Sponsor's submission vol 1.1, p.172

IV.B. Safety Results for Phase III Trials

IV. B.I. Results for Serum Calcium Phosphorus Levels :

The sponsor presented results of various comparisons for the mean serum calcium and mean serum phosphorus for every week of treatment, for the ITT population in the two pivotal studies. The sponsor's results are given in Attachment III. Table A.1, of Attachment III compares the weekly mean serum calcium for the first treatment period with that of the baseline for the California study. Table A.2 compares, for each treatment arm, the weekly mean serum calcium during the second treatment period with that of the baseline as well as with that of Week 16 (the

end of the first treatment period). In addition, it compares the mean serum calcium of hectorol and placebo treatments during this treatment period. Tables A.3 and A.4 gives analogous comparison to those of Tables A.1 and A.2 for the mean phosphorus in the California study. Finally, tables B.1 through B.4, which are analogous to tables A.1 through A.4, present the sponsor's results for the Memphis study.

The sponsor's results for both studies show that a significant increase in the mean serum calcium and phosphorus occurred when patients were on hectorol treatment compared to their baseline values, before the start of the treatment. In addition, the mean serum calcium for patients switched from hectorol to placebo during the second treatment period decreased significantly, but the decrease in the serum phosphorus was not significant. The results for comparing the mean serum calcium, and phosphorus, for hectorol and placebo treatments shows the difference between is, in general, not significant. It appears from the sponsor's results of Tables A.4 and B.4 that the number of patients for hectorol and placebo were switched in the second half of each table compared to the first half. .

IV. B.II. Adverse Events:

The sponsor reported that episodes of hypercalcemia and hyperphosphatemia were increased with hectorol therapy, but the incident rates for these side effects were low (Vol 1.1, p. 160), and that when hypercalcemia and hyperphosphatemia did occur, there were no symptoms of toxicity. The sponsor remarked also that no significant complications occurred as a result of treatment with oral 1α-OH-D_2 . Furthermore , they stated that ' All serious adverse events that occurred during the conduct of BCI's eleven clinical trials with oral 1α-OH-D_2 were determined to be not related to treatment with the test drug (Vol. 1.1, p.181). Instead, they were events commonly observed or expected in this seriously ill population of ESRD patients.

V. Reviewer's Comments and Re-analysis:

V. I. Reviewer's Comments:

In the previous section this reviewer raised several concerns during the description of the sponsor's statistical methodology and presentation of their results. Here we summarize the sponsor's response to these comments, and in Section V.II. we address some of these comments

when re-analyzing the sponsor's efficacy data. The main comments, aside from those related to the randomization, along with the sponsor's response to them, are listed below.

i) The comment about the period and primary efficacy analysis was addressed by the sponsor in a meeting on 10/26/98 during which the primary analysis was that based on comparison of the plasma PTH with that of placebo. Also, Dr. Troendle, Deputy Director for Division of Metabolism and Endocrine Drug Products, during a telephone conference with the sponsor on January 22, 1999, indicated to this reviewer that it is the policy of the medical division to compare active treatment against placebo for efficacy. Thus, the primary re-analysis of this reviewer will be based on comparing the plasma PTH reading for hectorol versus placebo patients during the second treatment period.

ii) Concerning this reviewer's comment about the choice of a certain week's data, or addressing the multiplicity, I have proposed in my request of October 20, 1998 that the sponsor carry a post-hoc analysis that takes into account the correlation expected between the weekly repeated measurements and for all patients enrolled in the first treatment period. This request was also repeated to the sponsor during a teleconference between the agency and the sponsor on January 22, 1999. This was also clarified to the sponsor's statistical consultant, Dr. Barry Storer, on January 28, 1999. The sponsor submitted the results of this analysis in their submission dated February 1, 1999 (see attachment IV).

This reviewer has the following comments about the sponsor's repeated measurements analysis as presented.

a) For patients with missing data, the sponsor carried forward the last value available. However, the sponsor's data in their submission of January 14, 1999 show that their are a total of 9 placebo-treatment patients (6 in Study 108-LA and 3 in Study 108-Memphis, as shown in Attachment V) with missing data for the entire second treatment period. Thus, carrying forward the last value observed when theses patients were on hectorol treatment to the placebo treatment period is expected to lead to bias (against hectorol) in the efficacy analysis. This reviewer's re-analysis of the sponsor's data excluded these 9 patients from the analysis.

b) In conducting the repeated measurements analysis for the first treatment period, the only covariate considered in the sponsor's fitted model is the treatment. However, since all patients

were on hectorol treatment during this period, the sponsor's fitted model are inappropriate for analyzing the efficacy data. The partial output, submitted by the sponsor (Attachment IV), shows that the 'Between Subject Effect', which measure the treatment effect, does explain the variation in the data. As can be seen from the attachment the p-values for treatment were 0.4309 for the California study and 0.4935 for the Memphis study. Thus the sponsors's fitted models for analyzing the first treatment period are inadequate for explaining the variability in the data.

As one interested in measuring the magnitude of decrease (if any) in the plasma PTH from that at the baseline, the baseline values should be included as a covariate in the model. Then with repeated measurements approach one could test whether there is an interaction between time and baseline plasma PTH through the first treatment period.

c) For the second treatment period with two treatment groups, the sponsor's fitted models included treatment as covariate in the model. However, one is still interested in finding out whether baseline plasma PTH at end of the first treatment period effect the plasma PTH during this period.

V. II. Results of Reviewer's Re-analysis

This reviewer's re-analysis of the sponsor's efficacy data, submitted on January 14, 1999, considers the comparison of plasma PTH for hectorol and placebo treatment during the second treatment period as the primary analysis. For this analysis we excluded 9 placebo patients (6 in Study 108-LA, and 3 in Study 108-Memphis) since their plasma PTH readings were missing for the entire second treatment period. The statistical methodology we consider here is analysis of covariance with repeated measurements (PROC GLM of SAS). For this analysis, plasma PTH weekly readings are taken as the dependent variables; and treatment and plasma PTH at the baseline (Week 26, which is the last observation of the first treatment period) are taken as the covariates in the model. For the first treatment period we analyze the change in plasma PTH, from their baseline values (the average readings of the last 3 weeks of the washout period). In addition, we fit repeated measurements model for the weekly plasma PTH readings with baseline measurements as a covariate in the model, to test the effect of time on the decline in the PTH weekly readings.

Table 7 presents the results for comparing the mean plasma PTH for 1α-OH-D_2 and placebo

Table 7 / Reviewer's Analysis

Efficacy Results For Hectorol and Placebo Treatments PTH Data, Second Treatment Period, Repeated Measurements GLM, ITT Population, Study 108-LA and Study 108-Memphis

	Study 108-CA						Study 108-Memphis					
Period / Covariates in GLM model	Mean (SE) plasma PTH			p-values for testing covariates effect (GLM)			Mean (SE) plasma PTH			p-values for testing covariates effect (GLM)		
	Hectorol (n = 30)	Placebo (n=26)	p-value [1]	Treatment	Week 26	Trt * Week 26	Hectorol (n = 41)	Placebo (n=32)	p - value [1]	Treatment	Week 26	Trt * Week 26
Week 26	381.8 (69.67)	525.6 (146.9)[2]					511.0 (74.7)	496.6 (72.9) [2]				
Week 28	366.8 (79.2)	755.9 (190.3)	.0001	.0007	.0001	.7920	463.3 (70.7)	747.8 (92.7)	.0001	.0015	.0001	.9527
Week 30	333.3 (58.2)	916.4 (212.3)	.0001	.0033	.0001	.0020	480.5 (70.4)	845.0 (125.9)	.0001	.1137	.0001	.0039
Week 32	373.9 (59.5)	910.9 (215.0)	.0001	.0290	.0001	.0016	406.6 (64.9)	833.8 (111.7)	.0001	.0187	.0001	.0289
Week 34	381.3 (48.5)	873.2 (213.4)	.0001	.1319	.0001	.0001	489.0 (73.5)	875.8 (109.9)	.0001	.0041	.0001	.2866
Between Subject Effect												
Treatment		.0015						.0072				
Week 26 PTH		.0001						.0001				
Trt*Week 26 PTH		.0027						.0813				
Within Subject Effect												
Time		.0026						.6148				
Time* Treatment		.3098						.0800				
Time * Week 26 PTH		.0275						.0042				
Trt* Time * Week 26 PTH		.0001						.0111				

[1] p-values are for comparing the mean PTH of the hectorol against placebo after adjustment for baseline measurements (Week 26 PTH), using the Least Squares Means in PROC GLM of SAS.

[2] Number of patients at Week 26 (baseline) is 32 for Study 108-LA and 35 for Study 108- Memphis

treatment for certain weeks during the second treatment period in the two pivotal studies, as well as for the entire period based on repeated measurements approach, for the two pivotal studies.

The results of Table 7 show the mean plasma PTH for patients on 1α-OH-D_2 treatment was significantly lower than those on placebo treatment for the individual weeks as well as for the entire period (p=0.0001). The reported p-values in Table 7 take into account adjustment for plasma PTH at the baseline, Week 26 readings, using the Least Squares Means.

The results for the between-subjects (patients) effect in Table 7, test the hypothesis that treatment, plasma PTH at baseline (Week 26), and their interaction have no effect on the plasma PTH levels during the second treatment period (the dependent variable), while ignoring the within patient effect. The results of Table 7 show there is a highly significant effect for the three factors. The within-subject (patient) effect results in Table 7 show the results of univariate analysis for testing the effect of time, and its interaction with the covariates in the model (treatment and Week 26 plasma PTH). The results of this analysis show that whereas the results for the Time-by-Week 26 PTH and Treatment-by-Time- by-Week 26 PTH interactions are significant across the two studies, the results for the Time and Time-by-Treatment interaction are not consistent across the two studies.

Now we consider analysis of plasma PTH analysis during the first treatment period, for ITT population in the studies. Table 8 shows the results testing the null hypothesis that the mean change plasma PTH from their baseline values is equal zero, using the t-test for paired comparison. In addition, Table 8 shows also the results of fitting GLM to plasma PTH data for which plasma PTH at baseline is taken as a covariate in the model.

The results of Table 8 show significant reduction in the mean plasma PTH, for both studies, during this treatment period from their baseline value, p-value = 0.0001. The results of fitting repeated measurements analysis to weekly plasma PTH readings, with plasma PTH at the baseline PTH taken as a covariate in the model, show that plasma PTH at the baseline is highly significant predictor for the plasma PTH readings during this period. The results for the within-subject effect shows that time effect is highly significant for the Los Angeles (p = .0001) study, and marginally significant for the Memphis study (p =.2509). However, the time-by-baseline interaction are highly significant for both studies. That is to say, as all patients were on active

treatment during this period, the effect of time, on the decline in PTH over time, was significant.

In addition to the ITT analysis, this reviewer carried out similar analysis on the per-protocol population. The results of the analysis were similar to that of the ITT analysis, and consequently not reported here.

Table 8 / Reviewer's Analysis

Efficacy Results For Hectorol Treatment PTH Data, First Treatment Period, Repeated Measurements ANOVA, ITT Population, Study 108-LA and Study 108-Memphis

	Study 108-CA				Study 108-Memphis			
	Mean (SE) plasma PTH (n = 62)	Change from baseline		Baseline p-value (GLM)	Mean (SE) plasma PTH (n = 76)	Change from baseline		Baseline p-value (GLM)
		Mean (S.E)	p-value			Mean (S.E)	p-value	
Week 10: Baseline [1]	822.9 (79.5)				981.5 (60.7)			
Week 12	623.8 (91.3)	-199.1 (31.7)	.0001	.0001	707.3 (60.7)	-274.2 (43.7)	.0001	.0001
Week 14	494.7 (77.5)	-328.2 (29.5)	.0001	.0001	708.9 (67.2)	-272.6 (46.6)	.0001	.0001
Week 16	489.5 (70.2)	-333.4 (37.2)	.0001	.0001	683.5 (89.1)	-298.0 (71.6)	.0001	.0001
Week 18	450.3 (62.0)	-372.6 (39.2)	.0001	.0001	692.3 (93.2)	-289.2 (72.5)	.0002	.0001
Week20	479.4 (98.5)	-343.5 (46.0)	.0001	.0001	583.2 (75.7)	-398.3 (71.7)	.0001	.0001
Week 22	524.7 (134.0	-298.2 (74.4)	.0002	.0001	504.3 (56.2)	-477.2 (56.9)	.0001	.0001
Week 24	469.1 (99.0)	-353.8 (48.4)	.0001	.0001	508.8 (54.8)	-472.7 (48.0)	.0001	.0001
	456.0 (82.8)	-366.9 (39.2)	.0001	.0001	504.4 (52.1)	-477.1 (51.7)	.0001	.0001
Between Subject Effect								
Week 10 PTH		.0001			.0001			
Within Subject Effect								
Time		.0001			.2509			
Time*Week 10 PTH		.0001			.0002			

[1] This is the average readings of the last 3 weeks during the washout period

VI. Overall Summary and Conclusion:

The sponsor in this submission is requesting approval for pulse dose oral 1-Alpha-hydroxy-vitamin D_2 (1α-OH-D_2), hectorol, for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on hemodialysis. The sponsor presented the results of

two multicenter studies, conducted under the same protocol in two different locations, Study # H-108-LA and Study H-108-Memphis.

Each of the two studies consisted of 3 periods: (i) an 8-week washout period, (ii) an open label 16-week active treatment period and (iii) an 8-week randomized, double-blind, placebo-controlled period. The randomization for the last period was carried out in blocks of size 10, upon enrollment, i.e at the start of the washout period. One hundred and six (106) patients enrolled in Study H-108-LA and 62 of them entered the first treatment period. For Study H-108-Memphis 107 patients were enrolled and of these 76 patients entered the first treatment period. This reviewer has concerns about the design and conduct of the two pivotal studies. Among these concerns is having the randomization carried out at the time of enrollment in the study, which is 24 weeks before the actual allocation of patients to 1α-OH-D_2 and placebo treatments. During this time interval a total of 73 patients out of a total of 211 patients enrolled (34.6%) dropped out after being randomized to the treatments. As it is difficult to test whether dropout occurred at random, one can not ensure that the integrity of the randomization was maintained after the dropout. In addition, a block of size 10 for the treatment assignment is an unusually large for the size of these trials, and makes it difficult to test for bias in treatment allocation. The importance of maintaining a proper randomization through the period of the trial should not be underestimated, because the validity of the statistical inference (calculated p-values for efficacy) is based on the integrity of the randomization.

In addition, there are several issues related to the sponsor's statistical analysis plan and their reported efficacy results. For example, the protocol did not define a criteria for treatment efficacy or a primary comparison or a certain period for efficacy assessment. Furthermore, as each of the two treatment periods involves weekly measurements, the statistical plan did not address the multiplicity issues. Concerning the sponsor's reported efficacy results, the analysis did not include all ITT. Instead, it was based on varying number of patients from week to week. Finally, the sponsor's re-analysis, in response to this reviewer's request, imputed for missing values of placebo treatment the last values reported when the patient was on active treatment. This is expected to lead to bias, in favor of placebo, when comparing hectorol and placebo responses.

This reviewer's re-analysis of the sponsor's efficacy data, of January 14, 1999, considers, following a comment by Dr. Troendle, the comparison of plasma PTH for hectorol and placebo as the primary efficacy analysis. The results of this analysis, as presented in Section V, show the

mean plasma PTH for hectorol is significantly lower than that placebo after adjustment for the baseline (Week 26 readings), p-values = 0.0001. These results for comparing the weekly measurements (least squares) means are consistent with the overall results of repeated measurements analysis for the entire second treatment period. In addition, the results of the weekly, as well as multiple measurements, for the first treatment period show also significant reduction in plasma PTH from that at the baseline (start of hectorol treatment). The efficacy findings are also consistent across the two studies. However, these ' apparently' highly significant results do not account for the issues raised about randomization and other aspects of the trials, as discussed above, which are difficult to make adjustment for them.

/S/ [redacted] 4/5/99
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APPEARS THIS WAY ON ORIGINAL

cc:
Archival/ NDA 20,862
HFD-510/ Dr. Lutwak// Mr. Hedin
HFD-510/File Copy
HFD-715/ Dr. Nevius/Dr. Sahlroot /Dr. Al-Osh
HFD-715/File Copy

This review contains 23 pages of text and 4 attachments.

Aloshm, nda510review (hectorol), 3/25/99

Attachment I

- Request to the sponsor for explanations concerning randomization, study conduct and analysis, dated 10/20/1998.

- Request to the sponsor for efficacy data, dated 1/21/1999.