

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-027

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-027 DATE REVIEWED: March 30, 2000 CHEMISTRY REVIEW #: 3

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	3/28/00	3/29/00? Not in DFS yet	

NAME & ADDRESS OF SPONSOR: Bone Care International, Inc.
One Science Court, Madison, WI 53711 (608) 236-2500

DRUG PRODUCT NAME:

Proprietary: Hectorol
Nonproprietary: 1-alpha-hydroxyvitamin-D₂, 1-alpha-hydroxyergocalciferol,
USAN name: Doxercalciferol
Chem.Type/Therapeutic Class: Type 3/ Class S

PHARMACOL. CATEGORY/INDICATION:

Treatment of secondary hyperparathyroidism in end stage renal disease (ESRD)

DOSAGE FORM:

Ampule, 1 and 2 mL

STRENGTHS:

2.0 microgram/mL

ROUTE OF ADMINISTRATION:

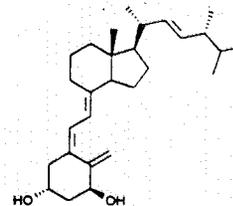
Intravenous Injection

Rx/OTC:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(1 α ,3 β ,5Z,7E,22E)-9,10-Secoergosta-5,7,10(19),22-tetraene-1,3-diol
CAS #: 54573-75-0, C₂₈H₄₄O₂, mol. wt. 412.66



REMARKS:

This NDA provides for an injectable dosage form containing the identical drug substance described in NDA 20-862 (oral soft gelatin capsule, approved 6/9/99). After the original NDA was refused to file, the NDA was Filed Over Protest on 10/21/99 and the current user fee date is 4/6/00. The 3/28/00 amendment contains updated stability data. The EER and microbiology review status is now acceptable.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint the application is approvable. The firm should be reminded of their Phase IV commitments to NDA 20862 in the approval letter.

Orig. NDA # 21-027
cc: HFD-510/Division file/D-G.Wu/M.Haber/R.Hedin

/S/

Martin Haber, Ph.D.

R/D Init by: Dr. D-G. Wu, Team Leader Chemist

/S/ 3/30/00

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-027 DATE REVIEWED: March 27, 2000 CHEMISTRY REVIEW #: 2

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	2/17/00	2/18/00	
Amendment	3/23/00	3/27/00	
Amendment	3/24/00	3/29/00? Not in DFS yet	

NAME & ADDRESS OF SPONSOR:

Bone Care International, Inc.
One Science Court, Madison, WI 53711 (608) 236-2500

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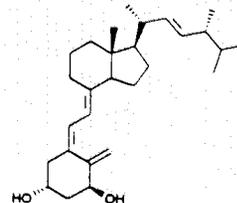
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X Rx OTC

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REMARKS:

This NDA provides for an injectable dosage form containing the identical drug substance described in NDA 20-862 (oral soft gelatin capsule, approved 6/9/99). The drug substance is a pro-drug for the native active form of vitamin D₂, 1 α ,25-dihydroxyvitamin D₂. After the original NDA was refused to file, the NDA was Filed Over Protest on 10/21/99 and the current user fee date is 4/6/00. A FDA CMC (including microbiology) information request letter was sent 2/3/00. The 2/17/00 and 2/24/00 amendments contain responses from the firm. The EER and microbiology review status is pending.

CONCLUSIONS & RECOMMENDATIONS:

The firm has provided an adequate response to CMC deficiencies. From a chemistry viewpoint the application is now approvable, pending only a recommendation for approval from the microbiology consult reviewer and the office of compliance. The firm should be reminded of their Phase IV commitments to NDA 20862 in the approval letter.

Orig. NDA # 21-027
cc: HFD-510/Division file/D-G.Wu/M.Haber/R.Hedin

/S/

Martin Haber, Ph.D.

R/D Init by: Dr. D-G. Wu, Team Leader Chemist

/S/ 3/28/00

5/10 /S/

FEB 1 2000

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-027 **DATE REVIEWED:** February 1, 2000 **CHEMISTRY REVIEW #:** 1

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	1/31/99	2/2/99	10/21/99 (see below)
Amendment	12/1/99	12/2/99	

NAME & ADDRESS OF SPONSOR: Bone Care International, Inc.
One Science Court, Madison, WI 53711 (608) 236-2500

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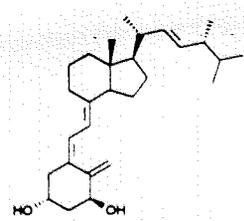
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REMARKS:

This NDA provides for an injectable dosage form containing the identical drug substance described in NDA 20-862 (oral soft gelatin capsule, approved 6/9/99). The drug substance is a pro-drug for the native active form of vitamin D₂, 1 α ,25-dihydroxyvitamin D₂. The division refused to file the original NDA for clinical and statistical deficiencies. Subsequently, the NDA was Filed Over Protest on 10/21/99 and the current due date is 2/15/00. The 12/1/99 amendment contains draft carton labels and a statement regarding the drug substance. The major chemistry deficiencies for this submission are related to [redacted]. The EER, microbiology and tradename review status is pending.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint the application is approvable, pending a satisfactory response to deficiencies delineated in the draft list of deficiencies and a recommendation for approval from microbiology and labeling consult reviewers and the office of compliance.

Orig. NDA # 21-027
 cc: HFD-510/Division file/D-G.Wu/M.Haber/R.Hedin

/S/

Martin Haber, Ph.D.

R/D Init by: Dr. D-G. Wu, Team Leader Chemist

/S/

2-1-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-027

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

MAR 24 2000

NDA: 21-027
Sponsor: Bone Care International
Drug: Hectorol (doxercalciferol) i.v. solution
Indication: Treatment of secondary hyperparathyroidism in end stage renal disease patients undergoing hemodialysis
Documents reviewed: Original volumes 1.1, 1.14 and 1.15, Volume 5.1 submitted December 20, 1999, submission dated February 22, 2000, and electronic data dated March 2, 1999
Medical Reviewer: Leo Lutwak, M.D. (HFD-510)
12-month User Fee date: April 6, 2000

Introduction

The sponsor has submitted one uncontrolled, open-label multicenter study of injectable Hectorol solution as treatment for secondary hyperparathyroidism in end stage renal disease (ESRD) patients undergoing hemodialysis. Patients who had previously completed treatment with oral Hectorol were treated at centers in two metropolitan areas, Memphis (9 centers) and Los Angeles (8 centers), under identical protocols.

During an 8-week pre-treatment period, patients were washed out of previous vitamin D treatment. After washout, all patients were given Hectorol i.v. for 12 weeks. Intact parathyroid hormone (iPTH) levels were measured weekly during washout and treatment. The starting dose of hectorol i.v. was 4 μ g for each of 3 weekly hemodialysis sessions. Treatment doses could be titrated to a maximum weekly dose of 18 μ g in an attempt to bring iPTH levels into the target range of (150, 300) mg/dL. The protocol endpoint was the change in iPTH level from baseline (average iPTH during the last three weeks of washout) to each post-treatment value.

This submission was originally filed on January 31, 1999. The DMEDP (HFD-510) sent the sponsor a Refuse-to-File letter on April 1, 1999, citing in part the lack of adequate well-controlled trials. On April 14, 1999, the sponsor asked that the submission be filed over protest; the Division filed the application on October 22nd. This review will present analyses of data from the original submission as well as additional statistical analyses submitted by the sponsor.

Patient disposition

Figure 1 (Appendix) shows the flow chart of subject participation in Trial 108 (oral hectorol) and Trial 114 (injectable). Out of 110 completers in Trial 108, 107 patients were considered eligible for participation in Trial 114. Twenty-seven subjects were dropped during washout (Table 1). The primary reason for discontinuation was low PTH during washout, a protocol exclusion criterion.

Table 1. Discontinuations during washout period

Reason for discontinuation	# of subjects
Low PTH ¹	14
Low serum phosphorus ¹	1
High serum phosphorus ¹	3
Low PTH and high serum phosphorus ¹	1
Received Albumin-based phosphate binders	1
Expired during washout	4
Concern for patient's safety – length of time w/o vitamin D therapy	1
Enrollment error	2
Total	27

¹ Classified by the sponsor as a protocol disqualification as opposed to a discontinuation.

Patients receiving hectorol i.v. treatment (n=70) were Black (84%), Caucasian (10%) or Hispanic (6%). Patients were evenly divided between males (51%) and females (49%). The mean age at entry was 52 years (range 23-76). Patients had been on hemodialysis a median of 44 months (range [redacted]).

Table 2 shows baseline iPTH values separately for patients receiving hectorol i.v. and washout discontinuations. Median iPTH values for hectorol i.v. patients were nearly twice as high as those for washout discontinuations (634 vs 329). Mean iPTH values differed by 200 mg/dL. The difference was statistically significant based on an analysis of ranks (p=.001). Much of the difference could be attributed to the 15 patients who were dropped during washout due to low iPTH levels per protocol (Table 1).

Table 2. Baseline¹ iPTH levels (mg/dL)

Statistic	Washout discontinuations (n=27)	Patients receiving hectorol i.v. treatment (n=70)
Min	86	266
10 th percentile	179	374
25 th percentile	214	458
Median	329	634
75 th percentile	728	915
90 th percentile	1120	1229
Max	1730	2039
Mean	536	736
SD	443	384
SE	85	46

¹ The sponsor computed a baseline mean for patients entering treatment as the average of the last three pre-treatment values (the average of Weeks -2, -1 and 0). This reviewer computed a baseline mean for all other patients by averaging the last three pre-treatment values for which data were available. In all instances, patients had at least three pre-treatment iPTH values in consecutive weeks, in most cases at Weeks -3, -2 and -1.

Results

Six patients receiving hectorol i.v. treatment were excluded from the sponsor's statistical analyses (Table 3). Four of these patients completed 12 weeks of treatment, and two completed 10 weeks. This reviewer's analysis results include all 70 patients receiving hectorol i.v.

Table 3. Sponsor's exclusions from statistical analysis

Reason for exclusion	# of subjects
Low dosing compliance ¹	2
Patient received Calcijex	1
Average serum phosphorus > 6.9mg/dL	2
Patient switched to a two times per week dialysis schedule	1
Total	6

¹One patient also hospitalized

The Wilcoxon one sample test was used to analyze Week 12 iPTH change from baseline. Values were carried forward for the two patients on-study for 10 weeks. Statistical tests were performed for all patients, and within metropolitan area. The nonparametric test was used in each case because the change from baseline data were not sufficiently normally distributed within the two metropolitan areas to justify the paired t test.

On-treatment iPTH levels were significantly reduced during treatment with Hecorol i.v. compared to baseline (Table 4). The results were significant for the individual protocols (Memphis, p=.001; LA, p=.004) and for the combined data as well (p<.001).

Table 4. iPTH summary statistics for patients receiving hectorol i.v.

iPTH Level	Memphis (n=42)	Los Angeles (n=28)	Combined protocols (n=70)
Baseline (Mean of Weeks -2, -1 and 0)			
Mean (SE)	762 (65)	698 (60)	736 (46)
Median	648	562	634
On-treatment (Week 12 ¹)			
Mean (SE)	426 (60)	406 (63)	418 (43)
Median	292	311	292
Change from Baseline ²			
Mean (SE)	-336 (41)	-292 (55)	-318 (33)
Median	-315	-274	-304
P-value ³	.001	.004	<.001

¹ Values were carried forward for the two patients on-study for 10 weeks

² Treatment iPTH minus baseline iPTH

³ Wilcoxon one-sample test

Figure 2 shows a cumulative distribution plot for iPTH change from baseline. The "curve" is clearly shifted to the left of zero on the horizontal axis, indicating the majority of patients experienced decreased iPTH during treatment.

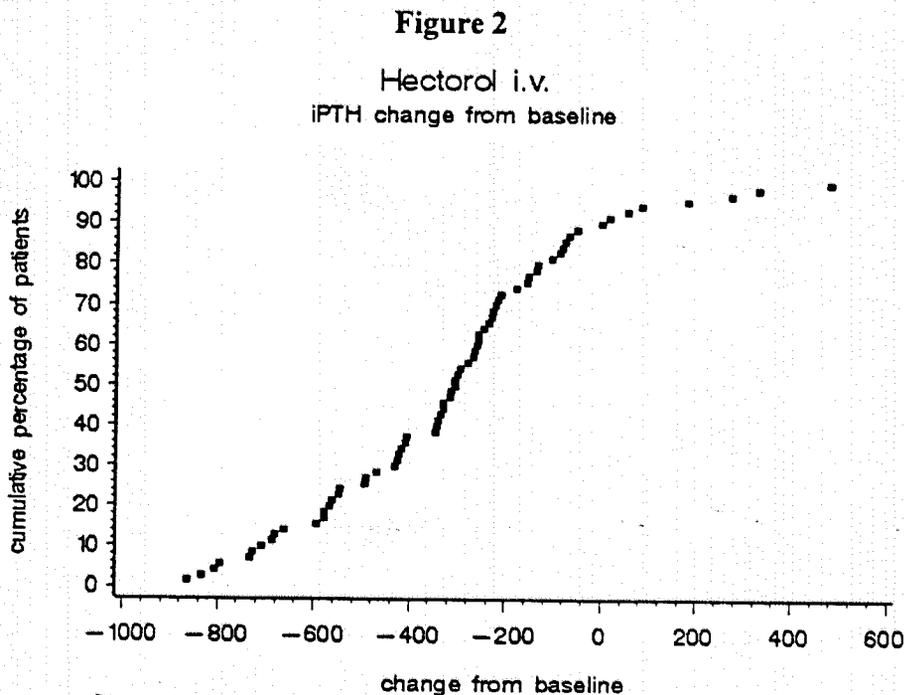


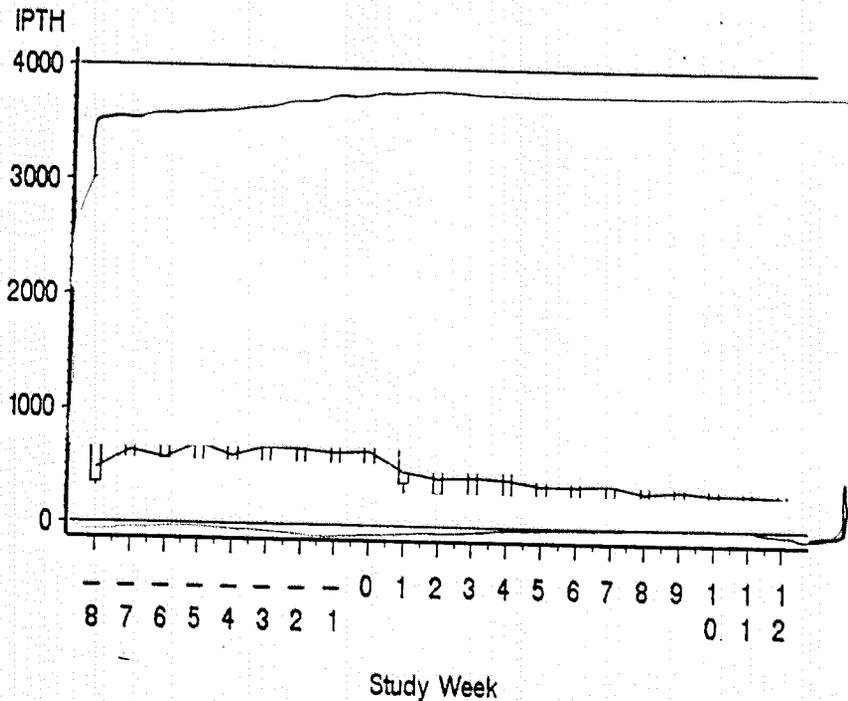
Figure 3 shows boxplots of iPTH over time. Median values are joined by a solid line. Some patients had missing values at some weeks, so week-to-week sample sizes were not identical, ranging from [redacted]. There is a clear downward shift in iPTH levels at Week 1, the start of hectorol i.v. treatment.

APPEARS THIS WAY
ON ORIGINAL

Figure 3

Hectorol i.v.

iPTH Boxplots by week for patients entering treatment



This reviewer examined whether baseline iPTH was a predictor of on-treatment response. Two subgroups of patients were analyzed as defined by the median baseline iPTH (641 mg/dL). Patients with baseline iPTH levels above 641 had larger changes from baseline (mean -466, median -519) than did patients with baselines below 641 (mean -179, median -221). The difference was statistically significant ($p < .001$). *Percentage changes* were also different between subgroups although the difference did not reach statistical significance ($p = .20$). Patients with high baselines experienced a 59% median decrease in iPTH levels, whereas patients with lower baselines experienced a 49% median decrease. The subgroup analysis suggests that, had the 27 patients who were discontinued during washout been given hectorol and followed to completion, their endpoint responses would probably have been less than responses for completers.

December 20, 1999 and February 22, 2000, submissions

The sponsor presented additional statistical analyses in response to the following concerns of the Medical Division and this reviewer expressed in a July 30, 1999, telecon:

- (1) The potential for bias in favor of Hectorol injection stemming from the relatively small number of patients treated with the i.v. formulation (n=70) relative to the number of patients initially enrolled in the trial of oral hectorol (n=211); and
- (2) The unpredictability of the natural course of hyperthyroidism during periods when Vitamin D treatment was withheld, e.g., during washout periods.

Sponsor's Response to item (1)

The sponsor addressed item (1) by comparing washout iPTH values *during the trial of oral hectorol* for patients treated with i.v. hectorol (n=70) with patients who were not (n=141). Two subsets of the latter group, patients who received open-label oral hectorol treatment (n=68) and patients who were treated during the double-blind period (n=52), also were compared to patients treated with i.v. hectorol.

Week -8 iPTH and Baseline iPTH were used as measures of comparison. Week -8 results were similar to the results for Baseline and for this reason are not shown here. The groups were compared using the Wilcoxon rank sum test.

Subjects receiving i.v. hectorol had significantly higher baselines than did subjects who were enrolled in the trial oral hectorol but did not receive hectorol i.v. (Table 5, p<.001). The sponsor claimed this result was expected because the non-i.v. group included approximately 50 subjects who were disqualified from treatment with oral hectorol due to low iPTH values during washout (iPTH < 400 pg/ml).

**Table 5. Subjects enrolled in (oral) Trial H-108:
iPTH at Baseline ¹**

Treated in H-114 (i.v.)	No	Yes
N	124 ²	70
Mean (pg/mL)	541	926
SD	538	530
SE	45	63
P-value ³	<.001	

¹ Baseline iPTH was the average of values at Weeks -2, -1 and 0.

² No Baseline iPTH values available for 17 subjects who discontinued prior to Week -2..

³ Wilcoxon rank sum test

Table 6 shows data for patients who were treated with oral hectorol. IPTH values at Baseline were not statistically different between patients who subsequently received i.v. hectorol and those who did not.

**Table 6. Subjects treated with oral hectorol in (oral) Trial H-108:
iPTH at Baseline ¹**

Treated in H-114 (i.v.)	No	Yes
N	67 ²	70
Mean (pg/mL)	841	926
SD	424	530
SE	52	63
P-value ³	.38	

¹ Baseline iPTH was the average of values at Weeks -2, -1 and 0.

² The 4 washout iPTH values available for one subject were taken to run from Week -8 to Week -4 in this analysis.

³ Wilcoxon rank sum test

Table 7 shows data for patients who entered the double-blind period of oral hectorol. IPTH values at Baseline were not statistically different between patients who subsequently received i.v. hectorol and those who did not.

**Table 7. Subjects who entered double-blind period in (oral) Trial H-108:
iPTH at Baseline ¹**

Treated in H-114 (i.v.)	No	Yes
N	51 ²	70
Mean (pg/mL)	836	926
SD	452	530
SE	63	63
P-value ³	.30	

¹ Baseline iPTH was the average of values at Weeks -2, -1 and 0.

² The 4 washout iPTH values available for one subject were taken to run from Week -8 to Week -4 in this analysis.

³ Wilcoxon rank sum test

The sponsor also conducted repeated measures ANOVA of washout iPTH levels in Trial 108. The analyses adjusted for Baseline differences between the groups (i.e., Baselines were forced to be equal) but allowed for a comparison of *the rate of change over time* during the washout period. The statistical model specified group and time as main effects and time*group as an interaction term. Two analyses were conducted, one for all enrolled patients and another for patients who entered the double-blind treatment period.

Results were consistent across the two analyses. The group effect was not statistically significant. The time effect was statistically significant ($p < .001$), reflecting the fact that iPTH values drifted upward during the washout. The interaction term was not statistically significant ($p > .3$), suggesting that baseline iPTH levels changed at rates that were not statistically different between the groups.

Reviewer's comments

To dispel the issue of the potential for bias in favor of Hectorol injection stemming from a possibly "enriched" population, the sponsor compared patients who received oral hectorol and not hectorol i.v., with patients who received both treatments. The measure of comparability used was baseline iPTH during the trial of oral hectorol.

The sponsor's analyses are not sufficient to address the *potential* for bias. The groups being compared are not the result of randomized assignment, but defined according to their response to oral treatment, ability to complete oral treatment, and other treatment-related factors. Although the sponsor has generated several non-significant p-values, for the reason just given it is difficult to assign any statistical meaning to these p-values. Furthermore, comparability is not a one-dimensional issue; other (possibly many) variables would have to be investigated as well.

The repeated measures ANOVA, as analyzed, will not produce a meaningful test for between-group differences. This is because iPTH values were normalized by forcing Baselines in the groups to be equal. This maneuver will make other (non-Baseline) washout values be more alike as well.

Sponsor's Response to item (2)

The sponsor conducted analyses to support the "predictability" of the natural course of hyperthyroidism when vitamin D treatment is withheld by examining iPTH data in the 3 periods of non-treatment with vitamin D therapy in the oral and i.v. studies:

- Period 1: Washout during H-108 (Weeks -8 to 0)
- Period 2: Washout during H-114 (Weeks -8 to 0)
- Period 3: Placebo treatment during H-108 (Weeks 16 to 24).

Mean normalized iPTH values were computed for each Week of each Period. Periods 1 and 2 were compared on Weekly iPTH levels, as were Periods 1 and 3, using t tests. The sponsor did not compare Periods 2 and 3.

iPTH levels generally rose monotonically within each Period. There were no significant differences between Periods at any timepoint for the comparisons that were conducted.

Reviewer's comments

The sponsor's analyses adequately address this issue.

**APPEARS THIS WAY
ON ORIGINAL**

Summary

Hectorol i.v. produced statistically significant reductions in iPTH levels from baseline in a selected group of patients who had previously completed treatment with oral hectorol. The magnitude of response varied with baseline. Because completers had statistically different baselines than discontinuations, the overall response might have been smaller if all patients had been followed until the end of the study.

None of the sponsor's analyses of washout iPTH values during the trial of oral hectorol for patients treated with i.v. hectorol compared to patients who were not resolves the issue of the *potential* for bias in favor of improved hectorol i.v. response in a possibly enriched population. The groups being compared were not the result of randomized assignment, but defined according to their response to oral treatment, ability to complete oral treatment, and other treatment-related factors. Therefore it is difficult to give any credance to the p-values comparing baseline iPTH values.

Suggestions for labelling

Labelling should reflect the fact that patients administered injectable Hectotol were a selected subset of patients who received oral Hectorol. As such, there should be no clinical data in the label directly comparing iPTH data for oral and i.v. formulations.

/S/

J. Todd Sahlroot, Ph.D.

Concur: Dr. Nevius /S/ 3/22/10

Cc:

Orig. NDA 21-027

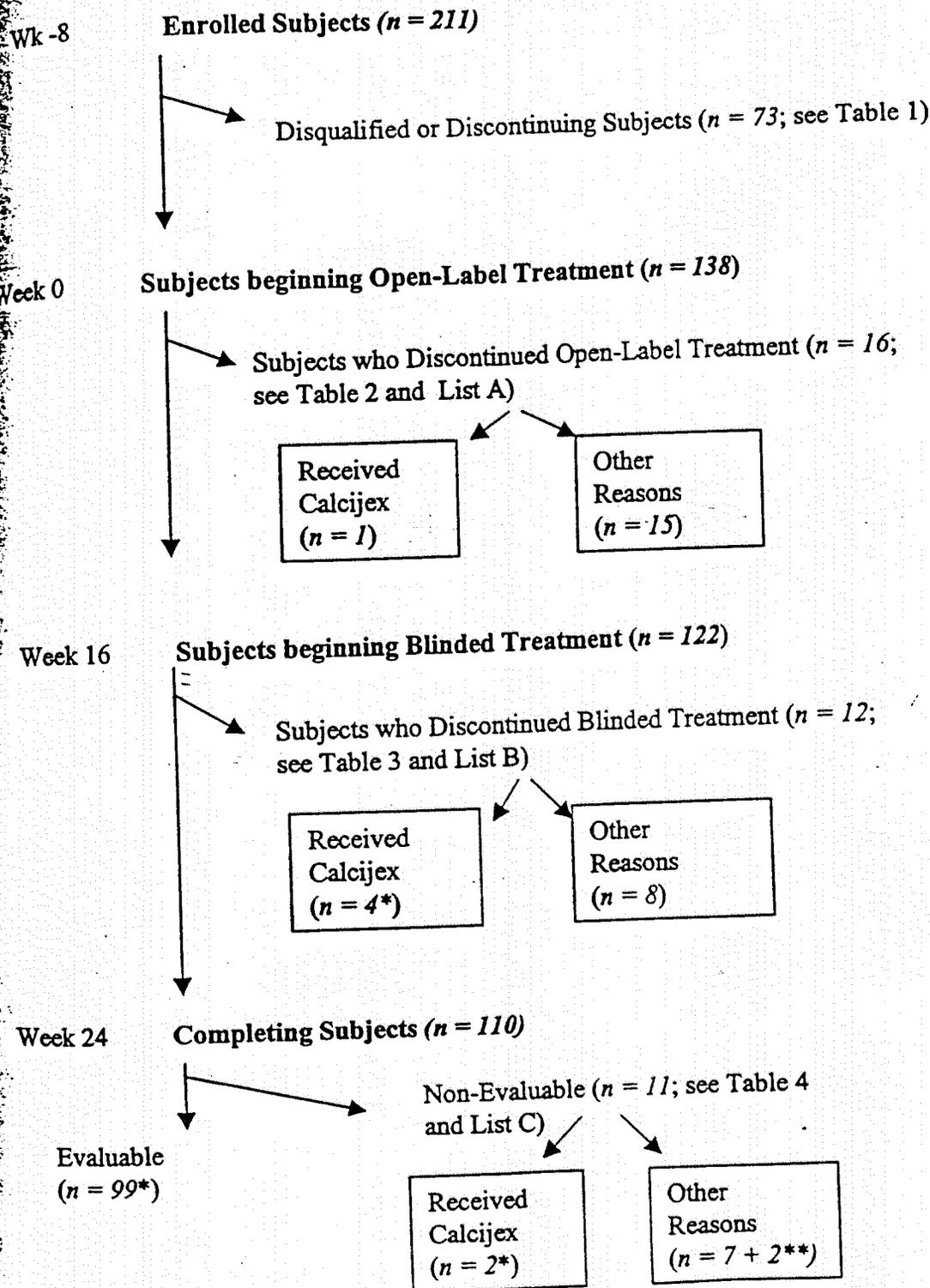
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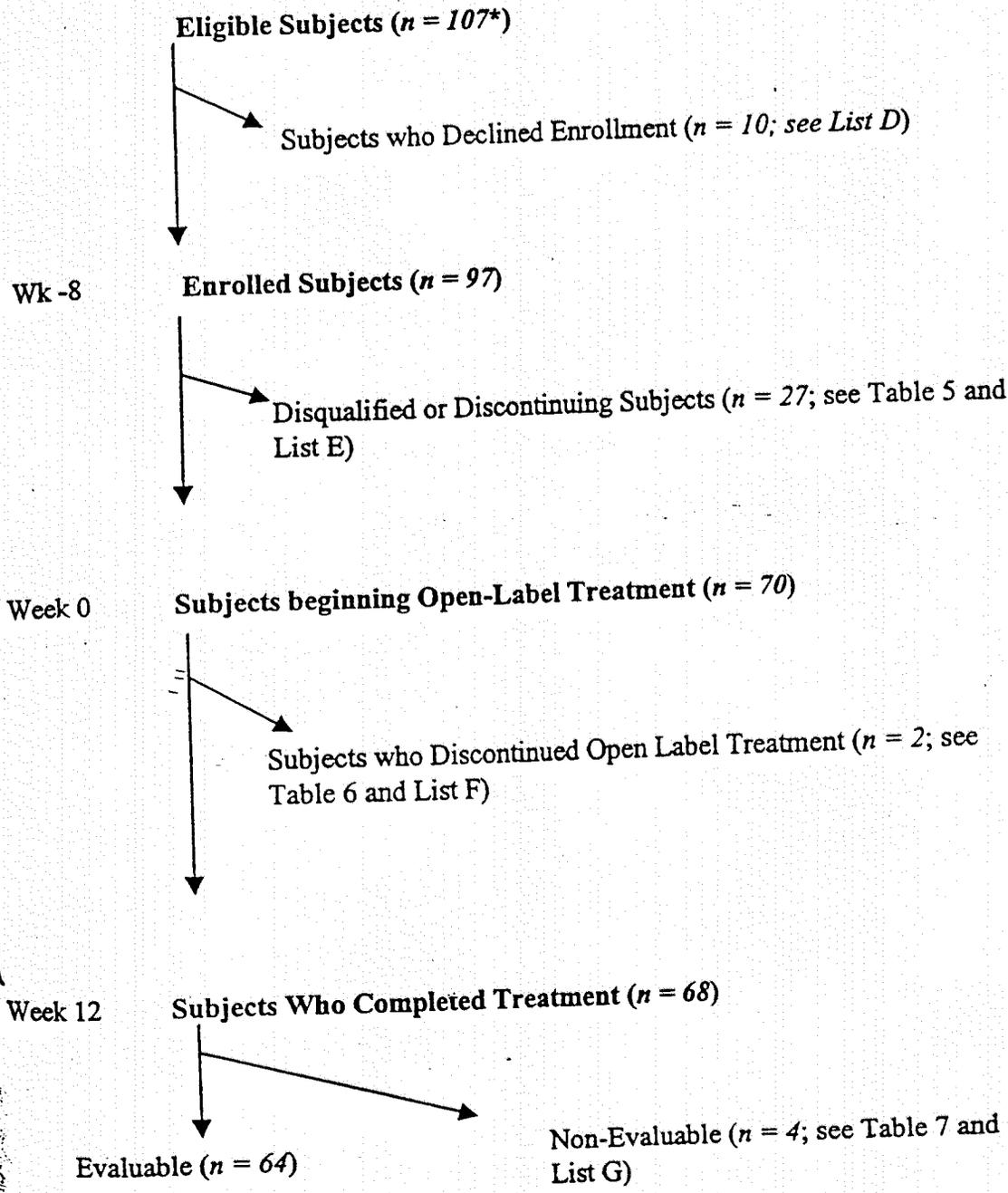
Flow Chart of Subject Participation in
Clinical Study Nos. H-108-LA and H-108-Memphis



Eligible for participation in Clinical Study Nos. H-114-LA and H-114-Memphis ($n=105$)

Two subjects from this group were initially considered eligible for participation in Clinical Study H-114-LA and H-114-Memphis but were found to be ineligible after enrollment in these studies.

**Flow Chart of Subject Participation in
Clinical Study Nos. H-114-LA and H-114-Memphis**



*All 107 subjects had participated in Clinical Study Nos. H-108-LA and H-108-Memphis. Of these, 99 were evaluable in the prior studies, 6 were evaluable except for receipt of Calcijex during Treatment Period #2, and 2 were enrolled in error.