

period) in this patient population. The agency indicated its belief that the natural history of untreated hyperparathyroidism was highly variable and unpredictable, in terms of iPTH levels. Dr. Sahlroot felt that the issue was not only the use of mean values but the variation around the mean as well as the discontinuation of patients. Dr. Bishop contested the notion that historical controls are inadequate or that the wash-out periods did not represent adequate historical controls. He noted that placebo controls were not appropriate or ethical in this patient population. He further stated that, with the study analysis of iPTH levels in the last 3 weeks of the 8-week wash-out as compared to each week during the treatment with Hectorol Injection, the analysis plan did in fact include sufficient compensation for week-to-week variability.

Finally, there was discussion about the potential for selection biases in the active treatment one-label group.

There followed a brief discussion of the procedural status. Dr. Strobos noted that it was his view that the NDA had been filed over protest. Dr. Sobel indicated that he understood our position and would have to review the regulatory situation with the appropriate people within the agency.

Action Items

- Bone Care would submit a written response that would include proposals for use of pharmacodynamic data to evaluate efficacy; development and demonstration of the appropriateness of a new historical control for Clinical Study Nos. H-114; and/or other analyses of existing data in NDA No. 21-027.
- The agency agreed to evaluate and respond to such a written proposal.
- The agency would internally evaluate its understanding of the status of NDA 21-027.

APPEARS THIS WAY
ON ORIGINAL

TAB B

An RTF letter (dated April 1, 1999) was received on April 5, 1999. An informal conference, following a written request filed with the agency on April 6, was held on April 9, 1999. Both the written request and the informal conference are described as preliminary to a filing over protest at § 314.101(a)(3). As set forth in the RTF letter:

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference.

Following the informal conference, Bone Care International filed, on April 14, 1999, a written clarification (with attachments) which specifically addressed the two objections in the RTF letter. This filing further thanked the agency "in advance for re-examining" the filing in light of the submission and requested that FDA "file the NDA without revision as soon as possible." We know of no clearer method of compliance with the provisions of 21 C.F.R. § 314.101(a)(3) relating to filing over protest, which state:

If, following the informal conference, the applicant requests that FDA file the application or abbreviated antibiotic application (with or without amendments to correct the deficiencies), the agency will file the application or abbreviated antibiotic application over protest under paragraph (a)(2) of this section, notify the applicant in writing, and review it as filed.¹

Additionally, following this filing over protest, Bone Care International made repeated verbal requests (April 29, May 14, June 14) for written confirmation of the filing and was assured, at each telephone call, that an agency response would be forthcoming. In any event, neither the regulations nor the RTF letter provide a time limit on the request for filing over protest.² We therefore request that the agency review the application as filed. Under the regulations, the appropriate filing date is 60 days after the date of submission of the request for the informal conference. Additionally, please note that we view the April 14th filing, as well as this correspondence and anticipated filings described in this correspondence, as falling within the amendments expressly permitted for a filing over protest ("to correct the deficiencies").

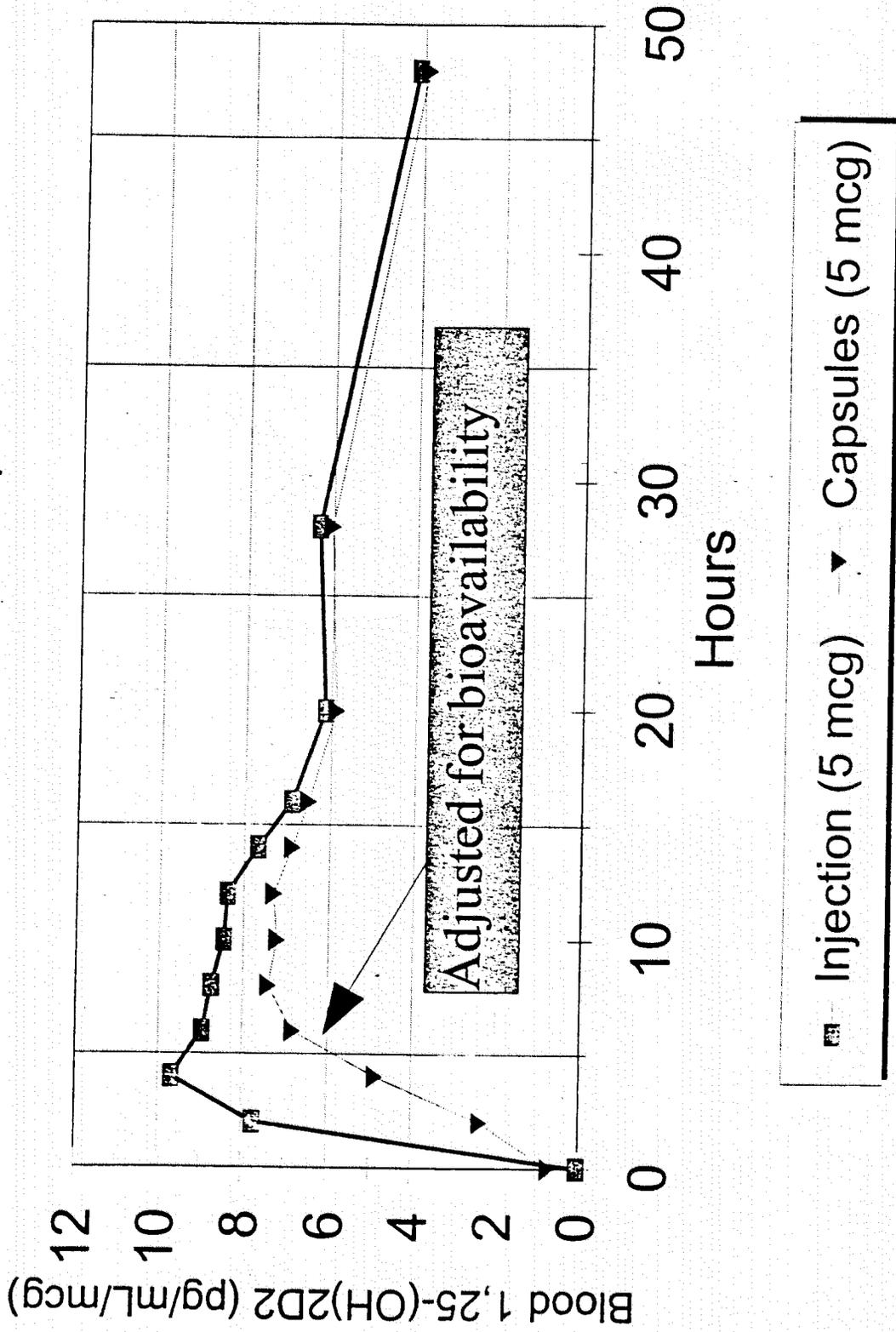
APPEARS THIS WAY
ON ORIGINAL

¹ Please note that these regulations do not specifically require the applicant to reference the filing as "over protest" in the applicant's correspondence—the applicant merely requests the filing. The regulations arguably require the agency to use this specific terminology when completing the filing of the application following the sponsor's request.

² The regulations do require that the written request for an informal conference be filed within 30 days of notification of the RTF letter. The written request was, in fact, filed within 24 hours of such notification.

Figure 1: Comparative Pharmacokinetics

Hectorol Injection vs. Capsules

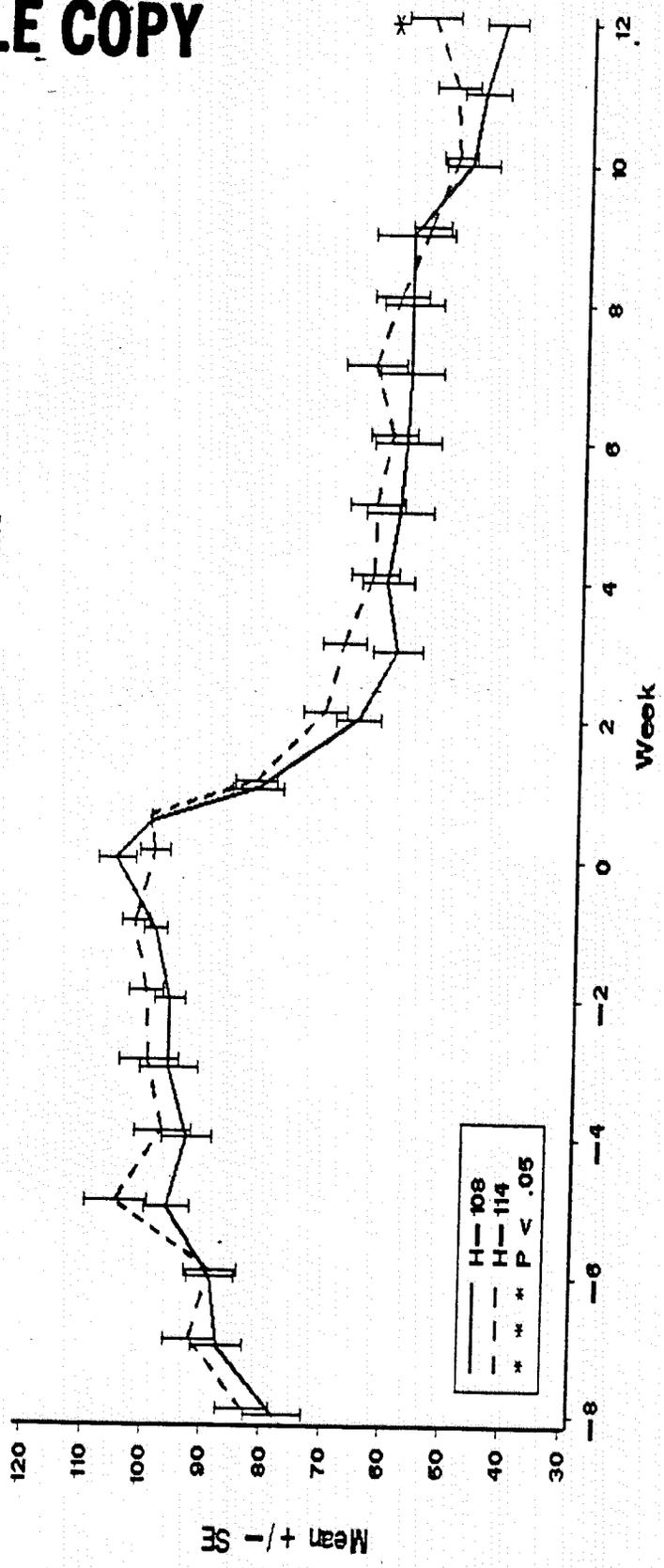


[Source: Study No. H-103; see NDA No. 21-027, Vol. 1.8, pp. 9-10.]

Figure 2: Comparative Pharmacodynamics (Per Protocol)
 Hecitorol Injection vs. Capsules

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Bone Care International
 Protocol H-114: All Per-Protocol Patients
 Plot of Mean PTH vs Time
 Data expressed as percent of baseline

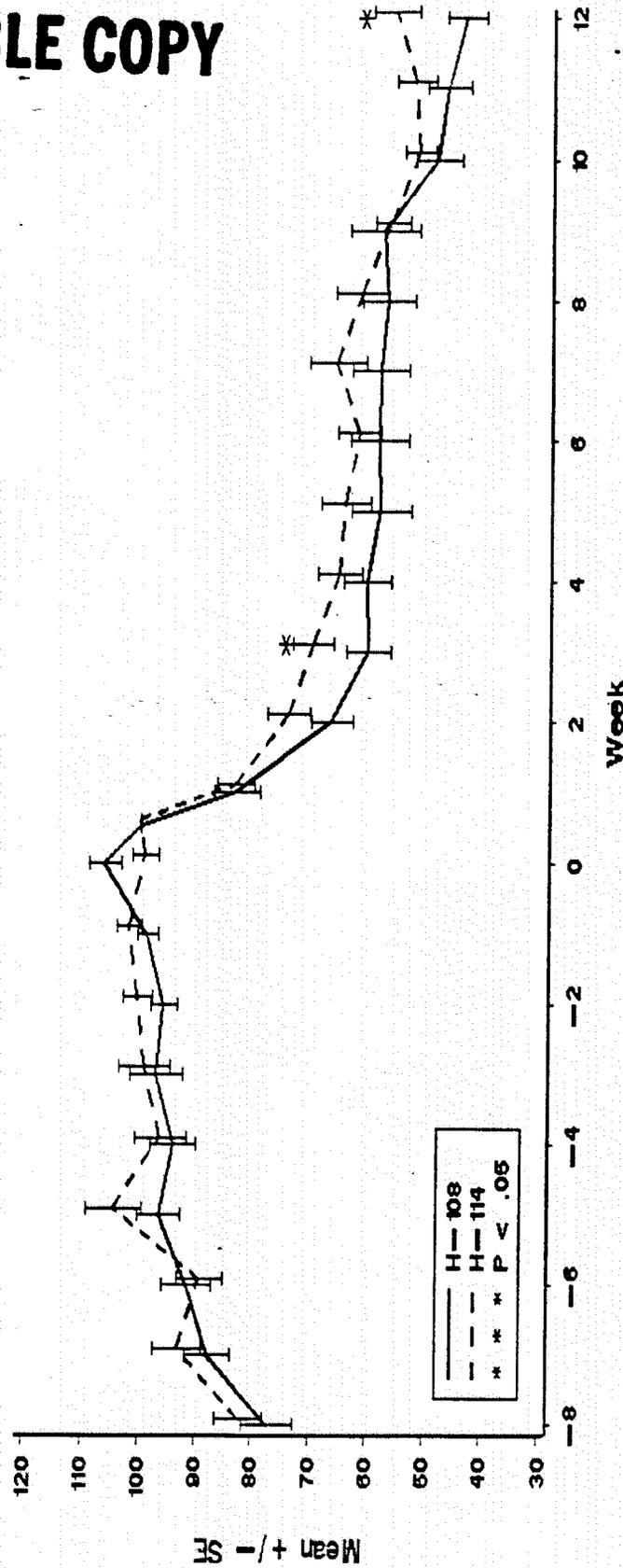


[Source: NDA No. 21-027, Vol. 1.15, p. 103.]

Figure 3: Comparative Pharmacodynamics (Intent-to-Treat) Hectorol Injection vs. Capsules

BEST POSSIBLE COPY

Bone Care International
Protocol H-114: All Intent-to-Treat Patients
Plot of Mean PTH vs Time
Data expressed as percent of baseline



Note: Baseline plotted at Week = 0
Note: Last value carried to end of study

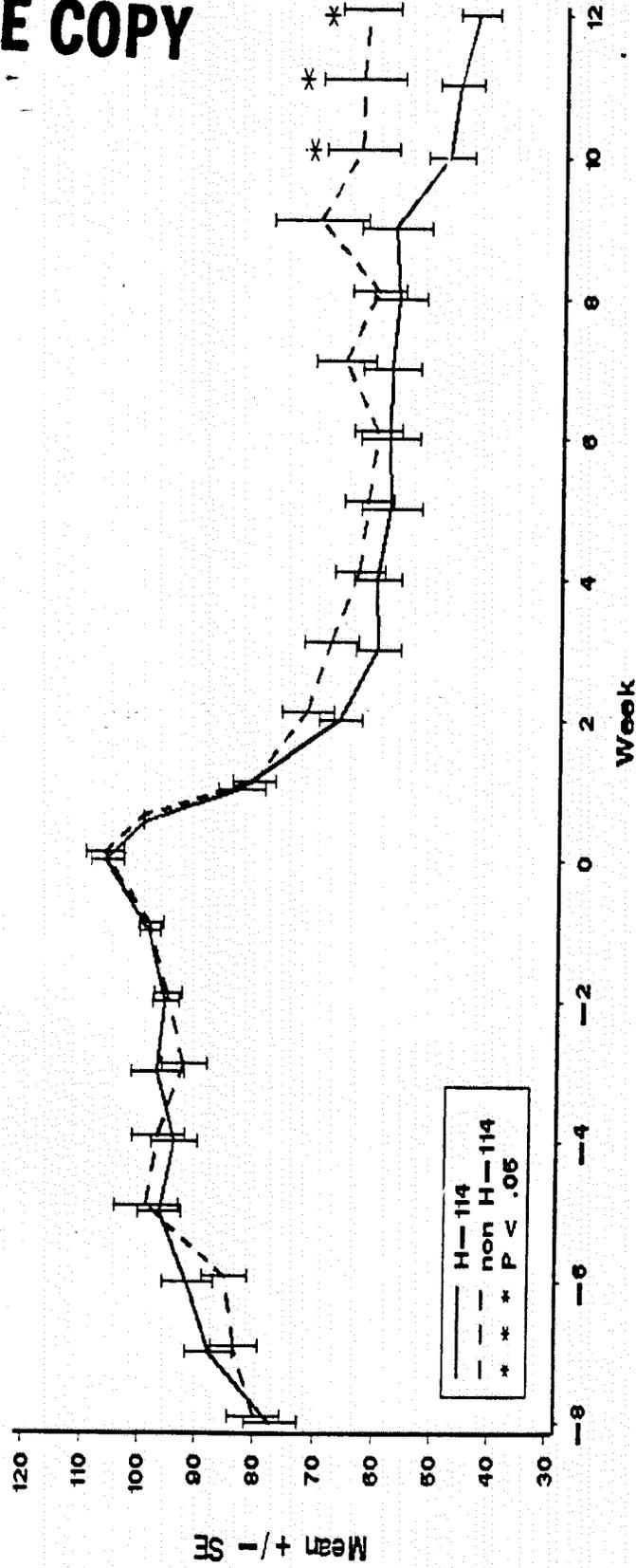
[Source: NDA No. 21-027, Vol. 1.14, pp. 248-253.]

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Figure 4: Comparative Pharmacodynamics (Intent-to-Treat)

H-114 cohort vs, non-H-114 cohort in Clinical Study Nos. H-108

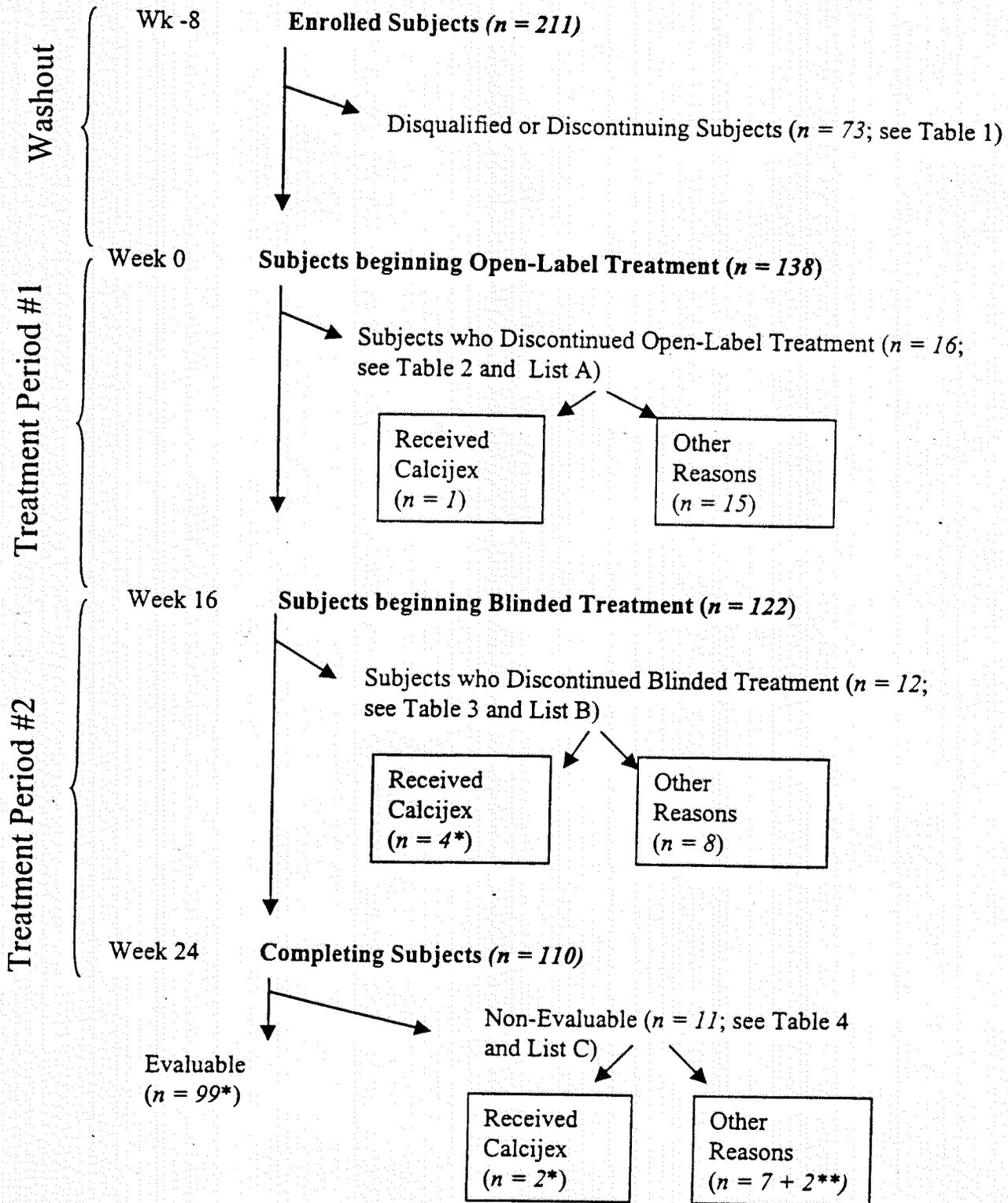
Bone Care International
 Protocol H-108: All Intent-to-Treat Patients
 Plot of Mean PTH vs Time
 Data expressed as percent of baseline



Note: Baseline plotted at Week = .0
 Note: Last value carried to end of study

[Source: NDA No. 20-862, Vol. 11.1, pp. 5-14.]

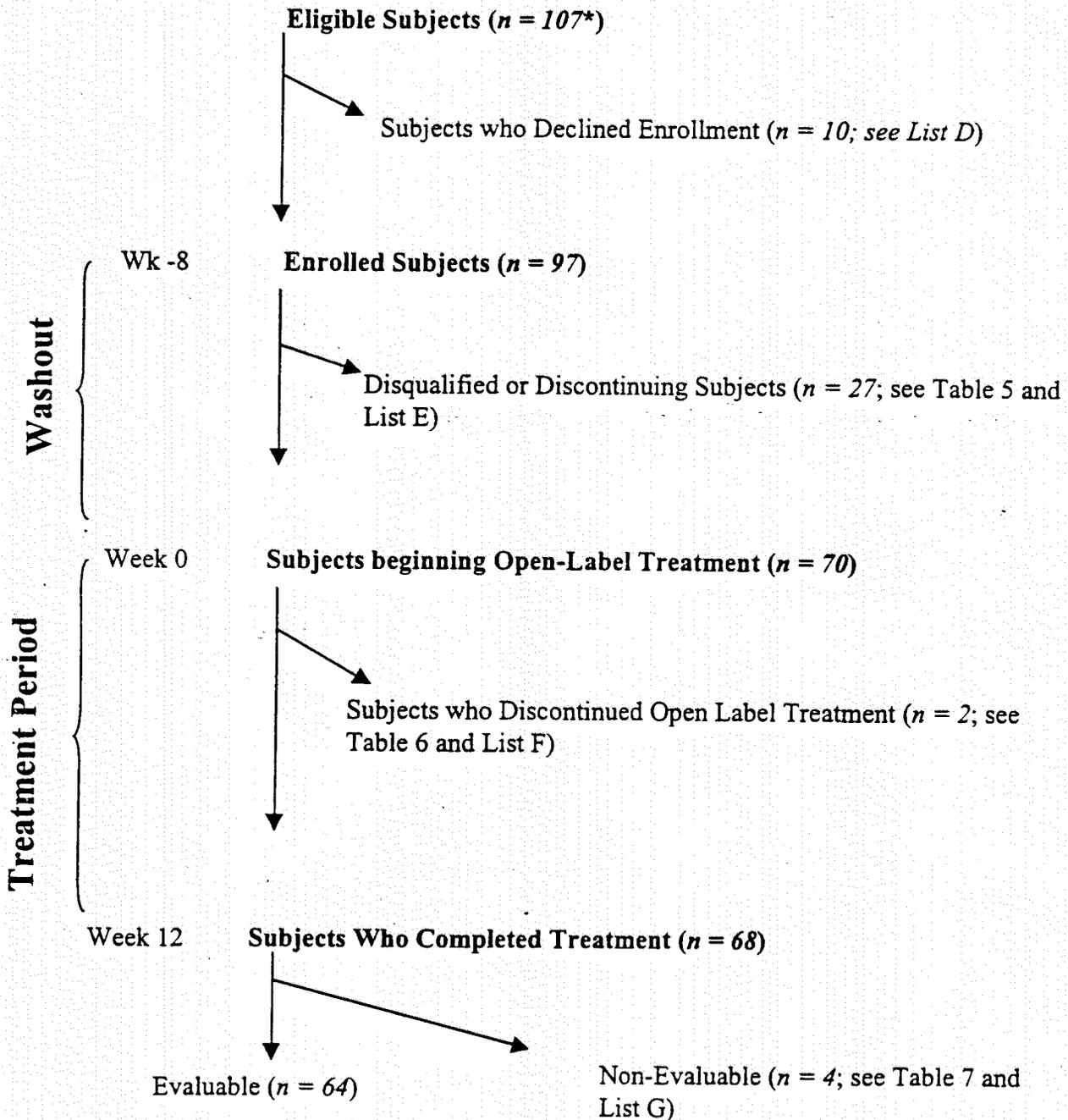
**Flow Chart of Subject Participation in
Clinical Study Nos. H-108-LA and H-108-Memphis**



*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 Nos. 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.

Bone Care

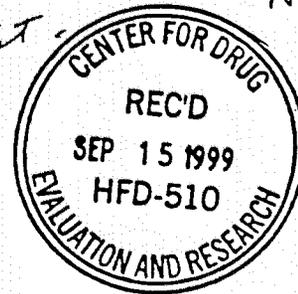
ORIGINAL

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-2500 **NEW CORRESP**

September 14, 1999

*Noted.
Previous review
of entire question
of filing over protest
151
11/2/99*



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center of Drug Evaluation and Research (HFD-510)
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857

*Noted
151
11/2/99*

*NC 151
11/2/99*

Correspondence
Hectorol® Injection (doxercalciferol)
NDA 21-027

Dear Dr. Sobel: -

On behalf of Dr. Jur Strobos, Ms. Darlene Kylo and myself, I am writing to thank Drs. Troendle, Lutwak, and Sahlroot; Ms. Hess, and you for meeting with Bone Care by teleconference on August 24, 1999. The time which you spent discussing the Phase 3 trials of Hectorol Injection (Clinical Study Nos. H-114-LA and H-114-Memphis) gave us a clearer grasp of the problems which DMEDP perceives with these studies. Specifically, we understand that DMEDP is reluctant to accept the 8-week washout period as an historical control by which the effectiveness of Hectorol Injection can be judged, preferring instead a placebo control like that used in the Phase 3 trials of Hectorol Capsules. We also understand that DMEDP has concerns as to the acceptability of the historical controls for Clinical Study Nos. H-114-LA and H-114-Memphis due to the large number of subjects who were disqualified or discontinued.

We are preparing, with Dr. Strobos, a proposal, as we suggested during the teleconference, which will be submitted to DMEDP shortly. We will propose that DMEDP review NDA No. 21-027 based on either, or both, pharmacokinetic and pharmacodynamic data which demonstrate the equivalence of Hectorol Injection and Hectorol Capsules.

An example of pharmacokinetic data included in this NDA appears in Figure 1 (attached). Here, the blood levels of $1\alpha,25$ -dihydroxyvitamin D_2 (the major active metabolite of doxercalciferol) are shown over 48 hours after both a 5 mcg intravenous and oral dose (oral dose

Solomon Sobel, M.D.
September 14, 1999
Page 2

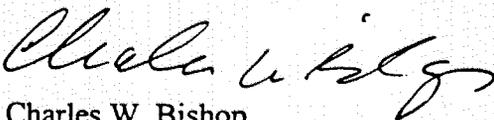
was adjusted by a factor of 0.41 to reflect documented lower bioavailability). The two formulations are equivalent (i.e., the areas under the curves are within 20% of each other) although, as expected, t_{max} occurs several hours sooner for the intravenous formulation.

There is also pharmacodynamic equivalence. Figure 2 (attached) shows the iPTH suppression observed in 138 patients treated with Hectorol Capsules (Clinical Study Nos. H-108-LA and H-108-Memphis) and the 70 patients treated with Hectorol Injection (Clinical Study Nos. H-114-LA and H-114-Memphis). The intent-to-treat responses to the two formulations of Hectorol are virtually indistinguishable. These responses compare favorably with intent-to-treat responses observed in two studies conducted by Abbott Laboratories (Study Nos. 95028 and 95034) which used Calcijex (calcitriol injection) and Zemplar (paricalcitol injection). The iPTH suppression during treatment with Hectorol Capsules and Hectorol Injection is at least equivalent to that during treatment with Calcijex or Zemplar. *(The data from Abbott's studies were obtained from pages 52 and 75 of the Medical Officer's Review of Zemplar, as obtained under Freedom of Information).* Unlike the latter agents, Hectorol was given without the need for any aluminum phosphate binders, which are problematic in dialysis patients because of aluminum-induced bone disease.

These two charts should alert you to the fact that both intravenous or oral formulations of Hectorol are bioequivalent.

As a final note, elevated PTH in dialysis patients is not only a problem for bone, but produces increased cardiovascular risks¹ and triples the rates of some cancers². Parathyroidectomy is contraindicated in renal patients, and leading nephrologists instead advocate close control of PTH through drug intervention.

Sincerely yours,



Charles W. Bishop
President & CEO

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

References

1. Maissonneuve P, Agodoa L, Gellert R, Steart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P. (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 354:93-99.
2. Rostand SG, Drueke TB. (1999) Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 56:383-392.

OLSSON, FRANK AND WEEDA, P.C.

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RICHARD L. FRANK
DAVID F. WEEDA
DENNIS R. JOHNSON
ARTHUR Y. TSIEN
JOHN W. BODE+
STEPHEN D. TERMAN
MARSHALL L. MATZ
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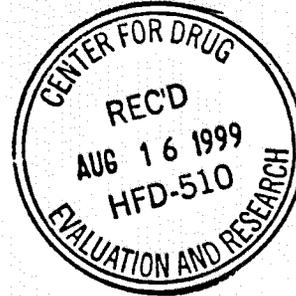
ORIGINAL

NDA SUPP AMEND

BM

Jur Strobos, MD
202/518-6377

August 13, 1999



Dr. Gloria Troendle
Division of Metabolic and Endocrine Drug Products
HFD-510; Parklawn Building Rm. 14B-19
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Note: This submission was reviewed in a 10/13/99 meeting in a RTF request in Dept. of Ad. further.

By Facsimile - 301-443-9282

REVIEWS COMPLETED
CSD ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSD INITIALS: <i>LSI</i> 10-25-99
DATE

Correspondence
Hectorol® Injection (doxercalciferol)
NDA 21-027

Dear Dr. Troendle:

This letter is to recapitulate our conversation of yesterday morning held on behalf of my client, Bone Care International ("Bone Care"), in regard to the above-captioned NDA. Briefly, this NDA was initially submitted on February 1, 1999. A Refuse-To-File ("RTF") letter, dated April 1, 1999, was received by Bone Care on April 5, 1999, which cited deficiencies in the clinical studies and supportive pharmacokinetic data. An informal conference was held on April 9, 1999, and a written follow-up provided by Bone Care on April 14th. My understanding is that the pharmacokinetic issues were fully resolved. An additional telephonic conference was held on July 30, 1999.

While I am new to the scientific issues, I have had some difficulty in understanding the Division's specific concerns with regard to the clinical studies. The RTF letter references potentially inadequate or non-existent controls and variable wash-outs. As noted in the April 14th submission, the design of the Hectorol® Injection studies was an open label 12 week treatment preceded by a uniform 8-week washout from oral Hectorol® before entry. Thus, each patient had a no-treatment historical control and the initial wash-out was consistent and standard

NC LSI 10/21/99

for this type of drug product. Comments provided to me by Bone Care on the July 30th conference, *see* attached letter, address a different issue: the potential that the clinical trials for Hectorol® Injection may have been limited to a subset of "enriched" patients in that the enrolled patients had previously demonstrated responsiveness to oral Hectorol®. This issue was not identified in the RTF letter and we know of no data to substantiate a clinical effect. Additionally, in the days immediately following the July 30th conference, this concern was not initially clear to us if only because internal and external advisers to Bone Care did not find this contention to be intuitive from a metabolic standpoint.

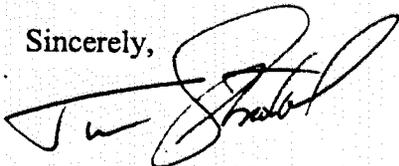
However, as per our teleconference, if the theoretical enrichment issue is the principal or only remaining concern, we believe that there may be a number of methods to address this concern through simple additions to the file. These potential additions could include: (1) re-analysis of the clinical data to capture a "worst case" response rate based on retrospective inclusion of "drop-outs," or those lost to follow-up, who were not entered into the Hectorol® Injection studies; (2) under the provisions of the Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," use of pharmacokinetic data from patients whose response to Hectorol® was unknown to calculate a response rate to Hectorol® Injection as an alternative to another supportive clinical trial;¹ (3) alteration of proposed labeling to add information about suspected response rates and the need for careful monitoring of blood parameters to detect response; or, (4) commitment to an open-label Phase IV study of rate of response (reduction in iPTH) in Hectorol® naïve patients. Alternatively, the indication for Hectorol® Injection could be simply limited to patients such as those entered into the H-114 trials.

From a procedural standpoint, we are certain that there are several available methods under the regulations to review the submission, as thus enlarged, provided that we can properly identify the correct substantive scientific approach to providing appropriate clinical evidence of safety and effectiveness.

As per our teleconference, we have also attached our 3 page response to Dr. Sobel following our teleconference of July 30th which addresses what we understood to be the other potential issues raised by the Division. Please note that the foregoing comments supplement the response to item # 2 in this attached letter.

I look forward to discussing these potential options with you on next Wednesday morning if that is a suitable time for you. You can reach me at 202-518-6377 or Darlene Kylo of Bone Care at 608-236-2530.

Sincerely,



Jur Strobos, MD

APPEARS THIS WAY
ON ORIGINAL

Attachment as in text.

¹ See section II.C.1.d and II.C.2.a, relating to approval of different dosage forms, since oral Hectorol® is approved.

Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

July 20, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

Dr. Charles Bishop and I request a teleconference with you regarding the filing status of NDA No. 21-027 for Hectorol Injection submitted on February 1, 1999.

We have been told informally that NDA No. 21-027 remains unfiled pursuant to your letter of April 1, 1999, which refused the application. According to Mr. Hedin, whom we contacted by phone on July 16, 1999, Dr. Lutwak holds the opinion that the two pivotal clinical trials included in this NDA are deficient in scientific design, execution, and statistical analysis. However, neither Dr. Lutwak nor DMEDP has communicated to Bone Care the exact nature of the deficiencies.

Your letter cites deficiencies pertaining to a hypothetical pivotal study which Bone Care did not conduct or submit for review. This inexplicable criticism prompted us to schedule a meeting with DMEDP on April 9, 1999. During this meeting, we and Drs. Jack Coburn and Russell Chesney, our Principal Investigators, reviewed the two pivotal studies which we actually designed, conducted, and submitted. We then documented our position on these studies in Volume 3.1, submitted on April 14, 1999. At the close of the meeting, Drs. Troendle and Lutwak agreed to reexamine NDA No. 21-027 for possible filing. However, we have not received further written communication from DMEDP regarding the filing status of this NDA.

We readily acknowledge that Bone Care did not conduct the pivotal study which Dr. Lutwak apparently envisioned. Instead, we conducted two 20-week studies, each containing 8-week historical control periods during which no vitamin D compounds were administered. These two studies (No. H-114-LA and H-114-Memphis) were designed by Drs. Coburn and Chesney, both experts in the clinical evaluation of vitamin D drugs. The studies were similar in scientific design to Phase 2 studies (Nos. H-106 and H-110) conducted earlier with Hectorol Capsules and identified by DMEDP as adequate and well-controlled studies (please refer to the final package insert).

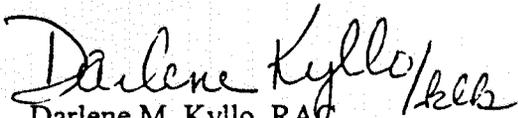
Solomon Sobel, M.D., Director

July 20, 1999

Page 2

We respectfully request a teleconference to ascertain from you exactly what is deficient in the two pivotal studies which we conducted with Hectorol Injection. Should you decide not to file NDA No. 21-027 because of deficiencies in the scientific design of these studies, what would you propose instead as an acceptable design for replacement studies?

Sincerely yours,

Handwritten signature of Darlene M. Kylo in cursive script.

Darlene M. Kylo, RAC

Director, Compliance, Quality & Regulatory Affairs

DMK/klb

APPEARS THIS WAY
ON ORIGINAL

Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

April 14, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

Enclosed is a submission, identified as Volume 3.1, to our New Drug Application for intravenous (IV) Hectorol (doxercalciferol, 1-alpha-hydroxyvitamin D₂, 1 α -OH-D₂), NDA No. 21-027.

This submission represents BCI's written clarification regarding the two objections cited in a Refuse to File (RTF) letter, dated April 1, 1999, received from DMEDP regarding NDA No. 21-027. These clarifications were discussed in an informal conference between DMEDP and BCI on April 9, 1999.

The basis for the first objection was that Bone Care International had inappropriately inserted the misleading term "cross-over" into the subtitle of Protocol No. H-114 under which the Phase 3 clinical trials were conducted with Hectorol Injection. This term was a misnomer in that the trials were never envisioned nor conducted as true cross-over trials; instead, they involved (1) only patients who had participated in studies previously completed under Protocol NO. H-108 and (2) incorporated historical controls as stated in the proposed analysis, final reports, and in the NDA. Unfortunately, this misnomer was confusing to both the Medical and Statistical Reviewers as the NDA did not contain a formal cross-over analysis. As we noted in the meeting of April 9, 1999, the concept of "crossing-over" patients from Protocol No. H-108 to Protocol No. H-114 was originally suggested by DMEDP and was incorporated into the revised version of Protocol No. H-114 after further communications between DMEDP and Bone Care.

The basis for the second objection was that Bone Care did not make it sufficiently clear that the starting clinical dose utilized in the Phase 3 clinical trials with Hectorol Injection was 4 μ g and not 10 μ g, as was used in the preceding Phase 3 clinical trials with oral Hectorol. This led DMEDP to conclude that the human pharmacokinetic data obtained after 5 μ g of Hectorol Injection were not clinically relevant. During the meeting on April 9, 1999, Bone Care requested that DMEDP consider

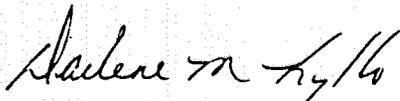
Solomon Sobel, M.D., Director
April 14, 1999
Page 2

the pharmacokinetic data at 5 µg as clinically relevant to the 4 µg starting dose in the Phase 3 clinical studies with Hectorol Injection. During these studies, the 4 µg starting dose often was increased to 6 µg.

The enclosed submission contains full clarifications, as discussed at the April 9th meeting, along with the appropriate documentation from the NDA and earlier IND submissions (IND No.)

We deeply appreciate your kindness in meeting with us on April 9, 1999, and we would like to thank you in advance for re-examining these two items. In the event that you accept our responses, we ask that you file the NDA without revision as soon as possible.

Sincerely,



Darlene M. Kylo, RAC
Director, Compliance, Quality & Regulatory Affairs

DMK/klb

Enclosure

c: Gloria Troendle, M.D.

APPEARS THIS WAY
ON ORIGINAL

Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

April 6, 1999

Randy Hedin, R.Ph., RMO
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857

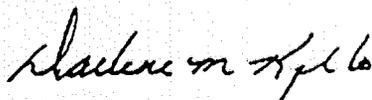
Dear Randy:

Thank you for your assistance this morning in rapidly scheduling a meeting for Bone Care with DMEDP personnel on Friday, April 9, 1999 at 2:30 p.m.

We feel the two reasons cited in Dr. Troendle's letter of April 1, 1999, are not justifiable reasons for a refusal to file and have requested this meeting to discuss the contents of NDA No. 21-027 with DMEDP.

Charles Bishop, President, and I will attend the meeting from Bone Care; Drs. Jack Coburn and Russell Chesney, Clinical Investigators, will attend as our consultants.

With best regards,



Darlene M. Kylo, RAC
Director, Compliance, Quality & Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

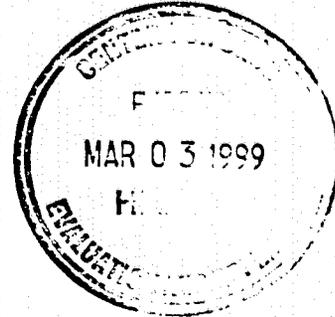
Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

March 2, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Sobel:

Enclosed, please find an information amendment to Bone Care International's New Drug Application for intravenous (IV) 1-alpha-hydroxyvitamin D₂ (1 α -OH-D₂) for the treatment of secondary hyperparathyroidism associated with end-stage renal disease (ESRD). This information is being submitted as Volume 2.1 to NDA No. 21-027.

This submission contains Bone Care's responses to the Medical Reviewer's request for electronic copies of the clinical data, relayed via Randy Hedin, R.Ph., RMO, in a telephone conversation on Wednesday, February 10, 1999.

The review copy and the archive copy each contain 2 Zip diskettes with the entire NDA in Word and a 3 1/2" diskette with the SAS datasets and programs.

The SAS programs and datasets used for analyzing the clinical data also are being submitted as hard copies and are incorporated into the submission.

Finally, a repeated measures analysis and a non-parametric analysis of the primary efficacy data also are included.

With best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo".

Darlene M. Kylo, RAC
Director, Compliance, Quality & Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

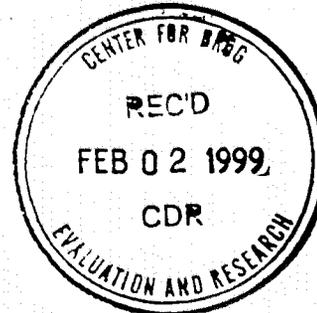
Bone Care

INTERNATIONAL

One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

January 31, 1999

Solomon Sobel, M.D. Director
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Documents Room
12229 Wilkes Avenue
Rockville, MD 20852



Dear Dr. Sobel:

Bone Care International is pleased to submit with this letter our New Drug Application for intravenous (IV) 1-alpha-hydroxyvitamin D₂ (1 α -OH-D₂, Hectorol), NDA No. 21-027.

BCI has been developing 1 α -OH-D₂ as a treatment for secondary hyperparathyroidism in end stage renal disease (ESRD) patients under IND File No. [redacted]. The proposed drug product is formulated as a sterile solution for injection that contains 2.0 μ g 1 α -OH-D₂/mL of solution. The recommended dosage is IV administration three times per week at the end of hemodialysis. We believe that IV 1 α -OH-D₂ offers a significant improvement in treatment over the currently available therapy with significant efficacy responses of 92.5% and 100.0% in treated patients participating in well-controlled clinical trials.

Enclosed, please also find a copy of the letter from Dale W. Gutman to the U.S. Food and Drug Administration, dated January 8, 1999, which documents the payment of the application fee [redacted] for the New Drug Application pertaining to User Fee ID #3609.

This submission contains the data from the two Phase 3 clinical trials and new CMC data for the drug product IV dosage form. Please note that all of the preclinical studies were previously submitted in NDA No. 20-862.

Thank you for your ongoing support of BCI's development program for 1 α -OH-D₂.

Best regards,

Darlene M. Kylo, RAC
Director, Compliance, Quality & Regulatory Affairs

Enclosures

FEB 2 1999

Bone Care

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One Science Court Madison, WI 53711 Phone: (608) 236-2500 Fax: (608) 236-0314

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March 28, 2000



John K. Jenkins, M.D., Acting Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Attn: Document Control Room - 14B19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA No. 21-027 for Hectorol Injection (doxercalciferol); Volume 16.1

Dear Dr. Jenkins:

This submission to NDA No. 21-027 is in response to a request for information received on Friday, March 24, 2000, from Dr. Martin Haber, Chemistry Reviewer.

Eighteen months of long-term storage stability data was submitted in the original application for Hectorol Injection. Dr. Haber requested the information for 2 years of long-term stability storage.

The following pages contain the 2-year stability data at long-term storage for the 3 lots of Hectorol Injection, 1 mL ampule, 2.0 mcg/mL and for the 3 lots of Hectorol Injection, 2 mL ampule, 2.0 mcg/mL. All 6 lots pass the specification for each parameter measured at 2 years.

I can be reached at (608) 236-2530 if you have any questions.

Best regards,

A handwritten signature in cursive script that reads "Darlene M. Kylo".

Darlene M. Kylo, RAC
Director, Compliance, Quality & Regulatory Affairs

Enclosure

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

APPEARS THIS WAY
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