CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-835/S001-004

CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: March 21, 2000

FROM: Eric Colman, MD

TO: NDA file 20-835/s-01-04

SUBJECT: Mortality Follow-up Study

RELATED REVIEWS: See reviews by Dr. Sue Jane Wang and Dr. Judy Chaio

Background

In my original review of NDA 20-835 (supplements 01-04), I deemed the supplements approvable [redacted] in which the imbalance in the incidence of lung cancer in the risedronate 2.5 mg groups compared with the placebo groups was discussed.

Since the date of the above review (August 10, 1999), the Division (including myself) decided that the lung cancer issue might be adequately addressed if the company conducted a mortality follow-up study. A mutually agreed upon study was in fact conducted during the Fall of 1999, and the results of that study were submitted to the Division on December 29, 1999.

While there was no doubt that a statistically significantly greater number (and percentage) of patients treated with 2.5 mg per day of risedronate were diagnosed with lung cancer compared with placebo-treated patients when the results of 10 phase 3 studies were analyzed in aggregate, a number of issues, most importantly, large dropout rates and incomplete and differential rates of follow-up, made it impossible to determine the nature of the association between risedronate and lung cancer. For these reasons, a follow-up study using the US National Death Index and the Canadian Provincial death indices was considered ideal for eliminating the problem of incomplete ascertainment of vital status for subjects who participated in the North American osteoporosis trials.

It was reasoned that comparing the rates of all-cause mortality, all-cancer mortality, and lung cancer mortality between the risedronate- and placebo-treated patients would generate an unbiased evaluation of risedronate's safety.

Mortality Study Results

Of the 8, 054 subjects randomized into the three North American trials (RVN, RON, and RHN), sufficient information was obtained for matching against the death indices for 7, 884 participants (98%). Because the study focused on the Intent-to-Treat population (subjects that received at least one dose of study medication), 69 subjects were excluded from the mortality follow-up database.

The time period covered in this study was 1993 (time of randomization into trials) through 1998 for all-cause mortality and 1997 for all-cause mortality, all-cancer mortality, and lung cancer mortality. The following table provides the results for all-cause mortality through 12/31/1998 and all-cancer and lung cancer mortality through 12/31/1997 for the two risedronate groups and placebo. The time period studied is

termed "All Time" and is defined as that period of time from initiation of study medication to the date of death or end date of mortality follow-up, whichever is earlier.

MORTALITY FOLLOW UP STUDY					
All-Cause Mortality Through 12/31/1998					
	Treatment	# of Deaths	Mortality Rate*	Relative Risk#	p-value
All Time	Placebo	210	18.9		
	Ris 2.5 mg	205	18.7	0.99	0.88
	Ris 5.0 mg	193	17.4	0.92	0.39
All-Cancer Mortality Through 12/31/1997					
All Time	Placebo	38	4.4		
	Ris 2.5 mg	43	5.0	1.15	0.54
	Ris 5.0 mg	26	3.0	0.68	0.14
Lung-Cancer Mortality Through 12/31/1997					
All Time	Placebo	14	1.6		
	Ris 2.5 mg	20	2.4	1.45	0.29
	Ris 5.0 mg	7	0.8	0.50	0.13

*per 1000 patient years #calculated using a Cox regression model

The results of the all-cause mortality analysis through 12/31/1997 were similar to the results shown through 12/31/1998.

The following table provides an analysis of lung cancer mortality through 12/31/1997 for patients without a diagnosis of lung cancer according to the company's clinical trial database. The results indicate that incomplete ascertainment of patients who dropped out of the trials affected the findings of lung cancer reported in the original sNDA. These cases of lung cancer mortality were determined to have occurred "off-study", or in other words, after the subjects discontinued from the trials and were originally deeded "lost to follow up".

LUNG CANER MORTALITY THROUGH 12/31/1997					
	Treatment	# of Deaths	Mortality Rate*	Relative Risk#	p-value
Off-Study	Placebo	8	2.96		
	Ris 2.5 mg	6	1.69	0.56	0.31
	Ris 5.0 mg	2	0.74	0.25	0.08

*per 1000 patient years #calculated using a Cox regression model

The "off-study" lung cancer mortality data, in particular the increased mortality rate in the placebo group, indicate that a follow-up bias influenced the imbalance in lung cancer cases reported in the original sNDA.

Comments

The finding of an increased incidence of lung cancer cases in risedronate- (2.5 mg) compared with placebo-treated patients in osteoporosis trials posed a vexing problem for this Reviewer and others in the Agency. On the one hand, the low bioavailability of risedronate, the occurrence of some lung cancers within months of randomization, the lack of a dose-response, and the absence of an increase in risk over time, all argued against a causal association between risedronate and lung cancer. In addition, the interpretation of the data was hampered by the high dropout rates, and the differential and incomplete rates of follow-up of subjects who discontinued early from the studies. Yet, on the other hand, given the extremely large target population for risedronate, the imbalance in lung cancer cases could not simply be dismissed as a chance finding or due to bias.

The mutually agreed upon mortality follow-up study provided unbiased ascertainment of approximately 98% of the subjects randomized into three large North American trials. The results of the study provide re-assurance that risedronate does not increase all-cause mortality, all-cancer mortality, and most importantly,

it does not increase the risk of death due to lung cancer. Statistical chance and/or follow-up bias appear to explain the imbalance noted in the original sNDA submission.

Regulatory Recommendation

The data submitted to date support the marketing of risedronate for the treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis.

/S/ 4/12/00

Eric Colman, MD

cc: HFD-510 NDA file
ODE II LRarick/JJenkins

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: February 24, 2000 Time: 3:30 – 3:45 PM Location: 14-56

NDA 20-835/S-001, S-002, S-003 & S-004 Actonel (risedronate sodium)

Type of Meeting: Teleconference

External participant: Procter & Gamble Pharmaceuticals

Meeting Chair: Dr. Bruce Stadel

External participant lead: Dr. Bruce DeMark

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Bruce Stadel, Medical Reviewer, DMEDP
Mr. Randy Hedin, CSO DMEDP

External participant Attendees and titles:

Dr. Nora Zorich, Director, Actonel Product Development, P&GP
Dr. Bruce DeMark, Section Head, Regulatory Affairs, P&GP
Dr. Arkadi Chines, Senior Medical Monitor, risedronate
Dr. Linda Manning, Senior Scientist, Regulatory Affairs, P&GP

Meeting Objectives:

The meeting was requested by the Division to ask Procter and Gamble to submit an analytical tree showing the number of patients in the histology/histomorphometry section of the label and how it relates to the bone histology and histomorphometric data submitted in the NDA.

Discussion Points and Decisions (agreements) reached:

- The Division asked the firm to submit an analytical tree showing the number of patients in the histology/histomorphometry section of the label and how it relates to the bone histology and histomorphometric data submitted in the NDA. A tree should be done for each section of the label that has histomorphometric data. Also, please explain in the trees any dropouts or discrepancies, and use the same logic in each tree.

- The Division asked the firm to use parallel language in all sections of the label

where histology/histomorphometry data is reported.

Unresolved or issues requiring further discussion:

- None

Action Items:

- The firm agreed to provide an analytical tree for the histology/histomorphometry sections of the label as soon as possible.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/2.24.99/N20835.MN8

Concurrences:

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

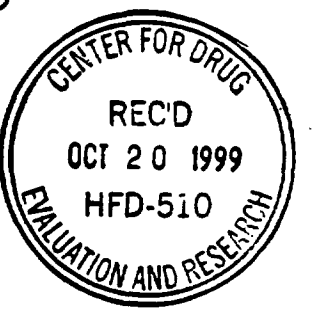
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-835/S-001, S-002, S-003, S-004

OCT 18 1999

In DFS



Procter and Gamble Pharmaceuticals
Attention: Linda Manning, Pharm. D.
Senior Scientist, Regulatory Affairs
11450 Grooms Road
Cincinnati, OH 45242-1434

Dear Dr. Manning:

Please refer to your supplemental new drug applications dated December 18, 1998 and received December 18, 1998 (S-001, S-002, and S-003), and August 27, 1999, received August 30, 1999 (S-004), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) Tablets.

We acknowledge receipt of your submissions dated January 11 and 28, February 3, 8, 9, 10, 15, 25, and 26, March, 1, 3, 5, 8, 12, 22, 26, 29, 30, and 31, April 5(2), 12, 20, and 22, May 7, 13, and 17, June 1, 10(2), 17, 18, 24, and 30, July 1, 2, 12(2), 13, 14, 28, and 30, August 3(2) 20, 27, and 30, September 3, 21, 22, 28, and 29, and October 8, 1999. Your submission of August 27, 1999, constituted a complete response to our August 20, 1999, action letter (S-001).

These supplements propose the following changes:

1. Supplement 001 provides for a new indication for the treatment of corticosteroid-induced osteoporosis.

2. Supplement 002 provides for a new indication for the prevention of postmenopausal osteoporosis.

3. Supplement 003 provides for a new indication for the treatment of postmenopausal osteoporosis.

4. Supplement 004 provides for a new indication for the prevention of corticosteroid-induced osteoporosis.

5. All four supplements provide for a new 5 mg strength tablet.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

1. While great doubt exists regarding risedronate's ability to promote existing lung tumors, it

is our opinion that you have not adequately addressed our concerns regarding the excess lung cancer found in the clinical trials submitted. Please conduct a follow-up study in, at a minimum, the North American osteoporosis trials in which all-cause mortality, all-cancer cases mortality and lung-cancer-specific mortality is reported in placebo and risedronate patients. Please submit a protocol for such a study for review and approval by the Division before initiating the followup.

2. Also, additional revisions of the draft labeling submitted on August 20, 1999, will be required after we have reviewed the additional material.

3. Further, a satisfactory current Good Manufacturing Practices inspection needs to be completed for your Longjumeau, France facility.

Also, your submitted stability data only support a — month expiry date.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDAs was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6430.

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 20-835/S-001

Procter and Gamble Pharmaceuticals
Attention: Linda Manning, Pharm. D.
Senior Scientist, Regulatory Affairs
11450 Grooms Road
Cincinnati, OH 45242-1434

AUG 20 1999

Dear Dr. Manning:

Please refer to your supplemental new drug application dated December 18, 1998, received December 18, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) Tablets.

We acknowledge receipt of your submissions dated January 11 and 28, February 3, 8, 9, 25, and 26, March, 1, 3, 5, 12, 22, 26, 29, 30, and 31, April 5, 13, and 22, May 7 and 13, June 1, 10(2), 17, 18, and 30, July 1, 12, 13, and 28, and August 3 and 20, 1999.

We also refer to your submissions dated June 10 and August 20, 1999. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

This supplemental application provides for a new indication

[ ]

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> Our review of your application has raised the question of whether the disproportionate number of lung cancer cases seen in the risedronate-treated group versus placebo constitutes a significant safety issue. We note that your June 10, 1999, submission contained a report from your Safety Advisory Panel which attempted to explain the disportionate number of lung cancer cases seen in the treated group versus placebo. If you have any additional safety information that explains this issue, please include it in your complete response to this letter.

Also, additional revisions of the draft labeling submitted on August 20, 1999, will be required after we have reviewed the additional material.

Further, a satisfactory current Good Manufacturing Practices inspection needs to be completed for your Longjumeau, France facility.

Also, the indication requested in supplement 001 was to [redacted] In the revised draft labeling submitted on June 30, 1999, the indication was changed to "ACTONEL is indicated for the prevention and treatment of corticosteroid-induced osteoporosis in men and women who are either initiating or continuing systemic corticosteroid treatment for chronic diseases." We consider the revised indication submitted in the June 30, 1999, revised draft labeling to be two separate indications. Therefore, another user fee for an additional supplement should be submitted if you submit a supplement that provides for the prevention of corticosteroid-induced osteoporosis.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ 8/20/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/S/ - 8/20/99

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 20-835
Div. File
HFD-510
HFD-150 / JChiao
/ DPaul

Memorandum

From: Judy H. Chiao, MD (Medical Officer, DODP) /S/ 2-16-00
Julie Beitz, MD (Medical Team Leader, DODP) /S/ 2/16/00

To: Bruce Stadel, MD
(Division of Metabolism and Endocrine Drug Products)

Date: February 10, 2000

Subject: NDA Amendment 9: Complete Response to October 18, 1999 Approvable Letter

We have reviewed the results of the follow-up mortality study in the North American osteoporosis trials submitted by Proctor & Gamble on December 29, 1999.

Table 1: Proctor & Gamble analysis of All Time All-cause Mortality through 12/31/97

Treatment	Number of Deaths	Mortality rate (per 1000 patient years)	Relative Risk	p-value
Placebo	157	18.13		
Ris 2.5 mg	141	16.53	0.91	0.413
Ris 5.0 mg	137	15.85	0.87	0.247
Ris Combined	278	16.19	0.89	0.249

Table 2: Proctor & Gamble analysis of All Time Lung Cancer Mortality through 12/31/97

Treatment	Number of Deaths	Mortality rate (per 1000 patient years)	Relative Risk	p-value
Placebo	14	1.62		
Ris 2.5 mg	20	2.35	1.45	0.21
Ris 5.0 mg	7	0.81	0.50	0.133
Ris Combined	27	1.57	0.97	0.927

Table 3: Accountability of the 42 patients with lung cancer reported in the clinical database as of 12/31/97

Number of patients	Placebo n=9	2.5 mg Risedronate n=23	5 mg Risedronate n=10	Total n=42
Died with lung cancer listed on death certificate	6	14	5	25
Died without lung cancer listed on death certificate	2	1	1	1
Were alive as of 12/31/97	1	8	4	13

The following are our comments and recommendation:

1. Only 41 out of 435 who died through 12/31/97 had a lung cancer diagnosis on the death certificate. Therefore analyses of all-cause mortality is unlikely to detect an excess of death related to lung cancer.

2. 42 patients had a diagnosis of lung cancer in the clinical database. 13 of these 42 patients were alive by 12/31/97. 25 out of 29 patients who died by 12/31/97 had lung cancer on their death certificates. In other words, 86% of patients who had a diagnosis of lung cancer and died had lung cancer on their death certificates. Among the 13 patients who were alive, 8 were on Risedronate 2.5 mg and 4 on Risedronate 5 mg. The possible reasons that these 13 patients were alive on 12/31/97 are listed as follows:

   - Relatively short period of time from the diagnosis of lung cancer to the cut-off date of 12/31/97. In the SAS dataset submitted by Proctor and Gamble on 5/24/99, 6 out of 41 patients were less than one year out from their diagnosis of lung cancer by the cut-off date of 12/31/97.
   - The diagnosis of lung cancer is incorrect.
   - Lung cancer was diagnosed at early stage.

3. In our consult on 7/7/99, we found that the increase in lung cancer was *only* seen in patients who were current or previous smokers and who have received risedronate. Proctor & Gamble did not perform a separate analysis of lung cancer mortality in smokers. We recommend that such an analysis be done to make sure that lung cancer mortality in smokers is not increased in those who took risedronate.

4. If the analysis under #3 shows no increase in lung cancer mortality in smokers, we would conclude that overall, treatment with risedronate is not associated with an increased risk of death due to lung cancer.

Memorandum

From: Judy H. Chiao, MD (Medical Officer, DODP)
Julie Beitz, MD (Medical Team Leader, DODP) /S/ 4/11/00

To: Bruce Stadel, MD
(Division of Metabolism and Endocrine Drug Products)

Date: April 13, 2000

Subject: Additional analyses related to lung cancer mortality submitted by Procter & Gamble on 2/28/00

We have reviewed the results of the submitted analyses related to lung cancer mortality stratified by smoking status.

Table 1: Proctor & Gamble analysis of Lung Cancer Mortality (i.e., lung cancer listed on death certificate) through 12/31/97 in current or previous smokers

Treatment	Number of Deaths	Mortality rate (per 1000 patient years)	Relative* Risk	p-value**
Placebo	11	2.76		
Ris 2.5 mg	18	4.62	1.67	0.18
Ris 5.0 mg	5	1.26	0.46	0.14
Ris Combined	23	2.93	1.07	0.864

*Relative risk based upon Cox regression model between individual residronate dose and placebo stratified by study.
**p-value for testing the difference between placebo and the risedronate groups using Cox regression stratified by study

Table 2: Proctor & Gamble analysis of All Time Lung Cancer Mortality through 12/31/97 in non-smokers and previous or current smokers

Treatment	Number of Deaths	Mortality rate (per 1000 patient years)	Relative Risk	p-value
Placebo	14	1.62		
Ris 2.5 mg	20	2.35	1.45	0.21
Ris 5.0 mg	7	0.81	0.50	0.133
Ris Combined	27	1.57	0.97	0.927

Table 3: Accountability of the 42 patients with lung cancer reported in the clinical database as of 12/31/97 in non-smokers and previous or current smokers

Number of patients	Placebo n=9	2.5 mg Risedronate n=23	5 mg Risedronate n=10	Total n=42
Died with lung cancer listed on death certificate	6	14	5	25
Died without lung cancer listed on death certificate	2	1	1	1
Were alive as of 12/31/97	1	8	4	13

The lung cancer mortality analyses through 12/31/97 in current or previous smokers (table 1) showed no increase in lung cancer mortality based on causes of death listed on the Death Certificate. In addition, lung cancer mortality based on causes of death listed on the Death Certificate was not increased in all patients, regardless of the smoking status (Table 2). Therefore, we conclude that overall, treatment with risedronate is not associated with an increased risk of death due to lung cancer.

APPEARS THIS WAY.
ON ORIGINAL

Meeting Date: May 24, 1999 Time: 2:00 - 4:00 pm Location: Conf. Rm. "M"

NDA 20-835/S-001, S-002, & S-003 Actonel (risedronate sodium)

Type of Meeting: General

External participant: Procter & Gamble Pharmaceuticals

Meeting Chair: Dr. Troendle

External participant lead: Dr. Bruce DeMark

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Director, DMEDP
Dr. John Jenkins, Director, ODEII
Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Bruce Stadel, Medical Reviewer, DMEDP
Dr. Eric Colman, Medical Reviewer, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. Bruce Schneider, Medical Reviewer, DMEDP
Dr. Joanna Zawadzki, Medical Reviewer, DMEDP
Dr. Sue-Jane Wang, Reviewer, Division of Biometrics 2
Dr. Judy Chiao, Medical Reviewer, Division of Oncology
Dr. Julie Beitz, Medical Team Leader, Division of Oncology
Mr. Randy Hedin, CSO DMEDP

External participant Attendees and titles:

Dr. Larry Versteegh, Vice President Global Regulatory and Clinical Development
Dr. Nora Zorich, Director, Actonel Product Development
Dr. Bruce DeMark, Section Head, Regulatory Affairs
Dr. Simon Pack, Section Head, Biometrics
Dr. Arkadi Chines, Senior Medical Monitor
Dr. Roger Phipps, Principal Scientist, Nonclinical Pharmacology
Dr. J. Michael Sprafka, Associate Director, Global Pharmacovigilance, Epidemiology and Pharmacoeconomics,
Dr. Ansu Vashishtha, Associate Director, Global Drug Surveillance, (HMR) Hoechst Marion Roussel
Mr. Fred Henry, Associate Director, Global Strategic Regulatory Development, HMR

[redacted]

(present via telephone conference)

Meeting Objectives:

To discuss the disproportionate number of lung cancer cases seen in the Actonel group versus the placebo group in the Actonel Phase 3 trials.

Discussion Points and Decisions (agreements) reached:

- Drs. DeMark and Zorich presented background information on the Safety Advisory Panel of experts that Procter and Gamble convened to address the discordance in the number of lung cancer cases seen in the treated group versus placebo.

- Dr. [redacted], a member of Procter and Gamble's Safety Advisory Panel, presented the overall conclusion of the panel that a causal relationship between risedronate treatment and lung cancer is unlikely for the following reasons:

  1. The short time to cancer diagnosis is inconsistent with known carcinogenic or tumor growth stimulatory mechanisms.
  2. There is no biologically plausible explanation
  3. No dose-response relationship exists.
  4. No time-dependent increase in cancer rate was evident.

Dr. [redacted] stated that in study RVN008993 nine cases of lung cancer were reported; one case in placebo, five cases in the 2.5 mg group, and 3 cases in the 5 mg group. Dr. [redacted] stated that five of the eight cases seen in the treated group were detected either before or within six months of randomization. The Division agreed that these five cases were probably not drug related; however, this type of assessment is not valid unless the whole data set is evaluated in the same manner.

Dr. [redacted] then presented lung cancer data from all studies excluding cases that were detected within six months of randomization; eleven cases in placebo, 22 cases in the 2.5 mg group, and eleven cases in the 5 mg group. He also presented the gastro-intestinal cancer data which showed a lower incidence of GI cancer in risedronate versus placebo treated patients.

Dr [redacted] summarized his presentation with the following:

1. Cancer was not a formal endpoint for analysis but one of the more than 600 adverse events collected and analyzed.
2. No formal screening prior to or during the study was done to rule out cancer.
3. Data on cancer site and histology are limited and often lacked radiological or pathological confirmation.
4. Some cases were reported after patients had dropped out of the studies, which had an overall dropout rate of 43%. Thus there are reasons to suspect incomplete ascertainment of cancer cases in this data set.
5. The overall number of lung cancer cases reported in the placebo arm (13) is significantly lower than the expected number for women of average age 70-75 years, further suggesting incomplete ascertainment.

- Dr [redacted] presented information on the biochemical and pharmacological aspects of bisphosphonates, and summarized the risedronate clinical pharmacokinetics, animal tissue distribution, and nonclinical genetic toxicity and carcinogenicity studies.

- Dr. [redacted] presented information about the timing for the development of lung cancer. He made the point that the entire carcinogenic process for all lung cancers, from initial mutation to a detectable level of tumor growth would be expected to be on the order of 10-20 years. Dr. [redacted] stated that this fact plus the lack of a dose response would exclude risedronate as a possible lung carcinogen. Dr. [redacted] then summarized the findings of the Procter and Gamble Safety Panel:

  1. There is no evidence to suggest that risedronate is a lung carcinogen.
  2. There is no evidence to suggest that risedronate accelerates the growth of lung cancer.
  3. There is no consistent evidence suggesting that risedronate causes lung cancers to become symptomatic

4. There is likely a lower than expected recognition of lung cancer in the study, particularly in the placebo group.

5. Random variation cannot be ruled out as an explanation for the increased recognition of lung cancers in the 2.5 mg treatment group.

6. A causal relationship between the risedronate treatment and lung cancer is unlikely for the following reasons:

   A. Short time to cancer onset is inconsistent with known carcinogenic or growth promotion mechanisms.

   B. There is no biologically plausible explanation.

   C. No dose-response relationship exists.

   D. No time-dependent increase in cancer rate was evident.

- Dr. [redacted] concurred with the finding of Procter and Gamble's Safety Panel, [redacted] He further stated that it would be helpful to evaluate the death registry data for the patients who had been enrolled in the risedronate clinical trials.

- [redacted]

- [redacted]

- The Division asked when the major amendment would be submitted to extend the user fee clock for the corticosteroid-induced osteoporosis supplement, and Dr. DeMark indicated that this would be submitted in early June prior to the June 18th goal date.

- The Division stated that it did not see a valid scientific reason for relating the lung cancer cases to risedronate; [redacted] The Division stated that it plans to meet with its own consultant, and will further evaluate the meaning of the lung cancer data. The

Division stated that the level of confidence needed to approve a drug to treat a relatively healthy population needs to be weighed very carefully against the lung cancer findings.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Post-meeting note: At a later date it was determined that a major amendment to a supplement does not extend the use fee goal.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/6.28.97/N20835.MN5
Concurrences: EColman/BStadel/LLutwak/JZawadzki/GTroendle/6.28/
SWang/7.1/SSobel/7.2/JJenkins/7.7.99

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: February 23, 2000 Time: 9:30 - 10:00 AM Location: 14-56

NDA 20-835/S-001, S-002, S-003 & S-004 Actonel (risedronate sodium)

Type of Meeting: Teleconference

External participant: Procter & Gamble Pharmaceuticals

Meeting Chair: Dr. Bruce Stadel

External participant lead: Dr. Bruce DeMark

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Bruce Stadel, Medical Reviewer, DMEDP
Mr. Randy Hedin, CSO DMEDP

External participant Attendees and titles:

Dr. Nora Zorich, Director, Actonel Product Development, P&GP
Dr. Bruce DeMark, Section Head. Regulatory Affairs, P&GP
Dr. John Taulbee, Director, Epidemiology and Biometrics, P&GP
Dr. Simon Pack, Section Head, Biometrics, P&GP
Dr. Gary Cline, Biometrics, P&GP
Dr. Linda Manning, Senior Scientist, Regulatory Affairs, P&GP

Meeting Objectives:

The meeting was requested by the Division to ask Procter and Gamble to do another analysis of their mortality study.

Discussion Points and Decisions (agreements) reached:

- Dr. Stadel spoke briefly about the mortality study, and the study report submitted on December 30, 1999. He then stated that the Division would like one additional analysis done. This request is being made in response to an oncology consultation received by the Division. The analysis should be a lung cancer mortality analysis similar to the analysis submitted in Vol. 1 Section 4.2.3 (page 49); however, it should be stratified bye smoking status (current or former versus never). The firm stated that they would do this, and proposed to also stratify analysis for lung cancer mortality and all cause mortality. We agreed that the further analysis

proposed by the firm would be beneficial.

ıresolved or issues requiring further discussion:

- None

tion Items:

- The firm agreed to provide an additional analysis as soon as possible, and will provide a timeline as to when it will be submitted.

ıature, minutes preparer: /S/

:urrence Chair: /S/

NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/2.23.99/N20835.MN7

ırrences:

APPEARS THIS WAY
ON ORIGINAL

9 PAGE(S) REDACTED

Draft Labeling

MEMORANDUM

U.S. Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products
HFD-510

October 8, 1999

RE: Response to Approvable Letter

NDA#: 20-835 S/01

Drug: Risedronate

Company: Procter and Gamble

Date of Submission: August 27, 1999

Date of Review: October 8, 1999

In response to the Division's approvable letter dated August 20, 1999, Procter and Gamble Pharmaceuticals submitted a letter dated August 27, 1999. In this response the company refers to a submission dated June 10, 1999, which contained a report from the Safety Advisory Panel that was convened by P&GP to evaluate the lung cancer cases.

In short, P&GP and its Safety Advisory Panel concluded that there was not strong support for the belief that risedronate acts as a lung carcinogen or promotes the growth of pre-existing lung tumors.

While great doubt exists regarding risedronate's ability to promote existing lung tumors, it is my opinion that the company has not adequately allied our concerns about the excess risk for lung cancer diagnosis found in the clinical trials submitted to date.

I recommend that the sponsor conduct a follow-up study in which all cause mortality, all cancer mortality, and lung-cancer specific mortality be calculated, at a minimum, from the North American osteoporosis trials. Until such data are submitted and reviewed I recommend that not only supplement 01 be considered approvable, but supplements 02, 03, and 04 also be considered approvable.

/S/

Eric Colman, MD

/S/ 10/14/99

cc: NDA Arch

SEL-001-000 SEL
SEL-003-004 SEL

Procter&Gamble
PHARMACEUTICALS

Health Care Research Center
8700 Mason-Montgomery Road
P.O. Box 8006
Mason, Ohio 45040-9462

ORIGINAL

March 16, 2000

John Jenkins, M.D., Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

/S/ 3/21/00

RE. NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL® (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Amendment 10: Safety Update

NO new safety issues
Unless identified to date

/S/ 3/13/00

Dear Dr. Jenkins:

The purpose of this amendment to NDA #20-835/S-001, S-002, S-003, S-004 is to provide updated safety information for ACTONEL. In the last safety update (Amendment 8, dated December 17, 1999) information from 3 ACTONEL studies, for which unblinded data had become available, was included in the submission. Per an agreement with the Division (teleconference with Mr. Randy Hedin on March 2, 2000), final reports which are now complete for each of these 3 studies are being provided in this safety update. The final reports for these studies have previously been submitted to risedronate IND ——— and are submitted to NDA #20-835 via cross-reference (IND serial no. and date submitted). The attached table provides these cross-references to the risedronate IND. The study type, number, and title are also provided in the table.

Should you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist, Regulatory Affairs
Phone: (513) 622-1114
FAX: (513) 622-5369

Desk Copies: Randy Hedin, R.Ph.
Eric Colman, M.D.

REVIEWS COMPLETED
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NDA 20-835/S-001
Actonel (residronate sodium) Tablets
Procter and Gamble Pharmaceuticals

Safety update review is included in medical officers' review.

21 F

MEMO TO THE FILE

RE: Safety Update (#2)

DATE OF SUBMISSION: 12/17/99

DATE OF REVIEW: 01/05/00

NDA#: 20-835 SE1 001, 002, 003, 004 B2

DRUG: Risedronate

COMPANY: Proctor and Gamble

As previously agreed upon, this second safety update for sNDA 001-004 contains information on GI adverse events, serious adverse events, and deaths that occurred during the conduct of the 4th and off-drug year of study RVN as well as during two phase 2 studies (1998012 and 1999033). The latter two studies examined the safety of modified dosing instructions (wait to lie down 30 minutes [redacted] and [redacted] dosing with risedronate [redacted] mg), respectively.

In RVN there were a total of 5 deaths during the 4th year: 2 in placebo and 3 in the risedronate 5 mg groups. No deaths were reported in studies 1998 and 1999. In general, there were no significant differences between active- and placebo-treated patients in the incidence of serious adverse events or GI-related adverse events. The upper GI adverse event profile observed during these studies was similar to that reported in the previous sNDA submissions.

Comment

I agree with the company that no changes are required to the proposed labeling based on the data submitted in the second safety update.

/S/

Eric Colman, MD
January 5, 2000

CC: NDA Arch
Hedin/Colman

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 24 2000

FROM: Sue-Jane Wang, Ph.D.
Mathematical Statistician, Division of Biometrics II (HFD-715)

SUBJECT: Lung cancer and death in risedronate (Trade name: Actonel) for treatment/prevention of corticosteroid-induced osteoporosis and post-menopausal osteoporosis

TO: File
(NDA# 20-835 SE1-001, 002, 003, 004 amendment #9 dated 12/29/1999)

This memorandum is a follow-up on "the sponsor's mortality study submitted 12/29/1999." Specifically, in response to the Medical Division's (HFD-510) request of further following-up on all patients' vital status, the sponsor conducted a mortality followed-up study using the National Death Index in patients from three (RON, RVN, RHN) trials conducted in the North American region out of the original 10 trials reviewed. These trials were to be indicated for treatment of post-menopausal osteoporosis (PMO).

SUMMARY OF THE SPONSOR'S ANALYSES

The sponsor submitted protocol amendments for the three US trials in September 1999 to include the Agency's request on mortality follow-up study. In this submission, the sponsor reported mortality rate per 1000 patient-years, 95% confidence interval, and p-values through December 31, 1997 (see sponsor's Table 1) and through December 31, 1998 (see sponsor's Table 2). In addition, the sponsor reported the above statistics for any cancer mortality rate (see sponsor's Table 3) and lung cancer mortality rate up to December 31, 1997 (see sponsor's Table 4 and sponsor's figures 19-24). The following summarizes the sponsor's analysis results.

- **ALL-CAUSE MORTALITY, ANY-CANCER MORTALITY, AND LUNG CANCER MORTALITY**

The "all-time" analysis of the pooled risedronate treatment groups compared with placebo provides no evidence for an increased relative risk of all-cause mortality (RR=0.89), any-cancer mortality (RR=0.91), or lung cancer mortality (RR=0.97). A similar result was also observed for the all-cause mortality (RR=0.95) through December 31, 1998. The corresponding 95% CI associated with the RR estimates through 1997 were 0.73, 1.08 for all-cause mortality; 0.62, 1.36 for any-cancer mortality; and, 0.51, 1.85 for lung cancer mortality.

The RRs of death from any-cancer or lung cancer were lower in the 5.0mg risedronate treatment group compared to the 2.5mg group for each of the analysis times ("all-time", "on-study", and "off-study"). For any-cancer mortality the RR compared with placebo for the "all-time" analysis was 1.15 for the 2.5mg treatment group and 0.68 for the 5.0mg treatment group. The RR for the 2.5mg group was 0.87 "on-

study" and 1.12 "off-study", while the RR for the 5.0mg group "on-study" and "off-study" was 0.47 and 0.90, respectively.

Lung cancer mortality data showed a similar pattern, with no evidence of a dose-response relationship. The RR compared with placebo for the 2.5mg group was higher than for the 5.0mg treatment group. The highest RR for the 2.5mg group compared to placebo was 1.69 for the "on-study" period. This relative risk was not replicated during the "off-study" period (RR=1.11), resulting in an overall "all-time" relative risk of 1.45 for this treatment group. In contrast, the 5.0mg risedronate treatment group had a consistently low RR of 0.44 to 0.60 during all analysis periods.

REVIEWER'S EVALUATION AND COMMENTS

- **REASONABLE ALL-CAUSE MORTALITY FROM THE FOLLOW-UP STUDY**

Based on the original NDA of risedronate, a crude estimate showed that an additional 1% of all cause mortality might be captured for an additional half-year follow-up. In this mortality study, approximately 2% increase in all cause mortality was shown between Dec. 31, 1997 and Dec. 31, 1998 in each treatment arm, confirming a reasonable projection from the original NDA data. Results are summarized in Table 1. If all-cause mortality could be assumed to be similar among placebo, risedronate 2.5mg and 5.0mg, such rates were 3.16% up to Dec. 31, 1997 and 5.16% up to Dec. 31, 1998.

Table 1. All-cause mortality reports during off-study period from the three US trials*

	Placebo	2.5mg ris	5.0mg ris	2.5mg+5.0mg ris
By Dec. 31, 97	3.15% 74/2348	3.34% 78/2333	3.00% 70/2334	3.17% 148/4667
By Dec. 31, 98	4.98% 127/2551	5.57% 141/2530	4.93% 126/2554	5.25% 267/5084

* extracted from the sponsor reports.

- **INTENT-TO-TREAT ANALYSIS**

The sponsor's analysis excluded those patients whose mortality status could not be determined. Discrepancies between the intent-to-treat patients and the patients with mortality status known up to Dec. 31, 1998 were very small, 26 patients (0.96%) in placebo, 26 patients (0.98%) in 2.5mg risedronate arm, and 21 patients (0.78%) in 5.0mg risedronate arm. This reviewer performed the relative risk analyses based on the intent-to-treat patients. Results of this reviewer's analysis were consistent with the sponsor's finding in terms of statistical evidence.

- **PERSON-YEAR APPROACH VS. PROPORTION APPROACH**

The sponsor focused on the person-year exposure to risedronate in the analysis of relative risk of all-cause mortality, any-cancer mortality, and lung cancer mortality. The sponsor stated that the person-years of exposure were similar among the three arms when the mortality follow-up periods were included. It is noted that in the three US trials, RON (n~200 per arm), RVN (n~800 per arm), and RHN (n~1650 per arm), the 2.5mg risedronate arm in Trial RVN was terminated earlier. The mortality follow-up study helped collect patients' vital status with use of the National Death Index, phone contact, and other means. According to the sponsor, it consisted of more than 98% (7845 patients out of 7981 patients in the original 3 US trials) follow-up of the original study cohort. Assuming there were no differential

ascertainments among the three arms, based on this reviewer's assessment, relative risk analysis using either proportion or person-year exposure all yielded similar results.

- **LUNG CANCER INCIDENCE, LUNG CANCER MORTALITY**

It is not surprising that all-cause mortality would resemble the trend seen in the original clinical trial. Any-cancer mortality seems likely to be similar since all cancer incidences were similar between placebo and risedronate. All-cancer incidences were similar among the three arms, odds ratio of 1.1 (95% CI 0.9 to 1.4) with 2.5mg ris relative to placebo, and 0.9 (95%CI 0.7 to 1.2) with 5.0mg ris relative to placebo. The puzzling disproportionate lung cancer incidences with relative risks (RR) of 2.9 (95% CI 1.6 to 5.7) in the 2.5mg risedronate and 1.6 (95% CI 0.8 to 3.2) in the 5.0mg risedronate prompted the focus of lung cancer incidence and cause-specific lung cancer mortality in this mortality study.

LUNG CANCER INCIDENCE OF THE BISPHOSPHONATE DRUG CLASS DURING THE ORIGINAL NDA REVIEW OF RISEDRONATE

In the memorandum dated 07/30/1999, the statistical analysis performed by this reviewer per Dr. Bruce Stadel's requesting on other drugs under the bisphosphonate class showed a relative risk of lung cancer relative to placebo of 1.5 (95% CI 0.8 to 2.6) with alendronate, 1.4 (95% CI 0.5 to 4.4) with etidronate, and 1.1 (95%CI 0.5 to 2.4) with tiludronate. With risedronate, however, the estimated overall odds ratio was 2.2 (95% CI 1.2 to 4.0). The twofold increase in lung cancer incidence with risedronate to be indicated for treatment of PMO was seen in both the US trials (RON, RVN, RHN) and the European trials (ROE, RVE, RHE) when the 2.5mg and 5.0mg risedronate were combined. These estimates were somewhat higher than other drugs under the same bisphosphonate class. It is noted that analogous to the risedronate study, clinical trials conducted for other drugs did not pre-specify consistent data collection on the lung cancer incidence.

LUNG CANCER INCIDENCE VS. LUNG CANCER MORTALITY OF RISEDRONATE

According to the sponsor, of the 42 patients (9 in placebo, 23 in 2.5mg ris, and 10 in 5.0mg ris) diagnosed with lung cancer during the on-study period from the clinical database, 13 (1 in placebo, 8 in 2.5mg ris and 4 in 5.0mg ris) were alive as of Dec. 31, 1997, 25 (6 in placebo, 14 in 2.5mg ris, and 5 in 5.0mg ris) died with lung cancer shown on the death certificate, and 4 (2 in placebo, 1 in 2.5mg ris and 1 in 5.0mg ris) without lung cancer on the death certificate.

Table 2. Lung Cancer deaths reported during trial periods, identified off-study, and total deaths

Lung cancer	US Trials (RON, RVN, RHN)				European Trials (ROE, RVE, RHE)			
	Placebo	2.5mg	5.0mg	2.5+5.0	Placebo	2.5mg	5.0mg	2.5+5.0
On-study								
Incidence	9	23	10	33	4	10	7	17
Death*	5	8	3	11	2	9	5	14
Off-study								
Death	9	12	4	16	na**	Na	na	na
All-time								
Death	14	20	7	27	na	Na	na	na

* based on those patients who died during the trial period and who reported lung cancer.

** not applicable

From the mortality study up to Dec. 31, 1997, a total of 41 lung cancer deaths were reported in the 3 US trials, 14 (0.52%) in placebo, 20 (0.76%) in 2.5mg ris, and 7 (0.26%) in 5.0mg ris [27 (0.50%) in

risedronate combined], as shown in Table 2. It appeared that not all reported lung cancer incidences from the clinical database were also reported as lung cancer death in the mortality study. Some lung cancer deaths (9 in placebo, 6 in 2.5mg ris, and 2 in 5.0mg ris) were identified through mortality follow-up study.

From the three US trials, the mortality study of risedronate (2.5mg and 5.0mg combined) showed a relative risk of lung cancer mortality obtained by following-up patients up to December 31, 1997 of 0.97 (95% CI 0.51 to 1.85), whereas a relative risk of lung cancer incidence 1.8 (95% CI 0.9 to 3.7) was obtained during the clinical trial period. In these trials, risedronate (2.5mg and 5.0mg combined) treated patients didn't show an excess of lung cancer mortality during the off-study period and the all-time analysis. The excess was primarily seen in the 2.5mg risedronate during the on-study period (RR=1.69, 95% CI of 0.55 to 5.17), and all-time analysis (RR=1.45, 95%CI 0.73 to 2.86).

LIKELIHOOD OF EUROPEAN TRIALS ON LUNG CANCER DEATH

The following observation was based on the on-trial information of the original clinical database.

COMPARISON BETWEEN EUROPEAN TRIALS AND NORTH AMERICAN TRIALS

Characteristics of age at study entry, % ever smoked, % lung cancer and % death between the North American trials (abbreviated as US) vs. the corresponding European trials from the original clinical trials, i.e., on-study, were summarized, see Table 3.

Table 3. Characteristics relating to lung cancer and death between US vs. European Trials (on-study)

Trial	% ≥ 65yrs	Median age(yr)	% ever smoked	# (% lung cancer) pbo	2.5mg	5.0mg	# (% death) pbo	2.5mg	5.0mg
RON (#pts)	41-46%	63-64	46-53%	0(0%) 220	1(.47%) 212	1(.46%) 216	0(0%)	0(0%)	0(0%)
RVN (#pts)	68-72%	68-69	48-51%	1(.12%) 820	5(.61%) 817	3(.37%) 821	22(2.7%)	15(1.8%)	20(2.4%)
RHN (#pts)	99%	76-77	42-44%	8(.48%) 1664	17(1.04%) 1633	6(.36%) 1651	61(3.7%)	49(3.0%)	47(2.9%)
US (#pts)				9(.33%) 2704	23(.86%) 2662	10(.37%) 2688	83(3.1%)	64(2.4%)	67(2.5%)
ROE (#pts)	52-56%	65-66	28-36%	0(0%) 180	2(1.09%) 184	1(.56%) 179	1(0%)	2(1.1%)	2(1.1%)
RVE (#pts)	80-84%	71-72	39-46%	1(.25%) 408	1(.24%) 410	2(.49%) 408	18(4.4%)	13(3.2%)	15(3.7%)
RHE (#pts)	97-98%	80	28-29%	3(.20%) 1520	7(.46%) 1518	4(.26%) 1511	114(7.5%)	127(8.4%)	122(8.1%
Euro (#pts)				4(.19%) 2108	10(.47%) 2112	7(.33%) 2098	133(6.3%)	142(6.7%)	139(6.6%

The impact of the two major prognostic factors (age and smoking history) at baseline relating to lung cancer risk and death were summarized. It appeared that the European trials, except for hip fracture studies, consisted of higher percentages of patients who were at least 65 years of age at study entry (corresponding to two-to-four years older in median age or average age) and lower percentages (about 10% to 20% lower) of patients in all three trials with smoking history in comparison to the US trials.

As shown in Table 3, lung cancer incidences were less in the European trials, 0.19% in placebo, 0.47% in 2.5mg risedronate, 0.33% in 5.0mg risedronate (0.4% in risedronate combined), than those in the US trials, 0.33% in placebo, 0.86% in 2.5mg risedronate, 0.37% in 5.0mg risedronate (0.62% in risedronate combined). Lower incidences of lung cancer seen in the European trials might be due to a smaller percentage of patients with smoking history. It is worthwhile to note that when the 2.5mg and 5.0mg risedronate were combined, lung cancer incidence were about twofold in risedronate compared to placebo in either the European trials (0.4% vs. 0.19%) or the US trials (0.62% vs. 0.33%). As for all-cause mortality, placebo treated patients in the European trials appeared to be twice as high (6.3%) than those in the US trials (3.1%), which might be due to higher percent of older patients. In the US trials, risedronate treated patients showed a slightly less percent of all-cause mortality compared to placebo, 2.5% in 5.0mg, 2.4% in 2.5mg, and 3.1% in placebo, whereas percentages were numerically slightly higher in the European trials, 6.6% in 5.0mg, 6.7% in 2.5mg, and 6.3% in placebo, respectively.

From Table 2, on-trial data of the US trials showed that less than 50% of patients were dead among those patients who reported lung cancer incidence (5 in 9 patients with placebo, 8 in 23 patients with 2.5mg risedronate, and 3 in 10 patients with 5.0mg risedronate). For the European trials, on-trial data showed that 82% of residronate treated patients were dead among those patients who reported lung cancer incidence (9 in 10 patients with 2.5mg risedronate, 5 in 7 patients with 5.0mg risedronate). Such percentage was 50% in the placebo treated patients (2 in 4 placebo patients).

No mortality follow-up study was performed for the European trials. It is worthwhile to note that the 2.5mg risedronate treatment was terminated earlier than expected in two (ROE and RVE) out of three European trials, which occurred in only one (RVN) of the US trials. Accurate estimate of off-study lung cancer mortality for the European trials, especially in the 2.5mg risedronate arm is important, but is not possible to obtain per the sponsor.

INDICATION APPLIES TO TREATMENT OF PMO ONLY

The three trials (RON, RVN, RHN) conducted in the North American region were to be indicated for treatment of post-menopausal osteoporosis (PMO). The corresponding three trials conducted in Europe were ROE, RVE, and RHE. These data do not provide mortality information regarding treatment/prevention of corticosteroid-induced osteoporosis indication or prevention of PMO.

CONCLUSION

In this mortality follow-up study containing three North American Trials (approximately 2,650 patients in each treatment arm), although the 2.5mg risedronate arm in Trial RVN was terminated earlier than the planned trial study period, more than 98% ascertainment of vital status resulted in approximately 2% increase in all cause mortality between Dec. 31, 1997 and Dec. 31, 1998. This is consistent with a crude estimate obtained from the original NDA data of "an additional 1% of all cause mortality for an additional half-year follow-up", see memorandum dated September 28, 1999 written by this reviewer.

Experience from the original NDA review showed that lung cancer incidence was somewhat higher with risedronate than other drugs under the same bisphosphonate class. All these clinical studies of drugs under the bisphosphonate class did not pre-specify systematic data collection regarding lung cancer. In addition, although lung cancer incidences were lower (see Table 1) in the European trials, possibly due to a 10% lower rate in patients with smoking history, twofold increase in the lung cancer incidence for the risedronate 2.5mg and 5.0mg combined was consistently observed in both regions (0.4% vs. 0.19% in the European trials and 0.62% vs. 0.33% in the US trials).

In the three US trials, Risedronate (2.5mg and 5.0mg combined) treated patients didn't show an excess of lung cancer mortality (RR=0.97 with 95% CI 0.51 to 1.85) obtained by following-up patients up to December 31, 1997, though the excess of lung cancer incidence and lung cancer death was primarily seen in the 2.5mg risedronate treated patients during on-study period and all-time analysis.

The sponsor did not perform a mortality follow-up study for the corresponding European trials, which was agreed upon by the Agency. From this reviewer's evaluation on the original "on-study" clinical database, all-cause mortality of placebo treated patients appeared to be two times higher with the European trials (6.3%) than with the US trials (3.1%), which might be due to somewhat higher % of older patients (65 ≥ years) recruited at baseline. Experience with the three North American trials showed that not all reported lung cancer incidences from the clinical database were also reported as lung cancer death in the mortality study. Some lung cancer deaths were identified through mortality follow-up study. Thus, a reasonable estimate of off-study lung cancer mortality up to Dec. 31, 1997 of the European studies, possibly caused by differential dropouts and caused by early termination of the 2.5mg risedronate arm in Trials ROE and RVE, is important. However, the impact to lung cancer mortality could not be directly assessed in the corresponding European trials.

In addition, these data do not provide lung cancer mortality information regarding indications for treatment/prevention of corticosteroid-induced osteoporosis or prevention of post-menopausal osteoporosis.

/S/

Sue-Jane Wang, Ph.D.
Mathematical Statistician

/S/ 2/24/00

Concurr: Edward Nevius, Ph.D.
Division Director

/S/ 2/24/00

Todd Sahlroot, Ph.D.
Team Leader

cc:
Archival sNDA#20-835 SE-001, -002, -003, -004
HFD510/Division File
HFD510/EColman
HFD510/BStadel
HFD510/RHedin
HFD715/Division file TSahlroot, SJWang, ENevius
HFD40RTemple

This memorandum consists of 16 pages, including 3 reviewer tables, 4 sponsor tables and 6 sponsor figures.

The mortality follow-up study results for all-cause mortality are provided in Table 1.

Table 1
All-Cause Mortality through December 31, 1997

Period	Treatment	N	No. of Deaths	Mortality Rate (per 1000 patient-years)	Relative Risk [95% CI]	p-value
"All-Time"	Placebo	2678	157	18.1	NA	NA
	Risedronate 2.5 mg	2636	141	16.5	0.91 [0.72, 1.14]	0.41
	Risedronate 5 mg	2667	137	15.8	0.87 [0.70, 1.10]	0.25
	Combined Risedronate	**5303**	**278**	**16.2**	**0.89 [0.73, 1.08]**	**0.25**
"On-Study"	Placebo	2678	83	13.9	NA	NA
	Risedronate 2.5 mg	2636	63	12.7	0.94 [0.67, 1.32]	0.71
	Risedronate 5 mg	2667	67	11.3	0.81 0.58, 1.11]	0.19
	Combined Risedronate	5303	130	11.9	0.86 [0.65, 1.14]	0.30
"Off-Study"	Placebo	2348	74	27.3	NA	NA
	Risedronate 2.5 mg	2333	78	21.9	0.86 [0.62, 1.19]	0.36
	Risedronate 5 mg	2334	70	26.0	0.95 [0.68, 1.31]	0.75
	Combined Risedronate	4667	148	23.7	0.89 [0.67, 1.18]	0.43

NA = not applicable.
N = No. of patients whose mortality status could be determined through December 31, 1997.
"All-Time" is the period from initiation of treatment until death or end of follow-up. "On-Study" is the period of time from the initiation of treatment until death or the date of last contact in the clinical trial database. "Off-Study" is the period of time from the date of last contact in the clinical database until the end of follow-up or death, whichever came first.

These analyses show that the risk of all-cause mortality in risedronate patients was similar to that of placebo subjects, regardless of the time period being considered. These data are consistent with the findings in the clinical trial database, which showed no increase in overall deaths in risedronate-treated patients during the studies.

APPEARS THIS WAY
ON ORIGINAL

All-cause mortality data through December 31, 1998 are provided in Table 2.

Table 2
All-Cause Mortality through December 31, 1998

Period	Treatment	N	No. of Deaths	Mortality Rate (per 1000 patient-years)	Relative Risk [95% CI]	p-value
"All-Time"	Placebo	2678	210	18.9	NA	NA
	Risedronate 2.5 mg	2636	205	18.7	0.99 [0.81, 1.19]	0.88
	Risedronate 5 mg	2667	193	17.4	0.92 [0.76, 1.12]	0.39
	Combined Risedronate	**5303**	**398**	**18.0**	**0.95 [0.81, 1.13]**	**0.56**
"On-Study"	Placebo	2678	83	13.9	NA	NA
	Risedronate 2.5 mg	2636	64	12.8	0.94 [0.67, 1.32]	0.72
	Risedronate 5 mg	2667	67	11.2	0.81 [0.59, 1.11]	0.19
	Combined Risedronate	5303	131	11.9	0.86 [0.65, 1.14]	0.30
"Off-Study"	Placebo	2551	127	24.7	NA	NA
	Risedronate 2.5 mg	2530	141	23.6	0.99 [0.78, 1.26]	0.93
	Risedronate 5 mg	2554	126	24.6	0.99 [0.78, 1.27]	0.96
	Combined Risedronate	5084	267	24.1	0.98 [0.80, 1.22]	0.88

NA = not applicable.
N = No. of patients whose mortality status could be determined through December 31, 1998.
"All-Time" is the period from initiation of treatment until death or end of follow-up. "On-Study" is the period of time from the initiation of treatment until death or the date of last contact in the clinical trial database. "Off-Study" is the period of time from the date of last contact in the clinical database until the end of follow-up or death, whichever came first.

All-cause mortality with an additional year of observation (through December 31, 1998) also showed no imbalance in deaths across treatment groups, with RRs of less than 1 for the active treatment groups for each time period. Cause of death information was not available for 1998.

APPEARS THIS WAY
ON ORIGINAL

The any-cancer mortality results are shown in Table 3.

Table 3
Any-Cancer Mortality through December 31, 1997

Period	Treatment	N	No. of Deaths	Mortality Rate (per 1000 patient-years)	Relative Risk [95% CI]	p-value
"All-Time"	Placebo	2676	38	4.4	NA	NA
	Risedronate 2.5 mg	2634	43	5.0	1.15 [0.74, 1.77]	0.54
	Risedronate 5 mg	2665	26	3.0	0.68 [0.42, 1.13]	0.13
	Combined Risedronate	**5299**	**69**	**4.0**	**0.91 [0.62, 1.36]**	**0.65**
"On-Study"	Placebo	2676	19	3.2	NA	NA
	Risedronate 2.5 mg	2634	15	3.0	0.87 [0.44, 1.72]	0.68
	Risedronate 5 mg	2665	9	1.5	0.47 [0.21, 1.05]	0.06
	Combined Risedronate	5299	24	2.2	0.67 [0.37, 1.22]	0.19
"Off-Study"	Placebo	2346	19	7.0	NA	NA
	Risedronate 2.5 mg	2331	28	7.9	1.12 [0.62, 2.06]	0.70
	Risedronate 5 mg	2334	17	6.3	0.90 [0.47, 1.72]	0.74
	Combined Risedronate	4665	45	7.2	1.02 [0.60, 1.76]	0.93

NA = not applicable.
N = No. of patients whose mortality status could be determined through December 31, 1997.
"All-Time" is the period from initiation of treatment until death or end of follow-up. "On-Study" is the period of time from the initiation of treatment until death or the date of last contact in the clinical trial database. "Off-Study" is the period of time from the date of last contact in the clinical database until the end of follow-up or death, whichever came first.

Any-cancer mortality (any cancer listed on the death certificate, with the exception of nonmelanotic skin cancer) in the risedronate groups was similar to that in the placebo group for each of the time periods. These results suggest that there is no association between risedronate treatment and an increased risk of death from all cancers. This finding is consistent with analyses of the clinical trial database, which found no increase in overall cancer reports in patients receiving risedronate treatment during the studies.

The lung cancer mortality results from the follow-up study are presented in Table 4.

Table 4
Lung Cancer Mortality through December 31, 1997

Period	Treatment	N	No. of Deaths	Mortality Rate (per 1000 patient-years)	Relative Risk [95% CI]	p-value
"All-Time"	Placebo	2676	14	1.6	NA	NA
	Risedronate 2.5 mg	2634	20	2.3	1.45 [0.73, 2.86]	0.29
	Risedronate 5 mg	2665	7	0.8	0.50 [0.20, 1.24]	0.13
	Combined Risedronate	**5299**	**27**	**1.6**	**0.97 [0.51, 1.85]**	**0.93**
"On-Study"	Placebo	2676	5	0.8	NA	NA
	Risedronate 2.5 mg	2634	8	1.6	1.69 [0.55, 5.17]	0.36
	Risedronate 5 mg	2665	3	0.5	0.60 [0.14, 2.51]	0.49
	Combined Risedronate	5299	11	1.0	1.16 [0.40, 3.34]	0.79
"Off-Study"	Placebo	2346	9	3.3	NA	NA
	Risedronate 2.5 mg	2331	12	3.4	1.11 [0.46, 2.69]	0.82
	Risedronate 5 mg	2334	4	1.5	0.44 [0.14, 1.44]	0.18
	Combined Risedronate	4665	16	2.6	0.79 [0.35, 1.81]	0.58

NA = not applicable.
N = No. of patients whose mortality status could be determined through December 31, 1997.
"All-Time" is the period from initiation of treatment until death or end of follow-up. "On-Study" is the period of time from the initiation of treatment until death or the date of last contact in the clinical trial database. "Off-Study" is the period of time from the date of last contact in the clinical database until the end of follow-up or death, whichever came first.

As was the case for all-cause mortality and any-cancer mortality, we observed no significant differences in lung cancer mortality between the combined risedronate groups and the placebo group. The relative risk of lung cancer for the combined risedronate groups decreased during the "off-study" period, especially in the 2.5 mg risedronate group. These data demonstrate no overall relationship between risedronate treatment and lung cancer death.

APPEARS THIS WAY
ON ORIGINAL

Figure 19
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
All Time Analysis: Placebo and Risedronate Combined

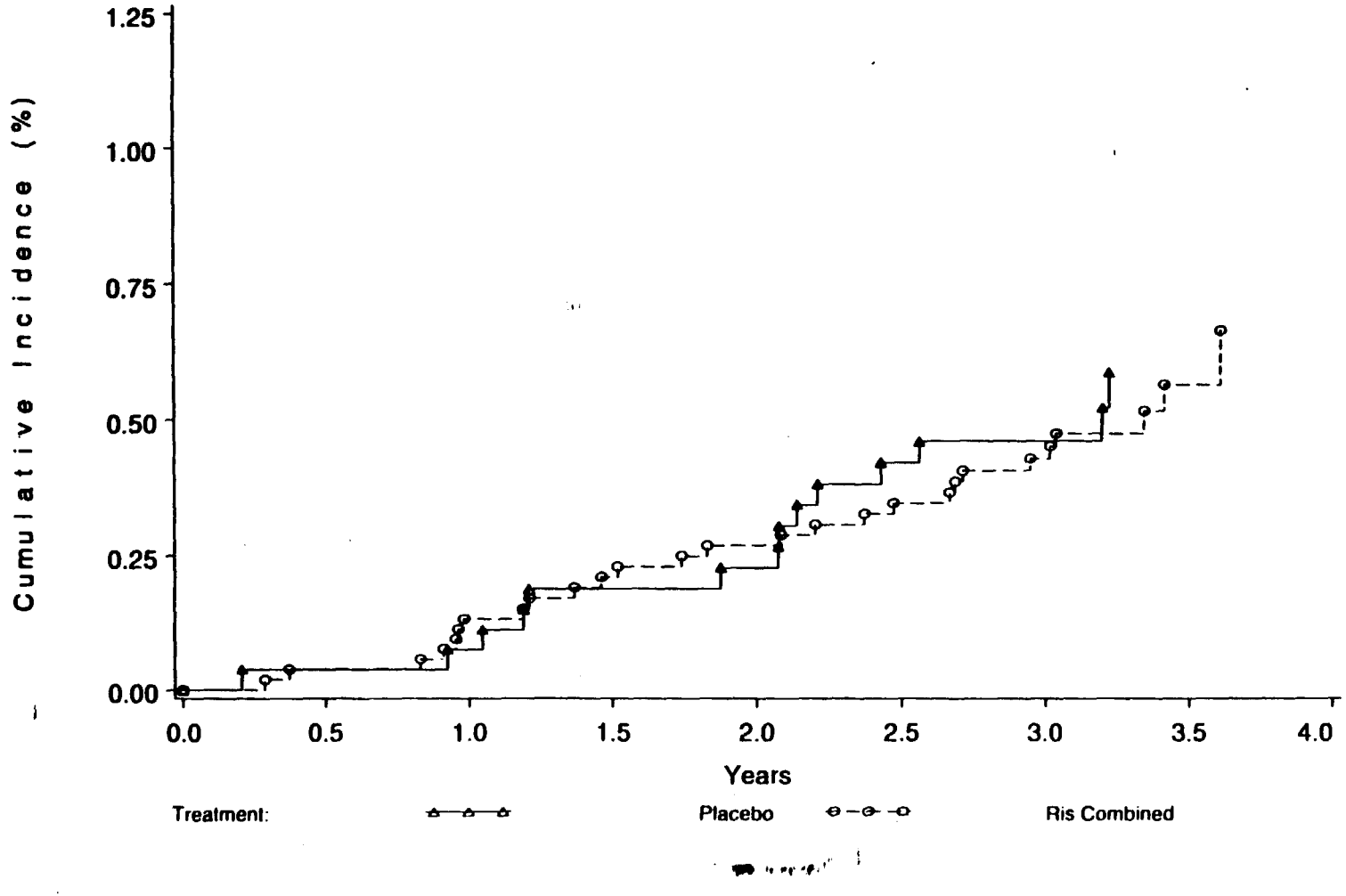


Figure 20
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
All Time Analysis: All Treatment Groups

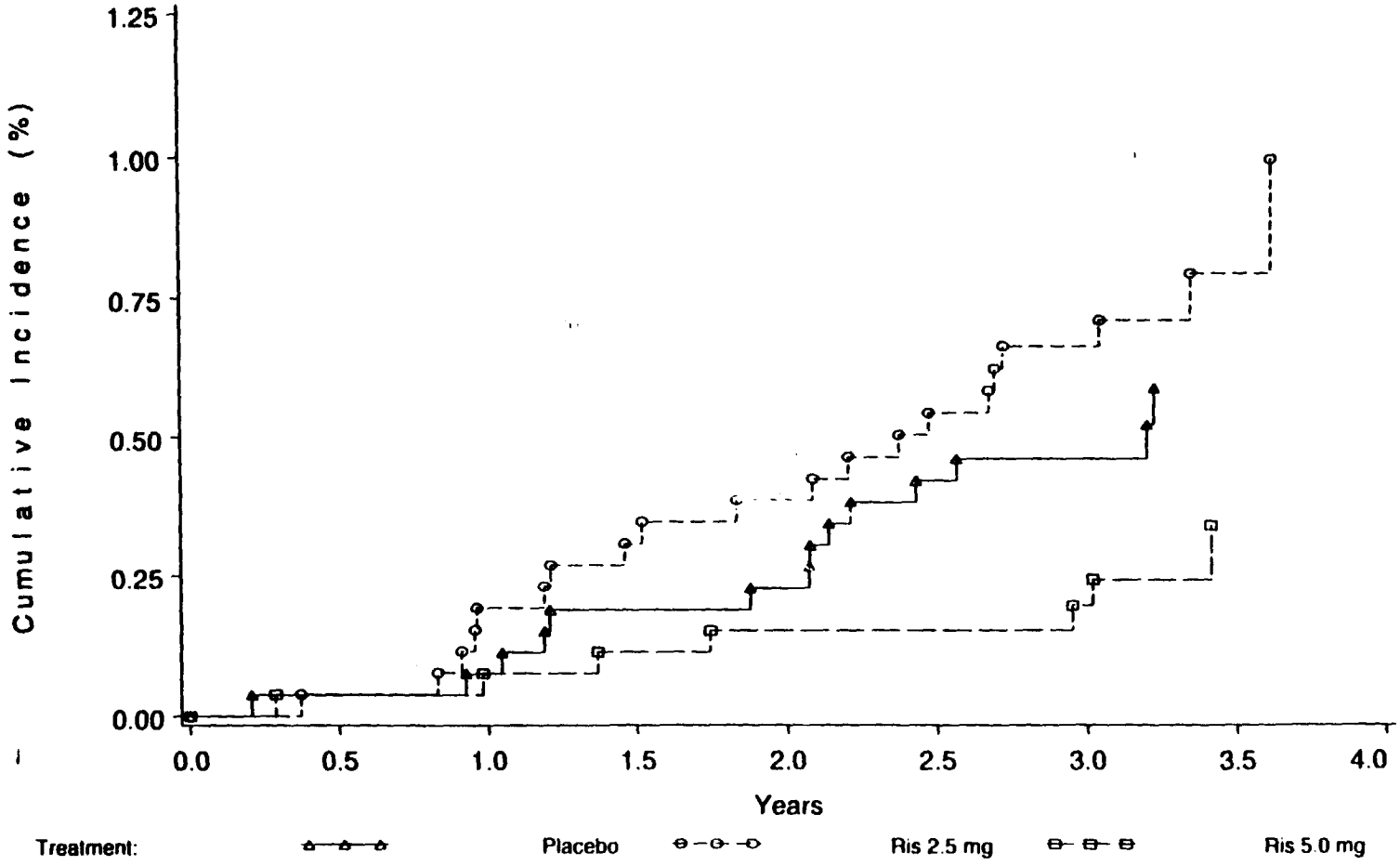


Figure 21
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
On Study Analysis: Placebo and Risedronate Combined

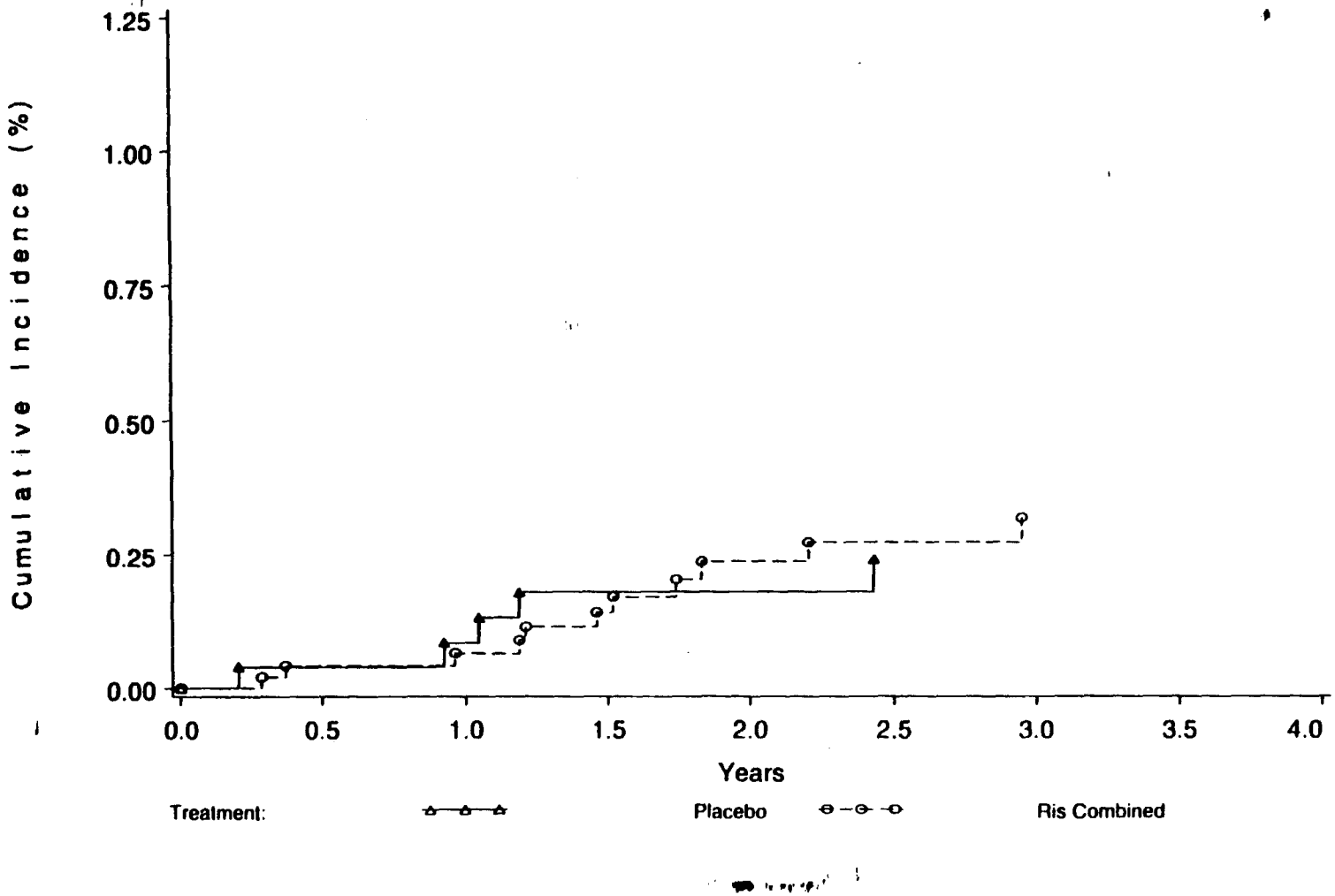


Figure 22
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
On Study Analysis: All Treatment Groups

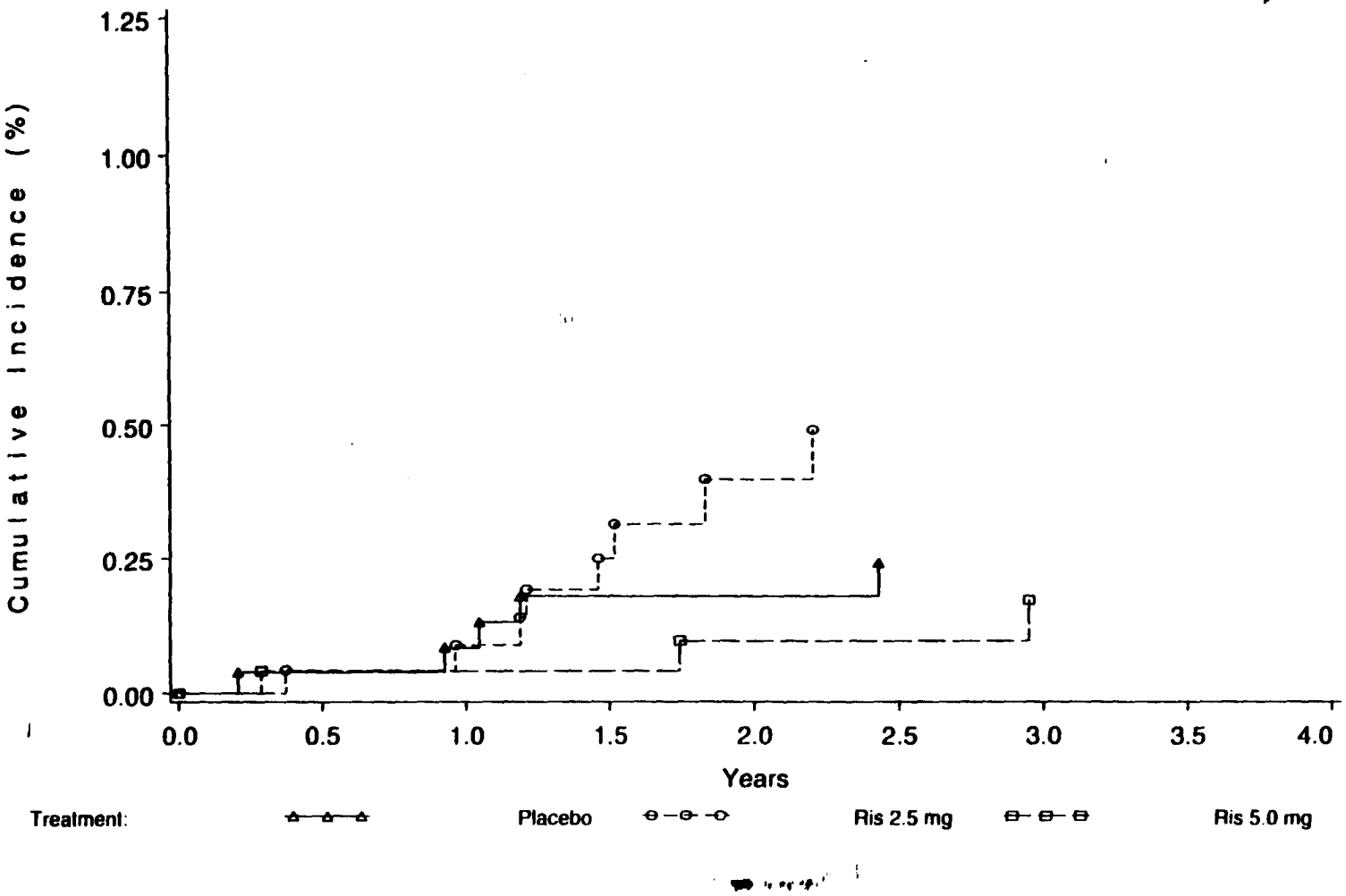


Figure 23
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
Off Study Analysis: Placebo and Risedronate Combined

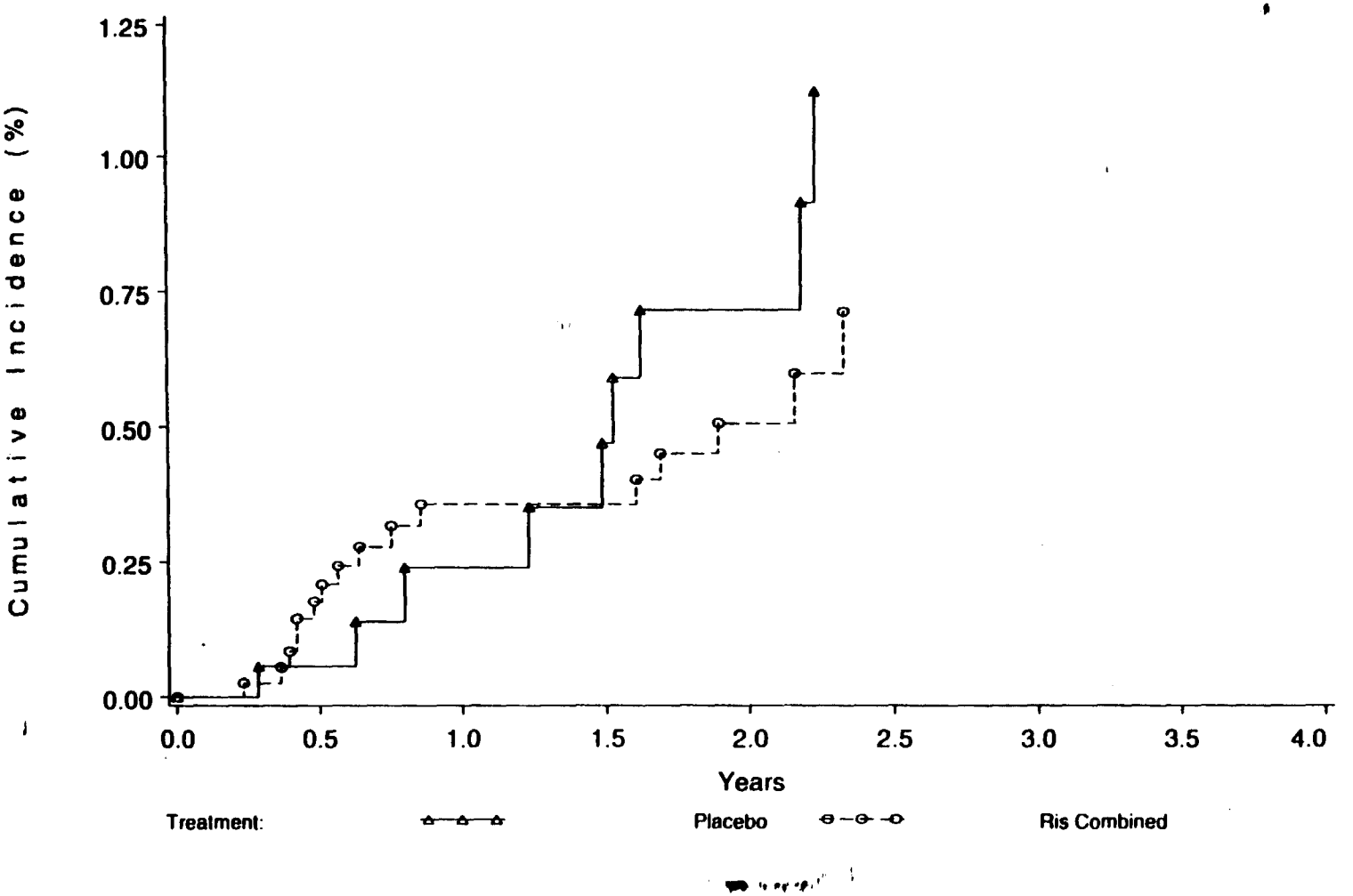
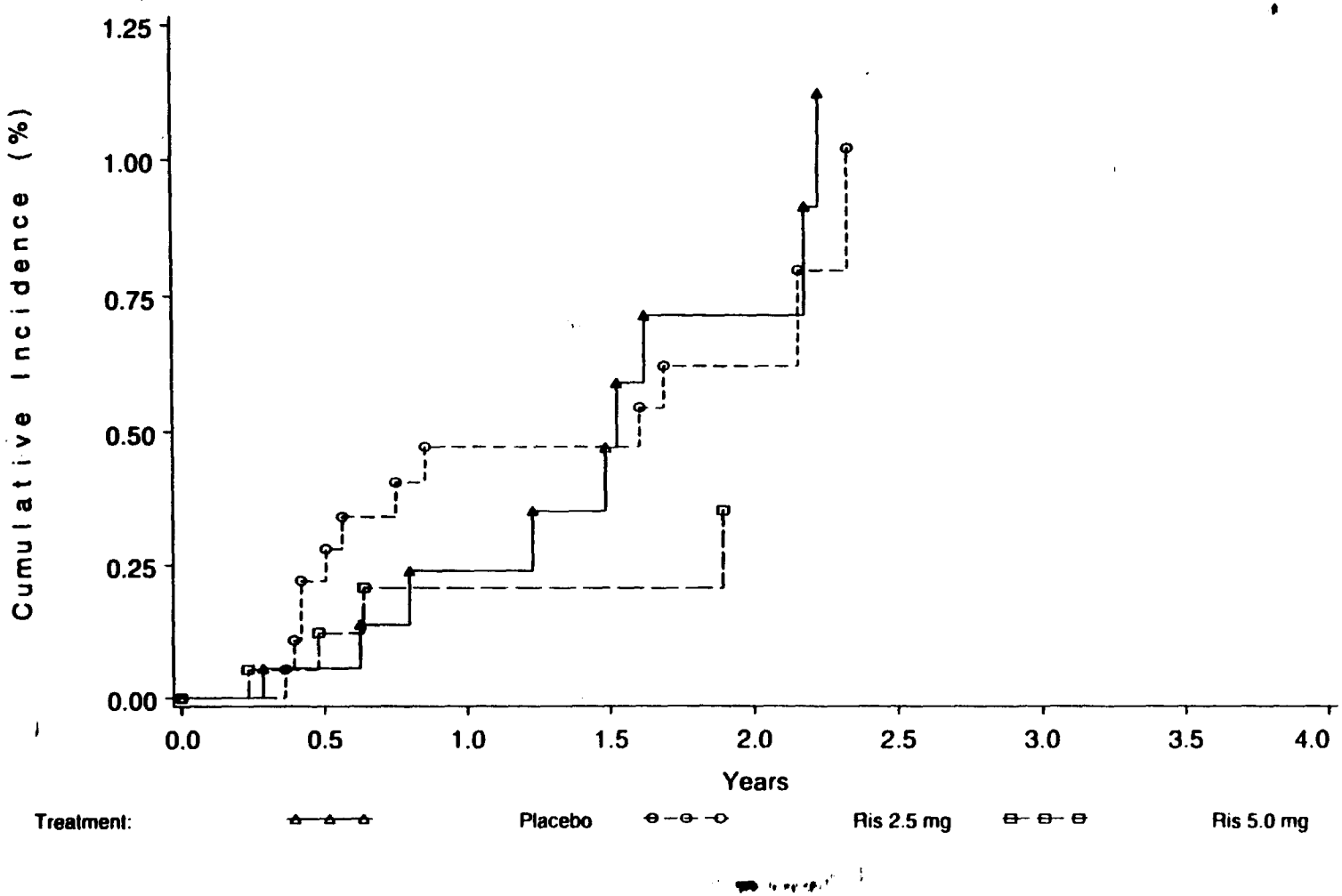


Figure 24
Mortality Comparisons across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)
Off Study Analysis: All Treatment Groups



21 PAGE(S) REDACTED

Draft Labeling

NDA 20-835/S-001
Actonel (risedronate sodium) Tablets

Dear Dr. Manning:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) Capsules.

We are reviewing the pharmacology section of your submission and have the following labeling comments. Please note that these are initial draft comments and additional comments should be expected.

1 PAGE(S) REDACTED

Draft Labeling

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the

user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ 5/17/99

Dr. Ronald Steigerwalt
Pharmacology Team Leader
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 20-835/S-001, 002, and 003
Actonel (risedronate sodium) Tablets

Dear Dr. DeMark:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) ———

We are reviewing the biopharm section of your submission and have the following comments:

1. Dosing in the phase III clinical trial was 0.5 – 1.0 prior to breakfast. When dosed 2 hours after dinner the relative bioavailability is 1.08 with a 90% confidence interval of 0.82 - 1.40 relative to dosing 0.5 hours before breakfast. However there is a delayed absorption resulting in a 64% decrease in Cmax. When dosed 3 hours after breakfast there is a decrease in relative bioavailability of 60%. Since the pharmacodynamic effect is concentration dependent, the proposed change in labeling ——— is unacceptable.
2. Drug administration in all trials was with 8 oz. of water. Due to safety concerns with alterations in esophageal transit with this class of drugs. The lack of bioavailability and safety data with administration of a smaller volume of water, and the use of larger volumes in all clinical studies, the proposed labeling change ——— is unacceptable.
3. The ———assay for residronate is biased and in-process quality control samples frequently indicated that the assay was performing outside the specifications specified by the sponsor. Any future submissions that are to include data generated with this ——— assay must have in-process controls that are acceptable to the agency. The high degree of bias with this assay indicates possible problems with the assay. If this assay is used in the future, this bias will also need to be addressed.
4. In the future, assays for pharmacodynamic measures in addition to assays for drug concentrations must be adequately validated and reports on their validation and in-process controls shall be submitted for review.

We also have the following preliminary labeling comments from the biopharm review. Additional labeling comments will be forthcoming.

~~Double-struck out~~ text should be removed from the proposed labeling; <u>double underlined text</u> should be added

➢ Indicates additional comments.

2 PAGE(S) REDACTED

Draft Labeling

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ 9/8/99

Dr. Hae-Young Ahn
Team Leader, OCPB/DPE-2 for the
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-835/S-001, 002, and 003
Actonel (risedronate sodium) Tablets

Dear Dr. Manning:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium)

We are reviewing the clinical section of your submission and have the following comments and information requests:

Integrated Summary of Safety

1. Please calculate the relative risk for death between the placebo and risedronate 2.5 mg groups, between the placebo and risedronate 5.0 mg groups, and between the placebo and combined risedronate groups. Please include all randomized, placebo-controlled phase 2 and 3 studies involving Risedronate 2.5 and/or risedronate 5.0 mg once daily. Subjects who died "off" study drug should be included in the analyses.

2. For the "combined" dataset, please provide a table that compares the number and percentage of patients in the placebo and risedronate 5.0 mg groups with adverse events occurring at a frequency > 2% and in more risedronate 5.0 mg-treated patients than in placebo-treated subjects. Please also provide statistical comparisons. Please also perform this type of analysis on the combined phase 3 CIO study database (I previously asked for this analysis for the individual CIO studies).

3. For the "combined" dataset, for all subjects in the placebo and risedronate 5.0 mg groups who had a high or markedly high AST, ALT, and/or GGT value at endpoint or on two or more occasions during the studies, please plot all of their values from baseline to endpoint. Please also mention whether the abnormal value resolved spontaneously or required specific intervention. It would also be helpful to see a statistical comparison of these analyses.

4. For the "combined" and phase 3 CIO databases separately, please statistically compare the incidence of all fractures [new (not worsening) vertebral and all other traumatic and atraumatic fractures] between the placebo and risedronate 5.0 mg groups.

5. Please refer to panel 139 (vol. 1.261/285). Please provide the actual number of patients in the placebo and risedronate 5.0 mg groups who had markedly low calcium levels at endpoint.

6. For study RVN, please provide a statistical comparison of the mean and median percentage changes from baseline to Month 12 in iPTH for the placebo and risedronate 5.0 mg groups. Please also provide a frequency distribution of the changes from baseline to Month 12 in iPTH in the placebo and risedronate 5.0 mg groups. For the placebo and risedronate 5.0 mg groups separately, we would also like to see the correlation coefficients for the changes from baseline to Month 12 in iPTH vs. midshaft radius BMD.

7. Are there vital sign data in the ISS for the "combined" dataset?

8. Are there EKG data in the ISS for the combined dataset? If not, are there any EKG data from placebo-controlled studies?

9. In the phase 3 combined and CIO databases, were any of the following terms captured as adverse events or funneled into another COSTART term: retching, hiccup, acid regurgitation, alkaline regurgitation, odynophagia, bloating, esophageal spasm, daytime heartburn, or nighttime heartburn?

RCP and RCT

1. For both studies separately, please perform LS, femoral neck, and femoral trochanter BMD responder analyses only on those placebo and risedronate 5.0 mg subjects who had a baseline and Month 12 BMD measurement. Please include statistical analyses of these data.

2. Please provide the details of the statistical model reported in response to my question #7 (both studies) in your February 25, 1999 submission.

RCT

1. Are the PTH data normally distributed? Please provide statistical analyses of the iPTH data shown in panel 308 (vol. 1.262/pg205). Please also provide statistical analyses of the mean and median percentage changes from baseline to Month 12 in iPTH for the placebo and risedronate 5.0 mg groups.

2. Please provide a frequency distribution of the changes from baseline to Month 12 in iPTH in the placebo and risedronate 5.0 mg groups. We would also like to see the correlation coefficients for the changes from baseline to Month 12 in iPTH vs. midshaft radius BMD in the placebo and Risedronate 5.0 mg groups separately.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization

agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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APPEARS THIS WAY
ON ORIGINAL

NDA 20-835/S-001, 002, and 003
Actonel (risedronate sodium) Tablets

Dear Dr. Manning:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) Capsules.

We are reviewing the biopharmaceutics section of your submission and have the following comments and information requests:

1. Please clarify: The synopsis for study RMD (Vs1.002/p206) indicates that the lot numbers of the 5 mg film-coated tablet used in the study were 73063 and 73077, and that the 2.5 mg tablets were from lots 72865 and 72867. However, Table TF-1 (Vs1.002/p97) does not include these lots for study RMD.

2. It would expedite the review process if you submitted on disk, in Word format, the proposed labeling with designation (e.g., redline, strikeout) to differentiate the current approved labeling from the proposed changes.

3. Panels 310A and 310B in Vs 1.1.262/p219-220 summarize the adverse events in patients exposed to concomitant therapy (users) for PMO and CIO, respectively. According to your minutes (Vs1.001/p79), the Agency had asked that duration, dose, and sample size be documented in the ISE for concomitant treatment statements. Please indicate where these data can be found. Also, please explain how a "user" is defined (e.g., minimum dose, frequency) and from which studies these data were derived.

4. Vs1.086/p74-87 discusses the dissolution of the 5 mg tablet. Please indicate from which 3 lots of clinical tablets the 12 tablets used in the dissolution testing were taken; also, in which clinical studies were these lots used? Please provide the individual tablet dissolution data that was used to generate the mean data presented in Vs1.086/p78-81, Tables 9.4.3 to 9.4.6.

5. Please submit on disk the data used in the PK/PD model from study RMD008894. The format (e.g. ASCII, Excel) of these data should be discussed with OCPB before submission.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and

should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ 2/2/99

Dr. Hae-Young Ahn
Team Leader, OCPB/DPE-2 for the
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 20-835/S-001, 002, and 003
Actonel (risedronate sodium) Tablets

Dear Dr. Manning:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) Capsules.

We are reviewing the clinical section of your submission and have the following comments and information requests concerning the safety review:

1. For the combined and phase 3 CIO databases, please provide by treatment group, the number and percentage of patients who started (on their own or by the investigator) antacids, H2-blockers (including OTC), proton-pump inhibitors, misoprostol, or any other medication for an upper-GI complaint (please exclude those taken for flatulence). Please also list by individual medication.

2. Please refer to panels 61 (Vol. 1.261/pg176) and 217 (Vol. 1.262/pg62). We would like to see similar tables in which all serious Aes are included regardless of incidence. Please also compare the incidence rates statistically between the placebo and risedronate 5.0-mg groups.

3. For subjects in the combined and phase 3 CIO databases, please provide, by treatment group, the number of patients who received empirical drug treatment for an upper GI complaint prior to endoscopy. Please also include the drug and dosage received, as well as the duration of treatment prior to the endoscopy.

4. Please refer to panels 85, 86, and 231 (Vol. 1.261/pgs220,221 and Vol. 1.262/pg87). Please stratify the data by age $\geq$ 65 years of age. For the users of NSAIDS or ASA, do you have estimates, by treatment group, of the doses of NSAID or ASA used?

5. For the two phase 3 CIO studies, please provide data like that shown in panels 79 and 80 (Vol. 1.261/pgs203,204).

6. Please refer to panel 220 (Vol. 262/pg68). Please stratify the data by mean and median dose of steroid.

7. Please refer to panel 231 (Vol. 1.262/pg87). Of NSAID users and ASA users (two left columns), there were more risedronate 5.0 mg subjects vs. placebo patients that complained of abdominal pain. Can you please describe what, if any, measures were taken in response to the complaint of abdominal pain in these 16 patients. For example, did some receive no specific treatment and the abdominal pain resolved spontaneously, did some discontinue the drug, did some received specific medication to treat the complaint?

8. Please refer to panel 124 (Vol. 1.261/pg272). Please indicate whether patients diagnosed with anemia received specific treatment in response to this finding. Please also indicate whether the anemia resolved by endpoint.

9. Please refer to panel 127 (Vol. 1.261/pg275). For total bilirubin, ALT, AST, and alk phos. please provide the number of patients in the risedronate 5.0 mg and placebo groups who had values above normal at endpoint. For these patients, provide the actual value at endpoint as well as all previous values for the specific parameter.

10. Please refer to panel 138 (Vol. 1.261/pg284). For endpoint values, please statistically compare the incidence rates for low calcium, low phos, and high phos between the placebo and risedronate 5.0 mg groups.

11. Please refer to panel 139 (Vol. 1.261/pg285). For endpoint values, please provide the number of patients in the risedronate 5.0 mg and placebo groups who had low calcium, low phos, and high phos values. For these patients, provide the actual value at endpoint as well as all previous values for the specific parameter.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Procter&Gamble
PHARMACEUTICALS

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8700 Mason-Montgomery Road
P O. Box 8006
Mason. Ohio 45040-9462

February 3, 2000

Bruce Stadel, M.D., M.P.H.
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention. Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE. NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-induced Osteoporosis

Dear Dr. Stadel:

This submission is in response to your question concerning the follow-up obtained on the 42 patients diagnosed with lung cancer (nine placebo, twenty-three 2.5 mg risedronate and ten 5 mg risedronate) during the 3 North American Phase III PMO clinical trials. As shown in Table 1 below (same as Table 5 in the mortality report), of these 42 patients, 29 patients' deaths (eight placebo, fifteen 2.5 mg risedronate, six 5 mg risedronate) were identified by the NDI database or the Canadian Provincial database mortality search process, and 25 of the 29 had lung cancer listed on the death certificate (six placebo, fourteen 2.5 mg risedronate, and five 5 mg risedronate). There were 4 patients who had lung cancer according to the clinical database, but lung cancer was not listed on the death certificate.

Table 1
Accountability of the 42 Patients with Lung Cancer Reported in the Clinical Database as of 12/31/97

	Placebo n = 9	2.5 mg Risedronate n = 23	5 mg Risedronate n = 10	Total n = 42
Patients who died with lung cancer listed on death certificate in mortality study	6	14	5	25
Patients who died without lung cancer listed on death certificate in mortality study	2	1	1	4
Patients with lung cancer in clinical studies who were alive as of 12/31/97	1	8	4	13

As stated in Section 4.1.4.3 of the mortality report, the analysis rules for the determination of any-cancer and lung cancer mortality were established such that the cause of death information was based on the external database searches for both "on-study" and "off-study" deaths. This rule maintained a consistent approach across these 2 time periods of the study

and the overall "all-time" analysis study period. Accordingly, the adverse event COSTART codes that were associated with cancer in the clinical database were not used to assign any-cancer and lung cancer cause of death.

Application of this rule resulted in the exclusion of the 4 patients (two placebo, one 2.5 mg risedronate, one 5 mg risedronate) listed in Table 1 above, who died without lung cancer listed on death certificate, from the lung cancer mortality analysis shown below in Table 2 (same as Table 10 of the mortality report). Therefore, for the all-time analysis in Table 2, six of the 14 placebo deaths, 14 of the twenty 2.5 mg risedronate deaths, and 5 of the seven 5 mg risedronate deaths are patients who were in the original group of 42 diagnosed with lung cancer in the clinical trial database.

All patients diagnosed with lung cancer in the clinical database and known to have died on-study were captured in the NDI or Canadian Provincial databases (five placebo, eight 2.5 mg risedronate, and three 5 mg risedronate).

Table 2
Mortality Comparisons Across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)

Time Period Treatment	N	Patient Years[a]	Number of Deaths	Mortality Rate (per 1000 Patient Years)	Relative Risk	95% CI[b]	P-value[c]
All Time							
Placebo	2676	8655.1	14	1.62	--	--	--
Risedronate 2.5 mg	2634	8527.8	20	2.35	1.45	(0.73, 2.86)	0.291
Risedronate 5 mg	2665	8640.7	7	0.81	0.50	(0.20, 1.24)	0.133
Risedronate Combined	**5299**	**17168.5**	**27**	**1.57**	**0.97**	**(0.51, 1.85)**	**0.927**
On Study							
Placebo	2676	5947.1	5	0.84	--	--	--
Risedronate 2.5 mg	2634	4973.8	8	1.61	1.69	(0.55, 5.17)	0.361
Risedronate 5 mg	2665	5945.1	3	0.50	0.60	(0.14, 2.51)	0.486
Risedronate Combined	5299	10918.9	11	1.01	1.16	(0.40, 3.34)	0.787
Off Study							
Placebo	2346	2708.0	9	3.32	--	--	--
Risedronate 2.5 mg	2331	3554.0	12	3.38	1.11	(0.46, 2.69)	0.817
Risedronate 5 mg	2334	2695.6	4	1.48	0.44	(0.14, 1.44)	0.177
Risedronate Combined	4665	6249.6	16	2.56	0.79	(0.35, 1.81)	0.584

N = Number of patients whose mortality status could be determined through December 31, 1997

-- = Not applicable or not performed

[c] P-value for testing the difference between placebo and the risedronate groups using Cox regression stratified by study

[a] "On study" patient years of observation (time from the start of the study to the last observation in the clinical database)
"Off study" patient years of observation (time from the last observation in the clinical database to December 31, 1997 or the date of death, whichever occurred first)

[b] Relative risk and 95% confidence interval based upon Cox regression model between individual risedronate dose and placebo stratified by study

[Source program: /home7/RISEDRONATE/mortality/survival.sas; program run on 17DEC99 at 10:50 by TF6225.]

[Source file code: aan.doc]

Of the 4 patients who died without lung cancer listed on the death certificate, three (1 in each treatment group) had another cancer listed, of which 1 patient had breast cancer and the other 2 patients had cancer of an unspecified site. All 4 patients were included in the all-cause mortality analysis (Table 7 of the mortality report), and the 3 patients with cancer were included in the any-cancer analysis (Table 9 of the mortality report).

Table 3 provides a tabulation of the deaths with lung cancer listed as identified by the mortality process. Twenty-five deaths were found from the cases in the clinical database (Line B). Sixteen new lung cancer deaths (eight placebo, six 2.5 mg risedronate, two 5 mg risedronate) were identified by the NDI or Canadian Provincial databases through 12/31/97 (Line C). Therefore, 41 patients (fourteen placebo, twenty 2.5 mg risedronate, seven 5 mg risedronate) deaths were identified with lung cancer listed on the death certificate through December 31, 1997 (Line D). This corresponds to the 41 all-time deaths in Table 2 above.

Table 3
Accountability of the Deaths with Lung Cancer Listed on Death Certificate as of 12/31/97

Line		Placebo	2.5 mg Risedronate	5 mg Risedronate	Total
A	Lung cancer cases recorded in clinical database	9	23	10	42
B	Clinical database cases identified in NDI or Canadian Provincial Database with lung cancer listed	6	14	5	25
C	New lung cancer deaths in NDI or Canadian Provincial Database	8	6	2	16
D	Total deaths (B+C)	14	20	7	41

Please call me if there are any questions and/or clarifications regarding this submission.

Sincerely,

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