X. MEDICAL OFFICER'S SUMMARY OF EFFICACY AND SAFETY OF RISEDRONATE FOR THE PREVENTION AND TREATMENT OF CORTICOSTEROID-INDUCED OSTEOPOROSIS

The pathogenesis of CIO is multifactorial[1]. Risedronate interacts at two points in the disease process: 1) It tends to decrease serum calcium levels, which in turn, tends to increase serum iPTH levels, and 2) It decreases osteoclast activity. Risedronate's anti-osteoclastic activity presumably explains its positive effect on BMD.

The data from studies RCP and RCT indicate that, in corticosteroid-treated patients, 5-mg once daily of risedronate increases LS BMD compared with treatment with 500 mg per day of calcium (prevention trial) or 1000 mg per day of calcium and 400 IU of vitamin D per day (treatment trial). In both studies the placebo-subtracted effect of 5 mg per day of risedronate on LS BMD after one year of treatment was about 3.0%. Similar results have been reported with the use of intermittent etidronate and alendronate in patients taking corticosteroids[2-4].

While the difference in LS BMD between active- and placebo-treated patients was statistically significant, the important question is whether risedronate decreases the risk for fractures in CIO patients? While a definitive answer cannot come from this small database, the results of logistic regression suggest a favorable reduction in vertebral deformity risk in patients treated with risedronate. This model indicated that a patient taking 5 mg once daily of risedronate was 2.5 times less likely to develop a vertebral deformity than a patient on placebo (calcium and/or vitamin D) after one year of treatment. Published results with alendronate and cyclical etidronate also indicate a trend for a lower incidence of vertebral fractures in drug-treated patients[2,4].

One concern about long-term concomitant use of corticosteroids and any anti-resorptive agent is the potential to slow or stop bone turnover to such an extent as to create "frozen bone." In this situation risk for fracture might well increase. The results from RCP and RCT do not suggest that the risk for non-vertebral fractures in patients taking an average of about 10 mg per day of prednisone is increased by concomitant use of risedronate for one year. And data for other bisphosphonates do not indicate that there is a significant increase in the risk for non-vertebral fractures during one year of treatment in patients receiving low to moderate doses of glucocorticoids[2,4]. The longer-term effects of concomitant use of risedronate and steroids on bone are unknown at this time and it would seem prudent for patients to receive this combination of drugs for less than one year, if possible.

Concern exists about the negative effects of bisphosphonates on the gastrointestinal (GI) tract, particularly the esophagus[5]. The concomitant use of risedronate with glucocorticoids and NSAIDs, agent also associated with GI irritation, is therefore of particular interest. Some GI adverse events were more common among risedronate/steroid-treated patients than placebo/steroid-treated subjects. These included abdominal pain, esophagitis, doudenitits, hemorrhage, nausea, and vomiting. Whether this safety profile will apply to the larger more heterogeneous population of patients likely to receive these agents in the market place is unknown.

References

1. Lane NE et al. The Science and Therapy of Glucocorticoid-Induced Bone Loss. Endo Met Clinics of North Am 1998;27:465.
2. Adachi JD et al. Intermittent Etidronate Therapy to Prevent Corticosteroid-Induced Osteoporosis. N Engl J Med 1997;337:382.
3. Roux C et al. Randomized Trial of Effect of Cyclic Etidronate in the Prevention of Corticosteroid-Induced Bone Loss. J Clin Endocrinol Metab 1998;83:1128.
4. Saag KG et al. Alendronate for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. N Engl J Med 1998;339:292.
5. DeGroen PC et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996;355:1016.

XI. Regulatory Recommendations

This Reviewer recommends that this sNDA (s001, 002, and 003) be designated approvable

This Reviewer also recommends that a formal meta-analysis of the lung cancer data be performed by the Agency using raw data from the appropriate sponsors. The sponsors should submit a general proposal for the statistical approach they feel most appropriate for this analysis.

/S/ 8/10/94

Eric Colman, MD

/S/

cc: NDA Arch (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S CONSULT REVIEW

NDA:	20-835/S-001
Sponsor:	Procter & Gamble Cincinnati, OH
Date Submitted:	January 26, 1999
Drug:	Risedronate sodium
Pharmacological Category:	Antipagetic, bone resorption inhibitor,
Mode of Administration:	5 mg coated tablets for oral administration
Material Reviewed:	Clinical Report Results of Study 1997037, an endoscopy study in healthy adult volunteers with aspirin-induced gastric erosions, comparing 5 mg risedronate and 10 mg alendronate [another suppressant of bone resorption]
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

FEB 11 1999

SUMMARY

The clinical report summarizes results of Study 1997037, an endoscopy evaluation using the Lanza's aspirin-damage model in healthy adult volunteers with aspirin-induced gastric erosions. The sponsor reached the conclusion that risedronate 5 mg/day and alendronate 10 mg/day given for up to 4 weeks following discontinuation of aspirin, did not interfere with the healing of the gastric mucosa. Although this consultant agrees with the sponsor's conclusions, there is little clinical relevance of the Lanza's bioassay to the larger and more important clinical issue: characterization of the local irritation (mainly the esophagus) that may be induced by risedronate and other bisphosphonates. Risedronate is intended for long-term use in postmenopausal osteoporotics who may need to take – simultaneously – other medications, such as aspirin or NSAIDs for rheumatoid arthritis or osteoarthritis. In such clinical setting, many questions – included those noted in Section IV. of this review, need to be answered. Adequate experimental/clinical studies are needed to properly characterize, treat and prevent this adverse experience.

I. BACKGROUND/INTRODUCTION

The compound which is the subject of the present consult is risedronate (NE-58095),[1] [RISE], a nitrogen-containing biophosphonate. Bisphosphonates[2] are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. RISE has a high affinity for hydroxyapatite crystals in bone and, according to the information in the Investigator's Brochure, is a highly potent antiresorptive compound. The sponsor of this NDA, Procter & Gamble, is developing RISE for the treatment of metabolic bone disorders such as post-menopausal osteoporosis. RISE is already approved for the treatment of Paget's disease of the bone. In pre-clinical studies in young or growing rats, no effect was observed on inhibition of bone mineralization with doses of RISE >3000 times the minimal effective dose for inhibition of bone resorption. There is no information available on possible ulcerogenic effects of this compound in animal models of gastro-duodenal ulcer or esophageal disease. According to the information included in the protocol and the clinical report, in Phase 1 clinical trials conducted in over 400 subjects, no clinically significant changes were observed in vital signs or laboratory parameters. In these studies, volunteers were administered either a single dose ranging from 0.25 to 40 mg, or multiple doses of 30 mg/day for 14 days.

One bisphosphonate now available in the US and many other countries for the treatment (10 mg per day for up to 4 years) and prevention (5 mg per day for up to 4 years) of post-menopausal osteoprosis and the treatment of Paget's disease of bone (40 mg for up to six months) is alendronate (FOSAMAX®) [ALEN]. In two placebo-controlled, double-blind, long-term, multicenter studies in postmenopausal women with osteoporosis, abdominal pain was significantly more frequent among subjects taking 10 mg/day of ALEN (20%) than among subjects receiving placebo (14%) (p=0.029). In an international multicenter fracture intervention trial with ALEN patients who experienced **erosive gastrointestinal disease** within the previous five years or who currently suffered from dyspepsia requiring daily treatment were excluded from participation. There have been several published case reports of **esophagitis** associated with the use of ALEN.

Currently, U.S. labeling for FOSAMAX® carries the following warning:

> FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa. Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia or retrosternal pain. The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with a full glass (6-8 oz) of water, and/or who continue to take FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

[1] 1-hydroxy-2-(3-pyridinyl) ethylidine bisphosphonic acid monosodium salt

[2] Other bisphosphonates include etidronate (DIDRONEL®, also a sequestring and chelating agent, pamidronate (AREDIA® a calcium metabolism regulator available for intravenous injection; structurally similar to etidronate), alendronate (FOSAMAX® inhibitor of bone resorption; structurally related to etidronate and pamidronate).

> Because of possible irritant effects of FOSAMAX on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

An additional PRECAUTION is included in the U.S. labeling:

> "To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow Fosamax® with a full glass of water (6-8 oz) and not lie down for at least 30 minutes and until after their first food of the day."

The Clinical Reports makes reference to two previous studies that were conducted using the aspirin-damage model by Dr. Lanza, the investigator for this current study.

- In the first study,[3] 10 or 40 mg of ALEN or 400 mg etidronate (Didronel®) were administered once a day for 28 days following an aspirin pre-treatment period. Two weeks after aspirin pre-treatment, fewer subjects in the ALEN 10 mg group demonstrated normal (healed) stomach scores compared to the no-treatment control group and the etidronate group. At 4 weeks after aspirin pre-treatment, fewer subjects in the no treatment control group had normal stomach scores than at 2 weeks after aspirin pre-treatment. The alendronate 10 mg group did not differ from the no-treatment control group at 4 weeks but did exhibit less healing than the etidronate group.

- In the second study,[4] 5 or 30 mg of RISE were administered once a day for 28 days following an aspirin pre-treatment period. It was concluded that RISE 5 mg did not interfere with the healing of the stomach mucosa compared to no treatment.

The sponsor now submits the results of study No. 1997037, a trial designed to evaluate the effects of ALEN and RISE at dose levels recommended for the treatment of postmenopausal osteoporosis, as compared to placebo. The endpoint is the healing of aspirin-induced erosions in normal subjects (40y of age or older). An additional objective of this trial was to assess the potential for RISE and ALEN to cause further esophageal, gastric, or duodenal mucosal injury.

II. SUMMARY REVIEW OF CLINICAL STUDY REPORT 1997037

"A Twenty-eight Day, Randomized, Single-blind, Gastrointestinal Endoscopy Study in Healthy Adult Volunteers with Aspirin-induced Stomach Erosions, Comparing 5 mg Risedronate and 10 mg Alendronate"
[07-Jun-97 to 08-Nov-97]

From the review of the evidence this was a single-blind, multiple dose, randomized, placebo-controlled, parallel-group, 3-arm study carried out at one center in Houston, TX. The principal investigator was Dr. Frank L. Lanza, a highly qualified expert in this field.

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[3] [M.R. Carlson et al. Medical Project Number 1995129. 29 May 1996; P&G Pharmaceuticals]
[4] [M.R. Carlson et al. Medical Project Number 1996028. 16 Jan 1997; P&G Pharmaceuticals]

Co-investigators (from the same Institution, the Houston Institute for Clinical Research) were Drs. R.E. Davis, P.M. Mauk, F.M. Sutton and J.G. Trabanino. The clinical report, dated 17 March 1998, was prepared by Dr. M.A. Blank et al. from Procter & Gamble Pharmaceut.

- The study **was set** to "compare the esophageal and gastroduodenal effects of RISE and ALEN in healthy adult volunteers with aspirin-induced erosions of the stomach mucosa".

- A **dose level** of 2600 mg/day of aspirin was chosen to induce stomach erosions. The dose of RISE selected for this trial, 5 mg/day, is the likely recommended therapeutic dose for the treatment of postmenopausal osteoporosis. The dose level and regimen for ALEN, 10 mg/day, is the labeled recommended dose for the treatment of postmenopausal osteoporosis.[5]

- The **study population** was adequate for this type of study. The study population consisted of generally healthy men and women who were nonsmokers; were at least 40y of age, had no Hx of peptic ulcer disease, esophagitis, GI bleeding or allergy to bisphosphonates, aspirin or other NSAIDs. The subjects had to have a normal esophageal and gastroduodenal mucosa at the screening endoscopy. The specific inclusion criteria and reasons for exclusion, were adequate to properly characterize a healthy individual with endoscopically proven lack of upper g.i. lesions who was not taking pro- or anti-ulcergenic medications that could potentially confound the results. It was anticipated that at least 50 subjects per treatment arm would complete the trial. This sample size was expected to have 90% power to detect a pairwise Tx difference in stomach scores among nonsmokers of 0.740, using a pairwise type I error rate of 0.05 and a conservative error estimate of 1.158 x 110% = 1.274.

- The study consisted of **3 periods**: a screening period (Days –13 to 1), after which eligible subjects were enrolled for aspirin pre-Tx; aspirin pre-Tx period (Days 1 to 7) during which a total of 8 aspirin tablets (2600 mg aspirin) per day were taken for 7 days at the end of which, eligible subjects were randomized to one of the three arms of the study; and a Tx-period (Days 8 to 35) during which subjects in each group took either one RISE tablet (5 mg), one ALEN tablet (10 mg), or one placebo tablet daily for 28 days.

[5] In the clinical report, the sponsor noted that due to their inability to produce or obtain an ALEN placebo, this study did not include double-dummy placebos. In order to minimize any potential bias associated with including only a RISE placebo, an unmatched (i.e., did not match either RISE or ALEN) placebo was used for the study. Results from study reported by M.R. Carlson et al. [Medical Project Number 1995129. 29 May 1996, P&G Pharmaceut]. evaluating etidronate (Didronel®) in the aspirin-damage model indicated that etidronate does not impair stomach healing. Therefore, the assumption was that the excipients in the etidronate placebo would not impair stomach healing. For these reasons, an etidronate (Didronel®) placebo was used for this study.

Diary cards were used to bolster medication compliance in both the aspirin pre-treatment and the treatment periods of the trial. The cards contained appropriate dosing instructions and provided a place for subjects to record when medication was taken.

- An adequate **method of assignment** [micro-computer-generated based program to balance within Tx groups for gastric endoscopy score] was used. Considered were the endoscopy score (3 vs 4 on the Lanza 0-4 scale), sex and age categories. The subject within each category was randomly assigned (block size of 3 generated by the sponsor prior to the start of the trial) to one of the 3 Tx groups.

- A summary of **clinical supplies** information is given below.

Clinical Supplies Information

Dosage Form	Drug Product Lot Number	Expiration Date
325 mg aspirin[a] tablets	1212	March 1999
Risedronate[b] 5 mg coated tablets	064781	August 1998
Fosamax® (alendronate sodium)[c] 10 mg tablets	82176/E2039	December 1998
Placebo[d] tablets for Didronel® 400 mg tablets	MAN211232	June 1999

a) Aspirin used for this study was purchased commercially from an independent pharmacist pre-packaged (sixty 325-mg tablets per container) and labeled as to content and usage. Tablets were manufactured by [redacted]
b) Each risedronate cellulose-film-coated tablet contained 5 mg risedronate sodium, monohydrate lactose, microcrystalline cellulose, crospovidone, and magnesium stearate.
c) Each alendronate cellulose-film-coated tablet contained 10 mg alendronate sodium.
d) Each placebo tablet contained the excipients lactose (anhydrous), microcrystalline cellulose, sodium chloride, and magnesium stearate. The risedronate tablets and the placebo tablets were manufactured by P&G Pharmaceuticals. All lots met the specifications set for them.

- On the subject of **blinding**, it is noted that the sponsor, investigator, physicians, and assistants participating in the endoscopic examinations did not know the treatment assigned to each subject. To protect the single-blind, all study medication (with the exception of aspirin) was dispensed by a designated member(s) of the Investigator's staff who was independent of subject evaluations, including EGDs. This individual(s) also had responsibility for reviewing the completed diary cards and for answering any questions that subjects might have about dosing instructions. Study medication was dispensed by qualified site personnel, under the direction of the investigator, but not directly by the investigator or sub-investigators.

  It is also noted that subjects were not blinded to treatments; however, to the extent possible, the subjects did not know the treatment to which they had been assigned. Although the three products (treatments) differed in appearance, the packaging for all three products were identical and the package label did not identify the product.

- **Compliance** with dosing regimen was adequately assessed. A subject that missed 2 days of test medication in either of the 14-day Tx periods was considered to be noncompliant for that period.

- All aspects of **safety assessment** were adequate.

- **Esophagogastroduodenoscopy (EGD) evaluations** were obtained at the screening visit (Day 1), on Day 8 (after 7 days of aspirin pre-treatment), and on Days 22 and 36 (after 14 and 28 days respectively, of risedronate, alendronate, or placebo treatment). At each evaluation, the esophageal and gastroduodenal mucosa were carefully examined. The condition of the mucosa in the stomach and duodenum was assessed using the following Lanza scale:

  0 = no visible lesions
  1 = mucosal hemorrhages only ($\leq$25)
  2 = 2 to 2 erosions, or >25 hemorrhages
  3 = 3 to 9 erosions
  4 = $\geq$10 erosions or an ulcer.

As reproduced below, the definitions of mucosal hemorrhage, erosion and ulcer were adequate.

Mucosal hemorrhage: a red spot with no mucosal defect.
Erosion An erythematous superficial mucosal defect that disrupted the epithelium and was not an ulcer as described below.
Ulcer: a break in the mucosa with depth that extended through the muscularis mucosa.

To qualify for entry into the study after the aspirin pre-treatment period, subjects had to have a **minimum stomach score of 3** on the Lanza scale.

The condition of the mucosa was also assessed in the esophagus, using the following Hetzel-Dent grading/scoring system:

0 = normal mucosa (no abnormalities noted)
1 = erythema, hyperemia, and/or friability present (no macroscopic erosions were visible)
2 = superficial ulceration or erosions involving <10% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
3 = superficial ulceration or erosions involving $\geq$10% but <50% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
4 = deep ulceration anywhere in the esophagus or confluent erosion of >50% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
5 = stricture that precludes the passage of the endoscope (if present, the subject was discontinued from the study).

- The clinical trial was conducted according to GCP principles. IRB approval and written IC were obtained. Adequate steps were taken to assure that data were

gathered and coded in a complete accurate and consistent fashion. An adequate CRF was used.

- For **statistical analyses,** EGD scores were recorded at the post-aspirin visit (Day 8), at Week 2, and at Week 4 for 3 sites: **stomach** (0-4 Lanza scale), **duodenum** (0-4 Lanza scale), and **esophagus** (0-5 Hetzel-Dent scale). Separate statistical analyses were performed for the 3 sites at Week 2 and at Week 4.

  - The **primary outcome variable** for this study was the stomach **score at Week 4.**

  - The primary statistical analysis was a pairwise Cochran-Mantel-Haenszel test (CMH) comparing the RISE 5 mg/day and ALEN 10 mg/day Tx groups, using the row mean scores to take into account the ordinality of the discrete response scores. In addition, each bisphosphonate treatment group was compared to placebo. This test was evaluated using a Type 1 error (alpha) rate of 0.05.

  - Post-aspirin scores were used as a stratification variable to take into account the pre-Tx severity of the specific EGD site. Differences in treatment effects for the stratum levels were investigated by carrying out a CMH test on each stratum separately, provided there were enough subjects in each stratum for a meaningful statistical analysis.

  - 2 secondary CMH tests were also performed to compare each bisphosphonate treatment group with the placebo group. These tests were performed in a manner similar to the primary test described above, and each was evaluated using a Type 1 error rate of 0.05.

  - To assess healing of the aspirin-induced erosions within each Tx group across the 4-week Tx period, the Week 2 and Week 4 EGD scores were compared to the post-aspirin EGD scores within each Tx group. In addition, the Week 2 and Week 4 scores were compared to each other within each Tx group.

  - Healing was evaluated as healed (score of 0 or 1) vs not healed (score of 2 or greater). This analysis was carried out using McNemar's test and was compared to its exact sampling distribution.

SUMMARY OF RESULTS

- Of 161 subjects enrolled in the aspirin pre-Tx period, 5 were not randomized (endoscopy finding too severe=1; AE=2; protocol violation=2).

- 2 of the 156 randomized subjects withdrew from the trial [AE=1 (unrelated to test med.); protocol violation (concomitant med.)=1].

- 154 (RISE=53; ALEN=50; PL-51) completed both the Week 2 and Week 4 EGD evaluations.

- The 3 Tx groups were comparable to each other in all respects, including demographic characteristics [mean age=49y (range: 40-66y, slightly more females (55%) than males (45%), 68% Caucasian, 22% blacks, 61% non-smokers] vital signs and concomitant medications. All subjects were compliant with their assigned test med.

- 18 subjects (RISE=7; ALEN=7; PL=4) had protocol deviations that were considered minor. These subjects were permitted to continue study participation.

- Of the 161 subjects enrolled in the aspirin pre-Tx period, 80 experienced a total of 116 AEs. None of these AEs were serious and all were considered doubtfully related to test medication. Of the 116 AEs, 93 were mild in severity, 18 were moderate, and 5 severe. There were no gross imbalances among the 3 Tx groups in the distribution of these AEs; as noted above, 2 subjects were withdrawn from the study due to AEs before being randomized into the bisphosphonate treatment period of the study. Narratives for these subjects were found in sponsor's Section 5.3.2.3.

- During the aspirin pre-Tx period, abdominal pain, nausea and dyspepsia were the most commonly reported AEs, with the following distribution:

AE	RISE [n=54]	ALEN [n=51]	PL [n=51]
Abdominal pain	24%	10%	24%
Nausea	4%	6%	12%
Dyspepsia	6%	8%	8%

- During the Tx period, headache, nausea, abdominal pain and dyspepsia were the most commonly reported AEs, with the following distribution:

	RISE [n=54]	ALEN [n=51]	PL [n=51]
Headache	11%	22%	35%
Nausea	7%	10%	4%
Abdominal Pain	7%	6%	8%
Dyspepsia	6%	6%	2%

When the pre-Tx AEs are compared to those occurring at the Tx period

- no dramatic changes are seen, other than a decrease in the proportion of patients experiencing abdominal pain in all 3 groups, including PL. Also seen is a numerical decrease in the PL subjects (12%→4%) experiencing nausea while there was a slight increase in the other 2 groups. Moreover, during the Tx period, a lower proportion of subjects in the PL group experienced dyspepsia when compared to the Pre-Tx period (8%→2%), while, for dyspepsia, there was virtually no difference among the subjects receiving RISE or ALEN.

These findings on symptoms are not easy to interpret. It appears that bisphosphonate treatment may be associated with nausea and dyspepsia..

EGD Results (Table 1)

- The EGD endoscopy after the aspirin pre-Tx (Day 8) revealed:

	Mean Scores
Minimum damage in the esophagus [Maximum score = 5][a]	(0.04 to 0.15)
Severe damage in the stomach [Maximum score = 4][b]	(3.85 to 3.88)
Moderate damage in the duodenum [Maximum score = 4][c]	(1.32 to 1.57)

a) Hetzel-Dent
b,c) Lanza

Irrespective of upper g.i. site examined, the three treatment groups were comparable to each other in regard to endoscopic scores. A remarkable reproducibility, from Tx group to Tx group, was seen in aspirin-induced **gastric lesions.**

- **At Week 2 (Table 1),** there was a lower proportion of subjects in each group with normal stomach scores compared to the proportion of subjects with normal scores for the esophagus and the duodenum.

  - There were no significant Tx differences with regard to EGD scores for each of the upper g.i. sites evaluated.

  - Since there were no overall treatment effects for any of the 3 sites, the pairwise analyses were not applicable.

- The results of the by-stratum analysis for the stomach and duodenum also showed no significant treatment differences. [No by-stratum analysis was done for the esophagus because the majority of subjects had EGD scores of 0.]

- **At Week 4 (Table 1),** the majority of the subjects showed normal scores in each of the three treatment groups.

  - There were no significant Tx differences with regard to EGD scores for the esophagus, stomach, or duodenum.

  - The primary statistical analysis comparing the RISE and ALEN Tx groups showed no statistically significant difference in the stomach scores.

  - Since there were no overall treatment effects for any of the sites, the pairwise analyses were not applicable.

  - The results of the by-stratum analysis for the stomach and duodenum also showed no significant Tx differences. [Again, no by-stratum analysis was done for the esophagus because the majority of subjects had EGD scores of 0.]

TABLE 1

Study 1997037

RESULTS OF ENDOSCOPY SCORES (LANZA) PER TREATMENT PERIOD AND TREATMENT GROUP

Endoscopy Score	End of Aspirin Period			TREATMENT PERIOD							
				Week 2				Week 4			
	RISE 5 mg [n=53]	ALEN 10 mg [n=50]	PL [n=51]	RISE 5 mg [n=52]	ALEN 10 mg [n=50]	PL [N=50]	Overall p-value[a]	RISE 5 mg [n=53]	ALEN 10 mg [n=49]	PL [n=51]	Overall p-value[b]
ESOPHAGUS											
0	90.6	94.0	98.0	94.2	90.0	94.0		94.3	89.8	94.1	
1	3.8	3.8	0	0	0	0		0	0	0	
2	5.7	2.0	2.0	3.8	8.0	6.0		5.7	10.2	5.9	
3	0	0	0	1.9	2.0	0		0	0	0	
4	0	0	0	0	0	0		0	0	0	
5	0	0	0	0	0	0		0	0	0	
Mean ± SEM	0.15 ±0.068	0.08 ±0.048	0.04 ±0.039	0.13 ±0.078	0.22 ±0.096	0.12 ±0.068	N.S.	0.11 ±0.064	0.20 ±0.087	0.12 ±0.067	N.S.
STOMACH											
0	0	0	0	40.4	42.0	52.0		81.1	77.6	70.6	
1	0	0	0	11.5	8.0	18.0		5.7	6.1	9.8	
2	0	0	0	28.8	34.0	14.0		5.7	12.2	7.8	
3	15.1	12.0	13.7	15.4	14.0	12.0		5.7	2.0	7.8	
4	84.9	88.0	86.3	3.8	2.0	4.0		1.9	2.0	3.9	
Mean ± SEM	3.85 ±0.050	3.88 ±0.046	3.86 ±0.049	1.31 ±0.175	1.26 ±0.171	0.98 (±0.175)	N.S.	0.42 ±0.133	0.45 ±0.134	0.65 ±0.163	N.S.
DUODENUM											
0	49.1	58.0	49.0	86.5	92.0	92.0		98.1	95.9	96.1	
1	5.7	0	0	5.8	2.0	4.0		0	2.0	0	
2	17.0	10.0	13.7	5.8	4.0	4.0		0	2.0	2.0	
3	18.9	16.0	19.6	1.9	2.0	0		1.9	0	2.0	
4	9.4	16.0	17.6	0	0	0		0	0	0	
Mean ± SEM	1.34 ±0.203	1.32 ±0.233	1.57 ±0.231	0.23 ±0.089	0.16 ±0.083	0.12 ±0.062	N.S.	0.06 ±0.057	0.06 ±0.045	0.10 ±0.070	N.S.

This table is a composite of sponsor's Tables 10, 11 and 12 (in the Clinical Report), with major modifications.

- Depicted are the proportion (%) of subjects with respective endoscopy scores.

a,b) p-values correspond to the Cochran-Mantel-Haenszel test using row mean scores. Post-aspirin scores were used as a strata.

Improvement Across the 4-Week Period (Table 2)

[NOTE: Because the majority of the subjects had normal scores at baseline (Day 8) in all 3 Tx groups and there were no statistically significant results found for the analysis of this site, esophageal scoring data are not depicted in this Table.

Stomach

- The proportion of patients with clinically normal stomach scores at Week 0 was 0.0 for each Tx groups, as expected.
- At Week 2, the proportions were 0.52, 0.50, and 0.70 for the RISE, ALEN, and PL groups, respectively.
- The proportion of subjects with clinically normal stomach scores at Week 4 was 0.87, 0.84, and 0.80 for the RISE, ALEN and PL groups, respectively.
- Within each Tx group, significant differences were found between the scores at Week 0 and Week 2, as well as Week 0 and Week 4.
- For the comparison between Week 2 and Week 4, both RISE and ALEN groups showed significant differences; there was no statistically significant difference between Week 2 and Week 4 in the PL group.

Duodenum

Results from the duodenum were similar to those of the stomach for comparisons between Week 0 vs Week 2 and Week 0 vs Week 4. For this site, however, no statistically significant differences were found between Week 2 and Week 4 in any of the three Tx groups.

TABLE 2
Study 1997037
Within-Treatment Assessment of Improvement Across 4-Week Treatment Period

		Proportion of Subjects with Clinically Normal Scores[a]			p-values[b]		
Treatment	Site	Week 0	Week 2	Week 4	Week 2 vs Week 0	Week 4 vs Week 0	Week 4 vs Week 2
RISE 5 mg	Stomach	0.00	0.52	0.87	<0.001	<0.001	<0.001
	Duodenum	0.55	0.92	0.98	<0.001	<0.001	N.S.
ALEN 10 mg	Stomach	0.00	0.50	0.84	<0.001	<0.001	0.002
	Duodenum	0.58	0.94	0.98	<0.001	<0.001	N.S.
PL	Stomach	0.00	0.70	0.80	<0.001	<0.001	N.S.
	Duodenum	0.49	0.96	0.96	<0.001	<0.001	N.S.

This Table corresponds to sponsor's Table 13 (in the Clinical Report) with major modifications.
a) Clinically normal was defined as a score of either 0 or 1 on either the Lanza scale (stomach or duodenum) or on the Hetzel-Dent Esophagitis grading scale (esophagus)
b) p-values from the exact distribution of McNemar's Test

Week 0=Visit 2 or Day 8 (post-aspirin visit); Week 2=Visit 3 or Day 22; and Week 4=Visit 4 or Day 36.

III. SPONSOR'S CONCLUSIONS

"In subjects with aspirin-induced stomach erosions, risedronate 5 mg/day and alendronate 10 mg/day did not interfere with the healing of the stomach mucosa compared to placebo-treated subjects after 2 or 4 weeks of treatment. There was no statistically significant difference in mean EGD scores between the risedronate and alendronate groups. Also, endoscopic evaluation demonstrated no additional effect on esophageal, gastric, or duodenal mucosa following treatment with risedronate or alendronate."

IV. REVIEWER'S ADDITIONAL COMMENTS

A. Comments Related to Study 1997037

According to the protocol-stipulated objective, study 1997037 was set to compare the esophageal and gastroduodenal effects of two bisphosphonates [in comparison to placebo], in healthy adult volunteers with aspirin-induced erosions of the stomach mucosa. In the clinical report this objective is more specifically stated as to compare the healing of aspirin-induced gastric erosions in subjects who subsequently received one daily dose of risedronate (5 mg), alendronate (10 mg), or placebo for two 2-week periods (28 days in total). The specified objectives of the trial were met.

The study was carried out at a single center, by Dr. Frank L. Lanza [the inventor of this aspirin model] and his co-workers. Adequate for this kind of study were the 2600 mg/day dose level of aspirin used to induce gastric lesions, the daily doses of risedronate and alendronate tested (likely recommended or already recommended doses, respectively, to treat postmenopausal osteoporosis) and the characteristics of the study population. The design of the study was that of a single-blind [the explanations not to double-blind the trial are reasonable], multiple dose, randomized, parallel-group, 3-arm trial where the effects of the test medications were compared to placebo. From the review of the evidence, the methods of randomization, clinical supplies, identity of test materials, methods to assess compliance and safety evaluations were all adequate. Considering the objective, the study was well-designed.

The primary endpoint result was endoscopic visualization of the upper g.i. mucosa at the end of Week 2 and Week 4 of treatment, in comparison to the scoring observed after lesions had been induced with aspirin for 7 days. The condition of the esophageal mucosa was assessed by the 0 to 5 Hetzel-Dent grading/scoring system, where 0=normal mucosa (no abnormalities noted) and 5=stricture that precluded the passage of the endoscope (a reason to discontinue the patient from the trial). In this trial, the definitions used for mucosal hemorrhage, erosion and ulcer were adequate. Also adequate was the approach that, to qualify for randomization into the study after the aspirin pre-treatment period, subjects had to have a minimum score of 3 (3 to 9 erosions).

The next highest score was 4, defined as $\geq$10 erosions or an ulcer. Here lies the first controversy when considering the LANSA scale: in these studies, the quantitation of the acute injury gives equal weight to 10 or more erosions [a very arbitrary number for lesions which, by themselves, may not have significant clinical meaning] and an ulcer [a deep break in the gastric mucosa

which may result in very significant clinical complications]. Incidentally, the clinical report does not make it clear if any aspirin-treated individual subject developed an (acute) ulcer.

The study was apparently well-executed. The randomization process resulted in three treatment arms (risedronate, n=54, alendronate, n=51 and PL, n=51) that were comparable to each other in demographic characteristics, vital signs and concomitant medications; all subjects were compliant. Potential confounders that may have obscured the interpretation of results were minimized and subjects with minor protocol violations (similarly distributed among the three treatment groups) were permitted to continue study participation. It is therefore reasonable to conclude that differences between groups being compared were not due to baseline imbalances.

After the end of aspirin pre-treatment (Day 8) revealed – not unexpectedly – damage of different severity according to the site: esophagus (minimum score, ———); stomach (severe, score ———); duodenum (moderate score, ——— At this point (end of aspirin treatment), regardless of upper g.i. site examined, the three treatment groups were comparable to each other with regard to endoscopic scores.

It is worth noting that the Lanza model is not fully characterized. Although endoscopy at the screening period showed no upper g.i. lesions, there were no data obtained at Day 1. Several studies, particularly with aspirin, have indicated that acute damage (first 24 h) is more widespread than damage observed after several days (Day 7 in this instance). This suggests that the mucosa possesses adaptive mechanisms that compensate for aspirin injury. It is also important to note that, since **biopsy examinations** were not carried out, it is not known if the groups were comparable with regard to histological characteristics (inflammatory cells, edema, hemorrhage, exudates, etc.). What is known, however, because of the many literature publications on this subject matter, is that a major feature of the acute aspirin-induced mucosal changes is their **tendency to revert to normal** (both endoscopically and histologically). The time over which this occurs depends on the method used to detect the endpoint. For example, in acute hemorrhagic gastritis the **endoscopic appearance** of the gastric mucosa may revert to normal within 24 to 48 h after bleeding has stopped. Histologic reversion to normal may require **a longer period of time**. Although acute gastritis **[this is a term that should be defined histologically, not endoscopically]** is a reversible lesion, histologic abnormalities may persist for months in some patients, particularly those infected with Helicobacter Pylori [this was not assessed in this trial].

Aside of the above-mentioned considerations, not addressed in the present study, the assumption that, in most patients, the aspirin-induced lesions will start improving, healing and eventually disappear once the noxious agent is discontinued, is correct. So, the design of study 1997037 is indeed testing the hypothesis that the bisphophonates do not interfere with the endoscopic healing of the gastric mucosa. And this was shown, since neither at Week 2 or 4 were there statistically significant differences between groups being compared (RISE vs PL; ALEN vs PL; RISE vs ALEN) in endoscopic scores in either of the three upper g.i. sites examined (esophagus, stomach and duodenum). Moreover, the reviewer agrees with the sponsor that endoscopic evaluation demonstrated no additional effect on esophageal, gastric, or duodenal mucosa following treatment with risedronate (5 mg/day) or alendronate (10 mg/day), at these specified doses and length of exposure. [NOTE: Since data on ref. 19 of the Clinical Report were not

available to this reviewer, it is not known what is the meaning of the last sentence in the fifth paragraph of page 42 of the Clinical Report: "with respect to alendronate 10 mg/day, the findings from this study and an earlier study[19] may not support each other"]. It is also concluded that it is not known if there were any differences between groups regarding histologic changes. In addition, results from study 1997037 appear to suggest (but do not prove) that bisphosphonate treatment in these healthy volunteers may be associated with a higher incidence of nausea and dyspepsia in comparison to placebo.

B. Comments on Bisphophonate Injury to the Upper G.I. Mucosa

Having agreed with the sponsor's conclusion from this study it is time to ask what is the clinical relevance of the observations in study 1997037. The answer to this question is that these observations are of limited clinical relevance.

First, the Lanza's acute aspirin bioassay is, as shown in this study and many publications, primarily a model for gastric lesions. Minimum damage to the esophagus is shown. Although the warning in the FOSAMAX® labeling, reproduced in section I of this review states that the drug, like other bisphonates, may cause local irritation to the upper g.i. mucosa, the emphasis is on **esophageal adverse experiences**. Included among these (according to the labeling) are esophagitis, esophageal ulcers and esophageal erosions... that in some cases have been severe and required hospitalization... patients should be instructed to discontinue the drug and seek medical attention if they develop dysphagia, odinophagia and retrosternal pain.

This emphasis on esophageal rather than gastric and duodenal lesions reflects the form of iatrogenic illness of the esophagus that has become evident with bisphosphonates and many other drugs. Ingested pills [included in this continuously growing list are emepronium bromide (an anticholinergic) tetracycline, doxycycline, mynocycline, potassium chloride and quinidine and less commonly, ascorbic acid, ferrous sulfate, aspirin, indomethacin, ibuprofen, clindamycin, teophylline and phenytoin] tend to lodge in the esophagus and damage the mucosa in a localized area. It would therefore be more useful to attempt to characterize the physiopathological/clinical nature of the [proposed] esophageal lesion with risedronate.

Among the clinical/experimental questions to be answered are: does the risedronate tablet disintegrate already in the esophagus so that there might be local irritation through the drug fragments (in addition that induced by the tablet proper) [for instance, in the stomach, aspirin has a caustic topical action inversely proportional to its solubility; phenylbutazone, a liposoluble substance, has a local action on the gastric mucosa which is directly related to dose], what is the histological picture of the risedronate-induced lesions? is there << restitutio ad integrum >> within a few weeks upon discontinuation of the drug? Does the drug damage the upper g.i. mucosa when administered parenterally? Is there an effect on prostaglandins production, mucus secretion, cell turnover, exfoliation of superficial epithelial cells and immunologic aspects? Does the drug alter cell metabolism? Is the "caustic" topical action of risedronate accentuated in patients with GERD, those with cardiac or pyloric narrowing or stricture, patients with bile/alkaline reflux esophagitis/gastritis, those that have undergone surgical operations resulting in esophageal reflux or those on the expanding number of medications capable of provoking

upper g.i. lesions that may further compound this situation? What is the possibility of developing clinically serious lesions? What is the role, if any, of alcohol and tobacco? Also needed are answers to questions such as: Does the drug (risedronate) fail to cause new erosions with subsequent usage? Do patients who previously tolerated the risedronate develop lesions with further use? If the clinical trials with risedronate excluded patients with GERD or dyspepsia, one would not know if patients with these underlying conditions may tolerate or get worse when they start taking the bisphosphonate.

The reviewer believes that answers to at least some of these questions are needed to better characterize, treat and prevent this adverse experience. Although the labeling for FOSAMAX® includes the warning that the risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking the drug, etc., it is worth noting that, according to textbook information, normal individuals can retain small capsules in the esophagus even when swallowing in the upright position.

Second the Lanza's bioassay appears to contribute little to the clinical situation at hand. The important question to answer is whether the known adverse events induced by aspirin (virtually any dose) are going to be compounded by risedronate taken concomitantly. Patients in this category might be those postmenopausal osteoporotic with rheumatoid arthritis or osteoarthritis **in need of high daily doses** of aspirin or NSAIDs or even those who – owing to cardiovascular conditions – are taking "low" doses of aspirin [this definition is inexact but includes doses of aspirin of 25 to 375 mg per day; even these low doses of this drug may, under certain conditions, be associated, for instance in predisposed individuals, with clinically serious complications] in whom risedronate would be indicated.

The Lanza model tested the effect of the bisphosphonates once the noxious agent (aspirin) had been discontinued. But in clinical practice, this may not be an option, especially in those osteoporotic arthritics that need to continue on NSAIDs or high dose aspirin because of severe pain and/or inflammation of the joints. Drug-drug interaction studies are therefore needed.

February 11, 1999

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-835
HFD-510
HFD-510/CSO
HFD-510/EColman
HFD-180/Consult File
HFD-180/LTalarico /S/ 2-11-99
HFD-180/HGallo-Torres
r/d 2/9/99 jgw
f/t 2/11/99 jgw

APPEARS THIS WAY
ON ORIGINAL

Medical Officer Consultation

Drug: Risedronate

Sponsor: Proctor and Gamble Pharmaceuticals

NDA #20-835 Supplements (Division of Metabolism and Endocrine Drug Products HFD-510): S-001, S-002, and S-003

Indications: Corticosteroid-induced osteoporosis; treatment of postmenopausal osteoporosis; prevention of postmenopausal osteoporosis

Date of requested inter-division consult: March 5, 1999

Reason for consult: an increased number of lung cancer cases were observed on risedronate arms in the randomized studies

Materials provided by HFD-510 for review: Meeting package (2/19/99); MedWatch Forms for 67 patients with lung cancers; Correspondence dated 5/13/99; SAS dataset dated 5/14/99

Medical Reviewer at CDER: Judy H. Chiao, MD

Statistical consultant at CDER: Gang Chen, PhD

Date of completed consult: July 7, 1999

REGULATORY BACKGROUND:

Risedronate is a bisphosphonate currently marketed for the treatment of Paget's disease. The sponsor, Procter and Gamble Pharmaceuticals, has been conducting randomized, placebo-controlled studies to demonstrate the efficacy and safety of risedronate in the treatment and prevention of corticosteroid-induced as well as postmenopausal osteoporosis. Supplement NDA S-001, 002 and 003 have been submitted to Division of Metabolism and Endocrine Drug Products (HFD-510) to seek marketing approval of the above indications.

The randomized studies in the supplemental NDAs involved 6300 patients. Twenty-three cases of lung cancer were observed in these studies (2 on placebo arm and 21 on risedronate arms). Subsequently, the sponsor unblinded the database from two 3-year hip fracture trials, RHN009193 (North American) and RHE009293 (Europe). These two studies randomized 9,497 patients and detected an additional forty-four cases of lung cancer (10 on placebo arm and 34 on risedronate arms).

In February 1999, a meeting was held between representatives from Procter and Gamble Pharmaceuticals and its development partner, Hoecht Marion Roussel and the Division of Metabolism and Endocrine Drug Products (HFD-510) to discuss the imbalance of lung cancer cases detected in the risedronate phase III clinical trials. An inter-divisional consult was generated on March 5, 1999. The Division of Oncology Drug Products (DODP) was asked to provide consultation on the lung cancer cases detected in the 10 randomized studies and the significance of these findings.

3/23/99: DODP asked for clarifications on the follow-up procedures used in the risedronate randomized studies.

3/26/99: Sponsor's response to DODP questions

3/30/99: DODP requested schedules of study visits on all risedronate randomized studies and an electronic database on the actual date of scheduled visits and other relevant information

4/5/99: DODP received schedules of study visits on 8 studies

4/27/99: DODP received correspondence dated 4/22/99 from the sponsor (Updates on GI cancers and lung cancers)

5/24/99: DODP received correspondence dated 5/13/99 and an electronic dataset in SAS. DODP participated in a meeting with HFD-510 to hear the the results of the sponsor's expert panel review of the lung cancer cases detected in risedronate trials

OVERVIEW:

Risedronate is a pyridinyl bisphosphonate which has been shown to be a specific inhibitor of osteoclast activity without interfering with osteoclast generation (1). There is also evidence that risedronate decreases metastatic MDA-231 breast cancer burden selectively in bone, suppresses progression of established osteolytic lesions, and prevents the development of new osteolytic lesions in nude mice (2)

Risedronate is an orally administered drug, which is absorbed throughout the upper gastrointestinal tract. Mean oral bioavailability of a 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%). Preclinical studies in rats and dogs dosed intravenously with single doses of [14C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. There is no evidence in support of systemic

metabolism of risedronate. Once absorbed, the serum concentration-time profile is multi-phasic with an initial half-life of about 1.5 hours and a terminal exponential half-life of 220 hours (3).

Risedronate has been evaluated in a battery of toxicology tests. The sponsor did not provide listings of toxicology studies for DODP review. The following is a summary of toxicology studies included in the sponsor's meeting package dated 2/19/99. Risedronate was found to be non-genotoxic in seven *in vitro* and *in vivo* genetic toxicity studies. In addition, risedronate did not increase tumors in lifetime bioassays conducted in both mice and rats. In agreement with the rodent bioassay results, no hyperplastic or neoplastic effects occurred in the lungs of dogs treated for two years with daily doses up to 2 mg/kg. The sponsor concluded that negative findings such as these would be unprecedented for a human carcinogen.

DESCRIPTION OF RANDOMIZED STUDIES

All ten studies were randomized, double blind, placebo-controlled trials. Baseline chest x-rays were not required. A total of 15,797 patients participated in these trials. Physical exam was performed at study entry and at the end of study. Adverse event assessment was done every 3 months.

Table 1: Ten risedronate randomized studies

Study No	Description	No. of patients (Start/stop date)
RVN-008993 (USA)	Treat postmenopausal women with established osteoporosis-related vertebral deformity (3 yrs); 2 doses of risedronate	N=2458 (12/3/93-1/19/98)
RVE-009093 (Europe and Australia)	Treat postmenopausal women with established osteoporosis-related vertebral deformity (3 yrs); 2 doses of risedronate	N=1226 (3/4/94-3/25/98)
RON-009393 (US and Canada)	Treat osteopenic postmenopausal women (1-1.5 yrs); 2 doses of risedronate	N=648 (3/8/94-4/12/96)
ROE-009493 (Europe and Australia)	Treat osteopenic postmenopausal women (2 yrs); 2 doses of risedronate	N=543 (4/19/94-4/11/97)
RHN-009193 (US and Canada)	Treat osteoporosis in elderly women (3 yrs); 2 doses of risedronate	N=4948 (11/24/93-3/4/98)
RHE-009293 (Europe)	Treat osteoporosis in elderly women (3 yrs); 2 doses of risedronate	N=4549 (2/22/94-4/15/98)
RBL-004494 (Australia)	Prevent postmenopausal bone loss (1-1.5 yrs); 2 doses of risedronate	N=383 (9/29/94-4/17/97)
RCP-009993 (US and Canada)	Prevent corticosteroid-induced bone loss (1 yr); 2 doses of risedronate	N=228 (4/25/94-12/11/96)
RCT-009893 (Europe)	Prevent corticosteroid-induced bone loss (1 yr); 2 doses of risedronate	N=290 (8/11/94-10/7/96)
RPE-004494 (Australia)	Prevent postmenopausal bone loss (1-1.5 yrs); risedronate + Estrogen	N=524 (8/31/94-6/5/96)

Age, sex, and smoking status were well balanced between the placebo arm and risedronate arms. There was a preponderance of older women on these trials. 40.4% of the participants were either current or previous smokers, reflecting the fact that smoking is a risk factor for developing osteoporosis.

Table 2: Patient demographics

	Placebo N=5372	2.5 mg N=5071	5 mg N=5354
Sex F/M	5311/61	5009/62	5291/63
Median age (range)	74 (18-98)	74 (19-99)	74 (26-100)
Smoker	2185	2036	2162
Non-smoker	3187	3033	3188
Smoking status unknown		2	4

REVIEW ISSUES:

1. Dropouts: 6776 patients (42.9%) dropped out of the studies. Follow-up data on those who dropped out are incomplete.

   Table 3: Number (percentage) of patients who dropped out of the studies

Study No	Placebo (%) N=2380	2.5 mg (%) N=2133	5 mg (%) N=2263
RVN-008993	370/820 (45.1)	220/817(26.9)	332/821 (40.4)
RVE-009093	176/408 (43.1)	143/410 (34.9)	145/408 (35.5)
RON-009393	55/220 (25)	38/212 (17.9)	47/216 (21.8)
ROE-009493	37/180 (20.6)	35/184 (19.0)	40/179 (22.3)
RHN-009193	862/1664 (51.8)	870/1633 (53.3)	846/1651(51.2)
RHE-009293	738/1520 (48.6)	765/1518 (50.4)	739/1511 (48.9)
RBL-004494	33/126 (26.2)	28/128 (21.9)	26/129 (20.2)
RCP-009993	21/77 (27.2)	22/75 (29.3)	16/76 (21.1)
RCT-009893	26/96 (27.1)	22/94 (23.4)	19/100 (19)
RPE-002494	76/261 (29.1)		65/263 (24.7)

Table 4: Information on patients who dropped out

Study No	Placebo N=2380	2.5 mg N=2133	5 mg N=2263
Median days on study (range)	313 (1-1348)	282 (1-1386)	301 (1-1317)
Reasons for Dropout (Number of patients)			
Adverse events	905	770	855
Treatment failure	28	12	11
Protocol violation	168	158	165
Patient withdrawal	980	874	922
Lost follow-up	110	109	111
Others	189	209	199
Unknown	0	1	1

Table 5: Percentage of dropouts with follow-up data (number of dropouts with follow-up data divided by the total number of dropouts of the study and multiplied by 100)

Study No	Placebo	2.5 mg	5 mg
RVN-008993	39.7	14.6	32.5
RVE-009093	24.4	16.8	20.7
RON-009393	5.5	13.2	8.5
ROE-009493	40.5	40	35
RHN-009193	25.6	28.2	25.7
RHE-009293	36.3	37.7	38.7
RBL-004494	30.3	39.3	38.5
RCP-009993	4.76	13.6	18.8
RCT-009893	15.4	40.9	36.8
RPE-002494	23.7		13.9

2. Lack of pathology reports in a significant number of lung cancer cases: There were a total of 69 cases of lung cancers in the most recent update submitted in the correspondence dated 5/13/99. No Medwatch forms were available for review on two patients (RCT-44492119 and RHN-41670006). According to the sponsor, pathologic diagnosis was available in 34 cases of lung cancers by either pathology report or pathology mentioned in the Medwatch forms. These patients are listed in Table 6. Information available on the remaining 35 patients is provided in Table 7. There was no central path review committee to review the slides of lung cancer cases to confirm the diagnosis.

Table 6: 34 lung cancers documented by pathology as per Sponsor

Patient ID	Rx	Best evidence	FDA path review	FDA comments
RHN-41130075	placebo	P	nsclc v. breast	Silicon inj/breast mass
RHN-41130070	placebo	P	nsclc	
RHN-39230018	placebo	PR	nsclc	
RHN-42170056	placebo	PR	nsclc	
RVN-43070628	placebo	PR	nsclc	
RHN-41570103	2.5 mg	PR	nsclc	never took study drug
RHN-10940049	2.5 mg	PR	nsclc	
RVN-25160621	2.5 mg	PR	nsclc	
RVN-41660642	2.5 mg	PR	nsclc	lung mass before study
RCT-41452053	2.5 mg	PR	nsclc	
RHE-41530020	2.5 mg	PR	nsclc	
RVE-44500634	2.5 mg	PR	nsclc	
RVN-25160633	2.5 mg	PR	nsclc	
RHE-42850010	2.5 mg	PR	nsclc	No lesion 1 year ago
RHN-10940022	2.5 mg	PR	nsclc	
RVN-45520657	2.5 mg	PR	nsclc	
RHN-42130005	2.5 mg	PR	nsclc	
RHN-41130065	2.5 mg	PR	sclc	
RHN-42170039	2.5 mg	PR	nsclc	
RHE-42700030	2.5 mg	PR	Mesothelioma	
RHN-39760021	2.5 mg	PR	nsclc	
RCT-44492119	2.5 mg	PR	Unknown	No medwatch form
RHE-41530062	5 mg	PR	nsclc	pre-existing lesion
RON-41740874	5 mg	PR	nsclc	
RHN-41570134	5 mg	PR	nsclc	
RVN-39460643	5 mg	PR	nsclc	
RHE-41430002	5 mg	PR	nsclc	
RVN-41130644	5 mg	PR	nsclc	
RHN-41840043	5 mg	PR	unknown	No path in Medwatch
RHE-45090025	5 mg	PR	nsclc	
RVN-39020644	5 mg	PR	nsclc	
RHN-14700034	5 mg	PR	nsclc	
RCP-41241978	5 mg	PR	nsclc	
RPE-39052231	5 mg	PR	nsclc	

nsclc: non-small cell lung cancer; sclc: small-cell lung cancer; PR: path report; P: path mentioned in notes

Reviewer's comments: No pathological diagnosis could be found in the Medwatch form on patient RHN-41840043. No Medwatch form was submitted for review on patient RCT-44492119.

Table 7: 35 cases of lung cancers without pathology as per sponsor

Patient ID	Rx	Best evidence	FDA path review	FDA comments
RHN-41110038	placebo	R	unknown	XRT given
RHN-42210022	placebo	R	unknown	No w/u
RHE-42090007	placebo	R	unknown	No w/u
RVE-33800656	placebo	H	nsclc	Path mentioned
RHE-38260017	placebo	H	unknown	
RHN-41700018	placebo	H	unknown	Path mentioned
RHE-42050009	placebo	H	unknown	insufficient inf
RHN-10940008	placebo	DC	nsclc	Bx done; XRT
RVN-42310630	2.5 mg	CRF	unknown	pre-existing on 9/22/94
RHN-39810005	2.5 mg	I	unknown	opacified left lung
ROE-33800801	2.5 mg	H	nsclc v. renal	Path mentioned
RHN-42150024	2.5 mg	R	nsclc	Resection of CNS mass
RON-41670867	2.5 mg	H	nsclc	Path mentioned
RHN-39290008	2.5 mg	H	nsclc	Path mentioned
RHE-43130026	2.5 mg	I	nsclc	Path mentioned
RBL-43232416	2.5 mg	I	Primary unknown	Path mentioned
RHE-41930056	2.5 mg	H	nsclc	Path mentioned
RHN-41670006	2.5 mg	H	unknown	No Medwatch form
RHN-42290003	2.5 mg	H	sclc	Path mentioned
RHN-39020007	2.5 mg	DC	nsclc	Path of met mentioned
ROE-41460971	2.5 mg	CRF	unknown	XRT given
RHN-41200098	2.5 mg	V	unknown	insufficient inf
RHN-39760017	2.5 mg	CRF	unknown	autopsy
RHE-41360036	2.5 mg	H	nsclc	Path mentioned
RHN-41860020	2.5 mg	V	unknown	Insufficient inf
RHE-41510056	2.5 mg	R	unknown	insufficient inf
RHN-39070020	2.5 mg	H	unknown	R-lobectomy
RHN-41590034	5 mg	H	nsclc	Path mentioned
RVE-43480632	5 mg	H	Primary unknown	Path mentioned
RHN-39150009	5 mg	R	nsclc	Lung nodule in 1990;
RBL-43232414	5 mg	I	sclc	Path mentioned
RHE-41920001	5 mg	H	nsclc	Path mentioned
ROE-33800876	5 mg	I	Pleural carcinom	Path mentioned
RVE-47210626	5 mg	H	Adenocarcinoma	insufficient inf
RHN-42120034	5 mg	H	nsclc	Path mentioned

R: radiographic evidence
H: hospital notes
I: investigator
CRF: case report form
V: verbatim patient report
DC: Death certificates

APPEARS THIS WAY
ON ORIGINAL

Reviewer's comments: After reviewing Medwatch forms and other submitted materials, FDA found that 18 out of these 35 patients had biopsies performed and pathology of the biopsy specimen mentioned in the Medwatch form or other submitted materials:

Patient (RVE-33800656) had pathology mentioned in hospital notes (bronchio-alveolar adenocarcinoma).

Patient (RHN-41700018) had bronchoscopy and brushings which documented large cell carcinoma.

Patient (RHN-10940008) had a biopsy which revealed cancer.

Patient (ROE-33800801) had a biopsy of the suprarenal mass which showed poorly differentiated adenocarcinoma or anaplastic cell carcinoma. FDA felt that this path was most consistent with primary lung cancer with metastasis to suprarenal area.

Patient (RON-41670867) had a CT guided biopsy of the lung lesion, which revealed non-small cell pathology.

Patient (RHN-39290008) had a biopsy done which revealed large cell carcinoma with neuroendocrine features.

Patient (RHE-43130026) was found to have squamous cell carcinoma of the right lung (Medwatch form).

Patient (RHE-41930056) had widely metastatic adenocarcinoma in lungs, liver, kidneys, spine and pancreas by autopsy report.

Patient (RHE-41930056) had a right superior lobectomy and pathology showed large malignant cells (Medwatch form).

Patient (RHN-42290003) underwent needle biopsy of the lung mass in the left lower lobe and pathology showed small cell lung cancer (Medwatch form).

Patient (RHN-39020007) had a biopsy of a left hip lesion and a biopsy of a lung lesion. Pathology of the left hip biopsy was mentioned in the Medwatch (malignant tumor). Patient received radiation therapy for metastatic lung cancer.

Patient (RHE-41360036) had a CT guided needle biopsy and pathology showed squamous cell carcinoma.

Patient (RHN-41590034) underwent needle biopsy of the lung mass, which revealed large cell tumor.

Patient (RVE-43480632) was coded as primary unknown by the sponsor. However, pathology mentioned in the Medwatch showed pulmonary adenocarcinoma of the left lung diagnosed in March 1995 when the lung cancer was resected. Patient developed metastasis to lymph nodes, bones and brain in October 1995. Biopsy of the metastatic sites showed poorly differentiated adenocarcinoma which looked different microscopically from the lung cancer resected in March 1995.

Patient (RHN-39150009) had a nodule in the right lower lobe of the lung in 1990 before enrolling on a risedronate study and work-up of this lung nodule included bronchoscopy (negative) and CT directed biopsy (non-diagnostic). Chest x-ray in March 1994 showed the nodular lesion was growing. She began taking risedronate 5 mg in May 1994. In January 1995, the same nodule got larger on chest x-ray and a needle aspiration biopsy revealed adenocarcinoma.

Patient (RHE-41920001) had a biopsy taken during bronchoscopy which showed poorly differentiated squamous cell carcinoma of the lung.

Patient (ROE-33800876) was diagnosed with pleural carcinomatosis by biopsy.

Patient (RHN-42120034) had pleural effusion and underwent thoracentesis, which removed 1600ml fluid. It was mentioned in Medwatch that she had lung adenocarcinoma.

3. Lung cancers which existed prior to study entry and cancers of histology other small cell or non-small cell lung cancer

Table 8: 9 patients had pre-existing lesions or histology other than lung cancer as per sponsor

Patient	Rx	Sponsor assessment	FDA agreement
RVN-42310630	2.5 mg	A, C	Yes
RHN-41570103	2.5 mg	A, C	Yes
RHN-39810005	2.5 mg	A, C	Yes
RVN-41660642	2.5 mg	A, C, E	Yes
RHE-41530062	5 mg	A, C	Yes
RON-41740874	5 mg	A, C	No: no documentation
RHN-39150009	5 mg	A, C	Yes
ROE-33800876	5 mg	D	Yes: pleural carcinomatosis
RHE-42700030	2.5 mg	D	Yes: Mesothelioma

A: primary lung cancer
C: pre-existing lesion
D: not consistent with lung cancer
E: less than 6 months into the study when lung lesion reported

Reviewer's comment:
Patient RON-41740874: There is no documentation of a pre-existing lung lesion in the Medwatch form or other submitted materials

FDA ANALYSIS:

1. Time of diagnosis

FDA analysis included 59 cases of lung cancers after excluding 6 cases of preexisting lesions, 2 cases of non-lung cancer histologies (mesothelioma and pleural carcinomatosis) and 2 cases (RCT44492119 and RHN41670006) which did not have date of lung cancer diagnosis in the SAS dataset.

Table 9: Time of diagnosis for 6 cases of preexisting lesions:

Days since randomization date	Placebo	2.5 mg	5 mg
<=30 (n=3)		2	1
>30 and <=90 (n=0)			
>90 and <=180 (n=1)		1	
>180 and <=360 (n=1)			1
>360 (n=1)		1	
Total	0	4	2

Time 10: Time of diagnosis for 59 cases of lung cancers

Days since randomization date	Placebo	2.5 mg	5 mg
<=30 days (n=0)			
<=90 days (n=6)	2	1	3
>90 and <=180 (n=7)	0	6	1
>180 and <=360 (n=13)	5	6	2
>360 (n=33)	6	16	11
Total	13	29	17

Reviewer's comment:
56% (33/59) of lung cancer cases were diagnosed more than one year after the randomization date. At 3-6 months and beyond 12 months from the randomization date, there was an excess number of lung cancer cases on risedronate arms compared to the placebo arm.

2. Incidence of lung cancers

Because of the missing follow-up dates on patients who dropped out of the studies, we define the incidence of lung cancer as the number of lung cancers per 1000 person-years of observation in these patients who had at least one adverse event (AE) assessment after enrolling on the study.

Person-years of observation = SUM of (last AE assessment date-randomization date)/365 days

There were 208 patients who did not have randomized dates and study start dates (66 on placebo, 71 on risedronate 2.5 mg, 71 on risedronate 5 mg) in the SAS dataset. 202 out of these 208 patients dropped out of the studies. In addition, there were 96 patients (30 on placebo, 45 on residronate 2.5 mg, 21

on risedronate 5 mg) did not have any adverse event assessment after randomization. All these patients were excluded from the analysis. Therefore, the calculation of person-years of observation included 15,493 patients (98.1% of the entire study population of 15,797 patients).

Table 11: Incidence of lung cancers based on 1000 person-years of observation

	placebo	2.5 mg	5 mg
Person-years obsv	12110.71	10535.05	11728.71
No. of lung cancer per 1000 person-years obsv	13/12110.71 (1.07)	29/10535.05 (2.75)	17/11728.71 (1.45)
Relative risk compared to placebo group		2.57	1.36

Reviewer's comment:

There were more patients on the risedronate arms being diagnosed with lung cancer when compared to patients on the placebo arm. The relative risk in the 2.5 mg dose group is higher than the relative risk in the 5 mg dose group. 4,914 out of 5,071 patients (96.9%) in the 2.5 mg dose group had both starting and stopping dates of risedronate treatment. The median duration of treatment for this group is 635 days with a standard deviation of 383 days. 5,207 out of 5,354 patients (97.3%) in the 5 mg dose group had both starting and stopping dates of risedronate treatment. The median duration of treatment for this group is 756 days with a standard deviation of 405 days. One possible explanation for the lower relative risk in the 5 mg dose group is that there are more patients with follow-up data and/or follow-up duration is longer in the 5 mg dose group. Since the incidence rate is calculated based on the number of lung cancers per 1000 patient years of observation, a higher number of patient years of observation because of better follow-up will result in a lower incidence rate and a lower relative risk when compared to the placebo group. 4,947 out of 5,071 patients (94.1%) in the 2.5 mg dose group had at least one follow-up after the start of treatment. The median duration of follow-up in this group of patients is 936 days with a standard deviation of 350 days. 5,258 out of 5,354 patients (98.2%) in the 5 mg dose group had at least one follow-up after the start of treatment. The median duration of follow-up in this group of patients is 1081 days with a standard deviation of 355 days.

3. The distribution of lung cancer cases in smokers and non-smokers

Table 12: Incidence of lung cancers in smokers (previous or current) and non-smokers

	placebo	2.5 mg	5 mg
No. of lung cancers			
Smoker	8	24	13
Non-smoker	5	5	4
Person-years obsv			
Smoker	4705.04	4014.4	4512.40
Non-smoker	7358.4	6423.56	7185.72
No. of lung cancer per 1000 person-years obsv			
Smoker	1.70	5.99	2.88
Non-smoker	0.68	0.78	0.56
Relative risk compared to placebo			
Smoker		3.52	1.69
Non-smoker		1.15	0.82

Reviewer's comment:

It appears that the increased number of lung cancer cases is only observed in smokers. To further explore the relationship between smoking (current or previous) and risedronate treatment (2.5 or 5 mg), we performed the proportional hazards analysis (SAS 6.12: The PHREG Procedure). The dependent variable is time to the diagnosis of lung cancer or last adverse event assessment. Patients who did not have lung cancer were censored at the last adverse event assessment. 208 patients who did not have a randomization date and 10 patients who had preexisting lung cancer, histologies other than lung cancers or uncertain diagnosis were excluded from the analysis. 96 patients who did not have an adverse event assessment after the randomization date were also excluded from the analysis. The covariates are smoking (current or previous), risedronate treatment (2.5 or 5 mg) and an interaction term (risedronate treatment *smoking). In the Cox regression analysis of the entire study population of 15,484 patients with 59 cases of lung cancer, there is a marked interaction between smoking and

risedronate treatment (p=0.16) although it does not reach statistical significance.

Table 13: Cox regression analysis in 15484 patients; P-values are from the maximum likelihood ratio test

Covariates	Risk Ratio	95% CI Lower	Upper	P value
Smoking	0.946	0.317	2.822	0.921
Risedronate Treatment	2.505	0.819	7.657	0.107
Sm*Risedronate Treatment	2.630	0.693	9.982	0.155

Because of the marked interaction between smoking and risedronate treatment, we further explored the smoking effect within the risedronate group and placebo group. In the subgroup of 10,208 patients who received risedronate (2.5 mg or 5 mg), there were 46 cases of lung cancer. Cox regression analysis showed that smokers (current or previous) had a statistically significant increase in the risk of being diagnosed with lung cancer.

Table 14: Cox regression analysis in the subgroup of patients who received risedronate treatment; P-value is based on logrank test

Covariates	Risk Ratio	95% CI Lower	Upper	P value
Smoking	6.617	3.193	13.713	0.0001

In the subgroup of 5276 patients who only received placebo, there were 13 cases of lung cancer. Cox regression analysis showed that smokers (current or previous) had a trend toward increased risk of being diagnosed with lung cancer.

Table 15: Cox regression analysis in the subgroup of patients who received only placebo; P-value is based on logrank test

Covariates	Risk Ratio	95% CI Lower	Upper	P value
Smoking	2.47	0.808	7.551	0.1128

DODP Comments:

1. DODP agrees with the sponsor that there is no evidence that risedronate is a human carcinogen in the *in vitro* and *in vivo* animal studies conducted to date. However, the possibility that risedronate may promote growth of existing lung cancers has not been investigated in appropriate animal models.
2. The large number of patients who dropped out from the ten randomized trials and the lack of follow-up data in a substantial number of these patients preclude us from reaching a definitive conclusion on the relative risk of developing lung cancers in patients who took risedronate.
3. The lack of pathological diagnosis in a significant number of patients who were coded to have lung cancers further reduces the reliability of these data.
4. Within the limitations of these data, there is a significant increase in the number of lung cancer cases in the risedronate arms (2.5mg and 5 mg) compared to the placebo arm when the incidence is calculated by the number of lung cancers per 1000 person-years of observation.
5. Exploratory subgroup analysis showed that the increase in the number of lung cancer cases was only seen in individuals characterized as previous or current smokers. Cox regression analysis showed a statistically significant increase in the risk of being diagnosed with lung cancer in smokers (current or previous) who received risedronate treatment when compared to nonsmokers who received risedronate.

DODP RECOMMENDATIONS:

1. The sponsor should use appropriate animal models to investigate whether risedronate promotes the growth of existing lung tumors.
2. The findings from the ten risedronate randomized studies suggest that patients who took risedronate had a higher risk of being diagnosed with lung cancer. In addition, the increased risk was only observed in previous and current smokers. Future prospectively conducted randomized studies are needed to confirm or refute these findings. A thorough evaluation for lung cancer should be performed at baseline prior to study entry in future studies.

Reference:

1. Lowik C et al: Mechanisms of action of bisphosphonates: Studies with bone culture systems, in Bijvoet HA, Fleisch H., Canfield RE, et al (eds): Bisphosphonates in Bones. 1995: 155-170
2. Saaki A et al: Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice. Cancer Res 55: 3551-3557, 1995.
3. Risedronate label in PDR 1999

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APPEARS THIS WAY
ON ORIGINAL

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