STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 20-835 SE1-002

Drug: Actonel (risedronate sodium)

Sponsor: Proctor & Gamble Pharmaceuticals

Indication: Prevention of osteoporosis in postmenopausal women

Date of Submission: January 19, 1999

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Volume Numbers in Statistical Section: Volumes 1-3, 169 to 198

Medical Input: Eric Colman, M.D. (HFD-510)

Introduction

The sponsor has submitted the results of two Phase III clinical trials (Table 1) to support an indication of prevention of osteoporosis in postmenopausal women. Two additional small Phase II studies (about 40 patients in each arm) are not reviewed here; one study showed no treatment effect for the 2.5 mg dose of Actonel and the other study showed a significant treatment effect for the 5.0 mg daily dose of Actonel (+1.4% change in lumbar spine BMD) compared to placebo (-4.3% change in lumbar spine BMD)

Table 1. Phase III Controlled Clinical Trials

Study	Design	Treatment (N)	Duration
RBL004494 Australia 11 sites	Rand, DB, parallel, placebo-controlled	Placebo (126) Actonel 2.5 mg (128) Actonel 5.0 mg (129)	2 years
RPE002494 North America 25 sites	Rand, DB, parallel, placebo-controlled	Estrogen 0.625 mg + Placebo (261) Estrogen 0.625 mg + Actonel 5.0 mg (263)	12-18 months

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Study RBL004494 (9/94 to 4/97)

Study RBL004494 is a Phase III, randomized, double-blind, parallel, placebo controlled trial designed to compare two doses of Actonel (2.5 mg and 5 mg) to placebo for the prevention of osteoporosis in women post-menopausal within 3 years of admission. All patients were administered 1 gram of calcium per day.

Percent change in lumbar spine BMD at Month 24 was the primary efficacy measure. A BMD>0.76 g/cm^2 by —— scanner or 0.86 g/cm^2 by — scanner was required to enter this prevention trial. To standardize BMD for machine type the following equations were used:

For —— scanner: Standardized BMD = ————

For — scanner: Standardized BMD = ————

Patient Disposition

A total of 383 patients were randomized to therapy; 126 to placebo, 128 to Actonel 2.5 mg and 129 to Actonel 5.0 mg (Table 2). About ¾ of the patients completed therapy. Included in this reviewer's ITT analysis of the primary efficacy variable are all patients who received medication and had any follow-up BMD data. The sponsor excluded from their ITT analysis BMD measurements not taken within 8 weeks of the scheduled visit date and also patients with no baseline or post-baseline radiograph.

Table 2. Study RBL004494 Patient Disposition

	Placebo	Actonel 2.5	Actonel 5.0
Randomized	126 (100%)	128 (100%)	129 (100%)
Received study drug	125 (99%)	127 (99%)	129 (100%)
Completed 24 mos.	93 (74%)	100 (78%)	103 (80%)
Reviewer's ITT	120 (95%	118 (92%)	125 (97%)
Sponsor's ITT	103 (82%)	108 (84%)	113 (88%)

The two major reasons for patient withdrawal from the study were adverse event and subject request (Table 3). More placebo patients withdrew voluntarily (13%) than in either Actonel group (5% and 9%). Most of the dropouts occurred during the first 3 months of the study.

Table 3. Study RBL004494 Reasons for Discontinuation

	Placebo	Actonel 2.5	Actonel 5.0
Total Discontinued	33 (26%)	28 (22%)	26 (20%)
Reason			
Never took drug	1 (<1%)	1 (<1%)	0
Adverse event	8 (6%)	12 (9%)	7 (5%)
Protocol violation	5 (4%)	7 (5%)	5 (4%)
Subject Request	16 (13%)	6 (5%)	12 (9%)
Lost-to-follow-up	1 (<1%)	0	0
Other	2 (2%)	1 (2%)	2 (2%)

Patient Baseline Characteristics

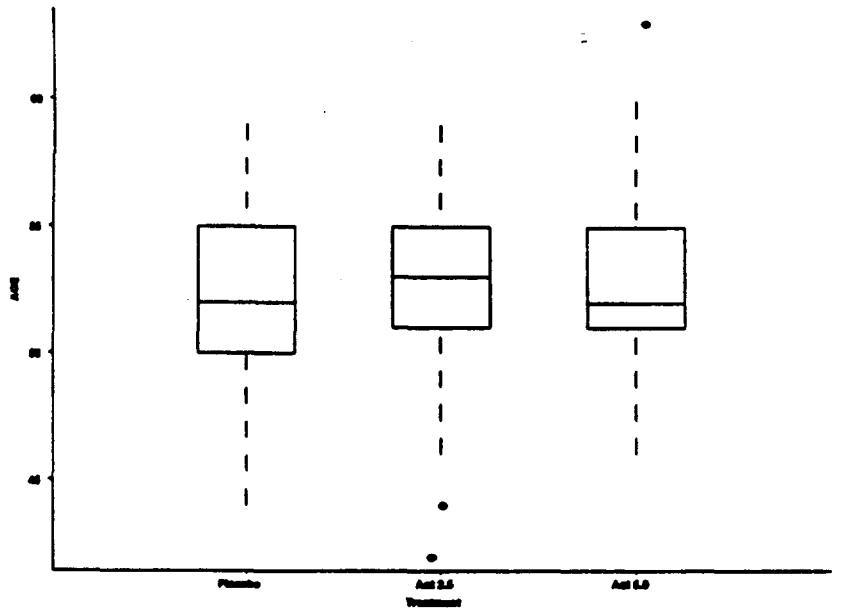
The treatment groups were well-balanced on all baseline characteristics except smoking status (Table 4). About 48% of the placebo patients were former or current smokers compared to 30% in the Actonel 2.5 mg group and 39% in the Actonel 5.0 mg group. Patients ranged in age from 42 to 63 with a mean of 53 years.

Table 4. Study RBL004494 Patient Baseline Characteristics

	Placebo (n=126)	Actonel 2.5 (n=128)	Actonel 5.0 (n=129)
Mean age (years)	53 (3.3)	53 (3.2)	53 (3.1)
% Caucasian	98%	98%	98%
Mean weight (kg)	70 (12)	70 (11)	69 (12)
Smoking status			
Never	52%	70%	62%
Former	30%	22%	27%
Current	18%	8%	12%
Time since last menstrual period (mos.)	47 (69)	49 (65)	43 (58)
% of patients with time since last menstrual period within 6-36 months of start of study drug	72%	77%	81%
% with prevalent vertebral deformities	19%	16%	20%

Figure 1 below shows the age distribution in each treatment group

Figure 1 Boxplots[1] for Age by Treatment Group

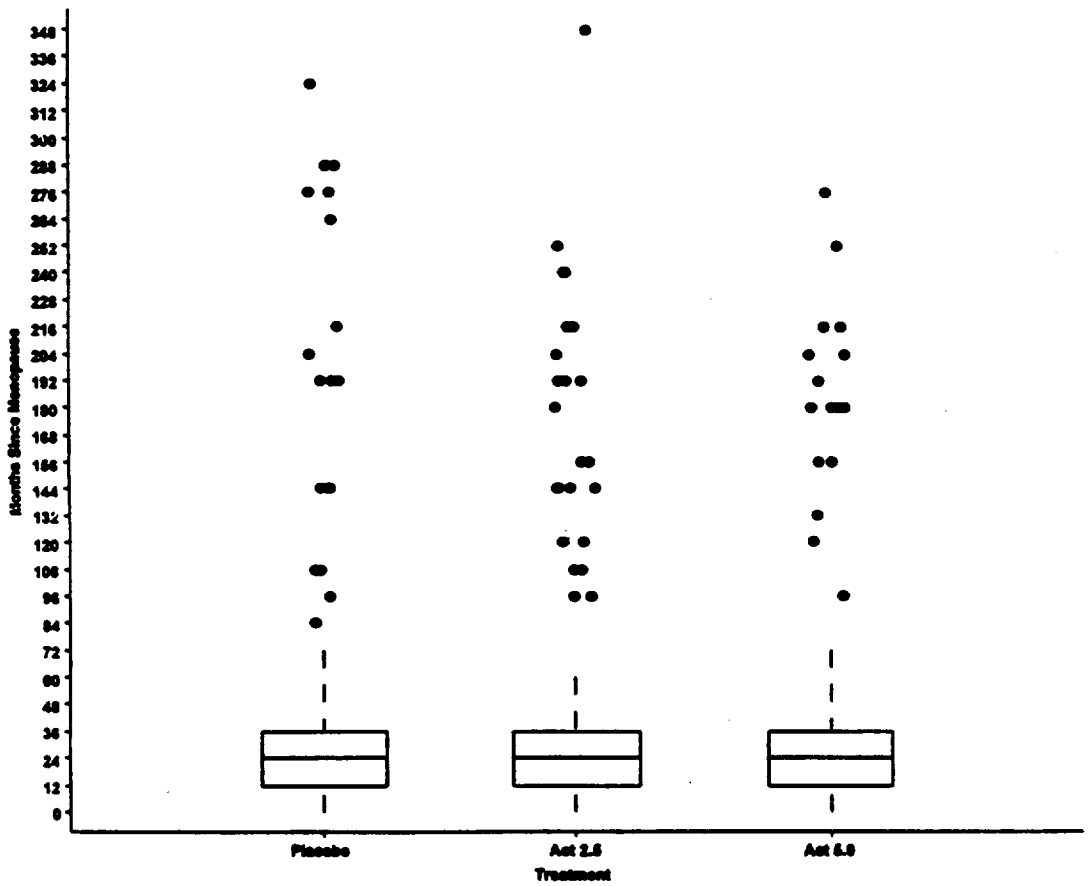


[1] The box represents the range from the 25th percentile to the 75th percentile; the line within the box represents the median. The lines from the box show the range of values within 1.5 times the interquartile range plus the 25th or 75th percentile; points beyond the lines are outliers.

The mean number of months since the last menstrual cycle was about 46 months for the database. According to the entry criteria, patients were to be between 6 and 36 months post-menopausal; patients with a hysterectomy without bilateral oophorectomy had to be at least 51 years old and under 61 years. There were 75 patients (about 25% of the patients) who were postmenopausal more than 36 months and qualified based on age. These patients were excluded by the sponsor from an "ITT subgroup" of 83 (66% of randomized patients) placebo patients, 85 (66%) Actonel 2.5 mg patients and 96 (74%) Actonel 5.0 mg patients analyzed by the sponsor.

Boxplots (Figure 2) illustrate the distribution of months since menopause to study start for each treatment group. The groups are comparable at baseline on this measure.

Figure 2 Boxplots for Months from Menopause to Study Onset by Treatment Group



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The treatment groups were comparable regarding baseline alkaline phosphatase, calcium, 25(OH)VitD_3 and four bone turnover markers (BAP, BGP, dPyr/Cr and Pyr/Cr). Baseline BMD was measured for lumbar spine, femoral neck, femoral trochanter, distal radius and midshaft radius. The treatment groups were comparable for all BMD sites except distal radius measured using an ——— instrument; placebo was 0.44, Actonel 2.5 was 0.39 and Actonel 5.0 was 0.43 ($p<.001$).

Primary Efficacy Results

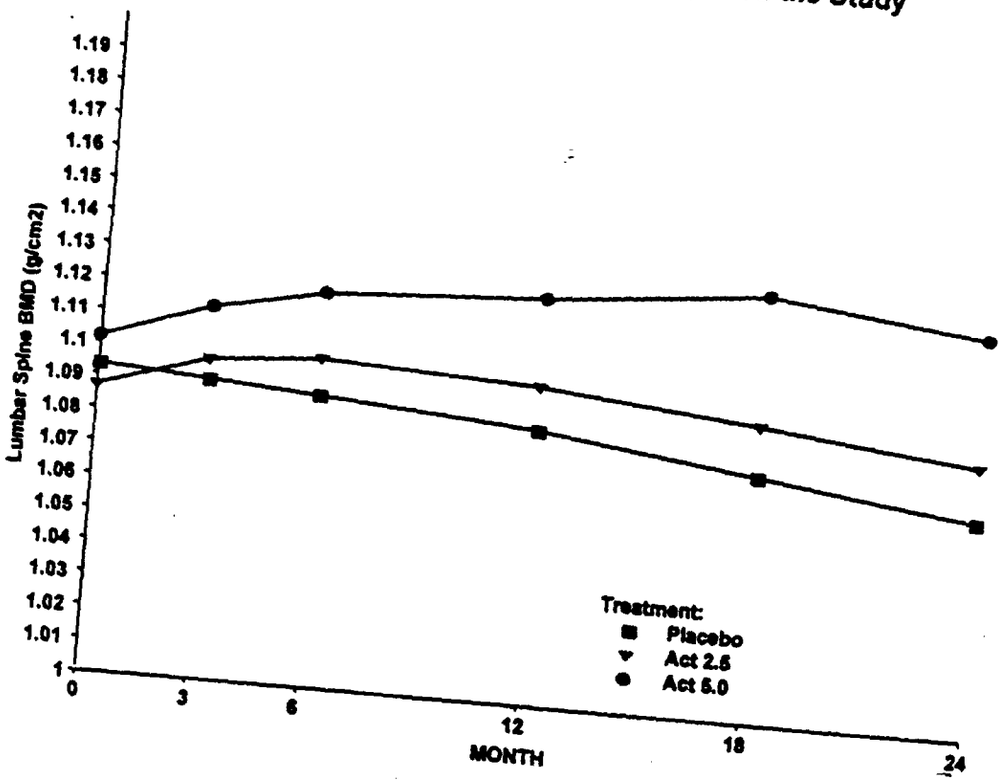
The primary efficacy variable designated in the protocol was lumbar spine BMD at Month 24. The results of an analysis of covariance with either baseline or months since menopause as a covariate for completers at Month 24 and for this reviewer's ITT sample with the last-observation-carried-forward (LOCF) show significant treatment effects for both doses of Actonel compared to placebo (Table 5, p<.0001). Consistent results across centers were observed.

Table 5. Reviewer's Results for Lumbar Spine BMD at Month 24 and at Endpoint (LOCF)

	Placebo	Actonel 2.5	Actonel 5.0	2.5 vs. Plac	5.0 vs. Plac
Baseline	1.09 (0.12)	1.09 (0.15)	1.09 (0.15)	NS	NS
% Change Month 24	-2.45% (3.09) (n=93)	-0.26% (3.28) (n=101)	+1.92% (3.00) (n=104)	p<.0001	p<.0001
LOCF	-2.32% (2.98) (n=120)	-0.27% (3.19) (n=118)	+1.87% (3.08) (n=125)	p<.0001	p<.0001

A plot of lumbar spine BMD means for patients who completed the 24 months of the trial (Figure 3) illustrate a steady increase in BMD overtime in the group treated with Actonel 5.0 mg compared to a decline in the placebo group and essentially no overall change in the Actonel 2.5 mg group.

Figure 3 Lumbar Spine BMD for Patients who Completed the Study



Based on the baseline differences noted among the treatment groups, this reviewer examined the lumbar spine BMD endpoint results by smoking status and by months since menopause (≤36 months versus >36 months). Figures 4 and 5 illustrate consistent treatment effects across the subgroups. Analyses by baseline BMD also revealed similar treatment effects regardless of baseline value.

Figure 4 Boxplots for Lumbar Spine BMD % Change from Baseline at Month 24 LOCF by Smoking Status and by Treatment Group

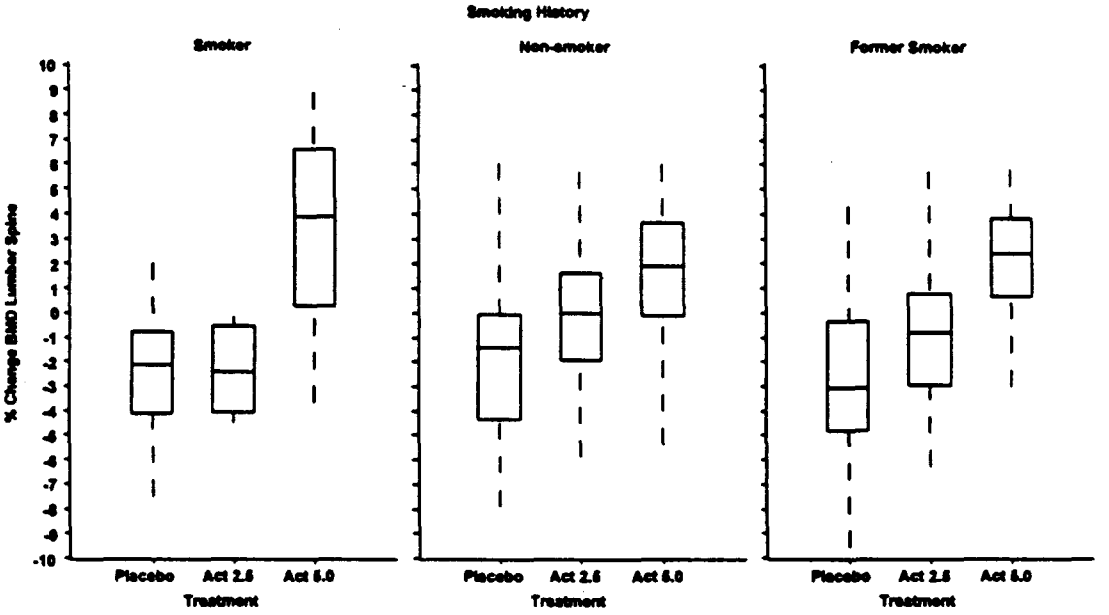
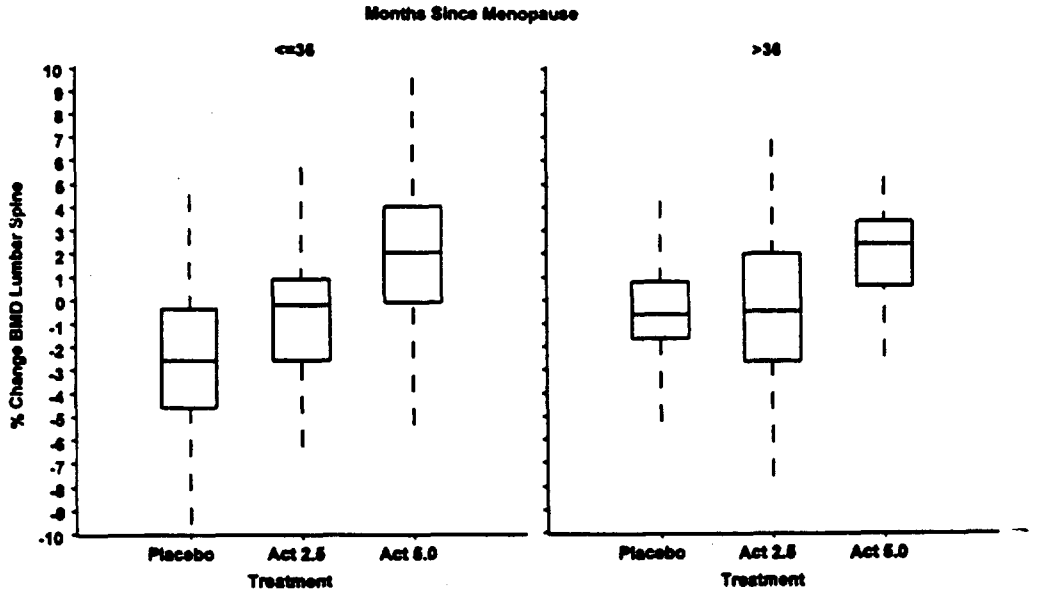


Figure 5 Boxplots for Lumbar Spine BMD % Change from Baseline at Month 24 LOCF by Months since Menopause (≤36 and >36 months) and by Treatment Group



Analyses of lumbar spine BMD adjusting for smoking status, months since menopause and presence of vertebral deformities at baseline yielded results consistent with the results presented in Table 5.

Secondary Efficacy Results

The results for BMD for two femoral sites (trochanter and neck) show significant increases in BMD for both doses of Actonel over placebo (Table 6). The results for both for these sites are presented in the sponsor's proposed labeling.

Table 6. Reviewer's Month 24 and Endpoint (LOCF) Results for Femoral Trochanter and Neck BMD

	Placebo	Actonel 2.5	Actonel 5.0	2.5 vs. Plac	5.0 vs. Plac
Trochanter					
Baseline	0.77 (0.12)	0.77 (0.13)	0.75 (0.11)	NS	NS
% Change					
Month 24	-1.88% (4.82) (n=91)	+1.32% (5.65) (n=100)	+2.45% (4.84) (n=104)	p<.0001	p<.0001
LOCF	-1.93% (4.67) (n=116)	+1.22% (5.42) (n=117)	+2.27% (4.89) (n=123)	p<.0001	p<.0001
Femoral Neck					
Baseline	0.89 (0.12)	0.88 (0.14)	0.87 (0.12)	NS	NS
% Change					
Month 24	-2.46% (3.29) (n=91)	-0.27% (3.81) (n=100)	+0.74% (3.26) (n=104)	p<.0001	p<.0001
LOCF	-2.21% (3.23) (n=116)	-0.12% (4.01) ((n=117)	+0.83% (3.38) (n=123)	p<.0001	p<.0001

The results for a third secondary endpoint, BMD of the distal radius were reported in the NDA but not in the labeling. No differences among the treatment groups was observed; the results at endpoint were –1.4% for placebo, -1.9% for Actonel 2.5 mg and –1.4% for 5.0 mg Actonel. Only descriptive statistics were provided for BMD of the midshaft radius (see Table 11 of this review); again no significant differences among treatment groups were noted.

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Study RBE002494 (8/94 to 5/96)

Study RBE002494 is a Phase III, randomized, stratified, double-blind, parallel trial designed to compare the combination of estrogen (Premarin 0.625 mg/day) plus Actonel 5 mg to estrogen alone for the prevention of osteoporosis in women post-menopausal for at least 12 months. All patients were administered 1 gram of calcium per day. Patients were randomly assigned to treatment stratifying on years postmenopausal (≤5 years and >5 years) and followed for at least 12 months at 25 centers. (This study was amended to reduce follow-up from 24 months to 12 months in August , 1995[1]; at that time, some patients had more than 12 months of follow-up so those patients have data past 12 months.)

BMD of the lumbar spine, proximal femur and distal radius were measured at 6, 12 and 18 months. Lumbar spine BMD at Month 12 was the primary efficacy endpoint. Adjustments for type of scanner were made as for the RBL Study.

The objective of this trial was to show that Actonel plus estrogen is superior to estrogen alone.

Patient Disposition

A total of 524 patients were randomized to therapy; 261 to estrogen alone and 263 to actonel 5.0 mg plus estrogen (Table 7). About ¾ of the patients completed therapy. The ITT population consisted of all patients randomized who took at least one dose of drug; for dropouts, the last observation was carried forward.

Table 7. Study RBE002494 Patient Disposition[2]

	Estrogen	Estrogen + Actonel 5.0
Randomized	261 (100%)	263 (100%)
≤5 yrs postmenopausal	62 (24%)	63 (24%)
>5 yrs postmenopausal	199 (76%)	200 (76%)
Received study drug	259 (99%)	261 (99%)
Completed 12 mos.	185 (71%)	198 (75%)
Completed 18 mos.	9 (3%)	6 (<1%)
Reviewer's ITT sample	201 (77%)	215 (82%)

The major reason for patient withdrawal from the study was adverse event (Table 8); there were about twice as many ADE withdrawals in the estrogen alone group (19%) than in the combination group (10%).

Table 8. Study RBE002494 Reasons for Discontinuation

	Estrogen (n=261)	Estrogen + Actonel 5.0 (n=263)
Total Discontinued	76 (29%)	65 (25%)
Reason		
Never took drug	2 (<1%)	2 (<1%)
Adverse event	49 (19%)	27 (10%)
Protocol violation	4 (2%)	2 (1%)
Subject Request	15 (6%)	17 (6%)
Lost-to-follow-up	6 (<2%)	12 (5%)
Other	0 (0%)	5 (2%)

[1] The study was shortened for [redacted] reasons according to the amendment.

[2] Note that this reviewer used the total randomized as the denominator when computing percentages for these tables; not the number taking drug as the sponsor did.

Patient Baseline Characteristics

The treatment groups were well-balanced on all baseline characteristics (Table 9). Patients ranged in age from 37 to 82 with a mean of about 59 years. The mean number of years since menopause was about 15 years (range of 0 to 48); about ¾ of the patients had been postmenopausal for more than 5 years. About 28% of the patients presented with vertebral deformities.

Table 9. Study RBE002494 Patient Baseline Characteristics

	Estrogen (n=261)	Estrogen + Actonel 5.0 (n=263)
Mean age (years)	59 (8)	58 (8.2)
%>65	28%	23%
Race		
% Caucasian	90%	92%
% Hispanic	6%	5%
% Other	3%	3%
Mean weight (kg)	72 (15)	71 (15)
Smoking status		
Never	55%	50%
Former	30%	34%
Current	15%	17%
Years since menopause (mean)	15 (10)	14 (10)
%≤5 yrs postmenopausal	24%	24%
%>5 yrs postmenopausal	76%	76%
% with prevalent vertebral deformities	28%	28%

The treatment groups were comparable regarding baseline alkaline phosphatase, calcium, 25(OH)VitD_3 and four bone turnover markers (BAP, BGP, dPyr/Cr and Pyr/Cr). Baseline BMD for lumbar spine, femoral neck, femoral trochanter, distal radius and midshaft radius were comparable for the two treatment groups.

Reviewer's comments

According to the FDA guideline for osteoporosis prevention trials, patients should be no more than 3 years post-menopausal and asymptomatic. In this study 76% of the patients are more than 5 years post-menopausal.

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Primary Efficacy Results

The primary efficacy variable was percent change from baseline of lumbar spine BMD at Month 12. Analyses of Month 12 data for completers and for an ITT sample with the last-observation-carried-forward showed no statistically significant difference between the treatment groups (Table 10).

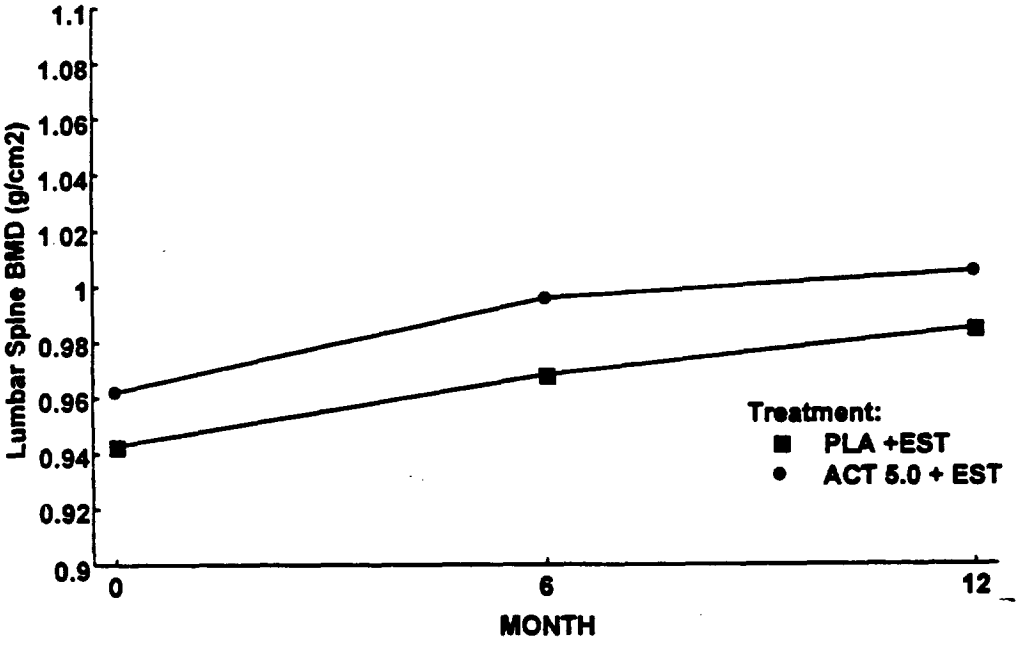
Table 10. Reviewer's Results for Lumbar Spine BMD at Month 24 and at Endpoint (LOCF)

	Estrogen (n=201)	Estrogen + Actonel 5.0 (n=215)	p-value*
Baseline	0.95 (0.18)	0.96 (0.18)	NS
% Change			
Month 12			
Mean (SD)	+4.5% (2.7)	+5.1% (3.2)	
LSM	+4.3% (n=185)	+4.9% (n=195)	.068
LOCF			
Mean (SD)	+4.4% (2.7)	+4.9% (3.2)	
LSM	+4.2%	+4.7%	.085

* p-values are results of the protocol-defined ANOVA model with treatment, center and stratum as main effects.

Figure 6 illustrates the mean lumbar spine BMD for patients who completed at least 12 months of therapy. An analysis of BMD adjusting for baseline yielded Month 12 least squares means of 0.991 for estrogen+placebo and 0.997 for estrogen+Actonel and p-value of .01; a statistically significant difference but most likely not a clinically relevant difference.

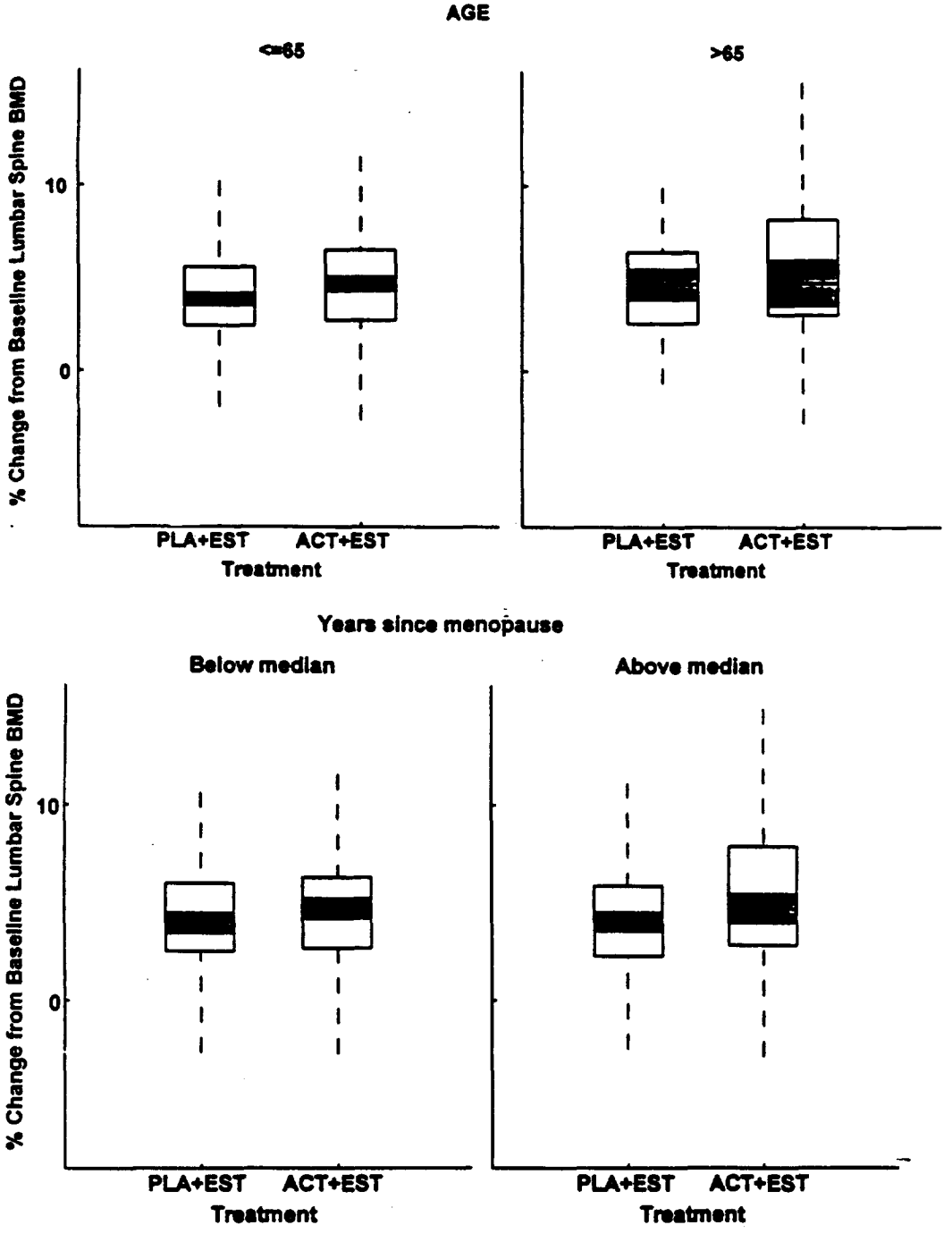
Figure 6. Mean Lumbar Spine BMD (g/cm^2) by Treatment Group and Month for Completers

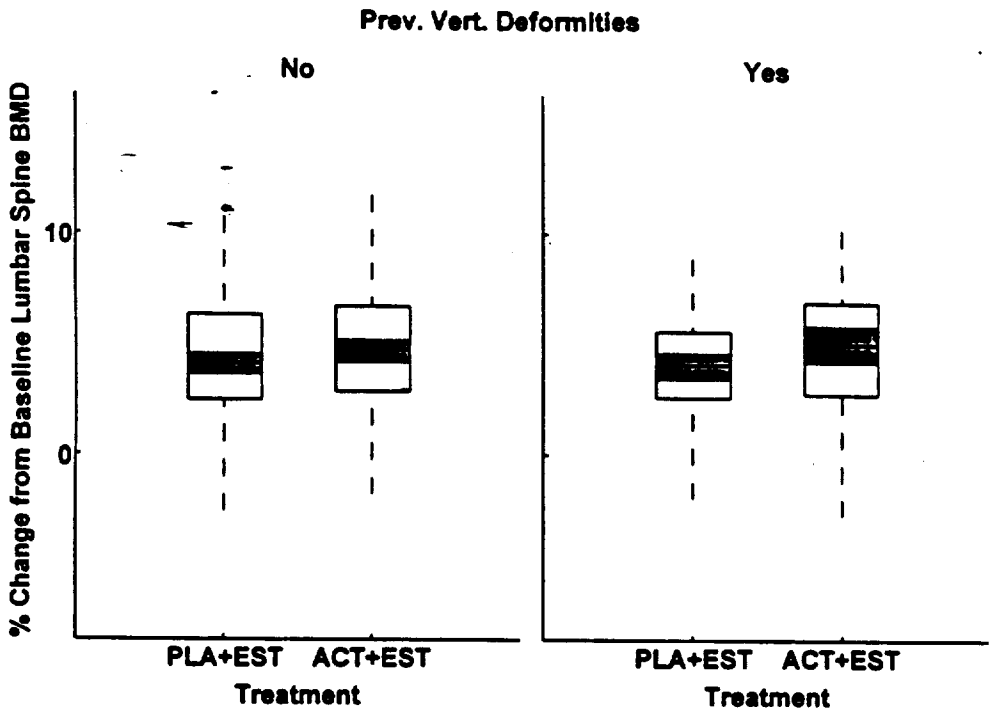


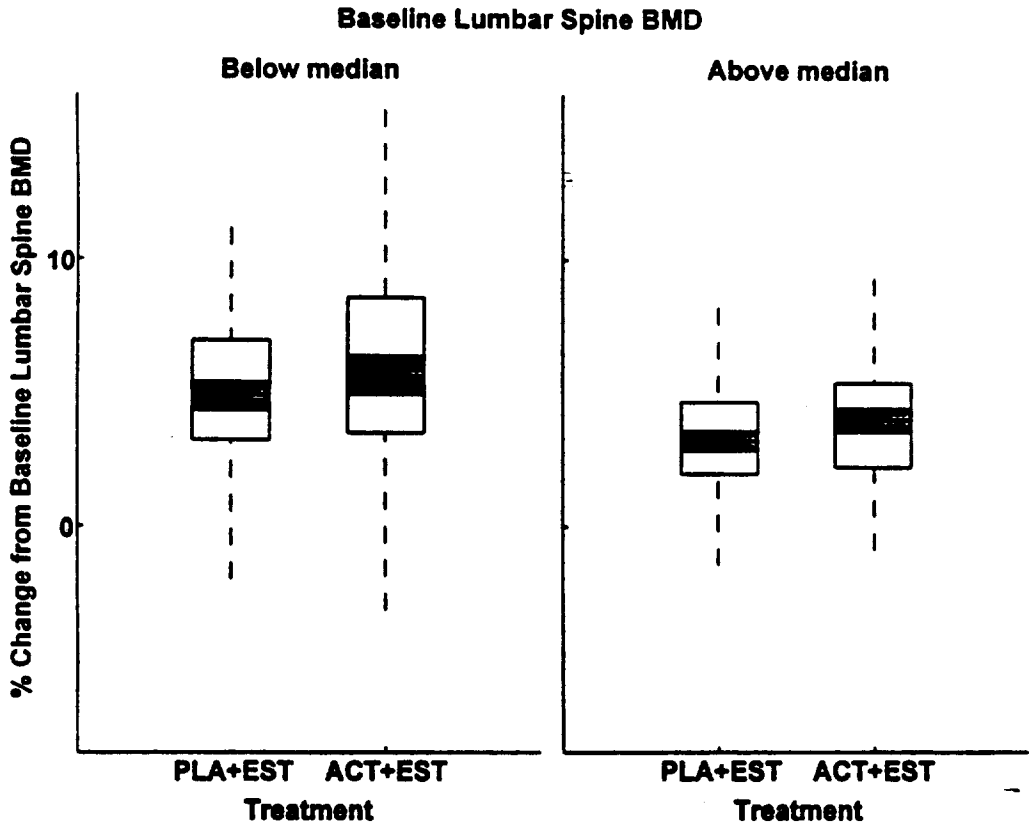
Subgroups

Subgroup results based on age (<65, ≥65), years since menopause (below and above the median of 11), vertebral deformities (present or not) and baseline BMD (below and above the median of .94) were examined by this reviewer. As for the overall sample, the treatment differences are small and non-significant (Figure 7).

Figure 7. Boxplots of Lumbar Spine BMD at Endpoint (LOCF) by Subgroup and Treatment




Prev. Vert. Deformities
No
Yes
% Change from Baseline Lumbar Spine BMD
10
0
PLA+EST
ACT+EST
Treatment
PLA+EST
ACT+EST
Treatment


Baseline Lumbar Spine BMD
Below median
Above median
% Change from Baseline Lumbar Spine BMD
10
0
PLA+EST
ACT+EST
Treatment
PLA+EST
ACT+EST
Treatment

Secondary Efficacy Results

In the protocol, three secondary efficacy variables are named; femoral neck, trochanter and distal radius. BMD of the midshaft radius was also measured by the sponsor. The results for all four secondary endpoints are presented in the sponsor's proposed labeling. The results for the distal radius were similar for both groups and are not presented here (+1.46% for Actonel plus estrogen versus +1.58% for estrogen alone). The LOCF results for BMD of the trochanter, the femoral neck and the midshaft radius show no significant treatment effects when one adjusts for multiple comparison. A Bonferroni adjustment for 4 comparisons would set alpha at .0125. The femoral neck results for completers are Month 12 show borderline significant results.

Table 11. Reviewer's Month 12 and Endpoint (LOCF) Results for Secondary Variables

	Estrogen (n=201)	Estrogen + Actonel 5.0 (n=215)	p-value
Fem. Trochanter			
Baseline	0.65 (0.13)	0.66 (0.13)	NS
% Change			
Month 12	+3.10% (3.73) (n=179)	+3.73% (3.41) (n=192)	.09
LOCF	+3.05% (3.71)	+3.52% (3.51)	.19
Femoral Neck			
Baseline	0.75(0.14)	0.76 (0.14)	NS
% Change			
Month 12	+1.75% (3.30) (n=179)	+2.64% (3.41) (n=192)	.01
LOCF	+1.83% (3.45)	+2.49% (3.39)	.05
Midshaft Radius			
Baseline	0.69(0.12)	0.68(0.11)	NS
% Change			
Month 12	+0.37% (1.83) (n=184)	+0.69% (2.30) (n=192)	.05
LOCF	+0.47% (1.95)	+0.63% (2.44)	.26

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Reviewer's Overall Comments

The BMD results for the primary endpoint (lumbar spine) and secondary endpoints for Studies RBL and RPE are summarized in Table 12.

Table 12. Summary of BMD % change at endpoint (LOCF) for Studies RPE and RBL

	Placebo	Act 2.5	Act 5.0	Act 5 + Est	Estrogen
Lumbar spine	-2.3%	-0.3%	+1.9%	+4.9%	+4.4%
Trochanter	-1.9%	+1.2%	+2.3%	+3.5%	+3.1%
Femoral Neck	-2.2%	-0.1%	+0.8%	+2.5%	+1.8%
Distal Radius	-1.4%	-1.9%	-1.4%	+1.5%	+1.6%
Midshaft Radius	-1.5%	-1.2%	-0.2%	+0.6%	+0.5%

Month 24 results for placebo, Act 2.5 and 5.0 and Month 12 results for Act 5 + Est and est alone.

1. The results of the RBL study are positive. Each dose of Actonel was statistically significantly different from placebo for the primary endpoint. Results were found to be consistent across many subgroups.

2. The sponsor presents the RPE study as a prevention study. This study design does not conform to the guidelines for an osteoporosis prevention study in that more than 75% of the patients were post-menopausal for more than 3 years.

3. Study RPE failed to show a significant difference between estrogen and Actonel plus estrogen. This BMD data suggests that patients did not benefit from the addition of Actonel to estrogen.

Comments on Labeling

Prevention of Osteoporosis in Postmenopausal Women:

1. The first sentence should describe the study design and include the number of patients in each treatment group.

2. [redacted] are misleading and not informative and should be replaced with the treatment group means.

/S/

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

/S/ 2/9/00

Todd Sahlroot, Ph.D.
Team Leader

/S/ 2/13/00

Ed Nevius, Ph.D.
Director of DOB2

cc:
Archival NDA#20-835
HFD-510
HFD-510/EColman, RHedin, JJenkins
HFD-715/Division 2 File, Chron, JMele

September 28, 1999

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STATISTICAL REVIEW AND EVALUATION

JUL 3 0 1999

NDA #	**20-835 SE-001**
Drug Name:	**Actonel (risedronate sodium) oral tablets**
Sponsor:	**Procter & Gamble Pharmaceuticals**
Indication:	**Treatment and Prevention of Corticosteriod Induced Osteoporosis**
Review Documents:	**Volume 1.1, 1.203-1.230, and 1.281 dated December 18, 1998, lung cancer related submissions dated 2/19/99, 4/22/99, 5/24/99, 6/18/99 and several faxes, SAS datasets, and related submissions dated 2/8/99, 3/30/99, 4/20/99**
Medical Reviewer:	**Eric C. Colman, M.D. (HFD510)**

The following review has been discussed with the review team. Tables are numbered within each Trial. On July 12, 1999, this reviewer gave a presentation on "Statistical review and evaluation of safety on cancer risks of Actonel" to the medical review team. For details, see Section 3 below.

HIGHLIGHTS OF STATISTICAL EVALUATION

- **The sponsor amended the protocol to drop the lower dose arm of 2.5mg risedronate halfway through the trial period in 4 of 10 trials without rigorous justification. The percentages of patients having completed trials at the time of terminating the 2.5mg arm ranged from 70% to 87%. The sponsor excluded already recruited patients in this arm, resulting in a 2-arm comparison.**
- **The medical division was concerned about a disproportionate lung cancer risk seen in the ten trials submitted by the sponsor to be indicated for treatment and prevention of corticosteroid-induced osteoporosis and postmenopausal osteoporosis.**
- **Early discontinuation rates ranged from 18% to 53% across the ten trials with the hip fracture study being the highest. The 2.5mg risedronate either had a dropout rate similar to the 5.0mg risedronate, or "a similar or lower" dropout rate compared to placebo within individual trials.**

1. BACKGROUND

Risedronate (Trade name: Actonel) has been approved for treatment of Paget's disease. In mid-December, 1998, Procter and Gamble Pharmaceuticals submitted risedronate NDA supplement for three indications (1) treatment and prevention of corticosteroid-induced osteoporosis (CIO) (2) treatment of postmenopausal osteoporosis and (3) prevention of postmenopausal osteoporosis (PMO). For the CIO indication, the sponsor met with the medical division on February 12, 1998 regarding whether their data package was sufficient to support the indication with appropriate labeling. In this meeting, the medical division stated that the division's tentative decision requires a two-year fracture study with 1-year follow-up for the CIO indication primarily due to a safety concern related to the quality of cortical bone. The requirement for the CIO indication was discussed at the May 13, 1998 Division of Metabolic and Endocrinologic Drug Advisory Committee Meeting. The sponsor stated that based on the discussions and conclusions stated by the Committee, they have included data to support the CIO indication in this supplement NDA.

Two phase II (Trial 89042 and Trial 89016) and two phase III (RCT009893 and RCP009993) studies were submitted for review in support for treatment of corticosteroid-induced osteoporosis. Of the two phase II studies, Trial 89042 consisted of 3 arms with approximately 25 patients in each arm, and about 70% dropouts due to early AE events. The other phase II trial enrolled only two patients (one male, one female).

This review pertains to the two well-controlled phase III studies for supplement #01, viz., treatment and prevention of corticosteroid-induced osteoporosis in patients between 18 and 85 years of age. In addition, the medical division's safety concern of a possible excess lung cancer risk seen in risedronate-treated patients in all 10 phase III trials was evaluated in-depth by this reviewer, see Section 3.

Keywords: percent change from baseline, ANOVA, lung cancer risk, corticosteroid-induced osteoporosis (CIO), postmenopausal osteoporosis (PMO), bone mineral density (BMD)

2. STUDY DESCRIPTION

2.1 Trial RCT 009893

Trial Design: This was to be a double-blind, stratified (by sex and menopausal status with 1=male patients, 2=premenopausal female patients, 3=postmenopausal female patients), randomized, parallel-group, placebo-controlled, multi-center (23 centers in Europe) study. The study was conducted in ambulatory patients ≥ 18 years and ≤ 85 years of age with documented rheumatoid arthritis, polymyositis, polymyalgia rheumatica, temporal arthritis, systemic lupus erythematosis, chronic interstitial lung disease, asthma, chronic obstructive pulmonary disease, skin disease (i.e. pemphigoid, pemphigus or dermatomyositis) or vasculitis requiring long-term corticosteroid treatment. Eligible patients were randomized to one of the three treatment arms: placebo once daily, 2.5mg risedronate once daily or 5.0mg risedronate once daily. The study consisted of a 12-month treatment phase and a 12-month follow-up phase without treatment (see bullet item#1 below). During both phases, patients received 1000mg elemental calcium and 400 IU of Vitamin D daily.

Trial Objective: The primary objective of the study was to determine the efficacy of risedronate versus placebo in maintaining or increasing lumbar spine bone mineral density (BMD) in patients receiving high dose corticosteroid therapy, ≥ 7.5mg mean daily dose prednisone or equivalent, for ≥ 6 months prior to study entry. The primary efficacy variable was BMD as measured by Dual Energy X-ray Absorptiometry (DXA) of lumbar spine. Secondary variables were BMD of proximal femur, BMD of distal and mid-radius. proportion of responders to risedronate therapy (in terms of lumbar spine, proximal femur, distal and mid-radius BMD), pharmacodynamic evaluations of bone turnover markers. A responder in terms of lumbar spine BMD is a patient who had a ≥ 1.5% increase in lumbar spine BMD over the first year of the study or up to the time of discontinuation, if the patient discontinues before completing one year. A responder in terms of femoral neck BMD, trochanter BMD and mid-radius BMD is defined as for lumbar spine BMD.

Assessments of safety of risedronate included monitoring the adverse event, hematologic, hepatic, renal and bone safety profiles [cortical bone mass (mid-radius and femoral neck) and vertebral and non-vertebral fracture rates].

Trial period was from 8/11/94 to 10/7/96. There were four protocol amendments, two of them (dated 3/94 and 5/94) were before trial initiation, one, dated 10/95, was during mid-course of the trial, and one, dated 3/97, was after trial completion. Points relevant to the statistical plan are summarized below by this reviewer, please refer to Section 2.1.2 for Reviewer Evaluation and Comments.

- The study was shortened from 24 months to 12 months of treatment by removing the 12-month drug-free period (Amendment 3, dated 10/95).
- Analysis of study results was changed to reflect the shortened study duration.
- [redacted] were deleted post-baseline. The objective of [redacted] was deleted.
- Definition of prevalent and incident vertebral deformities was changed after the study was clinically complete.

Statistical Plan: Analysis of variance (ANOVA) with treatment, center, and stratum for continuous variables, and extended Mantel-Haenszel tests with centers and strata as the blocking factors for categorical variables were protocol defined analysis methods. Primary parameter of interest was percent change from baseline. The main treatment group comparison for each variable was to be based on data at the one year time point. Analyses of interaction terms involving treatment were to be carried out prior to the interpretation of the analyses adjusted for center and strata effects in an ANOVA model for continuous variables and a logistic regression model for binary variables, at 0.10 significance level. Centers not having recruited at least 6 patients were to be pooled on the basis of geographic region for assessing interaction. Group comparisons at earlier time points were to be performed to explore possible earlier treatment group separation - to be commented on in Section 2.1.2 Reviewer Evaluation and Comments.

It was estimated that 91 patients per treatment arm would have at least 90% power to detect at least 3% difference in percent change from baseline in lumbar spine BMD between 5mg risedronate and placebo assuming a common standard deviation of 5%, 35% dropout rates, and at 5% two-sided significance. The sponsor stated in the protocol that 'a detailed statistical analysis methodology plan will be developed prospectively and filed with regulatory agencies prior to analysis initiation or breaking of the treatment blind'. In the NDA reports, the above detailed statistical analysis methodology was found and dated April 27, 1998, about 1.5 years after trial completion. Regarding multiple comparisons among treatment groups, the sponsor planned an overall F-test with SAS type III sums of squares. If the overall test was significant, then at least one of the 2.5mg risedronate vs. placebo or 5.0mg risedronate vs. placebo comparisons would also be required to be significant at the 0.05 level.

2.1.1 Sponsor Results and Reviewer's Comments

Two hundred ninety patients were enrolled at 23 centers in Europe; 5 patients withdrew prior to receiving any study drug. Of the 285 patients who were randomized and received study drug (i.e., the intent-to-treat ITT population), 62 patients withdrew before completing the 12-month treatment period. Table 1.1 presents the disposition of the patients in this study: 33 patients (11 in each arm) withdrew because of adverse experiences, five patients violated the protocol, 19 patients withdrew voluntarily and 4 patients were lost to follow up. One patient withdrew for other reasons – felt unable to cope with the demands of the study. Of the 223 patients who completed the 12-month treatment period, 115 patients had a Month-18 visit. Patients who were randomized were comparable in age (ranged from 19 to 85 years old with a mean age of 58.4 years), race (majority were Caucasian, 97%), smoking status (37% previous user, 24% current users, and 38% never used with a mean total # of years smoked among ever smoker of 27.5 years), alcohol consumption (17% previous users, 47% current users, 36% never used with a mean total # of years alcohol consumed among ever drinker of 31.0 years), sex (38% male and 62% female), stratum (38% males, 8% premenopausal female and 54% postmenopausal female), and percent of patients with prevalent vertebral deformities (35% from 99 patients with evaluable radiographs at baseline).

Table 1.1 Patient Accountability*(Trial RCT009893)

	Placebo n (%)	2.5mg risedronate n (%)	5.0mg risedronate n (%)
Randomized	96	94	100
Received study drug	94	92	99
Completed treatment period**	70(74%)	72(78%)	81(82%)
Males (stratum-1)	24	27	26
Premenopausal female (stratum-2)	6	6	8
Postmenopausal female (stratum-3)	40	39	47
Discontinued treatment **	24(26%)	20(22%)	18(18%)
Adverse event	11(12%)	11(12%)	11(11%)
Protocol violation	1(1%)	3(3%)	1(1%)
Voluntary withdrawal	9(10%)	6(7%)	4(4%)
Lost to follow-up	2(2%)	0	2(2%)
Other	1(1%)	0	0

* taken from sponsor panel 4: patient accountability in p.71 of vol.1.203.

** percentage (%) was calculated based on patients who received study drug in each treatment group during the 12-month treatment period.

Baseline BMD of the lumbar spine, femoral neck, femoral trochanter, distal radius, and midshaft (1/3) radius, as well as T-scores of the lumbar spine, were comparable across the three treatment arms and were comparable across the three treatment arms within each stratum (ref: panels 6 and 7 in p.73-75 of vol.1.203). According to the sponsor, there were no statistically significant differences among the treatment groups for any bone turnover marker. More within-strata variation was observed for the bone resorption markers. In Stratum-1 (males), bone resorption markers were within the normal ranges at baseline; mean values were at the midpoint of the normal ranges. In Stratum-2 (premenopausal females) and Stratum-3 (postmenopausal females), bone resorption markers were in the lower half of the normal

ranges although Stratum-3 mean and median values were higher and closer to the midpoint of the normal ranges (ref: panels 9 in p.78-79 of vol.1.203).

The most common conditions for which all randomized patients received glucocorticosteroid treatment were rheumatoid arthritis (41%), asthma (18%), and polymyalgia rheumatica (13%). All 285 patients (ITT) continued oral glucocorticosteroids during the study. The most common concomitant oral glucocorticosteroid therapy was prednisolone. The distributions of concomitant glucocorticosteroid therapy type, mean daily dose, and duration were comparable for the three treatment groups. Mean duration of glucocorticosteroid therapy was 10.55 months, which was the same as mean duration of study drug treatment (ref: Table 40.1 vol.1.204).

Of note, a higher percentage of patients in each of the active treatment groups (14.1% in 2.5mg and 13.1% in 5.0mg arm) took calcium channel blockers compared to the placebo group (3.2%). In addition, a higher percentage of patients in the placebo and 2.5mg groups were on thyroid replacement therapy compared to the 5.0mg group. According to the sponsor, these medications were begun prior to baseline in most cases. With respect to patient compliance, the majority of patients were at least 80% compliant (85% in placebo, 84% in 2.5mg arm, and 90% in 5.0mg arm). Non-compliance with the dosing schedule was highest during the first 3 months of the study, the sponsor stated that "the reason for this is unclear".

Primary efficacy endpoint – mean % change from baseline in BMD of the lumbar spine at month 12

The sponsor results for "mean percent change from baseline in BMD of the lumbar spine at month 12" are summarized in Table 1.2 (extracted from sponsor panel 17, p.91 of vol.1.203), also see Figure 1.1 (extracted from sponsor Figure 1 of p.90).

Reviewer Comments: From Table 1.2, we see that mean percent change from baseline in lumbar spine BMD was improved in risedronate-treated patients, however, lumbar spine BMD was no different from baseline in placebo-treated patients. Majority of early withdrawn patients occurred in the first 6-months. Risedronate 2.5mg treated patients was not shown to be superior than placebo-treated patients. Pease see Section 2.1.2 for further evaluation from this reviewer.

Table 1.2 Mean % change from baseline in BMD of the lumbar spine by visit - RCT 009893

Panel 17

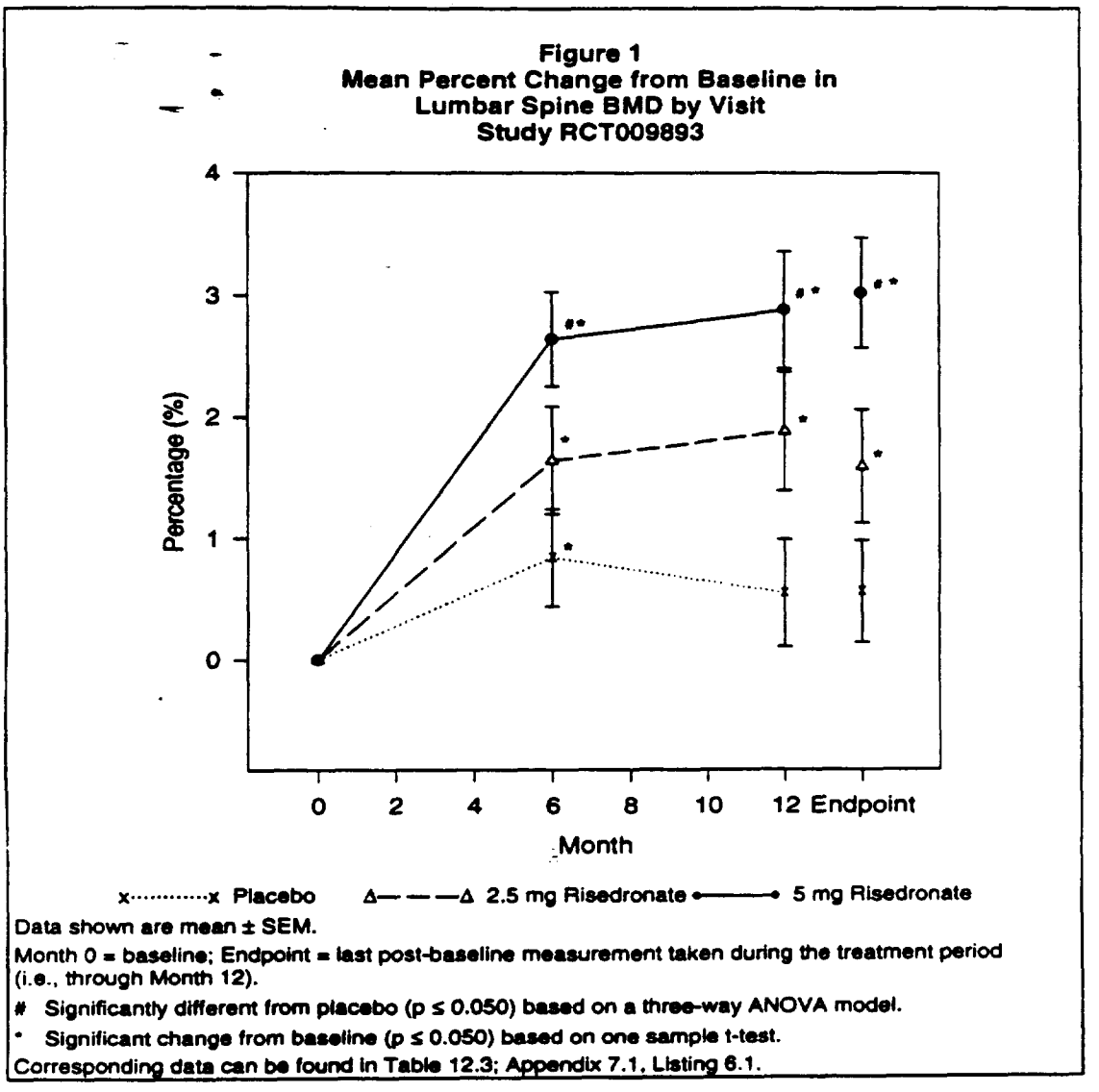
Mean Percent Change From Baseline in Bone Mineral Density of the Lumbar Spine by Visit

Study RCT009893

Treatment Group	Baseline BMD (g/cm²)	Percent Change From Baseline		
		Month 6	Month 12	Endpoint[a]
Placebo				
N	92	67	66	69
Mean (S.E.)	0.903 (0.0193)	0.85 (0.407)[c]	0.43 (0.435)	0.49 (0.420)
2.5 mg Risedronate				
N	92	75	70	76
Mean (S.E.)	0.935 (0.0168)	1.71 (0.465)[c]	1.88 (0.489)[c]	1.65 (0.491)[c]
5 mg Risedronate				
N	96	81	79	82
Mean (S.E.)	0.920 (0.0189)	2.71 (0.398)[c]	2.90 (0.469)[c]	3.02 (0.479)[c]
Overall P-Value[b]	--	0.004	<0.001	<0.001
5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	1.98 (0.598)[d]	2.68 (0.668)[d]	2.78 (0.650)[d]
2.5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	0.87 (0.601)	1.24 (0.679)	1.15 (0.656)
5 mg Risedronate vs. Placebo: 95% CI	--	0.805, 3.148	1.370, 3.982	1.500, 4.050
2.5 mg Risedronate vs. Placebo: 95% CI	--	-0.307, 2.050	-0.093, 2.571	-0.140, 2.430

[a] Endpoint is the last post-baseline measurement taken during the treatment period (i.e., through Month 12).
[b] P-value for testing the difference among treatments based on a three-way ANOVA model.
[c] Significant change from baseline ($p \leq 0.050$) based on one-sample t-test.
[d] Significantly different from placebo ($p \leq 0.050$)
N at baseline includes all patients who had values at baseline.
N at visits includes patients who had a value at baseline and visit.
-- = Not applicable
Corresponding data can be found in Table 12.3; Appendix 7.1, Listing 8.1.

Figure 1.1 Mean % change from baseline in lumbar spine BMD by visit - RCT 009893



Mean percent change from baseline in BMD of the lumbar spine by stratification

Few patients were premenopausal females (stratum II). Analysis results of percent change from baseline of lumbar spine BMD within each stratum are summarized in Table 1.3 (sponsor panel-18 of p.95), also see Figures 1.2 (male), 1.3 (premenopausal female) and 1.4 (postmenopausal female). The sponsor stated that "because many subgroups contained small patient numbers, definitive conclusions could not be drawn. However, the various subgroup analyses generally confirmed the efficacy of risedronate in patients receiving chronic glucocorticosteroid therapy. Furthermore, 5.0mg risedronate appeared to be more effective than 2.5mg risedronate".

Reviewer Comments: from Figures 1.2 to 1.4, the sponsor subgroup analysis results based on stratification factor at randomization showed that risedronate effect of 2.5mg and 5.0mg appeared to be similar in magnitude within postmenopausal females. The effect of risedronate seemed to be more prominent in male and premenopausal females.

Table 1.3 Mean % change from baseline in BMD of the lumbar spine by visit and stratum - RCT 009893

Panel 18

Mean Percent Change From Baseline in Bone Mineral Density of the Lumbar Spine by Visit and Stratum

Study RCT009893

	Baseline BMD (g/cm²)			Percent Change from Baseline					
				Month 6			Month 12		
	Stratum I	Stratum II	Stratum III	Stratum I	Stratum II	Stratum III	Stratum I	Stratum II	Stratum III
Placebo									
N	34	7	51	23	6	38	22	6	38
Mean (S.E.)	0.952 (0.0290)	1.064 (0.0609)	0.848 (0.0250)	1.71 (0.812)*	-1.30 (1.133)	0.67 (0.474)	1.17 (0.777)	-0.50 (0.967)	0.15 (0.587)
2.5 mg Risedronate									
N	36	9	47	27	8	40	26	6	38
Mean (S.E.)	0.977 (0.0227)	1.037 (0.0542)	0.884 (0.0237)	2.22 (0.784)*	-1.44 (1.373)	1.99 (0.607)*	2.07 (0.783)*	-0.29 (0.636)	2.08 (0.712)*
5 mg Risedronate									
N	35	9	54	27	8	46	25	8	46
Mean (S.E.)	0.939 (0.0325)	0.964 (0.0461)	0.899 (0.0261)	4.17 (0.631)*	2.89 (0.784)*	1.82 (0.546)*	4.81 (0.925)*	2.51 (0.795)*	1.93 (0.618)*
Overall P-value[a]	--	--	--	--	--	--	<0.001	0.141	0.073
5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	--	--	--	--	--	5.10 (1.137)#	2.47 (0.992)	1.77 (0.903)
2.5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)							1.54 (1.111)	0.54 (0.728)	1.96 (0.952)#
5 mg Risedronate vs. Placebo: 95% CI	--	--	--	--	--	--	2.871, 7.327	0.529, 4.418	0.002, 3.542
2.5 mg Risedronate vs. Placebo: 95% CI	--	--	--	--	--	--	-0.640, 3.717	-0.888, 1.966	0.096, 3.830

[a] P-value for testing the difference among treatments based on a two-way ANOVA model.
Stratum I = males; Stratum II = premenopausal females; Stratum III = postmenopausal females.
* Significantly different from baseline ($p \leq 0.050$) based on one-sample t-test.
# Significantly different from placebo ($p \leq 0.050$)
N at baseline includes all patients who had values at baseline.
N at visits includes patients who had a value at baseline and visit.
-- = Not applicable
Corresponding data can be found in Table 17.3; Appendix 7.1, Listing 6.1.

Figure 1.2 Mean % change from baseline in lumbar spine BMD by visit (Stratum I:Male) - RCT 009893

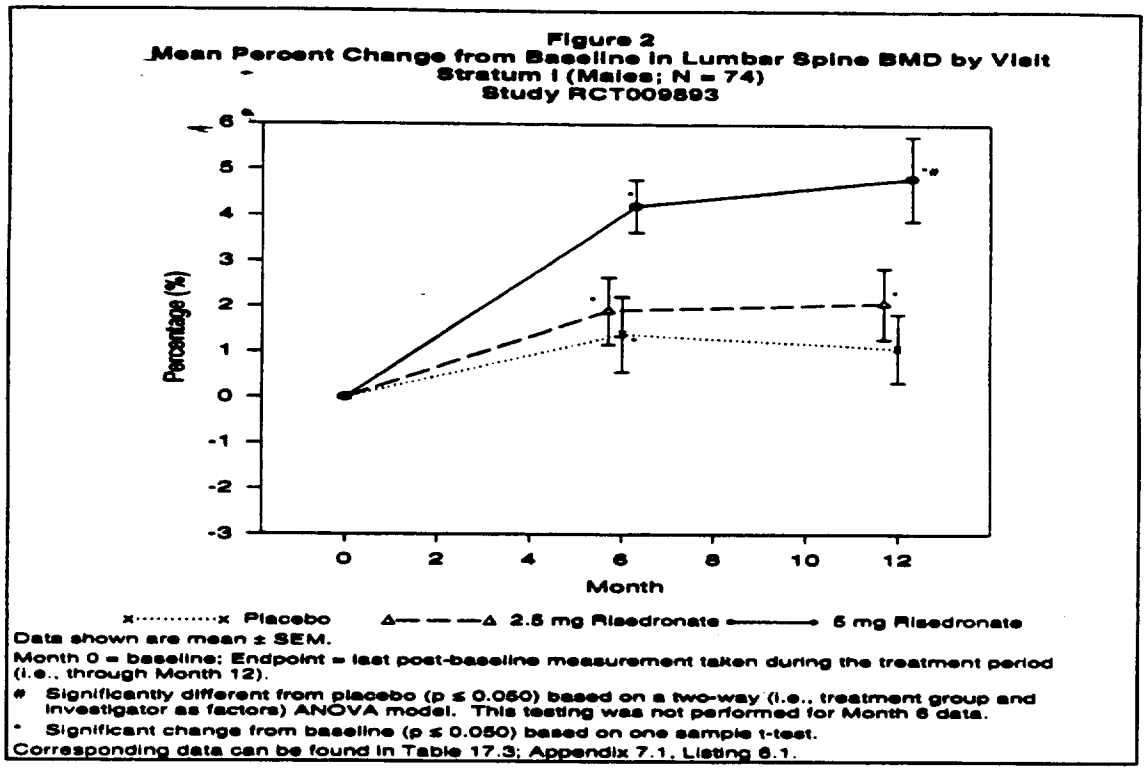


Figure 1.3 Mean % change from baseline in lumbar spine BMD by visit (Stratum II)- RCT 009893

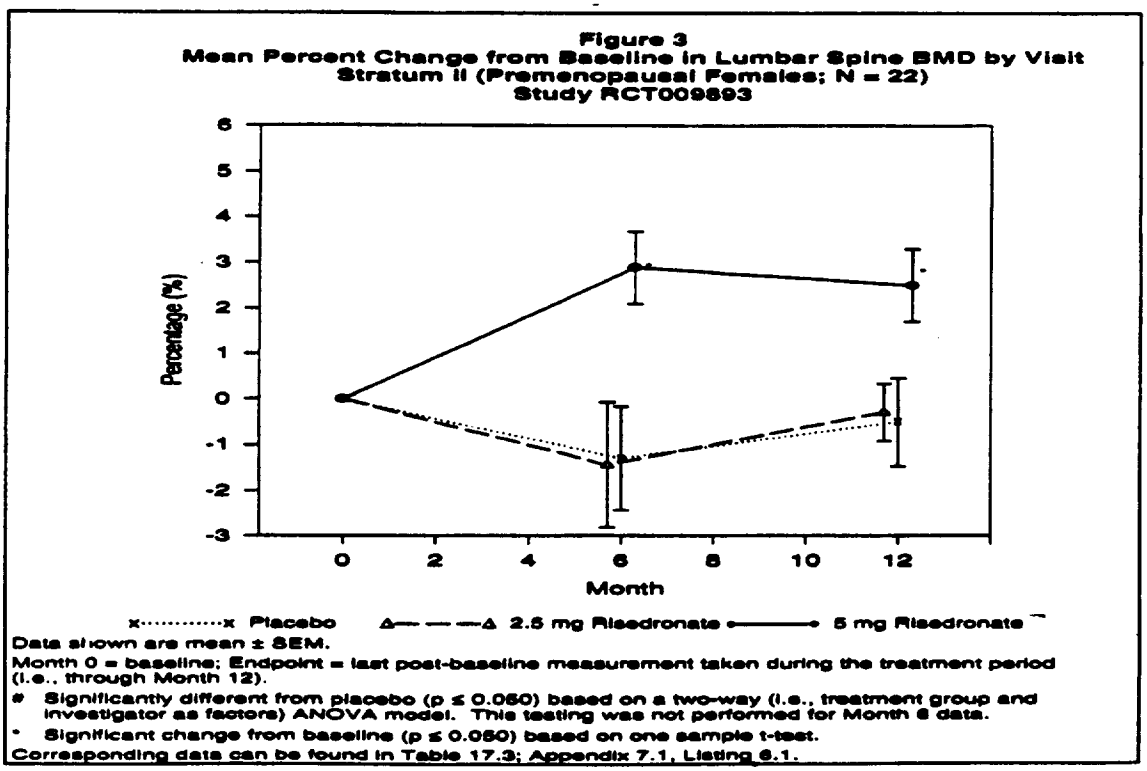
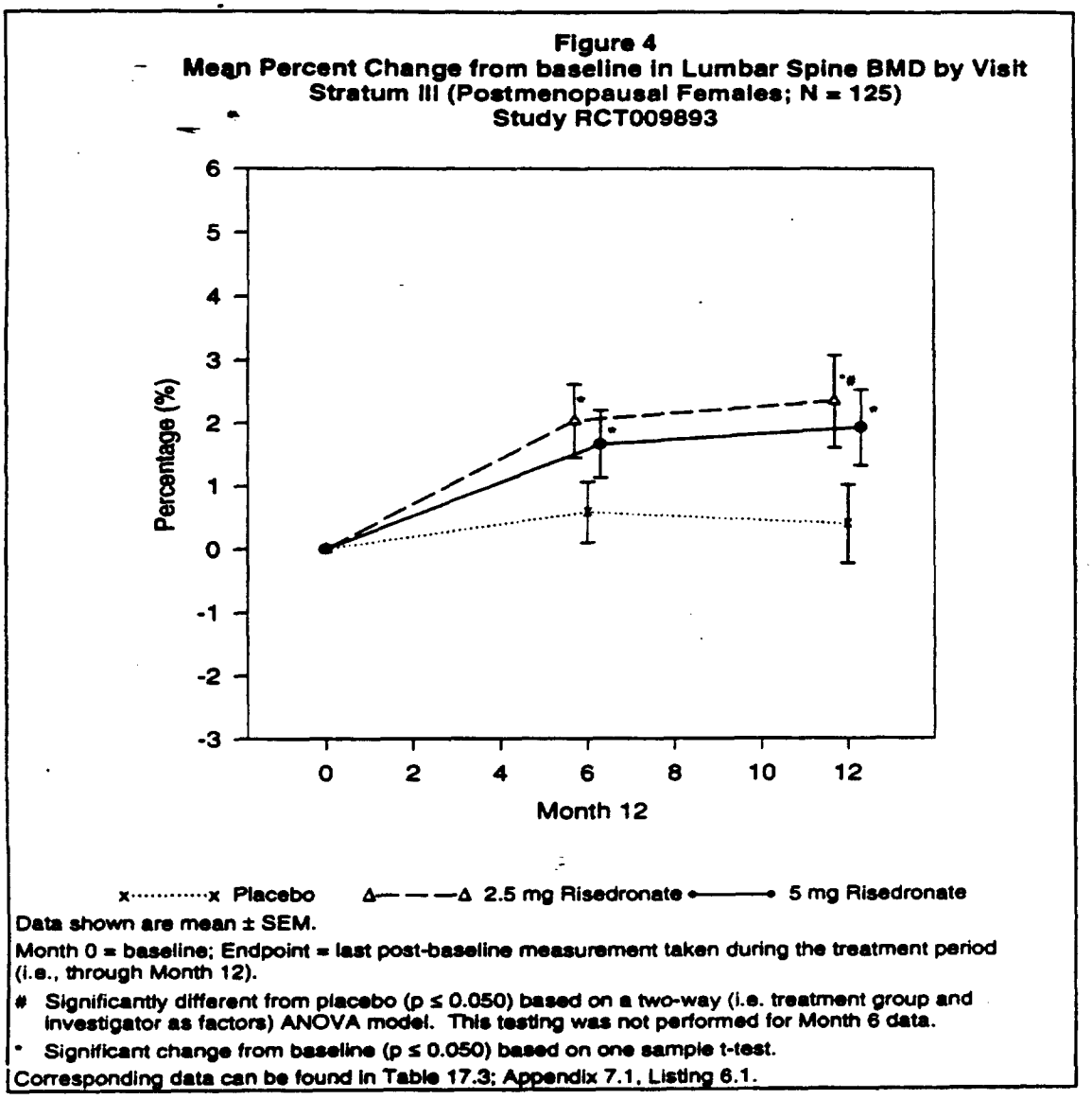


Figure 1.4 Mean % change from baseline in lumbar spine BMD by visit (Stratum III) - RCT 009893



Subgroup analysis on primary efficacy outcome

Demographic subgroup analysis results were presented. Table 1.4 (sponsor Panel-19 of vol.1.203) summarizes the sponsor's analysis by subgroup of age (<65 vs. ≥ 65 yrs), race (Caucasian vs. non-Caucasian), baseline iPTH level (< median vs. ≥ median), disease category (rheumatoid arthritis vs. lung diseases vs. other diseases), duration of pre-study glucocorticosteroid therapy (< median vs. ≥ median), and mean daily dose of pre-study glucocorticosteroid therapy (< median vs. ≥ median). Since more than 95% of patients were Caucasian, analysis of percent change from baseline in lumbar spine BMD by race may not be meaningful on non-Caucasian. The significant risedronate (5.0mg) effect appeared to be primarily attributed to patients who were less than 65 years of age, Caucasian, having baseline iPTH level ≥ median, under the disease category of rheumatoid arthritis, having duration of pre-study glucocorticosteroid therapy ≥ median, and having mean daily dose of pre-study glucocorticosteroid therapy < median.

Table 1.4 Mean % change from baseline in lumbar spine BMD at month 12 by subgroup – RCT009893

Panel 19

Mean Percent Change From Baseline in Bone Mineral Density of Lumbar Spine at Month 12 by Subgroup

Study RCT009893

Subgroup	Placebo		2.5 mg Risedronate		5 mg Risedronate		Overall P-Value[a]	2.5 mg Risedronate vs. Placebo		5 mg Risedronate vs. Placebo	
	N	Mean (S.E.)	N	Mean (S.E.)	N	Mean (S.E.)		LS Mean Difference (S.E.)	95% CI	LS Mean Difference (S.E.)	95% CI
Age											
< 65 Years	49	0.34 (0.491)	48	1.56 (0.538)*	58	2.74 (0.525)*	0.004	1.15 (0.764)	-0.350, 2.644	2.59 (0.762)[a]	1.100, 4.086
≥ 65 Years	17	0.70 (0.943)	22	2.56 (1.025)*	21	3.34 (1.151)*	0.472	1.03 (1.996)	-2.881, 4.943	2.23 (1.889)	-1.491, 5.952
Race											
Caucasian	64	0.41 (0.434)	69	1.88 (0.496)*	77	2.93 (0.501)*	<0.001	1.24 (0.692)	-0.112, 2.601	2.70 (0.682)[a]	1.367, 4.040
Non-Caucasian	2	1.10 (5.068)	1	1.20 (NA)*	2	1.66 (0.481)	NA	NA	NA	NA	NA
Baseline iPTH Level[b]											
< Median	31	0.90 (0.613)	34	1.97 (0.587)*	37	2.60 (0.677)*	0.153	0.83 (0.975)	-1.082, 2.741	1.88 (0.963)	-0.004, 3.771
≥ Median	30	-0.40 (0.631)	32	1.56 (0.829)	40	3.20 (0.736)*	0.007	1.14 (1.274)	-1.358, 3.638	3.60 (1.164)[a]	1.318, 5.880
Disease Category											
I - Rheumatoid Arthritis	29	0.08 (0.513)	27	1.96 (0.781)*	36	3.15 (0.746)*	0.011	1.62 (1.081)	-0.500, 3.736	3.24 (1.041)[a]	1.200, 5.283
II - Lung Diseases	12	1.38 (0.914)	14	1.09 (1.228)	15	2.46 (1.480)	0.787	0.59 (2.168)	-3.659, 4.840	1.57 (2.316)	-2.967, 6.111
III - Other Diseases	25	0.39 (0.887)	29	2.18 (0.736)*	28	2.82 (0.638)*	0.096	1.74 (1.158)	-0.530, 4.008	2.47 (1.135)[a]	0.241, 4.691[a]
Duration of Pre-Study Glucocorticosteroid Therapy[c]											
< Median	29	0.36 (0.789)	30	2.17 (0.757)*	43	2.79 (0.650)*	0.060	1.61 (1.095)	-0.535, 3.759	2.57 (1.065)[a]	0.477, 4.654
≥ Median	37	0.49 (0.479)	38	1.88 (0.641)*	36	3.04 (0.751)*	0.023	0.91 (0.915)	-0.881, 2.707	2.63 (0.953)[a]	0.767, 4.501
Mean Daily Dose of Pre-Study Glucocorticosteroid Therapy[d]											
< Median	35	0.76 (0.569)	35	2.64 (0.674)*	43	2.96 (0.629)*	0.015	1.99 (0.995)[a]	0.041, 3.941	2.71 (0.931)[a]	0.862, 4.530
≥ Median	31	0.06 (0.671)	33	1.34 (0.694)	36	2.84 (0.777)*	0.058	1.34 (1.003)	-0.627, 3.305	2.47 (1.022)[a]	0.466, 4.470

Secondary efficacy endpoints

BMD of femoral neck and BMD of femoral trochanter

The sponsor showed that there was a statistically significant difference among treatment groups in percent change from baseline in femoral neck BMD and femoral trochanter BMD at month-12. The difference between the 5.0mg risedronate group and placebo was statistically significant ($p<0.05$) at month-12 in femoral neck BMD and showed a numerical trend favoring risedronate in femoral trochanter BMD. The difference between the 2.5mg risedronate group and placebo was not statistically significant ($p>0.05$).

Reviewer Comments: Within individual study arms, there was no statistically significant mean percent change from baseline in the placebo and 2.5mg risedronate groups, but there was a significant change from baseline for the 5.0mg risedronate group at month-6 and month-12. It appeared that a significant increase from baseline in BMD of femoral neck and in BMD of femoral trochanter was observed in the 5.0mg risedronate group only.

BMD of distal radius

The sponsor claimed that neither of the active treatment groups showed a statistically significant difference in percent change from baseline compared with the placebo group. The within-treatment group 95% CI for the mean percent change from baseline in BMD of the distal radius did not demonstrate statistical significance at any time point for the active treatment groups. However, the 95% CI demonstrated statistical significance for the placebo group at Month-12, indicating a decrease from baseline.

Reviewer Comments: The trial period was two years. In the sponsor amendment 3, which was during the mid-course of the trial, i.e., about one year after trial initiation, [redacted] were deleted post-baseline. Therefore, only some patients may have had additional measurements taken prior to the implementation of amendment #3 to the protocol". The sponsor's analysis on the BMD of distal radius should be considered only exploratory in nature.

BMD responder analysis

For the lumbar spine, both active treatment groups had a significantly larger percent of responders than did the placebo group ($p=0.014$ and $p=0.003$ for the comparisons between 2.5mg risedronate and placebo and between 5.0mg risedronate and placebo, respectively). For the femoral neck and femoral trochanter, the 5.0mg risedronate group had a statistically significantly different proportion of responders than the placebo ($p=<0.001$ and 0.008, respectively), favoring risedronate.

Reviewer comments: The denominators for treatment groups in the BMD responder analysis performed by the sponsor were very similar to the number of patients completing the treatment periods shown in Table 1.1. This reviewer performed a robustness analysis using the ITT patients receiving at least one dose of study drug, but without adjustment on stratum, center and baseline BMD value. Results are summarized in Table 1.5.

It appeared that the results of this reviewer's analysis showed a 5% to 10% lower in responder rate with respect to lumbar spine, femoral neck and femoral trochanter outcomes. Statistical significance is consistent with the sponsor's conclusion. That is, statistically significantly higher responder rates were seen in the 5.0mg risedronate group (52% in lumbar spine, 43% in femoral neck, and 52% in femoral trochanter BMD) compared to the placebo (29% in lumbar spine, 19% in femoral neck, and 35% in femoral trochanter BMD) on all measurements of interest, but not so in the 2.5mg risedronate group (47% in lumbar spine with statistical significance, 28% in femoral neck and 25% in femoral trochanter BMD without statistical significance) after multiplicity adjustments.

Table 1.5 Reviewer results of the BMD responder analysis* - RCT009893

	Placebo (n=94)	2.5mg (n=92)	5.0mg (n=99)	Overall p-value	P-value (2.5mg vs. Pbo)	P-value (5.0mg vs. Pbo)
Lumbar Spine	27 (29%)	32 (47%)	51 (52%)	0.004	0.011	<0.001
Femoral Neck	18 (19%)	26 (28%)	43 (43%)	<0.001	0.144	<0.001
Femoral Troehanter	33 (35%)	23 (25%)	51 (52%)	<0.001	0.133	0.022

* no adjustment on stratum, center, and baseline BMD

Safety

A total of 12 patients died during the study (4 patients in the placebo group, 6 patients in the 2.5mg risedronate group, and 2 patients in the 5.0mg risedronate group). According to the sponsor, back pain, nausea, dyspepsia, arthralgia, depression, and dry mouth were reported more frequently in the 5.0mg risedronate group compared to placebo. Details of safety evaluation can be found in the medical reviewer's review. Concerns about the potentially increased risk of lung cancer in risedronate-treated patients are addressed in Section 3.

2.1.2 Reviewer Evaluation and Comments

- ***Impact of shortening study from 24 months to 12 months half-way after trial initiation***

The primary efficacy variable defined by the sponsor was percent change from baseline of lumbar spine BMD. The double-blind treatment period was 12 months, followed by a drug-free follow-up period of 12 months. According to the sponsor, the shortened study period was by removing the 12-month drug free period. Therefore, analysis of lumbar spine BMD at the end of treatment period (data at the one year time point per protocol definition), the primary efficacy outcome, and its conclusion based on the primary efficacy endpoint would not be affected by these later amendments.

- ***Validity of primary efficacy analysis***

The primary analysis for lumbar spine BMD at 12 months showed a statistically significant difference among the groups in mean percent change from baseline. The mean difference between the 5.0mg risedronate group and the placebo group was 2.68%. Risedronate 5.0mg daily for 12 months caused a statistically significant increase from baseline in lumbar spine BMD (2.9%), see Table 1.2.

The sponsor performed a 3-way ANOVA model including treatment, center (pooled), and stratum terms. If this overall test is significant at 0.05 level, then each treatment group is compared to placebo at the same 0.05 level. Such analysis approach is a closed testing procedure. Therefore, the experiment-wise type I error rate of 5% is controlled. This analysis is valid.

- ***Impact of early discontinuation on the primary efficacy analysis***

Percentage of early withdrawal showed a decreasing trend of 26% in placebo, 22% in 2.5mg risedronate arm and 18% in 5.0mg risedronate arm, see Table 1.1. The distribution of dropouts with respect to the reasons of treatment discontinuation was similar except a decreasing trend of 'voluntary withdrawal' (10% in placebo, 7% in 2.5mg group, 4% in 5.0mg group). From the primary efficacy analysis results of lumbar spine BMD shown in Table 1.2, it appeared that more than 95% of early discontinued patients withdrew from the study before month-6, but the percent of discontinuation due to adverse event was similar among the three groups.

The sponsor stated that in order for a BMD measurement to be included in the ITT analysis, the measurement had to have been taken within 8 weeks of the scheduled visit date. The sponsor's analysis results excluded patients who did not have (1) baseline BMD, (2) post-baseline BMD, (3) baseline radiograph, (4) post-baseline radiograph. From the study schema (Panel 2 of sponsor reports, p.20 of vol.1.203), BMD related post-baseline measurements were taken at month 6 and month 12. This reviewer

explored the baseline characteristics between the dropouts and the completers. It might be worth noting that baseline characteristics between dropouts and completers were somewhat different. From Table 1.6, it appeared that in contrast to completers, a greater percent of dropouts were males (48% vs. 35%, nominal p-value=0.050) and ever smokers (73% vs. 58%, nominal p-value=0.034).

Table 1.6. Comparison of baseline characteristics between early discontinued and completed patients

	RCT009893 (Europe)		
Completion Status	Completers	Dropouts	p-value*
Sample size	n=223(77%)	n=67(23%)	
Age			
< 51yr	27%	21%	0.328
51 - 65yr	44%	40%	
>= 65yr	30%	39%	
Smoking history			
Never	42%	27%	**0.034**
Ever	58%	73%	
Sex			
Male	35%	48%	**0.050**
Female	65%	52%	
Race			
Caucasian	97%	97%	0.620
Black	0.5%	1.5%	
Others	2.5%	1.5%	
Baseline Lumbar spine BMD	N=221	N=65	
Mean	933.8	985.3	0.030
SD	168.4	163.7	
Baseline femoral BMD	N=216	N=63	
Mean	0.69	0.68	0.476
SD	0.13	0.12	

* Chi-square test for categorical variables, and ANOVA for continuous variables

2.2 Trial RCP009993

Trial Design: This was to be a double-blind, stratified (by sex and menopausal status with 1=male patients, 2=premenopausal female patients, 3=postmenopausal female patients), randomized, parallel-group, placebo-controlled, multi-center (28 centers in North America) study. The study was conducted in ambulatory patients ≥ 18 years and ≤ 85 years of age, who had initiated treatment with glucocorticosteroids for rheumatoid arthritis, polymyositis, polymyalgia rheumatica, temporal arthritis, systemic lupus erythematosis, chronic interstitial lung disease, asthma, chronic obstructive pulmonary disease, skin disease (i.e. pemphigoid, pemphigus or dermatomyositis) or vasculitis requiring long-term corticosteroid treatment. Eligible patients were randomized to one of the three treatment arms: placebo once daily, 2.5mg risedronate once daily or 5.0mg risedronate once daily.

The study was originally planned for a 12-month treatment phase and a 12-month follow-up phase. During both phases, patients received 500mg elemental calcium daily. However, the 2.5mg risedronate treatment arm was removed by the sponsor [redacted] ' (p.8 of vol1.001) when the trial accrual was about 90% recruitement – to be commented on in Reviewer Evaluation and Comment Section 2.2.2.

Trial Objective: The primary objective of the study was to determine efficacy of risedronate versus placebo in maintaining or increasing lumbar spine bone mineral density (BMD) in patients initiating high dose corticosteroid therapy (≤ 3 months prior to study entry). The primary efficacy variable was BMD as measured by DXA of lumbar spine. Secondary variables were BMD of proximal femur; BMD of distal and mid-radius; proportion of responders to risedronate therapy in terms of lumbar spine, proximal femur, distal and mid-radius BMD; pharmacodynamic evaluations of bone turnover markers.

Trial period was from 4/25/94 to 12/11/96. There was one amendment, dated 2/94, before trial initiation, an amendment, dated 10/95, and an additional change to protocol, dated 3/97, after trial completion. Points in amendments after trial initiation and related to statistics evaluation were summarized by this reviewer, see Section 2.2.2 for Reviewer's Evaluation and Comment.

- The study was shortened from 24 months to 12 months by removing the 12-month drug-free period.
- The 2.5mg treatment arm was removed. The blind was maintained for the two remaining treatment arms (placebo and 5mg risedronate).
- Analysis of study results was changed to reflect the shortened study duration (24months to 12months) and elimination of one treatment arm (n=273 to n=231).
- [redacted] were deleted.
- Definition of prevalent and incident vertebral deformities was changed on 3/97.

Statistical Plan: Same as Trial RCT009893. The main treatment group comparison for each variable was to be based on data at the one year time point. Group comparisons at earlier time points will also be performed to explore possible earlier treatment group separation - to be commented on in Reviewer Evaluation and Comments Section 2.2.2.

The original protocol indicated that 91 patients per treatment arm would have at least 90% power to detect a 3% difference in percent change from baseline in lumbar spine BMD between 5mg risedronate and placebo assuming a common standard deviation of 5%, 35% dropout rates, and at 5% two-sided significance. In the October/95 protocol amendment, the sponsor stated that 77 patients per arm would be required assuming 18% dropout rate at the end of one year - to be commented on in Reviewer Evaluation and Comment Section 2.2.2.

The sponsor stated that the multiplicity issue does not apply since the 2.5mg arm was dropped and not used in the comparison - to be commented on in Reviewer Evaluation and Comments Section 2.2.2.

2.2.1 Sponsor Results and Reviewer Comments

Two hundred and twenty-eight patients were enrolled at 28 centers in North America, 4 patients withdrew prior to receiving any study drug. Of the 224 patients who were randomized and received study drug, 74 patients withdrew before completing the 12-month treatment period. Table 2.1 presents the disposition of the patients in this study. The sponsor considered the 23 patients in the 2.5mg risedronate arm who were dropped from the study per 10/95 amendment completed the treatment period. Of the 51 remaining withdrawals, 12 withdrew because of adverse experience, 16 patients violated the protocol, 15 patients withdrew voluntarily, 3 patients were lost to follow-up, and 5 patients withdrew for other reasons.

The sponsor's removal of the 2.5mg risedronate arm at 90% recruitment completion resulted in 42% patients completing 12-month treatment and 32% patients withdrawn from the study due to treatment

removal and 26% patients early discontinued due to reasons other than treatment removal, relative to the intended sample size of this arm. This indicated an equivalent completion rate of 74% for 2.5mg arm. Early discontinuation rates were slightly higher in placebo (25%) and 2.5mg risedronate arm (26%) than 5.0mg risedronate arm (17%). The distribution of dropouts with respect to reasons of withdrawal was similar among the three arms except a decreasing trend of voluntary withdrawal (8% in the placebo, 8% in the 2.5mg risedronate-arm, 4% in the 5.0mg risedronate arm, see Table 2.1).

Table 2.1 Patient Accountability* (Trial RCP009993)

	Placebo n (%)	2.5mg risedronate n (%)	5.0mg risedronate n (%)
Randomized	77	75	76
Received study drug	76	73	75
Completed 12-month treatment period**	57(75%)	31(42%)	62(83%)
Males (stratum-1)	20	9	25
Premenopausal female (stratum-2)	11	6	12
Postmenopausal female (stratum-3)	26	16	25
Amendment 10/95, completers	NA	23(32%)	NA
Discontinued treatment **	19(25%)	19(26%)	13(17%)
Adverse event	4(5%)	5(7%)	3(4%)
Protocol violation	6(8%)	5(7%)	5(7%)
Voluntary withdrawal	6(8%)	6(8%)	3(4%)
Lost to follow-up	1(1%)	1(1%)	1(1%)
Other	2(3%)	2(3%)	1(1%)

* Taken from sponsor panel 4: patient accountability in p.72 of vol.1.220.

** Percentage (%) was calculated based on patients who received study drug in each treatment group during the 12-month treatment period.

The three treatment arms were comparable in sex (34% male and 66% female), stratum (34% males. 20% premenopausal female and 46% postmenopausal female), race (majority were Caucasian, 88%), smoking status (37% previous user, 22% current users, and 41% never used with a mean total # of years smoked among ever smoker of 27.4 years), alcohol consumption (20% previous users, 40% current users, 40% never used with a mean total # of years alcohol consumed among ever drinker of 27.3 years), and percent of patients with prevalent vertebral deformities (30% from 68 patients with evaluable radiographs at baseline). Patients in the 5.0mg risedronate group appeared to have a higher mean age than patients in the other two treatment groups (nominal p=0.020). Patients in the 2.5mg risedronate group appeared to have a lower mean height and weight than patients in the other two arms. The sponsor stated that differences in age and height were not considered clinically significant.

Baseline BMD of lumbar spine, femoral neck, femoral trochanter, distal radius, and midshaft (1/3) radius were comparable across the three treatment arms and were comparable across the three treatment arms within each stratum (ref: panels 6 and 7 in p.75-77 of vol.1.220).

The most common conditions for which all randomized patients received glucocorticosteroid treatment were Rheumatoid Arthritis (39%), polymyalgia rheumatica (28%) and systemic lupus erythematosus (15%). All 224 patients (ITT) continued oral glucocorticosteroids during the study. The most common concomitant oral glucocorticosteroid therapy was prednisone. Of note, a higher percentage of patients in placebo was taking anticonvulsants (5%) compared to the 5mg group (0%). According to the sponsor, there were no clinically relevant differences among the three treatment groups with respect to concomitant medications that could impact the response to risedronate treatment or general safety profiles, and these medications were begun prior to baseline in most cases. With respect to patient compliance, the majority of patients were at least 80% compliant (93% in placebo, 89% in 2.5mg arm, and 94% in 5mg arm) (ref: Table 40.2 in vol.1.221). Non-compliance with the dosing schedule was highest during the first 3 months of the study. The sponsor stated that "the reason for this is unclear".

Primary efficacy endpoint – mean % change from baseline in BMD of the lumbar spine at month 12

The sponsor results on "mean percent change from baseline in BMD of the lumbar spine at month 12" are summarized in Table 2.2 (extracted from sponsor panel 17), see Figure 2.1(extracted from sponsor Figure1).

Reviewer Comments

From Table 2.2, it appeared that mean percent change from baseline at month 12 in lumbar spine BMD was significantly decreased in placebo-treated patients, and were not shown to increase BMD from baseline at one year in risedronate-treated patients. Majority of early withdrawal patients occurred in the first 6-months. Risedronate 2.5mg was removed before the end of the trial. Risedronate 5.0mg was shown to be no different from baseline.

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Table 2.2 Mean % change from baseline in lumbar spine BMD by visit - RCP009993

Panel 17

Percent Change From Baseline in Bone Mineral Density of the Lumbar Spine by Visit

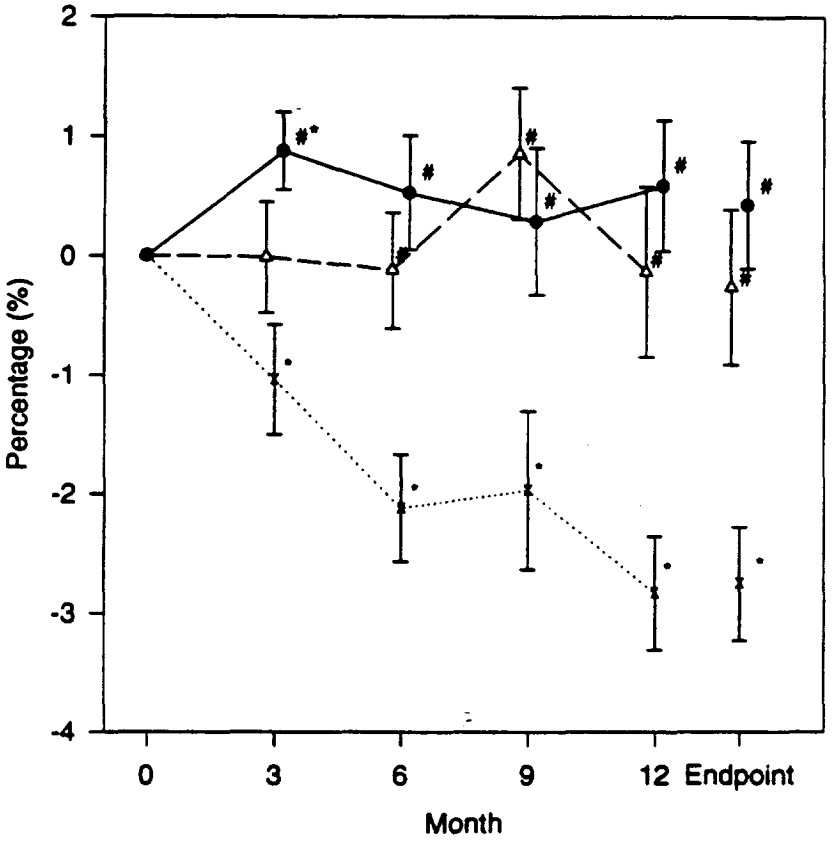
Study RCP009993

Treatment Group	Baseline BMD (g/cm^2)	Percent Change From Baseline				
		Month 3	Month 6	Month 9	Month 12	Endpoint[a]
Placebo						
N	73	46	56	34	52	57
Mean (S.E.)	1.020 (0.0227)	-1.04 (0.467)*	-2.12 (0.449)*	-1.97 (0.622)*	-2.83 (0.474)*	-2.75 (0.475)*
2.5 mg Risedronate[b]						
N	71	40	38	32	30	41
Mean (S.E.)	0.990 (0.2444)	-0.01 (0.463)	-0.12 (0.484)	0.86 (0.549)	-0.13 (0.713)	-0.26 (0.649)
5 mg Risedronate						
N	73	57	63	35	60	64
Mean (S.E.)	1.035 (0.2516)	0.88 (0.323)*	0.53 (0.481)	0.29 (0.619)	0.59 (0.548)	0.43 (0.534)
P-Value[c]	--	0.002	< 0.001	0.015	< 0.001	< 0.001
5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	2.04 (0.630)#	2.81 (0.665)#	2.53 (0.998)#	3.81 (0.781)#	3.51 (0.763)#
5 mg Risedronate vs. Placebo: 95% CI	--	0.791, 3.299	1.491, 4.133	0.525, 4.539	2.260, 5.363	1.996, 5.025
P-Value[d]	--	0.118	0.007	0.005	0.003	0.001
2.5mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	1.26 (0.795)	2.14 (0.772)#	3.03 (1.019)#	2.98 (0.954)#	3.03 (0.896)#
2.5 mg Risedronate vs. Placebo: 95% CI	--	-0.329, 2.851	0.598, 3.681	0.978, 5.086	1.067, 4.890	1.246, 4.818

[a] Endpoint is the last post-baseline measurement taken during the treatment period (i.e., through Month 12).
[b] This treatment group was discontinued per Amendment 2. Inferential statistics on this treatment group are presented here and discussed in Section 5.2.3.6.
[c] P-value for testing the difference between the 5-mg risedronate and placebo groups based on a three-way ANOVA model.
[d] Nominal p-value for testing the difference between the 2.5-mg risedronate and placebo groups based on a three-way ANOVA model.
* Significant change from baseline ($p \leq 0.050$) based on one-sample t-test.
# Significantly different from placebo ($p \leq 0.050$).
-- = Not applicable.
N at baseline includes all patients who had a value and a radiograph at baseline.
N at visits includes patients who had a value and a radiograph at baseline, a value at the visit, and a post-baseline radiograph.
Corresponding data can be found in Table 12.3; Appendix 7.1, Listing 6.1.

Figure 2.1 Mean % change from baseline in lumbar spine BMD by visit - RCP009993

Figure 1
Mean Percent Change from Baseline in Lumbar Spine BMD by Visit
Study RCP009993



x·····x Placebo Δ— — —Δ 2.5 mg Risedronate* •——• 5 mg Risedronate

Data shown are mean ± SEM.

Month 0 = baseline; Endpoint = last post-baseline measurement taken during the treatment period (i.e., through Month 12).

* This treatment group was discontinued per Amendment 2. Separate inferential statistics on this treatment group compared to placebo are presented in Section 5.2.3.6, but the nominal significance is indicated here for completeness (see Section 4.8).

\# Significantly different from placebo ($p \leq 0.050$) based on a three-way ANOVA model.

* Significant change from baseline ($p \leq 0.050$) based on one sample t-test.

Corresponding data can be found in Tables 12.3 A and 12.3B; Appendix 7.1, Listing 6.1.

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Table 2.3 Mean % change from baseline in lumbar spine BMD by visit and stratum – RCP009993

Panel 18

Percent Change From Baseline in Bone Mineral Density of the Lumbar Spine by Visit and Stratum

Study RCP009993

	Baseline BMD (g/cm^2)			Percent Change from Baseline					
				Month 6			Month 12		
	Stratum I	Stratum II	Stratum III	Stratum I	Stratum II	Stratum III	Stratum I	Stratum II	Stratum III
Placebo									
N	25	15	33	20	12	24	19	10	23
Mean (S.E.)	1.057 (0.0385)	1.101 (0.0324)	0.956 (0.0355)	-2.10 (0.687)*	-2.21 (0.860)*	-2.09 (0.789)*	-3.38 (0.783)*	-1.59 (0.626)*	-2.91 (0.807)*
2.5 mg Risedronate									
N	24	15	32	13	8	17	9	6	15
Mean (S.E.)	1.052 (0.0442)	1.103 (0.0362)	0.891 (0.0321)	0.08 (1.086)	-1.46 (1.228)	0.36 (0.395)	0.34 (1.254)	-0.07 (1.409)	-0.44 (1.127)
5 mg Risedronate									
N	27	14	32	24	13	26	24	12	24
Mean (S.E.)	1.134 (0.0385)	1.070 (0.0361)	0.936 (0.0404)	1.06 (0.576)	0.71 (0.781)	-0.06 (0.967)	0.76 (0.606)	-0.19 (1.318)	0.81 (1.063)
Overall P-value[a]	--	--	--	--	--	--	0.001	0.187	0.012
5 mg Risedronate vs. Placebo: LS Mean Difference (S.E.)	--	--	--	--	--	--	4.42 (1.210)[#]	2.43 (1.698)	3.92 (1.471)[#]
5 mg Risedronate vs. Placebo: 95% CI	--	--	--	--	--	--	1.919, 6.912	-1.413, 6.269	0.918, 6.917

[a] P-value for testing the difference among treatments based on a two-way ANOVA model.
Stratum I = males; Stratum II = premenopausal females; Stratum III = postmenopausal females.
* Significantly different from baseline ($p \leq 0.050$) based on one-sample t-test.
# Significantly different from placebo ($p \leq 0.050$)
N at baseline includes all patients who had values at baseline.
N at visits includes patients who had a value at baseline and visit.
-- = Not applicable
Corresponding data can be found in Table 17.3; Appendix 7.1, Listing 6.1.

Figure 2.2 Mean % change from baseline in lumbar spine BMD by visit (Stratum I:Male) – RCP009993

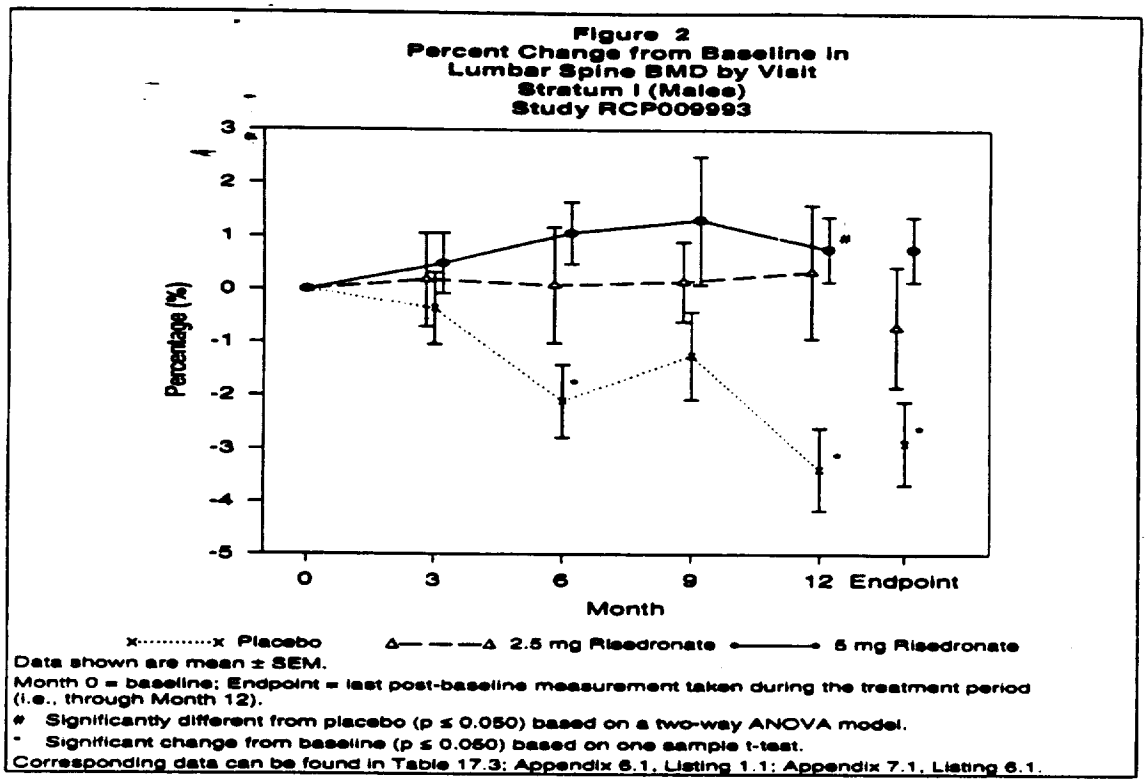


Figure 2.3 Mean % change from baseline in lumbar spine BMD by visit (Stratum II) – RCP009993

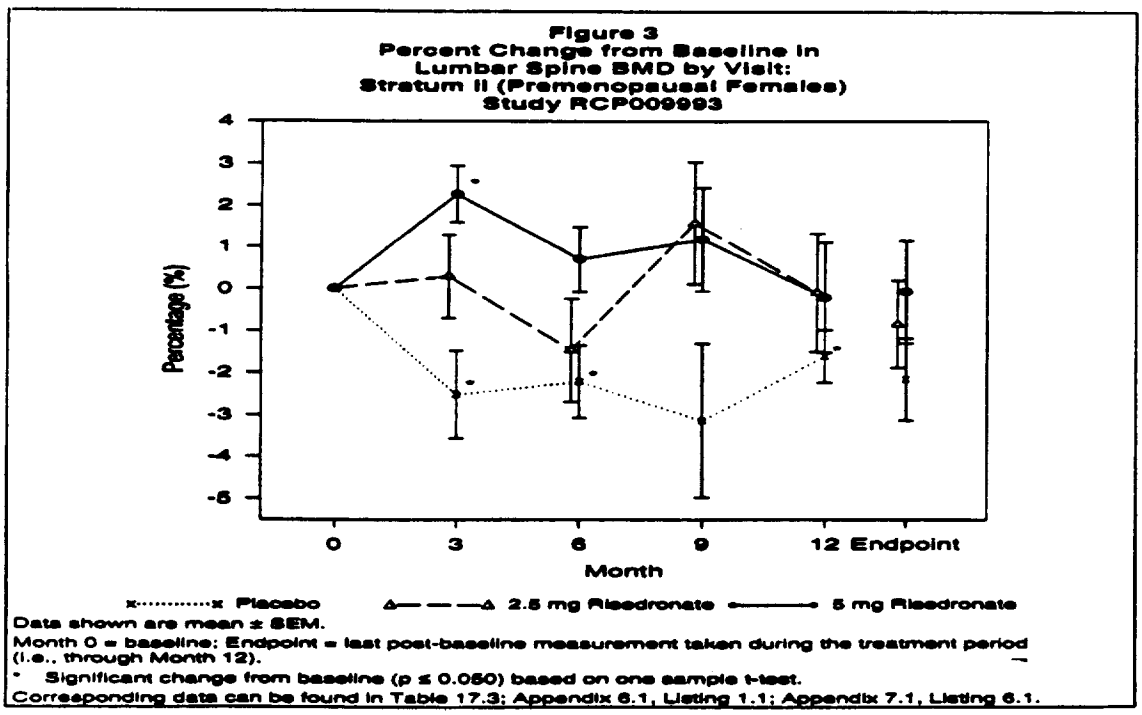
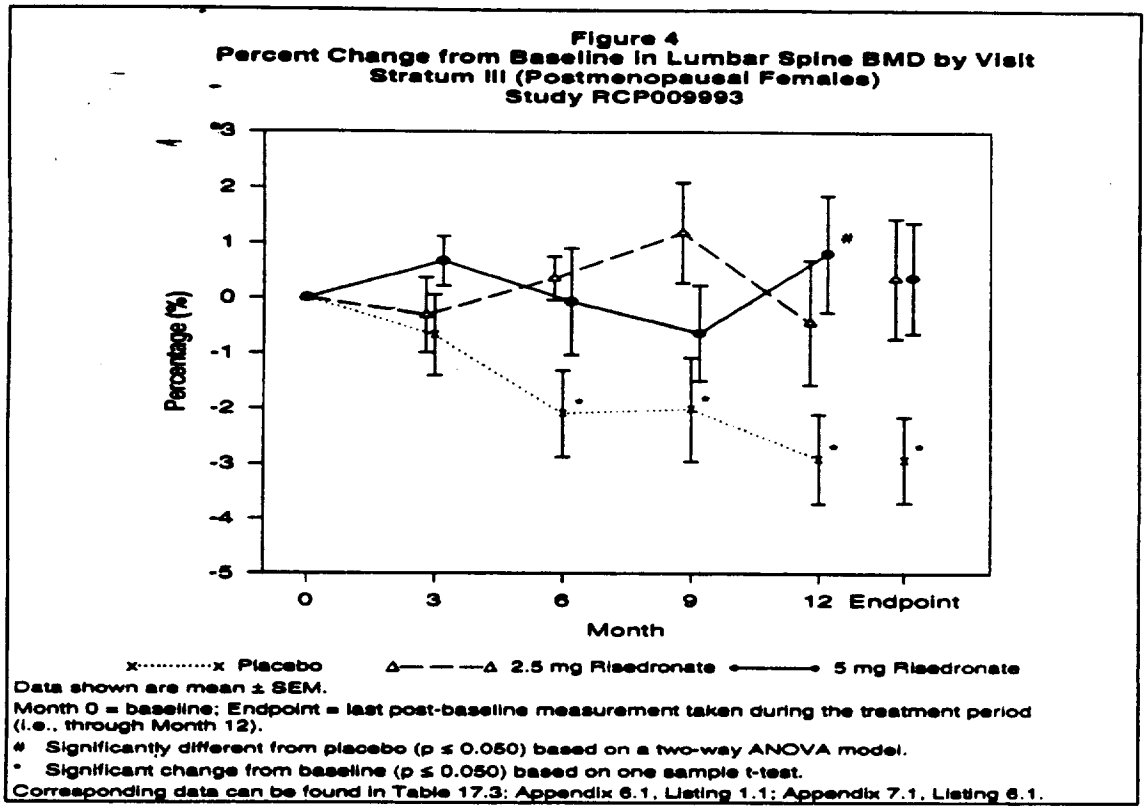


Figure 2.4 Mean % change from baseline in lumbar spine BMD by visit (Stratum III) – RCP009993



Mean percent change from baseline in lumbar spine BMD by stratification

The results of percent change from baseline of lumbar spine BMD within each stratum are summarized in Table 2.3 (sponsor panel-18, vol.1.220), also see Figures 2.2 (male), 2.3 (pre-menopausal female) and 2.4 (post-menopausal female).

Reviewer Comments: In general, the sponsor subgroup analysis results based on stratification factor at randomization showed that on average, risedronate-treated patients, either 2.5mg or 5.0mg, seemed to have maintained their lumbar spine BMD at one year compared to their baseline in males, pre-menopausal females, and post-menopausal females subgroups. This is consistent with the overall finding on percent change from baseline at one year in lumbar spine BMD.

Subgroup analysis on primary efficacy outcome

Demographic subgroup analysis results were presented. Table 2.4 (from sponsor Panel-19 of vol.1.220) summarizes the sponsor's analysis by subgroup of race (Caucasian vs. non-Caucasian), age (<65 vs. ≥ 65 years), disease category (rheumatoid arthritis vs. lung diseases vs. other diseases), duration of pre-study glucocorticosteroid therapy (< median vs. ≥ median), mean daily dose of pre-study glucocorticosteroid therapy (< median vs. ≥ median), mean daily dose of concomitent glucocorticosteroid therapy (< median vs. ≥ median) and baseline BMD. It seemed that significant risedronate (5.0mg) effect was homogeneous in subgroups explored except those with few patients.

Table 2.4 Mean % change from baseline in lumbar spine BMD at month 12 by subgroup – RCP009993

Panel 19

Percent Change From Baseline in Bone Mineral Density of Lumbar Spine at Month 12 by Demographic Subgroup

Study RCP009993

Subgroup	Placebo		2.5 mg Risedronate[a]		5 mg Risedronate		5 mg Risedronate vs. Placebo		
	N	Mean (S.E.)	N	Mean (S.E.)	N	Mean (S.E.)	P-Value[b]	LS Mean Difference (S.E.)	95% CI
Race									
Caucasian	49	-2.81 (0.493)*	26	-0.62 (0.755)	53	0.80 (0.607)	< 0.001	4.15 (0.838)#	2.483, 5.819
Non-Caucasian	3	-3.18 (1.975)	4	3.06 (1.455)	7	-0.98 (0.804)	0.047	--	--
Age									
< 65 Years	29	-2.35 (0.684)*	16	-0.08 (0.865)	29	0.62 (0.702)	0.003	3.83 (1.212)#	1.376, 6.290
≥ 65 Years	23	-3.42 (0.630)*	14	-0.19 (1.202)	31	0.56 (0.844)	0.004	4.20 (1.362)#	1.422, 6.969
Disease Category[c]									
I (Rheumatoid Arthritis)	19	-2.70 (0.886)*	10	-1.44 (1.199)	23	0.30 (0.800)	0.081	2.99 (1.641)	-0.400, 6.389
II (Lung Diseases)	1	-4.15 (--)	2	3.63 (1.790)	3	-0.08 (1.290)	--	--	--
III (Other Diseases)	32	-2.86 (0.572)*	18	0.18 (0.922)	34	0.85 (0.804)	< 0.001	4.53 (1.015)#	2.487, 6.577
Duration of Pre-Study Glucocorticosteroid Therapy[d]									
< Median	31	-2.89 (0.594)*	11	0.95 (1.261)	27	1.55 (0.816)	< 0.001	5.66 (1.004)#	3.627, 7.692
≥ Median	21	-2.74 (0.797)*	19	-0.75 (0.851)	33	-0.19 (0.723)	0.039	2.53 (1.172)#	0.139, 4.918
Mean Daily Dose of Pre-Study Glucocorticosteroid Therapy[e]									
< Median	25	-2.09 (0.668)*	17	-1.55 (0.853)	32	1.04 (0.846)	0.013	3.37 (1.300)#	0.737, 5.996
≥ Median	27	-3.51 (0.655)*	13	1.73 (1.030)	28	0.08 (0.671)	< 0.001	4.06 (1.072)#	1.876, 6.238
Mean Daily Dose of Concomitant Glucocorticosteroid Therapy[f]									
< Median	25	-2.71 (0.657)*	19	-0.87 (0.876)	32	1.03 (0.772)	0.002	3.87 (1.183)#	1.472, 6.270
≥ Median	27	-2.94 (0.691)*	11	1.15 (1.175)	28	0.09 (0.779)	0.019	2.90 (1.178)#	0.506, 5.300
Baseline BMD[g]									
< Median	29	-3.15 (0.672)*	17	-0.01 (1.137)	24	0.52 (1.071)	0.005	4.34 (1.450)#	1.387, 7.286
≥ Median	23	-2.42 (0.662)*	13	-0.28 (0.764)	36	0.64 (0.584)	0.004	3.25 (1.053)#	1.119, 5.390

[a] This treatment group was discontinued per Amendment 2. Data are displayed but are not included in treatment comparisons.
[b] Based on a three-way ANOVA model.
[c] Disease Category I = Rheumatoid Arthritis; II = Lung Diseases, III = Other Diseases.
[d] Median duration of pre-study glucocorticosteroid therapy = 0.13 years.
[e] Median daily dose of pre-study glucocorticosteroid therapy = 13.56 mg.
[f] Median daily dose of concomitant glucocorticosteroid therapy = 8.93 mg.
[g] Median baseline BMD = 1.017 g/cm^2.
* Significant change from baseline ($p \leq 0.050$) based on one-sample t-test.
# Significantly different from placebo ($p \leq 0.050$).
-- = Missing or not applicable.
Corresponding data can be found in Tables 17.1, 17.2, 17.4 - 17.8; Appendix 6.1, Listings 1.1 and 3.1; Appendix 7.1, Listing 6.1.

Secondary efficacy endpoints

BMD of femoral neck and BMD of femoral trochanter

The sponsor showed that there was a statistically significant difference between the 5.0mg risedronate treatment and the placebo in mean percent change from baseline in femoral neck BMD ($p<0.001$) and femoral trochanter BMD ($p<0.001$) at month-12, favoring risedronate. With the 2.5mg risedronate arm, no significant difference to the placebo in mean percent change from baseline at month 12 was found in BMD of femoral neck ($p=0.195$), but a significant difference was shown in BMD of femoral trochanter ($p=0.004$).

Reviewer Comments: For BMD of femoral neck, there was no statistically significant mean percent change from baseline at month 12 in either the 2.5mg or 5.0mg risedronate group, but there was a significant decrease in the placebo group. For BMD of femoral trochanter, a statistically significant decrease from baseline at month 12 in the placebo group was seen, while 5.0mg risedronate group showed a statistically significant increase in mean percent change from baseline at month 12. Comparison between 2.5mg group to placebo is only exploratory.

BMD responder analysis

In this study, a responder of lumbar spine BMD, femoral neck or trochanter BMD is a patient who did not show a decrease in corresponding measurements by the end of the study or up to the time of discontinuation. Based on the above criteria, 5.0mg risedronate group had a significantly greater proportion of responders than did the placebo group in lumbar spine BMD ($p<0.001$), in femoral neck ($p<0.001$) and in femoral trochanter ($p<0.001$), favoring risedronate, but not in the 2.5mg risedronate group.

Reviewer comments: The denominators for treatment groups in the BMD responder analysis performed by the sponsor were similar to the number of patients completing treatment period shown in Table 2.1. This reviewer performed a robustness responder analysis using the ITT patients receiving at least one dose of study drug, but without adjustments on stratum, center and baseline BMD value. Results are summarized in Table 2.5.

It appeared that the results of this reviewer's analysis showed a 2% to 22% lower rate of responders in lumbar spine, in femoral neck and in femoral trochanter outcomes. Statistical significance is consistent with the sponsor conclusion. That is, statistically significantly higher responder rates were seen in the 5.0mg risedronate group compared to placebo on all measurements of interests, but not in 2.5mg risedronate group. Comparison between the 2.5mg group to placebo is only descriptive.

Table 2.5 Reviewer results of BMD responder analysis*

	Placebo (n=76)	2.5mg (n=73)	5.0mg (n=75)	Overall p-value	P-value (2.5mg vs. Pbo)	P-value (5.0mg vs. Pbo)
Lumbar Spine	13 (17%)	20 (27%)	35 (47%)	0.0003	0.1325	<0.0001
Femoral Neck	14 (18%)	32 (44%)	36 (48%)	0.0002	0.0008	<0.0001
Femoral Trochanter	17 (22%)	30 (41%)	46 (61%)	<0.0001	0.0142	<0.0001

* no adjustment on stratum, center, or baseline BMD

Safety

Overall, five deaths were reported in this study. Three patients died after being discontinued for AEs, and two patients died after completing the treatment period. Details of safety analysis can be found in the medical officer's review. Concerns about potentially increased risk of lung cancer in risedronate-treated patients are addressed in Section 3.

2.2.2 Reviewer Evaluation and Comments

- ***Impact of shortening study from 24 months to 12 months half-way after trial initiation***

The primary efficacy variable defined by the sponsor was percent change from baseline of lumbar spine BMD. The double-blind treatment period was 12 months followed by a drug-free follow-up period of 12 months. According to the sponsor, the shortened study period was by removing the 12-month drug free period. Therefore, analysis of lumbar spine BMD at the end of treatment period (data at the one year time point per protocol definition), and its conclusion based on the primary efficacy endpoint would not be affected by these later amendments except possibly differential early withdrawals caused by moderate numerical differential dropout rates.

- ***Interim analysis***

From the sponsor's October/95 amendment, data from this protocol would be submitted to an external safety advisory group, who would, on an annual basis, or as required, unblindedly review safety data from the risedronate program. This group would not have the right to terminate the study for early efficacy results. However, the protocol also stated that "Group comparisons at earlier time points will be performed to explore possible earlier treatment group separation". There was no report on results of interim analyses included in this NDA submission. Although the protocol called for possible interim analyses, the sponsor presented results over 3-month intervals, viz., 3-, 6-, 9-, 12-month, and endpoint (protocol specified) without mentioning any interim analysis ever performed. According to the schema, BMD measurements of the lumbar spine were taken at baseline and Months 6 and 12. It appeared that had one interim analysis been performed at month-6, p-values reported for the endpoint analysis would still be statistically significant using a more conservative interim rule of O'Brien and Fleming (ref: panel 17, p.91 of vol.1.203 and p.266).

- ***Impact of dropping 2.5mg arm at 90% recruitment***

Using the sponsor results at endpoint of Table 2.2 as the point of illustration, original statistical decision rule should not be altered due to termination of the 2.5mg risedronate arm during the course of the trial. Global test of no differences among the three treatment arms in mean percent change from baseline of lumbar spine BMD at one year yielded a p-value <0.001. The 5.0mg arm vs. placebo comparison resulted in a p-value <0.001. These results are highly significant. Using either the closed test principle or two pairwise comparisons each being tested at two-sided 0.025 level, statistical significance for the comparison between 5.0mg risedornate arm versus placebo in mean percent change from baseline of lumbar spine BMD at one year still holds.

- ***Sample size reestimation at about 90% recruitment***

The trial was initiated on 4/25/94 and completed on 12/11/96. The sponsor amended the sample size from 91 patients per arm to 77 patients per arm on October/95, which was about 1.5yr after trial initiation and a little more than one year before trial completion. Justification of sample size reestimation was on a change of dropout rate from 35% to 18%. Meanwhile, the sponsor amended the protocol to remove the lower dose risedronate group (2.5mg). If the sample size was modified without breaking the blinded treatment assignment, the type I error rate would still be controlled. If sample size changed was based on the observed treatment contrast, the type I error rate would be affected to some extent. Since p-values of global test and the comparison of 5.0mg arm versus placebo were highly significant (< 0.001), the potential effect is not likely to negate the statistical significance.

- ***Impact of early discontinuation***

As in Study RCT 009893, in order for a BMD measurement to be included in the ITT analysis, the measurement had to have been taken within 8 weeks of the scheduled visit date. The sponsor's analysis results excluded patients who did not have (1) baseline BMD, (2) post-baseline BMD, (3) baseline

radiograph, (4) post-baseline radiograph. From the study schema (Panel 2 of sponsor reports, vol.1.220), BMD related post-baseline measurements were taken at month 6 and month 12. It appeared that these early withdrawal patients (23%) were mostly dropped out from the study before month 6. From Table 2.2, primary efficacy analysis results at month-6, at month-12 and at endpoint were very similar due to the sponsor's criteria of the ITT analysis. The conclusion drawn from the sponsor's primary efficacy analysis that the 5.0mg risedronate is effective in comparison to the placebo still holds since early discontinuation rate was higher in the placebo group (25%) than in the 5.0mg risedronate arm (17%), and distributions of early withdrawal were similar among the three arms studied. From Table 2.6, it is seen that baseline characteristics between dropouts and completers were somewhat different. It appeared that in contrast to placebo, a greater percentage of dropouts were females (78% vs. 62%, nominal p-value=0.027) and Black (12% vs. 2%, nominal p-value=0.014).

Table 2.6. Comparison of some baseline characteristics between early withdrawal and completed patients

	RCP009993 (North America)		
Trial Completion Status	Completers, n=169(74%)	Dropouts, n=59 (26%)	p-value*
Age			
< 51yr	27%	34%	0.318
51 - 65yr	27%	31%	
>= 65yr	47%	36%	
Smoking history			
Never	41%	39%	0.744
Ever	59%	61%	
Sex			
Male	38%	22%	**0.027**
Female	62%	78%	
Race			
Caucasian	91%	81%	**0.014**
Black	2%	12%	
Others	7%	7%	
Baseline Lumbar spine BMD	N=167	N=54	
Mean	1053.9	1086.4	0.318
SD	203.0	220.4	
Baseline femoral BMD	N=166	N=54	
Mean	0.73	0.74	0.831
SD	0.15	0.15	

* Chi-square test for categorical variables; ANOVA for continuous variables

3. EVALUATION OF LUNG CANCER RISK

3.1 Early termination of 2.5mg Risedronate Study Group

Although two studies were submitted for the CIO indication, there were a total of 10 studies reported by the sponsor regarding the lung cancer issue. In four of ten trials, the lower dose of 2.5mg risedronate arm was terminated during the course of the trial.

From the sponsor's response of June 18, 1999, the four trials were RCP009993 of CIO indication, ROE009493, RVE009093 and RVN008993 of prevention and treatment of postmenopausal osteoporosis indication. To determine the sample size in each arm at the time of dropping, the sponsor calculated it by determining the number of patients within each investigator site who were in the study on the date when the first 2.5mg patient completed according to the protocol amendment at that center. The total "sample size in each arm at the time of dropping" was then calculated by adding up the counts across the investigator sites. Table 3.1 displays the relative size between sample sizes in each arm as randomized compared to the sizes at the time of dropping.

Table 3.1. Summary of trials in which the 2.5mg risedronate arm was terminated during the trial period

	Start End (Trial period)	Sample size as randomized	Amendment date[*1]	Time since trial start	'n' at the time of dropping[*2]	Frozen date[*3]	% of 'n'[*4]
RCP009993	04/25/94 -12/11/96		10/10/95	1.5yr		01/02/98	
Pbo	(~2.5yr)	77			61		79%
2.5mg ris		75			55		73%
5.0mg ris		76			57		75%
ROE009493	04/19/94 -04/11/97		12/06/95	>1.5yr		10/30/97	
Pbo	(~3yr)	180			160		89%
2.5mg ris		184			160		87%
5.0mg ris		179			156		87%
RVE009093	03/04/94 -03/25/98		12/06/95	1.75yr		06/22/98	
Pbo	(~4yr)	408			279		68%
2.5mg ris		410			289		70%
5.0mg ris		408			281		69%
RVN008993	12/03/93 -01/19/98		10/10/95	<2.0yr		05/08/98	
Pbo	(~4yr)	820			628		77%
2.5mg ris		817			626		77%
5.0mg ris		821			633		77%

[*1] amendment date of dropping the 2.5mg Risedronate arm

[*2] sample size at the time of dropping the 2.5mg risedronate defined by the sponsor submission date 6/18/99

[*3] date the database was frozen for analysis

[*4] % of sample size available at the time of dropping

Among the four trials in which the 2.5mg risedronate arm was terminated during the trial period, the duration between the timing of trial initiation and the amendment ranged from 1.5 to 2.0 years corresponding to approximately half way of the trial period. Percents of patients available at the time of terminating the 2.5mg risedronate treatment were similar within trials (73% to 79% in RCP009993, 87% to 89% in ROE009493, 68% to 70% in RVE009093, and 77% in RVN008993), but varied across trials. It is noted that while the sponsor gave ———— for dropping the 2.5mg risedronate treatment, the percent of patients available at the time of terminating the lower dose 2.5mg treatment ranged from 70% to 87%, a high percentage of sample size available. Given that the percentages of patients available were similar among the three treatment arms within each trial in which the 2.5mg risedronate arm was terminated, an observation of increased risk of lung cancer incidence was made in the 2.5mg risedronate arm compared to placebo. For details, see Section 3.2.

It is not clear why the sponsor decided to drop the lower dose of 2.5mg arm during the courses of the trials in the four studies. From the efficacy review of the CIO indication, the sponsor's efficacy evaluation of Trial RCP009993, whose 2.5mg was terminated, seemed to indicate effectiveness of the primary efficacy endpoint relative to placebo ($p<0.001$, see Table 2.2), given available patients at the time of terminating the 2.5mg risedronate arm.

3.2 Increased Lung Cancer Risk in Risedronate-Treated Patients

From the sponsor's submission of safety data on eight clinical trials, the medical division noted a numerically-increased risk of lung cancer seen in risedronate-treated patients, particularly in the low dose 2.5mg group as well as a numerically-decreased risk of gastrointestinal cancer. The medical division further requested the sponsor to submit two other trials just completed for further investigation of the increased lung cancer rate. Following is a comprehensive statistical evaluation regarding this issue.

3.2.1 Brief summary of interaction between the sponsor, Dr. Richard Simon, and the review team

The sponsor requested to meet with the medical division on February 19, 1999 and on May 24, 1999 to discuss the disproportionate number of lung cancer cases seen in the risedronate group versus the placebo group in the risedronate phase III trials.

In addition, the medical division invited Dr. Richard Simon of the National Cancer Institute (NCI) on May 28, 1999 to consult on the possible excess of lung cancer risk. Eight studies had been submitted to this NDA; these studies showed numerically more lung cancer cases in risedronate-treated patients compared to placebo. The medical division then requested the sponsor to submit two additional studies recently completed for further evaluation. The medical division was concerned that this might be an issue for the biosphosphonate drug class in general. The medical division requested summary data on lung cancer cases and time in study prior to diagnosis of lung cancer from other bisphosphonate drugs, i.e., alendronate (including smoking history), etidronate, and tiludronate.

Regarding the numerical excess of lung cancer risk, Dr. Simon suggested that the original eight trials could be considered as a hypothesis generation. To test the hypothesis of a significantly increased lung cancer risk of the bisphosphonate drug class, one may consider looking at the two other studies later submitted and combining them with other bisphosphonate drugs for a confirmatory analysis. Please refer to a memorandum dated July 30, 1999 in response to Dr. Stadel's request for calculation of p-values on "lung cancer in clinical trials of bisphosphonates for osteoporosis". During the discussion, Dr. Simon also suggested that number of lung cancer incidence cases could be considered to follow a Poission distribution.

Since the numerical excess of lung cancer cases seen in the risedronate-treated patients, particularly in the 2.5mg risedronate arm, was not one of the objectives stated in the protocol plan for investigation, this reviewer conducted an in-depth evaluation. This reviewer incorporated Dr. Simon's suggestion, but applied it to just the risedronate evaluation. First, the sponsor's originally submitted eight trials were evaluated. Secondly, two additional studies were utilized to serve as some kind of confirmation. However, it should be noted that the study population was much older in the two hip fracture studies compared to the original eight trials. Thus, this reviewer took the totality of evidence from the ten trials submitted by the sponsor as the main focus for evaluation. Given that lung cancer risk of risedronate was not prespecified a priori, cancer risk by COSTART reported by the sponsor was evaluated. Findings of a decreased GI cancer risk and an increased lung cancer risk were further evaluated. This reviewer conducted in-depth analyses on death rate, time to death, patients with lung cancer or GI cancer among death, and moderate to high early withdrawal rate. This reviewer also evaluated the potential excess of lung cancer risk using a Bayesian view mentioned by Dr. Simon for breast cancer evaluation at an advisory committee meeting in 1997 and an epidemiologic view explored by the sponsor. The 2.5mg and 5.0mg risedronate arms were analyzed as is. It is noted that the 2.5mg arm was terminated in 4 of 10 trials at about 70% to 87% data completion and had similar or lower dropout rates compared to placebo.

3.2.2 Reviewer's evaluation of cancer risk in risedronate

In the ten double-blind placebo-controlled phase III clinical trials submitted, patients were randomized to one of the treatment arms. Treatment period within each trial varies from 1 to 2 years. Sample sizes among the placebo, 2.5mg and 5.0mg risedronate arm were similar, indicating that the results of analysis based on calculation of person-years per patient would be similar to those based on the number of patients studied, provided that there was no apparent differential early discontinuation.

This reviewer performed statistical analyses in two ways. One is the usual clinical adverse event approach of "Yes/No" a patient has lung cancer, and the other uses that number of lung cancer incidence cases follows a Poisson distribution as suggested by Dr. Simon. When the interest lies in proportion of patients having lung cancer during the trial period, the odds ratio, defined as ratio of odds of having lung cancer in the treated group to odds of having lung cancer in the placebo group, and its 95% confidence interval along with its nominal significance level will be presented. On the other hand, if Poisson rates are compared, the relative risk (RR), defined as ratio of incidence of lung cancer in the treated group to incidence of lung cancer in placebo, and its 95% confidence interval along with its nominal significance level will be summarized.

The total electronic database submitted by the sponsor regarding lung cancer risk has n=15797 patients from 10 trials. Of which, 233 patients had their time to lung cancer in days missing, one patient (subject id=41430002 of Trial RHE009293) in the 5mg risedronate arm had lung cancer and had the time to lung

cancer missing. Of the 233 patients, 5 of them did not have early withdrawal reasons. All 233 patients had at least one of the treatment start date and last visit date missing.

3.2.2.1 Sponsor's Original Safety Database of 8 trials

The sponsor reported lung cancer incidence per 1,000 person-years by trial and by dosage. This reviewer verified the results based on the sponsor's electronic database with small differences in total person-years calculation, see Table 3.2 and Table 3.4. In addition, this reviewer also tabulated the proportion of patients having lung cancer (per 1,000 persons) during the trial period, see Table 3.2 and Table 3.3.

Table 3.2. Lung Cancer summary in Risedronate from eight Phase III Trials [*1]

	PLACEBO				2.5mg Risedronate				5.0mg Risedronate			
Study	# rand.	Pyrs	#/1000 cases[*2]	#/1000 pyrs	# rand.	Pyrs	#/1000 cases^	#/1000 pyrs	# rand.	Pyrs	#/1000 cases [*2]	#/1000 pyrs
RBL004494	126	214	0 (0.0)	0.0	128	220	1 (7.8)	4.5	129	234	1 (7.8)	4.3
RCP009993[*3]	77	78	0 (0.0)	0.0	75	64	0 (0.0)	0.0	76	78	1 (13.2)	12.8
RCT009893	96	96	0 (0.0)	0.0	94	98	2 (21.3)	20.4	100	108	0 (0.0)	0.0
ROE009493[*3]	180	322	0 (0.0)	0.0	184	281	2(10.9)	7.1	179	307	1 (5.6)	3.3
RON009393	220	272	0 (0.0)	0.0	212	275	1 (4.7)	3.6	216	276	1 (4.6)	3.6
RPE002494	261	223	0 (0.0)	0.0	na	na	na	na	263	234	1 (3.8)	4.3
RVE009093[*3]	408	952	1 (2.5)	1.1	410	867	1 (2.4)	1.2	408	967	2 (4.9)	2.1
RVN008993[*3]	820	1850	1 (1.2)	0.5	817	1021	5 (6.1)	4.9	821	1906	3 (3.7)	1.6
Total [*4]	2188	4007	2 (0.9)	0.5	1920	2826	12 (6.3)	4.2	2192	4110	10 (4.6)	2.4

[*1] extracted from sponsor Table 4a of May 24, 1999 presentation
[*2] lung cancer cases (proportion of patients having lung cancer in per 1000 patients unit during trial period)
[*3] the 2.5mg risedronate arm was terminated during the course of the trial
[*4] these eight trials were from the original NDA submission

Table 3.3 Comparison on proportions of patients with lung cancer between placebo & risedronate in 8 trials

	Placebo n=2188	2.5mg ris n=1920	5.0mg ris n=2192	Nominal p-value [*1] (pooled)	Nominal p-value [*1] (stratified)	p-value [*2] 2.5mg vs. placebo	p-value [*2] 5.0mg vs. placebo
Lung cancer Cases	2	12	10				
Proportion [*3]	0.9	6.3	4.6	0.0074	0.0113	0.0161	0.0415

[*1] nominal p-value of the global test on lung cancer risk among the 3 arms
[*2] pairwise comparison adjusting for trial
[*3] Proportion of patients (in 1,000 persons unit) having lung cancer occurrence during the trial period

First, this reviewer performed the usual comparison of clinical adverse events that a patient either has lung cancer during the trial period or was free of lung cancer. Under the null hypothesis of no differential proportions of lung cancer among the three arms, the global test yielded a p-value of 0.0074 without stratifying on trials and a p-value of 0.0113 with stratifying. By adjusting trial differences, pairwise comparisons between 2.5mg vs. placebo with odds ratio and its 95% CI of 6.6 (1.4 to 30.7) and 5.0mg vs. placebo with odds ratio and its 95% CI of 5.0 (1.1 to 23.5) were both nominally significant, p=0.0161 and p=0.0415, respectively. Homogeneity across trials was tested and the result showed that there was no apparent heterogeneity across trials (p=0.678 for 2.5mg vs. placebo and p=0.937 for 5.0mg vs. placebo).

When Poisson rates calculated using person-years were used, the relative risk was 8.2 (95% CI of 1.8 to 37.1, asymptotic approach) in 2.5mg risedronate-treated patients compared to placebo. Noted that the odds ratio for this comparison was 6.6. The odds ratio (5.0) and the relative risk (4.9) were similar in the comparison between the 5.0mg risedronate and the placebo, using either the proportion approach or the Poisson rate approach. These two comparisons were both nominally statistically significant with p=0.0066 for 2.5mg risedronate vs. placebo and p=0.0405 for 5.0mg risedronate vs. placebo with asymptotic test. It is noted that result was slightly more significant with the exact test than with the asymptotic test, see Table 3.4.

Table 3.4 Comparison on lung cancer rates by person-years between placebo vs. risedronate across 8 trials

	Placebo pyrs=3939[*1]	2.5mg ris pyrs=2783[*1]	5.0mg ris prys=4038[*1]	p-value(asym)[*2] 2.5mg vs. pbo	p-value (asym)[*2] 5.0mg vs. pbo
Lung cancer Cases	2	12	10		
Poisson rate [*3]	0.5	4.3	2.5	0.0016 (0.0066)	0.0387 (0.0405)

[*1] Applied the algorithm used by the sponsor, i.e., if exposure time >1100 days, then exposure time=1100 days, if exposure time < 0, then exposure time=2 days, then normalize the exposure time in years by dividing exposure time by 365.25.

[*2] exact p-value (asymptotic p-value)

[*3] Incidence of lung cancer per 1,000 person-years during the trial period

3.2.2.2 Sponsor's two additional Trials (hip fracture) just completed in the middle of sNDA evaluation

The sponsor was asked to submit two hip fracture studies (RHE009293 and RHN009193) in view of the significant excess risk of lung cancer seen in the risedronate-treated patients. According to the sponsor, [redacted] that patient population in these two trials were generally older than those eight trials evaluated above.

This reviewer summarized and verified the sponsor's lung cancer reports in these two studies with a minor difference in time in study prior to known lung cancer incidence, see Tables 3.5 and 3.6.

Table 3.5. Lung Cancer reports in two hip fracture Risedronate Phase III Trials [*1]

	PLACEBO				2.5mg Risedronate				5.0mg Risedronate			
Study	# rand.	Pyrs	#/1000 cases	#/1000 pyrs	# rand.	Pyrs	#/1000 cases	#/1000 pyrs	# rand.	Pyrs	#/1000 cases	#/1000 pyrs
RHE009293	1520	3124	3 (2.0)	1.0	1518	3087	7 (4.6)	2.3	1511	3084	4 (2.6)	1.3
RHN009193	1664	3357	8 (4.8)	2.4	1633	3250	17 (10.4)	5.2	1651	3331	6 (3.6)	1.8
Total [*2]	3184	6481	11(3.5)	1.7	3151	6337	24 (7.6)	3.8	3162	6415	10 (3.2)	1.6

[*1] extracted from sponsor Table 4a of May 24, 1999 presentation

[*2] these two trials were from medical division's additional request

A global test of no difference among the three arms in terms of proportion of lung cancer cases yielded a p-value of 0.0204 using pooled analysis and a p-value of 0.0206 using analysis stratified by two trials. Further pairwise comparisons showed that the difference was pronounced in the 2.5mg risedronate vs. placebo (p=0.0295) and not in the 5.0mg risedronate vs. placebo (p=0.8407) comparison. The results of analysis with Poisson rate assumption gave similar p-values of pairwise comparisons, as shown in Table 3.6. There was no statistical evidence that the proportions of patients having lung cancer during the trial periods were heterogeneous across the two studies (p=0.929 for 2.5mg risedronate vs. placebo and p=0.537 for 5.0mg risedronate vs. placebo). The odds ratio and its 95% CI was 2.2 (1.1, 4.5) for the 2.5mg risedronate relative to placebo and 0.9 (0.4, 2.2) for the 5.0mg risedronate relative to placebo.

Table 3.6 Comparison on lung cancer risk between placebo and risedronate in the two hip fracture trials

	Placebo N=3184 Pyrs=6372	2.5mg ris n=3151 pyrs=6226	5.0mg ris n=3162 pyrs=6311	Nominal p-value[*1] (pooled)	Nominal p-value[*1] (stratified)	p-value[*2] 2.5mg vs. placebo	p-value[*2] 5.0mg vs. placebo
Lung cancer Cases	11	24	10				
Proportion [*3]	3.5	7.6	3.2	0.0204	0.0206	0.0295	0.8407
Poisson Rate [*3]	1.7	3.9	1.6			0.0267[*4]	0.8443[*4]

[*1] nominal p-value of the global test on lung cancer risk among the 3 arms

[*2] pairwise comparison adjusting for trials was performed after significance shown from the global test

[*3] proportion of patients (in 1,000 persons unit) having lung cancer occurrence during the trial period

[*4] asymptotic test of Mantel-Haenszel inference on common relative risk adjusting for trial differences.

Since analysis results based on proportion of lung cancer cases versus Poisson rates by person-years were similar in terms of statistical significance, this reviewer will report the analysis results using proportion approach for the rest of the evaluation. Breslow and Day (1980) and others pointed out that when proportions are very small, relative risk is well approximated by odds ratio of the disease probabilities - the ratio of the odds of disease occurrence in the exposed group (risedronate-treated patients) and non-exposed sub-groups (placebo-treated patients). This reviewer reported odds ratio and its 95% CI when appropriate.

3.2.2.3 Sponsor's total database of the 10 trials on GI cancer and lung cancer occurrence

3.2.2.3.1 GI Cancer Evaluation

The sponsor and the medical division observed a numerically decreased risk of GI cancer in risedronate-treated patients. This reviewer performed a global test on GI cancer risk among the 3 arms. Based on the global test, there was no statistical significance found (nominal p-value ranged from 0.100 to 0.219, see Table 3.7). Since the global test was not significant, no pairwise comparisons were performed. Note that our specific interest with respect to cancer occurrence evaluation was on GI and lung cancers. If one were to adjust for multiplicity due to the fact that two cancer risks were evaluated, adjusted p-values would be twice higher than those shown in Table 3.7. While there was a numerical trend in decreased risk of GI cancer over placebo, 2.5mg to 5.0mg risedronate, the trend was not statistically significant.

Table 3.7 Comparison of GI cancer among placebo, 2.5mg, and 5.0mg risedronate across trials

	Placebo # Prop[*1] Incid[*2]	2.5mg ris # Prop[*1] Incid[*2]	5.0mg ris # Prop[*1] Incid[*2]	Nominal p-value[*3] (pooled)	Nominal p-value[*3] (stratified)
Original 8 trials Odds Ratio (95%CI)	12 5.5 3.1	4 2.1 1.4 0.4 (0.1,1.2)	10 4.6 2.5 0.8 (0.4, 1.9)	0.219	0.164
2 hip trials Odds Ratio (95%CI)	29 9.1 4.6	21 6.7 3.4 0.7 (0.4,1.3)	17 5.4 2.7 0.6 (0.3, 1.1)	0.196	0.196
Total evidence Odds Ratio (95%CI)	41 7.6 4.0	25 4.9 2.8 0.6 (0.4, 1.1)	27 5.0 2.6 0.7 (0.4, 1.1)	0.120	0.100

[*1] Proportion of patients (in 1,000 persons unit) having GI cancer occurrence during the trial period
[*2] Incidence of GI cancer per 1,000 person-years
[*3] Nominal p-value of the global test on GI cancer risk among the 3 arms

3.2.2.3.2 Lung Cancer Evaluation

Table 3.8 Comparison of lung cancer risk among placebo, 2.5mg, and 5.0mg risedronate across trials

	Placebo # Prop[*1] Incid[*2]	2.5mg ris # Prop[*1] Incid[*2]	5.0mg ris # Prop[*1] Incid[*2]	Nominal p-value[*3] (pooled)	Nominal p-value[*3] (stratified)
Original 8 trials Odds Ratio (95%CI) [*4]	2 0.9 0.5	12 6.3 4.3 6.6 (1.4, 30.7)	10 4.6 2.5 5.0 (1.1, 23.5)	0.0074	0.0113
2 hip trials Odds Ratio (95%CI) [*4]	11 3.5 1.7	24 7.6 3.9 2.2 (1.1, 4.6)	10 3.2 1.6 0.9 (0.4, 2.2)	0.0204	0.0206
Total evidence Odds Ratio (95%CI) [*4]	13 2.4 1.3	36 7.1 4.0 2.9 (1.6, 5.7)	20 3.7 1.9 1.6 (0.8, 3.2)	0.0012	0.0017

[*1] Proportion of patients (in 1,000 persons unit) having lung cancer occurrence during the trial period
[*2] Incidence of lung cancer per 1,000 person-years
[*3] Nominal p-value of the global test on lung cancer risk among the 3 arms
[*4] Odds ratio was obtained by adjusting for trials evaluated

Analysis of the original 8 trials, analysis of the 2 hip fracture trials, and analysis of all 10 trials were tabulated in Table 3.8. This reviewer performed a global test on lung cancer risk among the 3 arms. The global test indicated a significant increase in lung cancer risk (common odds ratio estimate after adjustment of 10 trials was 2.9 with 95% CI of 1.6 to 5.7) in the 2.5mg risedronate-treated patients. The 2 hip fracture studies also showed a significant increase. However, for the 5.0mg risedronate-treated patients, statistical significance was not shown in the 2 hip fracture studies. A numerical increase of 1.6 times higher (95% CI of 0.8 and 3.2) of lung cancer risk was seen in 5.0mg risedronate arm after adjustment of 10 trials. The results based on the pooled analysis and the stratified analysis were similar. For details, see Table 3.8. It is noted that diagnosis of lung cancer was not a required procedure defined in the protocol.

3.2.2.3.3 Was the increased lung cancer risk mainly due to factors other than risedronate treatment?

3.2.2.3.3.1 Probabilistic View

The sponsor presented the distribution of cancer cases by COSTART. Specific sites were bladder, breast, endometrial, GI, leukemia, Lung, Lymphoma, Myeloma, and skin, see Table 3.9. This reviewer calculated the odds ratio and the relative risk for cancer risk in general, as in the last row of Table 3.9. When COSTART cancer risk was evaluated without breaking down to specific cancer site, odds ratio and relative risk were similar. From 95% CI estimates, it appeared that there was a numerically increased cancer risk of 0.9 to 1.4 times higher in 2.5mg risedronate than in placebo, and no apparently increased risk seen (from 0.7 to 1.2) in 5.0mg risedronate versus placebo.

Table 3.9 Distribution of cancer cases by COSTART reported by the sponsor from all 10 trials

Cancer Type	Placebo N=5,372 Pyrs=10,488	2.5mg risedronate n=5,071 pyrs=9,163	5.0mg risedronate n=5354 pyrs=10,525
Bladder	4	9	2
Breast	35	39	28
Endometrial	6	4	7
GI	41	24	27
Leukemia	5	5	4
Lung	13	36	20
Lymphoma	6	4	6
Myeloma	4	3	5
Skin	97	91	106
Total [*1]	144	151	133
# / 1000 cases	26.8	29.8	24.8
(Odds ratio) [*2]		**1.1 (0.9, 1.4)**	0.9 (0.7, 1.2)
# / 1000 yrs	13.7	16.5	12.6
(relative risk) [*2]		**1.2 (1.0, 1.5)**	0.9 (0.7, 1.2)

[*1] Excluding non-melanotic skin cancer

[*2] Odds ratio estimate and relative risk estimate with 95% CI calculated by this reviewer

What may be the major cancer site contributing to the potentially increased cancer risk seen in 2.5mg risedronate compared to placebo? When a more liberal type I error rate of say 5% for every cancer risk evaluated without multiplicity adjustments was considered, only lung cancer from 9 cancer sites listed in Table 3.9 would be identified. If one were to specifically test for possible decreased GI cancer risk and possible increased lung cancer risk, significantly increased risk of lung cancer would be the only site identified. In this reviewer's analyses summarized in Tables 3.2 to 3.8, the increased risk of lung cancer was highly statistically significant in the comparison between the 2.5mg risedronate and placebo. There was only a numerical increase seen in the 5.0mg risedronate arm.

Was any imbalance seen between the 2.5mg risedronate arm versus placebo and the 5.0mg risedronate arm?

This reviewer explored potential baseline imbalance and potential death rate imbalance among the placebo, 2.5mg and 5.0mg risedronate-treated patients. Smoking history of never (60%), prior (13%), versus current (27%) smoker was similar among the three arms, nominal p=0.395. That is, on average, approximately 40% of patients were ever smokers in all 10 trials studied. Male:female ratio (99:1) was the same (p=0.918) among the three arms. Age distribution at baseline, required by the FDA of <65yrs versus ≥ 65yrs, was significantly different between 2.5mg risedronate-treated patients (84%) versus placebo/5.0mg risedronate-treated patients (81%), nominal p<0.001. Menopausal status was also significantly different between 2.5mg risedronate-treated patients (98% female postmenopausal) versus placebo/5.0mg risedronate-treated patients (93% female postmenopausal), nominal p<0.001. The above summary is only descriptive, indicating that the 2.5mg risedronated treated patients had a higher percent of patients who were at least 65 years of age and that higher percent of patients was female postmenopausal.

Cumulative Incidence of Lung Cancer and Cumulative Incidence of GI cancer

The medical division requested the sponsor to perform analyses of cumulative incidence of lung cancer and GI cancer among the three arms. This reviewer summarized the sponsor's report in Table 3.10, also see Figure 3.1 for lung cancer (the sponsor's Figure 1) and Figure 3.2 for GI cancer (the sponsor's Figure 2).

Table 3.10 Summary of the p-values of test for cumulative incidences of lung cancer and GI cancer*

	Global test	2.5mg vs. placebo	5.0mg vs. placebo
Lung Cancer	P<0.001	P<0.001	P=0.295
GI Cancer	P=0.160	P=0.115	P=0.091

* p-values were reported by the sponsor from all 10 trials

SEE THE ATTACHED FIGURE 3.1 (THE SPONSOR'S FIGURE 1) FOR LUNG CANCER AND FIGURE 3.2 (THE SPONSOR'S FIGURE 2) FOR GI CANCER INCIDENCE EVALUATION

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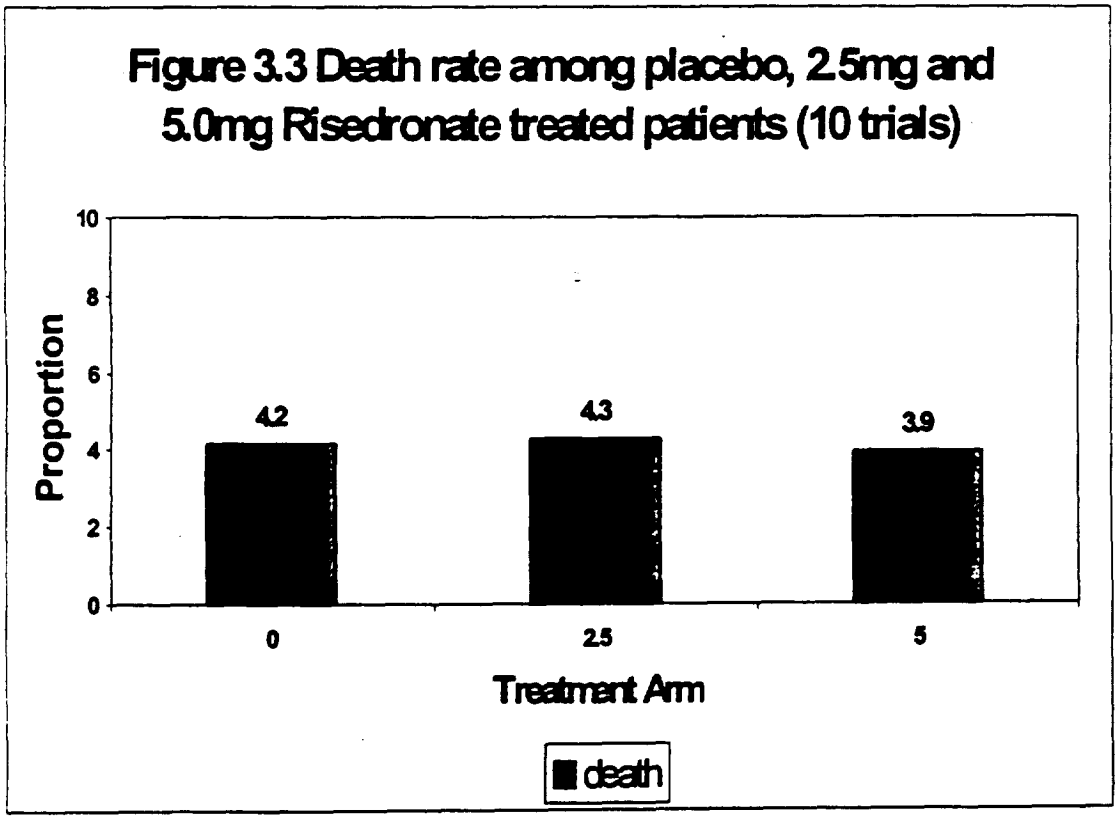
Is lung cancer risk associated with death rate?

Table 3.11 Distribution of death, lung cancer, and GI cancer across 10 trials

	Placebo (n=5372)	2.5mg ris (n=5071)	5.0mg ris (n=5354)
Death rate	224 (4.2%)	216 (4.3%)	211 (3.9%)
GI cancer risk	0.8%	0.5%	0.5%
GI cancer among death	4.5%	3.2%	2.8%
GI cancer and died	0.2%	0.1%	0.1%
Lung cancer risk	0.2%	0.7%	0.4%
Lung cancer among death	3.6%	7.9%	3.3%
Lung cancer and died	0.2%	0.3%	0.1%

This reviewer summarizes the distribution of death rate, lung cancer risk, and GI cancer risk across all 10 trials. Death rates among the placebo (4.2%), 2.5mg risedronate (4.3%), and 5.0mg risedronate (3.9%) arms were similar, see Figure 3.3. From Sections 3.2.2.3.1, 3.2.2.3.2 and Table 3.11, GI cancer risks among the placebo (0.8%), 2.5mg risedronate (0.5%) and 5.0mg risedronate (0.5%) arms were not statistically significantly different with nominal p=0.12 from pooled analysis and p=0.10 from an analysis stratified by trial. Lung cancer risk, on the other hand, was significantly higher in the 2.5mg risedronate arm (0.7%), less so in the 5.0mg risedronate arm (0.4%) than the placebo arm (0.2%), p=0.0012 from pooled analysis and p=0.0017 from stratified analysis.



Given that death rates were similar among the three arms, differential lung cancer risks were still seen when patients were categorized into "lung cancer and died" (0.2% in placebo, 0.3% in 2.5mg risedronate arm, and 0.1% in 5.0mg risedronate arm).

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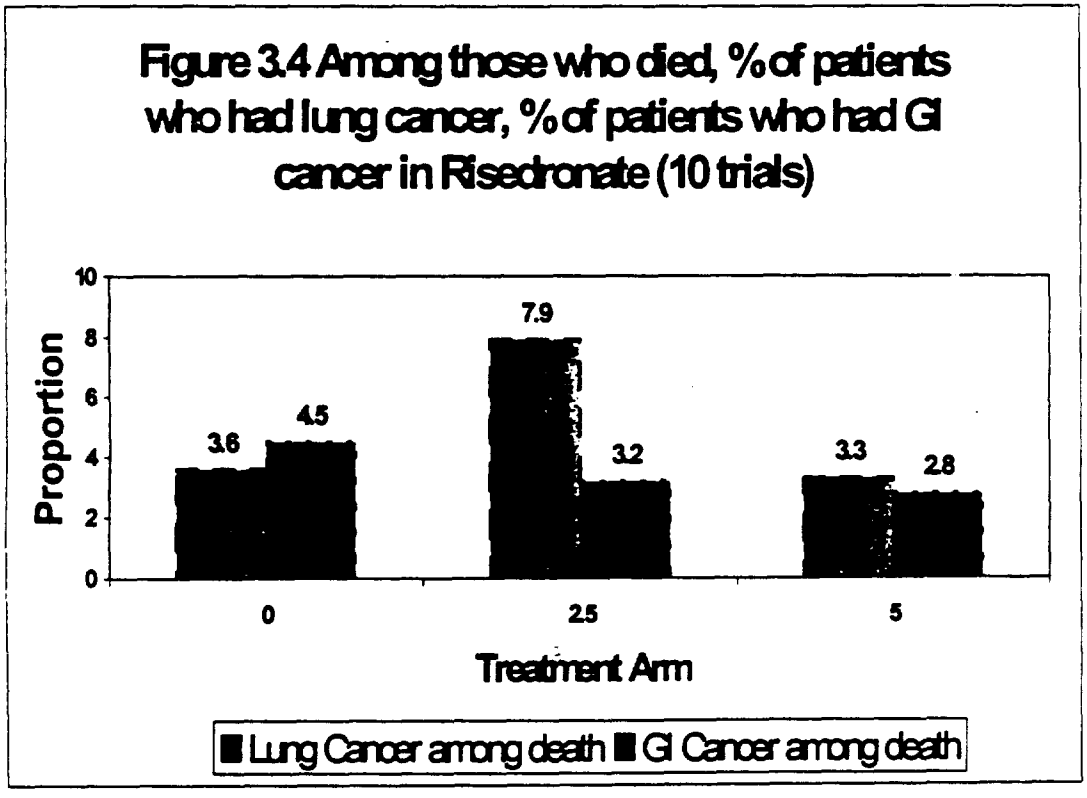
It is noted that among those who died (224 in placebo, 216 in 2.5mg risedronate arm, and 211 in 5.0mg risedronate arm) in these 10 phase III clinical trials, percent of patients who had lung cancer though they might not die of lung cancer was more than twice higher in the 2.5mg risedronate arm (7.9%) than either the 5.0mg risedronate arm (3.3%) or the placebo arm (3.6%), see Table 3.11 and Figure 3.4. Of those 32 patients who had lung cancer and died, none of them had GI cancer, one was a male, remaining 31 patients were all female and postmenopausal. Reasons of early withdrawal of those patients who had lung cancer and died were coded as "adverse event", "other reasons", and "voluntary withdrawal". As for GI cancer, among those who died, percents of patient having GI cancer were 4.5% in placebo, 3.2% in 2.5mg risedronate, and 2.8% in 5.0mg risedronate.



Time to Death

The medical division was interested in exploring if there are differences among the three arms in terms of time to death. Since patients who had lung cancer or GI cancer during the trial and who eventually withdrew from the trial had their reasons of withdrawal coded as voluntary withdrawal, other reasons, and adverse event, the distribution of time to death may not properly reflect patients' alive status at the end of the trial because of early discontinuing patients had not been followed through the end of the trial. It is worthwhile to note that there were a total of 69 patients who had lung cancer during the trial. From the electronic database of all 10 trials submitted by the sponsor, among the 26 patients who had lung cancer and who died during the trials, 22 patients had their time to onset of death in days identical to their time to lung cancer in days, the other 4 patients had their time to onset of death missing.

It is also troubling that there were 4 patients who had lung cancer during the trial but whose time to onset of death was earlier than their time to lung cancer.

Table 3.12 Early discontinuation rates among the placebo, 2.5mg, 5.0mg risedronate arms from 10 trials*

Trials	Placebo % (#dropped/n)	2.5mg risedronate % (#dropped/n)	5.0mg risedronate % (#dropped/n)	Total % (#dropped/n)
CIO-indication				
RCP009993**	27.3% (21/77)	**29.3%** (22/75)	21.1%(16/76)	25.9%(59/228)
RCT009893	27.1% (26/96)	23.4% (22/94)	19.0%(19/100)	23.1%(67/290)
PMO-indication				
ROE009493**	20.6% (37/180)	**19.0%** (35/184)	22.4% (40/179)	20.6% (112/543)
RON009393	25.0% (55/220)	17.9% (38/212)	21.8% (47/216)	21.6% (140/648)
RBL004494	26.2% (33/126)	21.9% (28/128)	20.2% (26/129)	22.7% (87/383)
RPE002494	29.1% (76/261)	-----	24.7% (65/253)	26.9% (141/524)
RVE009093**	43.1%(176/408)	**34.9%** (143/410)	35.5% (145/408)	37.9% (464/226)
RVN008993**	45.1%(370/820)	**26.9%** (220/817)	40.4% (332/821)	37.5% (922/2458)
RHE009293	48.4%(735/1520)	50.3% (764/1518)	48.7% (736/1511)	49.1% (2235/4549)
RHN009193	51.8%(862/1664)	53.3% (870/1633)	51.2% (846/1651)	52.1% (2578/4948)
Total	44.5%(2391/5372)	42.2%(2142/5071)	42.4%(2272/5354)	43.1%(6805/15797)

* Based on total randomized patients

** The 2.5mg risedronate treatment was terminated

This reviewer further summarized the early discontinuation rates by trials from the sponsor' electronic database, see Table 3.12. Dropout rates were calculated based on total patients randomized. Among these 10 trials, the highest dropout rates were seen in the two hip fracture trials (49.1% in RHE009293 and 52.1% in RHN009193). That is, half of the randomized patients discontinued early from the hip fracture trials. It is followed by the two vertebral fracture trials (RVE009093 and RVN008993), in which placebo had the highest dropout rates (43% to 45%) followed by the 5.0mg risedronate arm (35% to 40%), then the 2.5mg risedronate arm (27% to 35%). Even though the 2.5mg risedronate arm had the lowest dropout rates, the sponsor terminated the 2.5mg risedronate treatment at about 70% to 77% patients data available for analysis in these two vertebral fracture trials. The remaining six trials had dropout rates ranging from 18% to 29% and the rates were not too different among the placebo, 2.5mg and 5.0mg risedronate arms within individual trials. Still, the sponsor terminated the 2.5mg risedronate treatment at about 73% patients data available for analysis in Trial RCP009993 and about 87% patients data available for analysis in Trial ROE009493. It is difficult to rationalize the sponsor's terminating the 2.5mg risedronate treatment in four out of 10 trials, given that the 2.5mg risedronate arm had either a similar dropout rate as the 5.0mg risedronate arm or a similar or smaller dropout rate than placebo within individual trials.

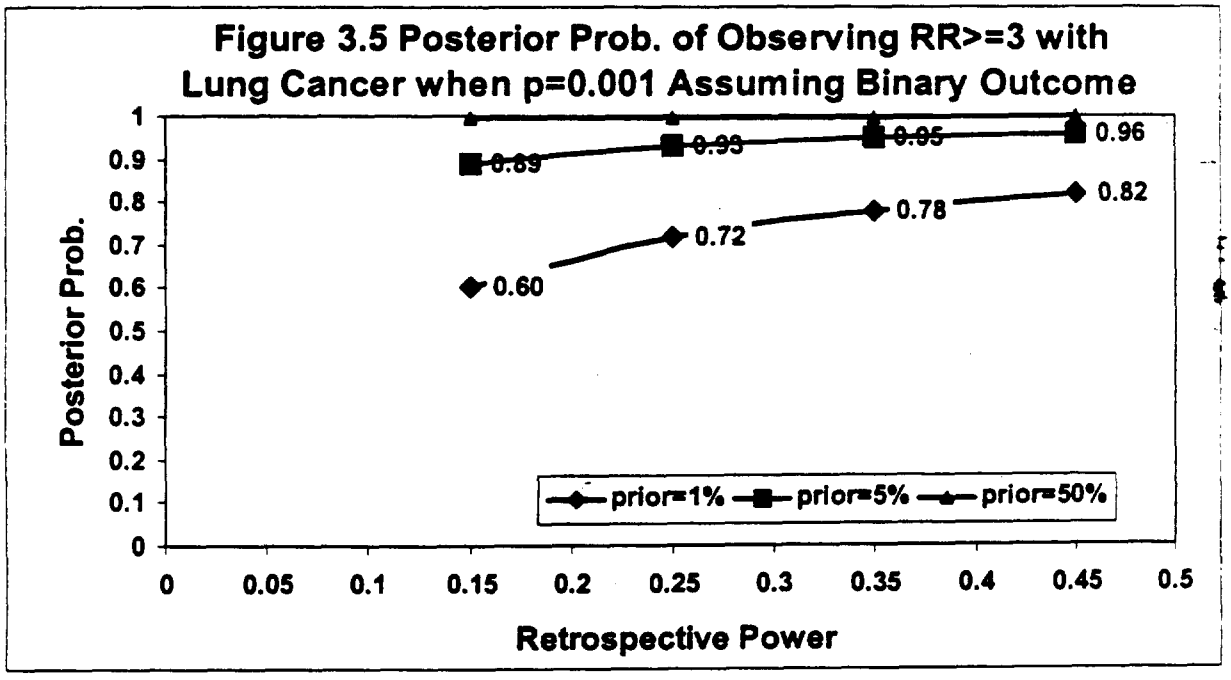
3.2.2.3.3.2 Bayesian View

Dr. Richard Simon from the NCI made comments concerning an NDA submission at the Division of Metabolic and Endocrinologic Drug Product (DMEDP) advisory committee meeting held in 1997 regarding a potentially increased breast cancer risk seen in the treated patients (p~0.07). He stated that

- Whether we believe that the study drug causes an increase in breast cancer, we have to take into account that a priori this finding is unexpected. Dr. Simon suggested that if a priori of 1% probability of believing at the outset of a relative risk ≥ 3 for breast cancer, but statistical power for detecting an effect of this size is probably about 30% or 40%, and there is some uncertainty as to what we would all feel comfortable with

a p-value, say, p-value maybe is 0.10, something like that, or 0.15, in that range, then Dr. Simon stated that "my posterior probability of believing RR≥ 3 after seeing the data is only about 4% or 5%".

One may question that lung cancer risk was not a priori hypothesis of interest clearly stated in the protocol. Finding of increased adverse event of lung cancer risk, based on the binary outcome of "Yes/No" a patient has lung cancer during the trial period, might be considered due to chance. Based on my calculation by applying Dr. Simon's use of 1% prior probability to the risedronate case, the posterior probability of believing a relative risk (RR, approximated by odds ratio) of 2.9 or higher after seeing the data is about 72%. This calculation was based on the observed nominal p-value of 0.001 and power of detecting an effect of this size of about 20% to 30%, see Table 3.8 and Figure 3.5. When one's prior probability is raised to 5%, the posterior probability of believing RR of 2.9 or higher after seeing the data becomes 93%. Indeed, if one does not have any preference of believing such a finding, that is, when the prior probability of believing is 50%, the posterior probability of observing a relative risk as high as 2.9 or higher with lung cancer in the 2.5mg risedronate-treated patients compared to placebo would be almost 100%.



3.2.2.3.3.3 Epidemiologic View

Based on the discussion from the risedronate NDA review team, smoking history and age are known significant risk factors for lung cancer. From epidemiologic reports, individuals who ever smoked are at higher risk than those who never smoked. In general, cancer risk is increased with age. The above a priori knowledge led this reviewer to believe that if increased lung cancer risk was primarily caused by smoking history and older age, such increased risk in risedronate-treated patients would not be seen after evaluation of lung cancer risk is adjusted for smoking history and age of patients. This reviewer performed a generalized linear model analysis assuming binary (Yes/No) outcome of lung cancer risk per patient and adjusting for 10 protocols, smoking history of ever versus never smoked, and age of <65yrs versus ≥65yrs. Age grouping criterion was used by the FDA medical division and stated in the sponsor's report. Results of this analysis are summarized in Table 3.13.

Table 3.13 Generalized linear model of lung cancer risk in risedronate adjusting for smoking, age, protocol

	Main effect p-value	Contrast p-value	Relative risk (95%CI)
Treatment	0.0023	0.0015 (2.5mg vs. pbo)	2.9 (1.5 to 5.8)
		0.2268 (5.0mg vs. pbo)	1.6 (0.8 to 3.3)
Protocols (block factor)*	0.7579	N/L**	
Smoke (ever versus never)	0.0001	<0.0001 (ever vs. never)	3.9 (2.3 to 7.0)
Age (≥65yrs vs. < 65yrs)	0.0488	0.0678 (≥65yrs vs. < 65yrs)	2.7 (1.0 to 8.8)

* 10 protocols were treated as blocking factor in the model due to their having entry criteria differences
** N/L indicates not listed

From Table 3.13, it appeared that smoking history and age well explained the lung cancer risk. Patients who ever smoked were 3.9 (95%CI of 2.3 to 7.0) times higher of lung cancer risk compared to those who never smoked. Patients who were 65 years of age or older were 2.7 (95%CI of 1.0 to 8.8) times higher of lung cancer risk compared to those who were younger than 65 years of age. However, after explaining away the excess of lung cancer cases by smoking history and age, the increase in lung cancer risk in the 2.5mg risedronate arm relative to placebo was still highly statistically significant (p=0.0015). The increase in lung cancer risk of 1.6 (95%CI of 0.8 to 3.3) times higher in the 5.0mg risedronate arm than in placebo was not significant (p=0.23).

Could excess lung risk seen in risedronate be due to lower than expected lung cancer cases seen in the placebo group?

On February 19, 1999, the sponsor presented their concern that their placebo lung cancer cases were lower than general population, which may prompt the increased risk seen in risedronate-treated patients. Information source used by the sponsor's presentation is the external SEER, which reported the cancer incidence by cancer site per 100,000 subjects by age group – female, USA White, between 1983 to 1987, see Appendix I.

Since these 10 trials were mainly conducted in early 1990s to late 1990s and the most recent reports on cancer incidence by SEER are those between 1988 to 1992 (see Appendix II), this reviewer performed an epidemologic analysis of standardized incidence rates comparison (Statistical Methods in Cancer Risk by Breslow and Day, 1987). The standardization combines a set of age-specific rates into a synoptic figure and provides a quantitative measure of the difference in rates between the study cohort and a standard population that is free from the effects of age. The analysis helps explain if lung cancer incidence in the placebo, 2.5mg, and 5.0mg risedronate arms from 10 clinical trials was each different from USA population.

Nighty-nine percent of patients were female in each arm. This reviewer summarizes the results of comparison in females alone in Tables 3.14 to 3.16. There was only one male lung cancer case. The expected number of lung cancer cases for the placebo arm in Table 3.14 is 21.9, and thus the standardized incidence ratio is 13/21.9=0.6 with 95%CI of 0.3 to 1.0, indicating a somewhat underestimated lung cancer incidence in placebo patients from the 10 trials as opposed to the USA general population from SEER database.

The expected number of lung cancer cases for the 2.5mg risedronate arm in Table 3.15 is 19.4. The standardized incidence ratio is 35/19.4=1.8 with 95%CI of 1.3 to 2.5, indicating a significantly increased lung cancer incidence in the 2.5mg risedronate-treated patients as compared to the USA general population (SEER).

Table 3.14 Expected placebo lung cancer cases using SEER White female incidence as a standard population [*1]

AGEG[*2]	PLACEBO LUNG CANCER EVENTS	E[*3]	PLACEBO EXPOSURE TIME	PLACEBO #/1000 PYRS	SEER INCIDIDENCE RATE
≥85	2	0.90679	699.69	2.85843	1.296
80-85-	2	3.91328	1923.93	1.03954	2.034
75-80-	4	5.37413	2160.89	1.85109	2.487
70-75-	4	7.77417	3046.31	1.31307	2.552
65-70-	0	2.15122	976.05	0.00000	2.204
60-65-	1	1.10464	650.55	1.53715	1.698
55-60-	0	0.48311	406.32	0.00000	1.189
50-55-	0	0.19048	274.47	0.00000	0.694
45-50-	0	0.02770	88.49	0.00000	0.313
40-45-	0	0.00158	14.11	0.00000	0.112
35-40-	0	0.00015	4.11	0.00000	0.036
30-35-	0	0.00004	3.96	0.00000	0.011
25-30-	0	0.00001	1.05	0.00000	0.007
TOTAL	13	21.9			

[*1] See Appendix II
[*2] There were no female patients younger than 25 years of age in the placebo arm
[*3] Expected number of lung cancer cases in placebo

Table 3.15 Expected lung cancer cases in the 2.5mg risedronate arm using SEER White female incidence as a standard population [*1]

AGEG[*2]	2.5mg risedronate LUNG CANCER EVENTS	E[*3]	2.5mg risedronate EXPOSURE TIME	2.5mg risedronate #/1000 PYRS	SEER INCIDIDENCE RATE
≥85	2	0.87021	671.46	2.9786	1.296
80-85-	8	3.68947	1813.90	4.4104	2.034
75-80-	8	5.12203	2059.52	3.8844	2.487
70-75-	9	7.16350	2807.01	3.2063	2.552
65-70-	4	1.34429	609.93	6.5581	2.204
60-65-	2	0.73578	433.32	4.6155	1.698
55-60-	0	0.32440	272.84	0.0000	1.189
50-55-	1	0.14402	207.52	4.8189	0.694
45-50-	1	0.01486	47.49	21.0592	0.313
40-45-	0	0.00225	20.12	0.0000	0.112
35-40-	0	0.00006	1.59	0.0000	0.036
30-35-	0	0.00004	3.27	0.0000	0.011
25-30-	0	0.00001	1.04	0.0000	0.007
TOTAL	35	19.4			

[*1] See Appendix II
[*2] There were no female patients younger than 25 years of age in the 2.5mg risedronate arm
[*3] Expected number of lung cancer cases in the 2.5mg risedronate arm

Table 3.16 Expected lung cancer cases in the 5.0mg risedronate arm using SEER White female incidence as a standard population [*1]

AGEG[*2]	5.0mg risedronate LUNG CANCER	E[*3]	5.0mg risedronate EXPOSURE	5.0mg risedronate #/1000	SEER INCIDIDENCE

	EVENTS		TIME	PYRS	RATE
≥85	1	0.91325	704.67	1.41910	1.296
80-85-	1	4.02253	1977.65	0.50565	2.034
75-80-	4	5.43662	2186.02	1.82981	2.487
70-74-	8	7.58739	2973.11	2.69078	2.552
65-70-	4	1.95372	886.44	4.51241	2.204
60-65-	1	1.22351	720.56	1.38781	1.698
55-60-	0	0.46002	386.90	0.00000	1.189
50-55-	1	0.23265	335.23	2.98302	0.694
45-50-	0	0.02482	79.29	0.00000	0.313
40-45-	0	0.00183	16.38	0.00000	0.112
35-40-	0	0.00051	14.21	0.00000	0.036
30-35-	0	0.00002	2.04	0.00000	0.011
25-30-	0	0.00000	0.33	0.00000	0.007
TOTAL	20	21.9			

*1 See Appendix II

*2 There were no female patients younger than 25 years of age in the 5.0mg risedronate arm

*3 Expected number of lung cancer cases in the 5.0mg risedronate arm

The expected number of lung cancer cases for the 5.0mg risedronate arm in Table 3.16 is 21.9. The standardized incidence ratio is 20/21.9=0.9 with 95%CI of 0.6 to 1.4, seemed to indicate a comparable lung cancer incidence in the 5.0mg risedronate-treated patients as opposed to the USA general population (SEER).

There was one male patient who had lung cancer during the trial period. Thus, including or excluding this patient, the above findings were almost unchanged using SEER data between 1988 to 1992 with male patients included. It is noted that the above findings were also similar to using SEER data between 1983 to 1987 with or without male patients.

4. SUMMARY AND CONCLUSION

4.1 Efficacy

The sponsor has submitted two pivotal studies in support of treatment and prevention of corticosteriod induced osteoporosis in male and female patients aged 18 to 85 years. The European Study (RCT009893) was for treatment and the North American Study (RCP009993) for prevention. The study designs between the European study (RCT 009893) and the North American study (RCP009993) were somewhat different. For instance, patients in the European study received 1000mg elemental calcium and 400 IU of Vitamin D daily, whereas patients in the North American study received 500mg elemental calcium daily during both the 12-month treatment period and the 12-month drug-free follow-up period. In the European study, the entry criteria required patients to initiate high dose glucocorticosteroid therapy for ≥ 6 months, but the North American study requires high dose glucocorticosteroid therapy for ≤ 3 months prior to study entry.

An interesting difference between the two studies is noted. In the European study, to be used in support of treatment of corticorsteroid induced osteoporosis, 2.5mg and 5.0mg risedronate showed a significant change from baseline of lumbar spine BMD at one year. Placebo was not shown to have a significant change from baseline at 12 months. In the North American study, to be used in support of prevention of corticorsteroid induced osteoporisis, neither 2.5mg nor 5.0mg risedronate had a significant change from baseline of lumbar spine BMD at one year, but average placebo patients were worse at 12 months than at baseline. In the latter study, the sponsor amended the study design about halfway of the trial. Consequently, patient size per arm was modified from 91 patients to 77 patients and the lower dose of 2.5mg risedronate treatment was terminiated at 90% recruitment, which amounts to approximately 73% to 79% patients available for analysis.

Both studies showed a statistically significant difference favoring 5.0mg risedronate-treated patients in lumbar spine BMD, femoral neck BMD, and trochanter BMD. For the primary efficacy outcome of percent change from baseline in lumbar spine BMD, the estimated treatment effect of difference between 5.0mg risedronate and placebo was 2.8% with 95% CI of 1.5% to 4.1% in RCT009893 study and 3.5% with 95% CI of 2.0% to 5.0% in RCP009993 study. The efficacy of 2.5mg risedronate was not shown in the European Study. The North America study seemed to suggest possible efficacy of 2.5mg risedronate in BMD of lumbar spine and trochanter, but not femoral neck, given the partial enrollment for this dose arm.

In RCT009893 European study, early withdrawal rates showed a decreasing trend (26% in placebo, 22% in 2.5mg group and 18% in 5.0mg group). In RCP009993 North American study, early discontinuation rates were slightly higher in placebo (25%) and 2.5mg risedronate arm (26%) than 5.0mg risedronate arm (17%). Although early withdrawal rates between two studies were not too different, characteristics were somewhat different between the two studies. It appeared that in contrast to completers, in the European study, a greater percentage of dropouts were male (48% vs. 35%, nominal p-value=0.050) and ever smokers (73% vs. 58%, nominal p-value=0.034), whereas in the North American study, a greater percentage of dropouts were female (78% vs. 62%, nominal p-value=0.027) and Black (12% vs. 2%, nominal p-value=0.014).

4.2 Risks of on Lung cancer and GI cancer of risedronate

Potentially increased lung cancer risk and decreased GI cancer risk with administration of risedronate were seen in the ten trials submitted by the sponsor to be indicated for treatment and prevention of corticosteroid-induced osteoporosis (CIO) and postmenopausal osteoporosis (PMO). The following summarizes this reviewer's in-depth evaluation. Probabilistically, it appeared that increased lung cancer risk in both the 2.5mg and the 5.0mg risedronate-treated patients was statistically significant (Odds ratio: 6.6 with 95% CI of 1.4 to 30.7, nominal p=0.0161 for 2.5mg vs. placebo and Odds ratio: 5.0 with 95% CI of 1.1 to 23.5, nominal p=0.0415 for 5.0mg vs. placebo) based on the sponsor's original 8 trials. However, statistical significance was shown only for the 2.5mg risedronate arm (Odds ratio: 2.9 with 95%CI of 1.6 to 5.7, p=0.0011 for 2.5mg vs. placebo and Odds ratio: 1.6 with 95%CI of 0.8 to 3.2, p=0.2232 for 5.0mg versus placebo) when all 10 trials were included. The results of the additional two hip fracture trials were parallel with the results from all 10 trials. For details, see Section 3.2.2. The following summary refers to all 10 trials.

While there was a numerically decreasing trend in GI cancer risk over the range of placebo, 2.5mg to 5.0mg risedronate, the trend was not statistically significant (see Section 3.2.2.3.1 for details).

The above test for lung cancer risk was not specified a priori. By applying a Bayesian approach previously used at a DMEDP advisory committee meeting by Dr. Richard Simon from the NCI, the posterior probability of observing a relative risk of 2.9 or higher in the 2.5mg risedronate arm relative to placebo was as high as 72% with 1% prior probability of believing the finding. The relative risk was approximated by the odds ratio. This posterior probability drastically increased to 93% with 5% prior probability and to almost 100% when no prior preference of the finding (i.e., prior probability of 50%) was used in the calculation.

From an epidemiologic view point, if one expects that there is no difference in lung cancer risk among the placebo, 2.5mg, and 5.0mg risedronate arms, one would not see a significant treatment effect when lung cancer risk was adjusted for important known risk factors of smoking history and age. Based on this reviewer's generalized linear model analysis, it appeared that a significant increase in lung cancer risk was still seen in the 2.5mg risedronate-treated patients (nominal p=0.0015) and a numerical increase in lung cancer risk was also seen in the 5.0mg risedronate-treated patients (nominal p=0.2268) after adjusting for smoking history and age. The estimated relative risk after adjustment was 2.9 with 95% CI of 1.5 to 5.8 for the 2.5mg risedronate arm and was 1.6 with 95% CI of 0.8 to 3.3 for the 5.0mg risedronate arm.

The sponsor pointed out at the February 19, 1999 meeting that the proportion of patients with lung cancer seen in placebo might be underestimated and that comparison between risedronate vs. placebo needs be carefully evaluated. The sponsor used external SEER 1983-1987 as the reference. When person years were standardized in reference to SEER incidence rate by race, sex and age 1988-1992 (which is the most recent

SEER report and the time period is closer to the clinical trial periods compared to SEER 1983-1987), it appeared that age adjusted observed lung cancer cases was somewhat underestimated in the placebo arm (the standardized incidence ratio being 0.6 with 95%CI of 0.3 to 1.0) of the 10 trials. The standardization was calculated using the SEER's projected general population rate of USA White, 1988-1992 females. Using SEER as the reference, the incidence in lung cancer risk was still significant in the 2.5mg risedronate arm (the standardized incidence ratio being 1.8 with 95%CI of 1.3 to 2.5), not in the 5.0mg risedronate arm (the standardized incidence ratio being 0.9 with 95%CI of 0.6 to 1.4). For details, see Section 3.2.2.3.3.3.

Given that (1) death rates were similar among the placebo (4.2%), 2.5mg risedronate (4.3%), and 5.0mg risedronate (3.9%) arms, (2) the 2.5mg risedronate arm had either a similar dropout rate compared to the 5.0mg risedronate or a "similar or smaller" dropout rate compared to the placebo in all 10 trials, (3) a seemingly superior treatment effect of % change from baseline of lumbar spine BMD (nominal $p<0.001$) seen in RCP009993 for the CIO prevention indication (1 of 4 trials in which the 2.5mg risedronate arm was terminated and was reviewed by this reviewer, the remaining 3 trials will be reviewed by Dr. Lee-Ping Pian under the PMO indication), it is difficult to rationalize the sponsor's terminating the 2.5mg risedronate treatment in four out of ten trials. Meanwhile, it is worthwhile noting that a significantly increased lung cancer risk was seen in the 2.5mg risedronate (nominal $p=0.0011$) either statistically, epidemiologically, or under Bayesian framework, and that patients' data available for analysis ranged from 70% to 87% at the time of terminating this 2.5mg risedronate treatment.

In summary, this statistical evaluation focused on risedronate alone in providing statistical findings regarding a significant increase of lung cancer risk seen in the 2.5mg risedronate arm with the complication of sponsor's dropping this 2.5mg risedronate arm at more than 2/3 data completion in 4 of 10 trials. There was only a numerical increase seen in the 5.0mg risedronate arm. No detailed data of other bisphosphonate drugs were available for in-depth evaluation. Whether a look at data from the entire class would be preferable than risedronate alone calls for clinical judgement. Please see Dr. Stadel's evaluation and a memorandum from this reviewer dated July 30, 1999 in response to Dr. Stadel's request for calculation of p-values on "lung cancer in clinical trials of bisphosphonates for osteoporosis".

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AVERAGE ANNUAL INCIDENCE PER 100,000 BY AGE GROUP (YEARS) - FEMALE

T E	ALL AGES	AGE UNK	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+	CRUDE RATE	%	CR 64	CR 74	AGE WORLD	ICD (9th)
	201	0	-	-	-	-	0.0	0.0	0.1	0.1	0.1	0.3	0.4	0.5	0.8	1.1	1.6	2.8	3.5	3.9	0.4	0.1	0.0	0.0	0.2	140
ue	787	0	-	-	0.0	0.0	0.1	0.2	0.3	0.5	0.7	1.5	2.4	4.3	5.2	7.0	6.3	7.7	4.9	5.7	1.7	0.4	0.1	0.1	1.2	141
vary gland	624	0	-	0.1	0.1	0.3	0.2	0.3	0.6	0.8	0.9	1.0	1.1	1.6	2.0	2.1	2.5	3.0	3.7	4.9	0.9	0.2	0.8	0.1	0.7	142
h	1253	0	-	-	0.1	0.0	0.0	0.2	0.3	0.5	0.9	2.2	3.4	7.1	8.2	10.5	11.8	10.3	11.0	11.5	2.7	0.7	0.1	0.2	1.8	143-5
aryrx	414	0	-	0.1	-	-	0.0	-	0.0	0.1	0.5	1.1	1.6	3.1	3.8	4.2	3.3	2.5	2.1	1.6	0.9	0.2	0.0	0.1	0.7	146
pharynx	135	0	-	0.0	-	0.1	0.1	0.1	0.1	0.1	0.2	0.5	0.5	0.7	0.9	1.2	0.7	0.7	0.7	0.7	0.3	0.1	0.0	0.0	0.2	147
pharynx	254	0	-	-	-	-	0.0	0.0	-	0.0	0.1	0.5	0.8	1.7	2.0	3.7	2.0	1.5	0.8	0.9	0.5	0.1	0.0	0.1	0.4	148
yrx unspecified	127	0	-	0.0	-	-	0.0	-	-	0.1	0.0	0.0	0.5	0.7	1.5	1.5	1.0	0.8	0.6	0.1	0.3	0.1	0.0	0.0	0.2	149
phagus	980	0	-	-	-	-	-	0.0	0.0	-	0.1	0.6	1.0	4.1	6.8	7.9	9.9	11.7	12.7	13.2	2.1	0.5	0.1	0.2	1.3	150
ach	2979	0	-	-	-	0.1	0.1	0.2	0.5	0.7	1.6	3.8	4.8	7.7	11.7	16.6	27.3	40.8	51.1	62.9	6.4	1.6	0.2	0.4	3.5	151
l intestine	666	0	-	-	-	-	0.1	0.0	0.1	0.2	0.3	1.1	1.5	2.1	1.9	3.7	4.0	5.0	6.3	4.8	1.0	0.2	0.0	0.1	0.6	152
e	20175	0	-	-	-	0.0	0.4	0.6	1.8	3.5	7.8	16.1	34.4	58.2	85.5	123.4	194.8	275.5	348.9	385.5	43.3	10.7	1.0	2.7	23.6	153
um	7385	0	-	-	-	0.1	0.2	0.2	0.8	2.0	4.2	10.0	17.5	27.5	40.9	53.6	72.9	82.4	102.8	105.4	15.9	3.9	0.5	1.1	9.6	154
r	786	8	0.5	-	0.2	0.2	0.2	0.2	0.2	0.3	0.6	0.8	1.7	2.2	3.3	5.3	7.1	8.8	10.7	12.5	1.7	0.4	0.1	0.1	1.1	155
bladder etc.	1520	0	-	-	-	-	-	-	0.1	0.1	0.6	0.9	3.2	3.2	7.0	9.6	14.1	20.2	29.1	31.1	3.3	0.8	0.1	0.2	1.7	156
reas	4985	0	0.0	-	-	0.0	0.1	0.1	0.4	0.7	1.9	4.3	7.1	14.2	24.1	37.6	50.4	61.8	79.3	92.2	10.7	2.6	0.3	0.7	6.0	157
tonum	794	0	0.4	0.0	0.1	0.0	0.1	0.1	0.1	0.3	0.3	0.8	0.6	1.3	1.5	1.6	3.0	3.7	1.9	1.5	0.6	0.2	0.0	0.1	0.5	158
, sinuses etc.	271	0	0.1	0.1	-	0.0	0.1	0.1	0.1	0.3	0.3	0.6	0.9	0.8	1.5	1.8	2.0	2.4	2.9	2.8	0.6	0.1	0.0	0.0	0.4	160
se	815	0	-	-	-	-	0.1	0.1	0.0	0.3	0.4	1.7	3.8	5.4	8.0	9.5	6.5	4.3	2.7	2.5	1.8	0.4	0.1	0.2	1.4	161
chus, lung	29995	0	-	-	0.1	0.2	0.3	0.6	1.4	4.5	10.7	24.6	66.3	130.1	151.8	185.9	202.8	179.7	143.9	101.0	42.9	10.6	1.9	3.9	29.9	162
ra	141	0	-	-	-	-	0.0	-	0.0	0.1	0.2	0.3	0.3	0.5	0.7	0.9	1.2	1.9	2.4	1.0	0.3	0.1	0.0	0.0	0.2	163
r thoracic organs	108	0	0.5	0.0	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.1	0.4	0.4	0.7	0.7	0.4	0.4	0.2	0.7	0.2	0.1	0.0	0.0	0.2	164
	345	8	0.1	0.6	1.2	1.2	0.5	0.3	0.4	0.4	0.6	0.8	0.5	0.4	1.4	1.5	1.5	1.3	1.6	1.4	0.7	0.2	0.0	0.1	0.7	170
ective tissue	988	0	1.4	0.3	0.8	1.1	1.0	1.0	1.0	1.3	1.7	1.3	2.6	3.0	3.6	4.9	6.3	5.4	10.5	8.4	2.1	0.5	0.1	0.2	1.7	171
nma of skin	5136	0	0.1	0.1	0.2	1.7	4.2	8.7	12.3	15.5	16.3	17.1	19.0	20.5	19.2	16.6	20.9	23.0	22.2	23.3	11.0	2.7	0.7	0.9	8.8	172
r skin	677	0	0.0	0.0	0.1	0.2	0.4	0.6	0.7	0.8	0.7	1.0	0.8	1.0	1.2	2.2	1.8	3.5	5.6	5.4	0.9		0.0	0.1	0.6	173
st	57094	0	-	-	-	0.0	1.0	7.6	26.6	66.1	126.5	186.5	221.0	272.1	334.6	392.2	417.8	443.0	442.1	410.8	122.5	30.2	6.2	10.3	89.2	174
s unspecified	173	0	-	0.0	0.0	-	0.0	-	0.0	0.1	0.2	0.4	0.5	0.3	0.7	0.8	1.4	2.1	2.5	4.2	0.4	0.1	0.0	0.0	0.2	179
x uteri	4269	0	0.0	-	-	0.3	2.0	7.2	11.9	16.5	15.7	14.9	15.0	15.9	15.6	17.5	16.6	15.8	17.1	9.2	2.3	0.6	0.7	7.3	180
nta	62	0	-	-	0.0	0.3	0.3	0.3	0.4	0.1	0.2	-	-	0.2	-	-	-	-	-	0.1	0.0	0.0	0.0	0.1	181
s uteri	12547	0	-	-	0.0	0.1	0.5	2.3	5.9	12.4	25.4	43.3	66.1	98.7	119.5	117.3	99.0	81.9	59.1	26.9	6.6	1.3	2.5	19.2	182
, etc.	7950	0	-	0.2	0.6	1.5	2.0	3.0	3.9	7.1	12.4	21.7	29.0	38.9	51.3	55.9	60.6	57.5	59.1	51.3	17.1	4.2	0.9	1.5	12.5	183
f female genital	1464	0	0.0	-	0.0	0.0	0.3	0.3	0.8	1.2	1.0	2.2	3.6	4.0	6.4	8.1	11.5	17.1	19.8	29.0	3.1	0.8	0.1	0.2	1.9	184
ter	4705	0	-	0.0	-	0.2	0.1	0.5	0.6	1.3	2.3	4.9	9.4	15.1	24.9	34.2	46.0	54.2	70.0	81.2	10.2	2.5	0.3	0.7	5.9	188
y etc.	3331	0	1.9	0.7	0.1	0.2	0.2	0.4	0.8	1.3	3.3	6.1	8.9	12.9	19.1	26.5	29.9	37.2	32.1	31.1	7.1	1.8	0.3	0.6	4.9	189
	319	0	1.5	0.1	0.0	-	0.1	0.2	0.3	0.1	0.4	0.8	0.8	1.6	1.0	2.0	2.2	1.7	2.4	2.3	0.7	0.2	0.0	0.1	0.6	190
, nervous system	2810	0	3.5	3.1	2.0	2.2	1.7	2.9	3.2	4.0	4.0	5.2	7.8	9.9	12.6	17.4	18.8	18.9	17.4	8.6	6.0	1.5	0.3	0.5	5.0	191-2
ld	3181	0	-	0.1	0.9	3.1	6.1	7.8	9.6	10.0	9.6	11.2	10.8	9.3	10.0	9.0	8.6	6.5	9.5	7.4	6.8	1.7	0.4	0.5	5.8	193
: endocrine	163	0	1.2	0.3	0.1	0.1	0.1	0.0	0.1	0.2	0.2	0.2	0.6	0.4	0.7	0.6	1.3	0.5	0.6	0.5	0.3	0.1	0.0	0.0	0.4	194
in's disease	1139	0	-	0.3	1.5	4.5	6.2	4.9	3.6	2.8	1.8	1.5	1.6	2.4	2.8	2.7	3.4	3.9	3.8	2.3	2.9	0.7	0.2	0.2	2.5	201
dgkin lymphoma	6356	0	0.5	0.6	0.6	1.1	1.4	1.8	2.9	3.8	7.4	11.0	14.9	24.3	31.7	42.7	56.2	70.1	78.5	68.8	13.6	3.4	0.5	1.0	8.9	200,202
ple myeloma	1932	0	-	-	-	-	-	0.0	0.1	0.4	0.8	1.9	3.6	5.8	10.0	15.0	18.2	27.3	29.5	27.6	4.1	1.0	0.1	0.3	2.4	203
eid leukemia	1864	0	5.4	2.4	1.7	0.8	0.4	0.4	0.4	0.8	0.8	1.3	2.3	4.1	7.8	9.3	14.7	17.7	24.6	31.6	4.0	1.0	0.1	0.3	3.8	204
id leukemia	1857	0	0.4	0.3	0.6	0.7	0.7	0.9	1.5	2.1	1.9	2.8	4.5	5.3	7.3	9.2	14.3	17.6	27.6	27.0	4.0	1.0	0.1	0.3	2.6	205
ytic leukemia	143	0	0.1	0.1	0.1	0.2	0.1	0.0	0.1	0.2	0.2	0.3	0.3	0.5	0.5	0.8	0.7	0.8	2.4	2.0	0.3	0.1	0.0	0.0	0.2	206
: leukemia	80	0	0.1	-	-	-	0.0	0.0	-	0.1	0.1	0.1	0.2	0.4	0.3	0.7	0.6	0.6	1.5	0.6	0.2	0.0	0.0	0.0	0.1	207
mia unspecified	461	0	0.2	0.2	0.2	0.0	0.1	0.1	0.2	0.3	0.3	0.3	0.9	1.0	1.7	2.3	2.6	5.0	7.5	12.6	1.0	0.2	0.0	0.1	0.6	208
ry site uncertain	5694	0	0.2	0.0	0.0	0.2	0.2	0.2	0.7	1.3	3.2	5.5	10.8	16.1	24.9	34.9	50.1	63.9	96.5	134.0	12.2	3.0	0.3	0.7	6.7	PSU
sites	189245	0	18.4	9.8	11.5	20.7	30.7	53.1	91.6	157.2	281.8	409.2	567.6	787.9	1056.4	1324.2	1549.5	1723.3	1867.1	1894.0	406.2		17.4	31.7	277.0	ALL
sites but 173	188818	0	18.4	9.8	11.4	20.4	30.3	52.5	90.9	156.3	280.6	408.2	566.8	787.0	1055.2	1322.0	1547.7	1719.7	1881.5	1888.5	405.3	100.0	17.3	31.7	276.3	
from 39 cases			0.300	0.342	0.331	0.312	0.252	0.231	0.248	0.281	0.353	0.441	0.469	0.445	0.454	0.507	0.616	0.789	1.159	1.233						

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ANNUAL INCIDENCE PER 100,000 BY AGE GROUP (YEARS) - FEMALE

TE	ALL AGES	AGE UNK	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+	CRUDE RATE	%	CR 64	CR 74	ASR (W)	ICD (9th)
	216	0	-	-	-	-	0.0	0.1	0.2	0.1	0.1	0.3	0.3	0.7	0.8	1.7	1.8	1.9	3.5	3.0	0.4	0.1	0.01	0.03	0.3	*140*
igue	776	0	0.0	-	-	0.0	0.1	0.2	0.3	0.5	0.6	1.1	2.3	4.0	5.0	6.1	6.4	5.7	5.9	6.8	1.6	0.4	0.07	0.13	1.1	*141*
ivary gland	450	0	0.0	0.1	0.1	0.2	0.2	0.5	0.3	0.6	0.8	1.1	1.2	1.2	1.6	3.1	3.1	2.9	3.4	4.2	0.9	0.2	0.04	0.07	0.7	*142*
uth	1180	0	-	-	0.1	0.1	0.2	0.2	0.2	0.5	0.9	1.7	3.3	5.1	7.6	8.2	11.1	9.9	11.6	10.6	2.4	0.6	0.10	0.20	1.6	*143-5*
pharynx	430	0	0.0	-	-	-	-	-	0.0	0.2	0.1	0.9	1.6	2.4	3.8	3.5	4.5	3.3	1.9	1.0	0.9	0.2	0.05	0.09	0.6	*146*
opharynx	132	0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.4	0.6	0.6	0.9	1.1	1.1	0.5	0.7	0.3	0.1	0.01	0.02	0.2	*147*
opharynx	243	0	-	-	-	-	-	-	-	-	0.1	0.2	0.5	2.1	1.8	2.2	2.8	1.9	1.3	1.1	0.5	0.1	0.02	0.05	0.3	*148*
rynx unspecified	134	0	-	-	-	-	-	-	-	-	-	0.2	0.4	0.7	0.9	1.1	1.4	1.2	1.0	1.4	0.3	0.1	0.01	0.02	0.2	*149*
sophagus	1044	0	-	-	-	-	-	0.1	0.0	0.1	0.2	0.4	1.7	3.8	6.2	8.2	11.1	11.6	13.0	13.1	2.2	0.5	0.06	0.16	1.2	*150*
mach	2822	0	-	-	-	0.0	-	0.2	0.4	0.9	1.3	2.1	5.0	6.5	10.9	16.1	23.7	35.5	44.5	54.2	5.9	1.4	0.14	0.34	3.1	*151*
all intestine	616	0	-	-	-	-	-	0.2	0.1	0.4	0.7	1.0	1.6	2.1	2.8	4.9	5.4	5.0	6.8	7.5	1.3	0.3	0.04	0.10	0.8	*152*
lon	19227	0	-	-	0.0	0.1	0.1	0.8	1.7	3.5	7.7	15.3	26.5	48.9	78.8	115.6	169.2	240.4	312.2	351.9	39.9	9.4	0.92	2.34	20.8	*153*
ctum	7176	0	-	-	-	0.1	0.1	0.4	1.0	2.1	4.4	8.0	16.4	23.6	36.2	50.5	65.7	78.4	89.2	94.0	14.9	3.5	0.46	1.04	8.7	*154*
ver	969	0	0.5	0.1	0.0	0.0	0.1	0.2	0.2	0.3	0.4	1.2	1.5	2.6	5.0	5.3	8.7	11.3	14.8	11.7	2.0	0.5	0.06	0.13	1.2	*155*
llbladder etc.	1552	0	-	-	-	-	0.0	0.0	0.1	0.5	0.7	0.9	2.1	4.4	6.3	8.8	14.6	18.8	24.8	28.6	3.2	0.8	0.08	0.19	1.7	*156*
ncreas	5166	0	0.0	0.0	0.0	0.1	0.1	0.1	0.3	0.7	1.2	3.4	7.4	14.2	20.9	35.2	49.9	65.3	76.6	88.5	10.7	2.5	0.24	0.67	5.7	*157*
se, sinuses etc.	268	0	-	0.1	0.1	-	0.1	0.1	0.1	0.4	0.3	0.2	0.8	1.0	1.4	1.6	1.7	2.5	2.6	3.0	0.6	0.1	0.02	0.04	0.4	*160*
rynx	901	0	-	-	-	-	-	0.1	0.2	0.2	0.4	1.4	3.2	6.2	7.8	8.4	8.1	5.9	4.2	3.0	1.9	0.4	0.10	0.18	1.4	*161*
onchus, lung	24781	0	-	-	-	0.2	0.4	0.7	1.1	3.6	11.2	31.3	69.4	118.9	169.8	220.4	255.2	248.7	203.4	129.6	51.4	12.1	2.03	4.41	33.8	*162*
ther thoracic organs	136	0	0.4	0.1	0.1	0.0	0.0	0.0	0.2	0.3	0.1	0.2	0.4	0.5	0.6	0.5	1.0	0.9	0.9	0.4	0.3	0.1	0.01	0.02	0.2	*163-4*
one	399	0	0.2	0.6	1.5	1.0	0.8	0.5	0.5	0.6	0.6	0.5	0.7	0.7	1.2	1.1	1.5	2.2	2.2	1.4	0.8	0.2	0.05	0.06	0.8	*170*
onnective tissue	1105	0	1.4	0.4	0.5	0.7	0.8	1.2	1.1	1.6	1.8	1.9	2.4	3.0	4.4	5.1	6.0	7.6	8.4	11.3	2.3	0.5	0.11	0.16	1.7	*171*
lesothelioma	219	0	-	-	-	0.0	-	0.0	0.1	0.1	0.3	0.2	0.6	0.6	1.4	1.6	1.4	2.8	2.2	1.5	0.5	0.1	0.02	0.03	0.3	*MES*
aposi's sarcoma	80	0	-	-	-	-	-	0.1	0.1	0.2	0.0	0.1	-	0.1	0.0	0.0	0.3	1.1	1.5	2.5	0.2	0.0	0.00	0.00	0.1	*KAP*
lelanoma of skin	6383	0	0.0	0.1	0.5	2.0	5.7	9.3	13.9	16.0	18.5	20.8	20.3	22.2	23.8	22.9	25.2	26.2	27.6	32.3	13.2	3.1	0.77	1.01	10.2	*172*
ther skin	472	0	0.0	0.1	0.2	0.2	0.4	0.9	0.6	0.8	0.9	0.9	1.4	1.4	1.8	1.3	2.3	3.0	4.7	5.1	1.0		0.05	0.06	0.7	*173*
reast	62413	0	-	-	0.0	-	0.9	7.0	23.8	61.0	121.2	194.5	231.5	273.2	340.5	403.6	439.4	466.3	459.4	415.8	129.6	30.4	6.27	10.48	90.7	*174*
terus unspecified	188	0	0.0	-	-	-	-	-	0.0	0.2	0.2	0.4	0.4	0.4	0.5	0.9	1.2	1.5	2.2	5.3	0.4	0.1	0.01	0.02	0.2	*179*
ervix uteri	4650	0	-	0.0	-	0.2	2.0	8.8	12.4	15.1	15.7	16.0	15.7	13.5	17.3	17.3	13.1	15.0	15.3	15.7	9.7	2.3	0.58	0.74	7.5	*180*
lacenta	48	0	-	-	0.0	0.1	0.2	0.3	0.3	0.2	-	0.1	-	-	0.0	0.0	-	-	-	-	0.1	0.0	0.01	0.01	0.1	*181*
orpus uteri	12727	0	-	-	-	0.1	0.1	1.0	2.1	5.6	12.1	22.7	43.2	63.2	87.8	107.6	116.1	107.0	87.2	63.1	26.4	6.2	1.19	2.31	18.2	*182*
vary etc.	8259	0	0.1	0.2	0.4	1.6	1.5	3.1	3.6	7.6	11.0	20.0	26.6	38.4	46.3	54.2	61.3	63.9	62.7	58.8	17.1	4.0	0.80	1.38	11.9	*183*
ther female genital	1628	0	0.1	-	-	0.1	0.3	0.4	0.7	1.4	1.7	2.7	2.8	5.6	6.6	8.4	12.7	15.7	20.4	27.0	3.4	0.8	0.11	0.22	2.0	*184*
ladder	5225	0	0.0	-	-	0.1	0.3	0.5	0.7	1.1	2.2	4.8	9.5	17.7	25.4	36.9	46.6	57.0	67.5	83.0	10.8	2.5	0.31	0.73	6.2	*188*
idney etc.	3994	0	2.2	0.6	0.2	0.2	0.1	0.5	0.8	1.4	3.7	6.3	11.4	15.6	22.6	27.6	34.2	39.8	38.2	34.7	8.3	1.9	0.33	0.64	5.5	*189*
ye	357	0	1.1	0.2	0.0	0.1	0.1	0.2	0.2	0.3	0.3	0.3	0.8	1.6	1.5	2.4	2.6	2.7	2.4	2.5	0.7	0.2	0.03	0.06	0.6	*190*
rain, nervous system	3047	0	3.7	3.0	2.6	2.1	2.4	2.7	2.8	3.6	4.9	5.8	7.8	9.5	11.7	16.6	20.3	21.7	18.4	11.2	6.3	1.5	0.31	0.50	5.1	*191-2*
Thyroid	3719	0	-	0.0	0.8	2.7	7.0	9.1	10.2	11.8	11.8	12.3	11.1	10.7	10.2	9.9	10.0	9.1	8.7	7.1	7.7	1.8	0.49	0.59	6.4	*193*
Other endocrine	176	0	1.2	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.5	0.4	0.4	0.9	0.8	0.6	0.8	0.5	0.3	0.4	0.1	0.02	0.03	0.4	*194*
Hodgkin's disease	1441	0	0.0	0.3	1.4	4.7	6.8	5.8	3.9	3.2	2.4	1.7	1.3	1.9	2.0	2.8	3.3	3.8	5.0	3.0	3.0	0.7	0.18	0.21	2.7	*201*
Non-Hodgkin lymphoma	7693	0	0.4	0.4	0.6	1.3	1.7	2.7	3.1	4.6	7.8	11.7	18.4	26.2	36.9	48.9	65.8	76.0	85.4	79.8	16.0	3.7	0.58	1.15	10.1	*200,202*
Multiple myeloma	2177	0	-	-	-	-	0.1	0.1	0.0	0.3	0.8	2.4	4.0	5.6	11.2	15.3	20.8	26.9	33.0	26.5	4.5	1.1	0.12	0.30	2.5	*203*
Lymphoid leukaemia	2123	0	5.8	2.4	1.6	0.8	0.5	0.5	0.5	0.5	1.3	1.2	2.3	4.9	6.6	11.1	16.5	19.3	25.5	31.7	4.4	1.0	0.14	0.28	3.2	*204*
Myeloid leukaemia	2054	0	0.9	0.3	0.6	1.1	0.6	1.2	1.4	1.8	2.5	3.1	4.3	5.2	7.4	10.9	14.3	18.8	24.4	27.2	4.3	1.0	0.15	0.28	2.7	*205*
Monocytic leukaemia	118	0	0.1	0.1	-	-	0.1	0.1	0.1	-	0.1	0.2	0.2	0.3	0.4	0.6	0.9	1.1	0.9	1.9	0.2	0.1	0.01	0.02	0.2	*206*
Other leukaemia	65	0	0.2	-	0.0	-	-	-	-	0.0	0.1	0.0	0.1	0.1	0.3	0.4	0.5	0.6	1.1	0.4	0.1	0.0	0.00	0.01	0.1	*207*
Leukaemia unspecified	449	0	0.1	0.1	0.0	0.0	0.1	0.2	0.1	0.2	0.2	0.4	0.5	0.7	1.4	2.5	3.7	4.0	7.7	10.6	0.9	0.2	0.02	0.05	0.5	*208*
Other and unspecified	6535	0	0.9	0.1	0.0	0.2	0.3	0.3	0.9	1.4	2.8	5.3	8.4	16.9	27.5	36.9	54.0	70.6	103.4	143.3	13.6	3.2	0.32	0.78	7.1	*O&U*
All sites	205963	0	19.7	9.5	11.5	20.3	34.6	60.1	90.6	155.1	256.6	408.1	572.1	789.2	1066.4	1350.0	1620.9	1816.4	1938.3	1917.2	427.5		17.47	32.32	281.6	*ALL*
All sites but 173	205491	0	19.7	9.5	11.3	20.1	34.2	59.3	90.0	154.3	255.7	407.3	570.8	787.9	1064.6	1348.7	1618.6	1813.3	1933.6	1912.1	426.5	100.0	17.42	32.26	280.9	*ALL-b*
Rate from 10 cases			0.299	0.309	0.327	0.432	0.295	0.251	0.234	0.252	0.278	0.356	0.446	0.489	0.476	0.486	0.572	0.708	1.012	1.105						

Important - see notes on population page