CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-835/S001-004

MEDICAL REVIEW(S)

U.S. FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS
HFD-510

MEDICAL REVIEW

Supplemental NDA for Risedronate Sodium Actonel®

DRUG: Risedronate (Actonel®)

NDA#: 20-835 S001, S002, and S003

COMPANY: Procter & Gamble

PHARMACOLOGICAL CATEGORY: Bisphosphonate/Bone Anti-Resorptive

ROUTE OF ADMINISTRATION: Oral

PROPOSED INDICATIONS: Treatment and Prevention of Postmenopausal Osteoporosis and Corticosteroid-Induced Osteoporosis

PROPOSED DOSAGE: 5 mg once daily

DATE SUBMITTED: December 18, 1998

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I. RELEVANT BACKGROUND INFORMATION

1995 Clinical Phase III Clinical Program Changes - May 1995 FDA Meeting

As presented by P&G:

In early 1995, P&G approached the Division regarding changes to the Phase III clinical program. An important meeting was held with the Division on May 31, 1995 to discuss proposed changes in the overall program to develop risedronate. P&G indicated that the scope of the program for developing risedronate was to be restructured for business reasons. The program would be revised so that only essential elements of the program would be maintained with respect to FDA guidelines and for patient safety. P&G further stated that, even though it needed to reduce costs, the objectives of the program remained unchanged. There were five general areas proposed for program modification, as follows:

1 [redacted]

2. Discontinuing one of the two dosing arms (2.5-mg risedronate dose) in all osteoporosis trials;

3. Eliminating the 1-year calcium follow-up from all studies except the North American vertebral fracture trial and Paget's trial;

4. Discontinuing trials which were not needed for regulatory approval; and

5. Modifying some protocol procedures not expected to effect safety or efficacy.

The Division did not object to P&G's proposed plan to discontinue the 2.5-mg dosing arm from all osteoporosis treatment and prevention trials. As part of the discussion on this topic, P&G presented results from the completed Phase II studies. These results confirmed the trends observed in the corresponding 9-month interim analyses presented during the End of Phase II meeting, namely that the 5-mg dose was providing superior BMD efficacy. Before making this change, P&G agreed to provide the Division with the algorithm that was used to evaluate Phase III efficacy (bone mass) and safety parameters (adverse GI events and bone turnover markers) for dose selection. The algorithm was subsequently supplied to the Division (IND [redacted]) and P&G received no objections to this approach.

Assuming P&G had demonstrated fracture efficacy, the Division reaffirmed that the single Australian Prevention trial (RBL004494) would be sufficient to obtain an indication for prevention of post-menopausal osteoporosis.

The Division agreed that the one-year follow-up period (calcium-supplementation) in each of

the osteoporosis trials could be eliminated with the exception the North American vertebral fracture trial (RVN008993) and the Paget's disease trial (RPD001694). It was agreed that the follow-up data need not be submitted with the initial NDA.

The Division had no objection to the early discontinuation of one of the osteopenia trials (either ROE009493 or RON009393) and the estrogen combination trial (RPE002494).

Vertebral Fracture Definition

On February 5, 1997 P&G met with the Division to discuss proposals to change the criteria for defining prevalent and incident vertebral deformities in the Phase III osteoporosis studies. These proposals were based on recently analyzed vertebral fracture data from Study RON009393 and a blinded analysis of vertebral fracture data from a random sample of 300 patients from ten Phase III osteoporosis protocols. These analyses indicated that the protocol-specified quantitative morphometry criteria for the determination of
prevalent and incident vertebral deformities were highly sensitive but resulted in a high false positive rate for the determination of vertebral fractures.

During this discussion, the following changes to the definition of prevalent and incident vertebral deformities were agreed to by the Division:

· For the pivotal vertebral fracture and hip fracture trials (RVN008993, RVE009093, RHN009193, RHE09293).

- Prevalent deformities: The Eastell published "trimming" method was to be used in place of the current procedure which was based on a 20% reduction in vertebral body height ratios.
- Incident deformities: The current quantitative morphometry (15%/4 mm) and semiquantitative analyses were to continue in parallel. However, where there were discrepancies, a different radiologist would make the final yes/no/cannot assess deformity determination (adjudication).

· For the supportive bone mineral density endpoint studies (RCT009893, RCP009993, RBL004494, ROE009493, RPE002494).

- Prevalent deformities: The Eastell published "trimming" method was to be used in the same manner as with the pivotal vertebral fracture and hip fracture trials.
- Incident deformities: The current quantitative morphometry (15%/4 mm) criteria were to be used. Vertebrae which were not identified as deformed by morphometry were not to be considered fractures. Vertebrae which were identified by morphometry as deformed were to be verified by a radiologist who would make a yes/no/cannot assess final determination (visual verification).

II. PRECLINICAL PHARMACOLOGY/TOXICOLOGY (see approved NDA for Paget's Disease and the pharmacology review by Dr. Gemma Kuijpers)

Animal and Human Exposure Comparison

Animal and human pharmacokinetic data were compared in terms of multiples of human exposure to provide an index of human safety. Multiples of human exposures were calculated from AUC obtained on the terminal sampling day in toxicity studies, expressed as a ratio to the steady-state AUC from pharmacokinetics studies in humans AUC was based on total drug

concentration and not corrected for protein binding. Plasma protein binding in rats, dogs, and humans was 98%, 37%, and 24%, respectively. Human data were from postmenopausal women receiving a 5 mg oral dose for approximately 6 months. The steady-state AUC was 6.06 ng*hr/mL, with an accumulation ratio of approximately 2. These data are consistent with the findings in a 14-day multiple dose study and predicted values from a single dose study.

For rats, relative exposure based on AUC progressively increased with dose from ——— (dose range 2-4 mg/kg) to ——— (64 mg/kg), and tended to increase as the duration of dosing increased past 4 weeks. At the NOAEL in rats (8 mg/kg), relative exposure ranged from 13.5 to 47.0. For dogs, AUC-based relative exposure also progressively increased with dose from about ——— (dose range 4-12 mg/kg). Relative exposure at the minimally toxic dose in dogs (8 mg/kg) ranged from 227 to 312, and at the NOAEL in dogs (4-6 mg/kg), relative exposure was approximately 103, indicating a wide safety margin. Although the multiples of human exposure ratios would be lower if corrected for species differences in plasma protein binding, the demonstrated clinical safety data is more in agreement with AUC comparisons based on total drug concentration.

III. HUMAN PHARMACOLOGY/PHARMACOKINETICS (See the approved NDA for Paget's Disease and the reviews by Drs. Gemma Kuijpers and Ronald Kavanagh)

Metabolism

Similar to other bisphosphonates, there is no evidence to indicate systemic metabolism of risedronate occurs in humans or animals. Although an in vivo metabolism study has not been conducted in humans, in vivo metabolite profiling studies were completed in rats and dogs. No metabolites were detected in bone, plasma or pre-bladder urine (collected via ureteral cannula) from rats dosed orally or intravenously with risedronate. Two known chemical degradation products, 1-oxo-2-(3-pyridinyl)ethylidene]-phosphonic acid and 3-pyridyl acetic acid, were found in rat and dog urine samples after oral dosing. These amounts represented less than 0.1% of the oral dose. In vitro experiments indicated that the amount of degradation was 1% in human urine incubated at 37°C over 24 h. No degradation occurred in urine stored at 5°C. In vitro studies with liver slices, plasma, serum and fecal flora from humans, dogs and rats indicated no metabolism of risedronate. No evidence of hepatic microsomal enzyme induction was detected in rats dosed daily with 0.1 to 16 mg/kg/day risedronate for 14 days.

Intravenous Single Dose Studies

Multiphasic risedronate serum concentration-time and urinary excretion rate-time profiles were observed following intravenous administration. Risedronate pharmacokinetics in healthy subjects indicate that following intravenous administration, 45-65% of the dose is excreted in the urine within 24 hours, and 85% of the dose can be recovered in the urine over 28 days. Since CLR comprised 86% of the CL, only a small percentage (14%) of a systemically available dose is "cleared" or incorporated into bone.

The VSS was large (6.3 L/kg) probably resulting from the distribution of risedronate to the surface of bone. The 33-fold difference in VC (0.19 L/kg) and VSS (6.3 L/kg) indicated a large fluctuation in peak to trough risedronate serum concentrations will occur with daily dosing. The difference in VZ (27 L/kg) and VSS (6.3 L/kg) was indicative of a drug where most of the dose eliminated relatively rapidly, and a small fraction of the dose persisting with the long $t_{½,z}$ (201 h). The $t_{½,1}$, $t_{½,2}$ and $t_{½,Z}$ were 0.85, 9.9 and 201 h. Based on the mean coefficients and exponents, the $t_{½,1}$, $t_{½,2}$ and $t_{½,Z}$ for risedronate account for 61.2%, 16.4% and 22.4%,

respectively, of the total AUC.

Intravenous Multiple Dose Studies

The dose proportional increase in excretion with increasing dose from 0.1 mg to 0.5 mg following a single dose and from 0.25 mg/day to 0.50 mg/day for 7 days of daily dosing suggested risedronate pharmacokinetics are linear across these doses. Urinary excretion increased 1.2- to 1.6-fold following multiple dosing, which indicated that systemic exposure to risedronate upon multiple dosing will increase less than 2-fold with respect to the first dose.

Oral Single Dose Studies

Bisphosphonates are known to have low oral bioavailability. The oral bioavailability of risedronate was 0.63%. Absorption was relatively rapid (tmax ~1 h). The extent of absorption was similar throughout the upper gastrointestinal tract, and the extent of absorption was not significantly influenced by the rate of drug delivery. Serum risedronate concentration-time profiles and cumulative urinary excretion of risedronate increased proportionally with single dose administration. The rate (Cmax) and extent (AUC and Ae) of risedronate absorption increased dose proportionally from 2.5 to 30 mg (Panel 2). Based on simultaneous analysis of serum concentration and urinary excretion data, the terminal exponential half-life was 220 hours.

Oral Multiple Dose Studies

Steady-state was achieved within 57 days of daily dosing. Risedronate pharmacokinetics were dose proportional following multiple dose, oral administration of 2.5 and 5 mg to postmenopausal women. Approximately 2-fold increase in extent of exposure occurred at steady-state when compared to single dose pharmacokinetic parameters, with a 15% increase in the Cmax and an 8- to 10-fold increase in Cmin. Similar accumulation (2- to 3-fold) was observed at higher doses, based on cumulative urinary excretion (3 and 14 days of dosing, respectively). The terminal exponential half-life was approximately 480 hours, which is longer than that observed in single dose studies (220 hours). The difference in half-life may be due to the ability to quantitate risedronate in urine for a longer period of time upon multiple dose administration of 2.5 and 5 mg (672 h after last dose) as compared to single dose administration of 2.5 and 5 mg (168 and 480 h, respectively), or due to renal function as the multiple-dose study utilized older subjects with diminished renal function (meanCLcr of 67 and 70 mL/min) as compared to the young subjects (mean CLcr of 105-115) utilized in single dose studies.

Influence of Food

Phase II studies were conducted with risedronate administered 2 h after a meal (generally dinner) and the phase III study was conducted with risedronate administration 0.5-1 h prior to breakfast. Therefore, a study was conducted to compare the bioavailability of risedronate administered 0.5-1 h before breakfast and 2 h after dinner. Serum concentrations were measured in all 127 subjects, indicating that risedronate was absorbed after all dosing conditions. Furthermore, the extent of absorption (AUC) was not statistically significantly different between dosing 2 h after dinner and 0.5 h before breakfast, and were equivalent based on the criteria for highly variable drugs; however, the rate of absorption (Cmax) was 2.5- fold greater when risedronate was administered before breakfast. The rate and extent of absorption were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. These results indicate that the phase III dosing regimen should

provide extent of absorption equal to, or greater than, the phase II dosing regimen, and a significantly greater rate of absorption.

The effects of a meal on the absorption of risedronate after a single oral 5-mg dose (two 2.5-mg risedronate capsules with 150 mL of water) was also evaluated in healthy adult male (Japanese) volunteers (Study 92115). Plasma concentrations indicate that risedronate was absorbed after all dosing conditions studied, including dosing 30 minutes after breakfast, although absorption was clearly affected by food. The extent (AUC (0-24), urinary excretion) and rate (C max) of absorption showed the following tendency: fasting conditions > dosing 30 minutes before breakfast > dosing 3 hours after breakfast > dosing 30 minutes after breakfast.

Influence of Renal Impairment

The regression analysis of renal clearance and creatinine clearance indicated a significant correlation between renal function and the clearance of risedronate. Risedronate renal clearance was reduced (77%) with a decrease in creatinine clearance (120 to 20 mL/min). Consistent with renal clearance was a trend toward a lower oral clearance when creatinine clearance was decreased. This trend was the consequence of a reduction in renal clearance which resulted in a decrease (44%) in predicted oral clearance. Although these results suggest that only patients with severe renal impairment (creatinine clearance <20 mL/min) may require a dosage adjustment, risedronate is not recommended for patients with creatinine clearance less than 30 mL/min due to a lack of clinical experience.

Pharmacokinetic/Pharmacodynamic Relationships

Markers of bone resorption (dPyr/crt and Pyr/crt) were reduced by 10-15% from baseline after 8 days of treatment with 5 mg risedronate. PK/PD relationships could be defined between the decrease in the bone resorption markers Pyr/crt and dPyr/crt and an increase in Cmin. These results suggested a direct effect of risedronate on osteoclast activity, with the Cmin reflecting the concentration of risedronate on bone that inhibits the osteoclast activity. No direct PK/PD relationship could be identified linking risedronate concentration or exposure to the decrease in bone formation markers.

IV. CLINICAL BACKGROUND

Risedronate was approved by the FDA on March 27, 1998, for the treatment of Paget's Disease of the bone.

[ ]

A PubMed search for risedronate identified 78 papers published from 1991 to December 23, 1998. Most of these papers were preclinical.

V. DESCRIPTION OF CLINICAL DATA SOURCES

Of greatest relevance to this review, both from an efficacy and safety standpoint, the sponsor has conducted two 3-year phase III studies for the treatment of PMO and two one-two-year phase III studies for the prevention of PMO. Additionally, two one-year phase III studies for the treatment and prevention of CIO were conducted.

The following table outlines all the phase III studies for the treatment and prevention of PMO and the treatment and prevention of CIO.

OVERVIEW OF RANDOMIZED DOUBLE-BLIND PHASE III STUDIES			
Study	Duration	Groups	N Randomized
Treatment of PMO			
RVN	3 years	Plo	815
		Ris 2.5 mg	811
		Ris 5.0 mg	813
RVE	3 years	Plo	407
		Ris 2.5 mg	408
		Ris 5.0 mg	407
RON	12-18 months	Plo	217
		Ris 2.5 mg	210
		Ris 5.0 mg	216
ROE	2 years	Plo	180
		Ris 2.5 mg	184
		Ris 5.0 mg	177
Prevention of PMO			
RBL	2 years	Plo	125
		Ris 2.5 mg	127
		Ris 5.0 mg	129
RPE	12-18 months	Plo + Estrogen	259
		Ris 5.0 mg + Estrogen	261
Treatment of CIO			
RCT	12 months	Plo	94
		Ris 2.5 mg	92
		Ris 5.0 mg	99
Prevention of CIO			
RCP	12 months	Plo	76
		Ris 2.5 mg	73
		Ris 5.0 mg	75

Additional data are culled from 15 assorted clinical pharmacology and special studies, which in general are short-term.

Drug Exposure

Drug exposures for patients in the phase 3 studies for the treatment and prevention of PMO (combined dataset) and for patients in the phase 3 studies for the treatment and prevention of CIO are shown in the following tables. The mean number of months and the total patient-months of exposure were comparable for the placebo and Ris 5.0 mg groups.

PATIENTS RANDOMIZED AND EXPOSURE TO STUDY DRUG - COMBINED DATASET			
Study	Plo	Ris 2.5mg	Ris 5.0mg
RVN	820	817	821
RVE	408	410	408
RON	220	212	216
ROE	180	184	179
RBL	126	128	129
Mean Exposure (months)	24	19	25

Total Patient-Months	42348	31169	43377

RCP + RCT	173	169	176
Mean Exposure (months)	10	10	11
Total Patient-Months	1734	1623	1881

Patient Demographics

The baseline characteristics of the study groups were similar. Detailed accountsof baseline characteristics for subjects in the Combined and CIO databases are shown below.

Age (yrs)			
Mean	67	67	67
Range	38-85	42-85	39-85
Race			
Caucasian	97%	98%	97%
Oriental	1.3%	1.1%	0.7%
BMI (kg/m2)	26	26	26
Months Since Last Period	21	21	21
Smoking Status			
Never	56%	54%	54%
Current	16%	15%	15%
Current Alcohol Consumption	49%	49%	50%
% Patients with Prevalent Vertebral Fractures	61%	64%	62%

As seen above, the randomization process was very successful in that the groups were almost identical in the parameters measured.

The baseline characteristics of the patients in the CIO studies are shown in below table.

Age (yrs)	58	59	59
Range	18-84	19-85	26-85
% Female	65	63	64
% Caucasian	94	92	93
% Postmenopausal	52	48	51
Smoking Status (% current)	26	25	19
Alcohol Consumption (% current)	42	49	39
% Patients with Prevalent Vertebral Fractures	33	29	35

The groups were fairly well matched at baseline. A slightly greater percentage of placebo patients vs. Ris 5.0-mg patients were current smokers. This is unlikely to significantly affect the BMD results.

Patient Disposition

In the combined dataset, a total of 5258 patients were randomized; of these, 3533 (68%) completed. The percentages of patients completing were 62% vs. 67% in the placebo and Ris 5.0-mg groups, respectively. Adverse events were the most common reason for early discontinuation with approximately 15% of patients in the placebo and Ris 5.0-mg groups. About 14% of placebo patients and 13% of Ris 5.0-mg patients were recorded as having voluntarily withdrawn from the studies.

In the CIO studies, a total of 518 patients were randomized; of these, 396 (78%) completed the one-year trials. The percentages of patients completing were 75% vs. 82% in the placebo and Ris 5.0-mg groups, respectively. Adverse events were the most common reason for early discontinuation, with approximately 9.0% of patients in the placebo group and 8.0% of the Ris 5.0-mg subjects discontinuing for this reason. About 9.0 % of placebo patients and 4.0% of Ris 5.0-mg patients were recorded as having voluntarily withdrawn from the studies.

VI. INTEGRATED SUMMARY OF SAFETY (ISS)

This ISS will focus on the combined study database: treatment studies RVN, RON, ROE, and RVE and the prevention study RBL, and the two phase 3 CIO studies: RCP and RCT. The sponsor has defined the intent-to-treat (ITT) population as those patients who were randomized and received at least one dose of drug; in practice, however, only patients who had a baseline measurement and at least one postbaseline measurement for a given safety parameter were included in the analyses for that parameter. The endpoint analysis includes the last postbaseline measurement for a parameter.

In the combined study database, there were a total of 5258 subjects randomized to treatment; 32 did not receive study drug and therefore there are 5226 patients included in the ITT safety assessment.

Deaths

The number of deaths reported for all of the phase 2 and 3 randomized, placebo-controlled studies are shown below. The numbers of patients who died on and off study drug are shown as well. The risk for death was not significantly altered by treatment with Ris 5.0 mg when compared with placebo.

Number Randomized	5535	5199	5390
Patient-Years	11007	9614	10818
Number of Deaths	205	217	211
RR vs. Placebo		1.02	0.96
Exposure Adjusted RR		1.1	**0.95**
95% CI		0.91, 1.33	0.78, 1.15

Studies included: RBL, RCP, RCT, ROE, RON, RPE, RVN, RVE, RHN, RHE, 89019, 90019, 89042, 90002

Serious Adverse Events

Serious adverse events are defined as those events that were fatal or life-threatening, were severely or permanently disabling, required (or prolonged) inpatient hospitalization, required intervention to prevent impairment or damage, or was a congenital anomaly, cancer, or overdose.

Combined Database

There were a total of 420 (24%), 311 (18%), and 451 (26%) serious adverse events reported by the placebo, Ris 2.5 mg, and Ris 5.0 mg groups, respectively. These numbers do not raise any serious concerns.

A table of the most common serious Aes reported in each major body system is shown below. P-values are shown for events in which the probability that the difference in incidence rates between the two groups was less than 0.20.

Cardiovascular System	103 (6%)	126 (7%)
Angina	12 (0.7%)	20 (1.1%) p=0.16
MI	17 (1.0%)	19 (1.1%)
CVA	9 (0.5%)	15 (0.9%)
DVT	2 (0.1%)	8 (0.5%) p=0.06
Digestive System	81 (4.6%)	83 (4.8%)
Colitis	9 (0.5%)	13 (0.7%)
Cholelith	6 (0.3%)	10 (0.6%)
Endocrine System	2 (0.1%)	6 (0.3%)
Goiter	1 (0.1%)	3 (0.2%)
Hematologic System	7 (0.4)	12 (0.7%)
Anemia	0	4 (0.2%) p=0.06
Metabolic and Nutritional	6 (0.3%)	4 (0.2%)
Hyponatremia	1 (0.1%)	2 (0.1%)
Musculoskeletal System	109 (6%)	112 (6%)
Traumatic Bone Fracture	79 (4.5%)	57 (3.3%) p=0.07
Arthritis	12 (0.7%)	18 (1.0%)
Bone Disorder	2 (0.1%)	8 (0.5%)
Nervous System	19 (1.1%)	23 (1.3%)
Vertigo	1 (0.1%)	5 (0.3%) p=0.12
Respiratory System	47 (2.7%)	43 (2.5%)
Pneumonia	18 (1.05)	11 (0.6%)
Lung Cancer	2 (0.1%)	8 (0.5%) p=0.06
Urogenital System	42 (2.4%)	42 (2.4%)
Uter Disorder	3 (0.2%)	8 (0.5%) p=0.15
Skin	37 (2.1%)	46 (2.6%)
Skin Carcinoma	30 (1.7%)	37 (2.1%)
Melanoma	2 (0.1%)	5 (0.3%)

Phase III CIO

There were a total of 57 (34%), 46 (28%), and 53 (31%) serious Aes reported by the placebo, Ris 2.5 mg, and Ris 5.0 mg groups, respectively. The body systems with the most frequent reports of serious Aes were the cardiovascular system (8% vs. 6%, Plo vs. Ris 5.0 mg), musculoskeletal

system (10% vs. 8%), and the respiratory system (7% vs. 9%). Within all body systems, there were no significant imbalances in single Aes between the placebo and Ris 5.0-mg groups. None of the comparisons between the placebo and Ris 5.0-mg groups in the incidence of serious Aes were associated with a p-value of less than 0.20.

Withdrawals Due to Adverse Events

Combined Database

There were a total of 261 (15%), 186 (11%), and 245 (14%) Aes leading to withdrawal in the placebo, Ris 2.5 mg, and Ris 5.0 mg groups, respectively. In the digestive system, a total of 6% of placebo subjects and 5% of Ris 5.0-mg subjects withdrew because of an AE.

As a rule, in all treatment groups, there were few patients coded to any single adverse event. Of potential interest there were 15 atraumatic fractures in the placebo group compared with only 4 in the Ris 5.0-mg group.

Phase III CIO

There were a total of 15 (9%) placebo patients and 13 (8%) Ris 5.0-mg patients with adverse events leading to withdrawal from the 2 phase III CIO studies. The cardiovascular and digestive systems were the most commonly cited body systems from which patients had serious Aes leading to study withdrawal. Five (2.9%) placebo subjects and 4 (2.3%) Ris 5.0-mg subjects withdrew from the study because of a cardiovascular AE. There were no significant imbalances between the two groups for individual cardiovascular Aes. Three (1.8%) placebo patients and 5 (2.9%) Ris 5.0 mg patients withdrew from the study because of a GI AE. Again, there were no significant imbalances between the two groups for any individual GI Ae.

Given the small number of patients per adverse event it is not possible to make reliable inferences about causality.

Incidence of All Adverse Events

Combined Database

Body as a Whole	70%	71%
Infect	30%	31%
Pain Back	25%	27%
Pain	14%	14%
Pain Abd	10%	12%
Pain Neck	5%	5%
Asthenia	5%	5%
Pain Chest	5%	5%
Neopl	3%	4%
Hernia	3%	3%
Cardiovascular System	27%	32%
Angina	3%	3%
Hypertension	9%	11%
Cardiovascular Dz	2%	3%
Vasodilatation	2%	2%
Digestive System	50%	52%

Constipation	13%	13%
Diarrhea	10%	11%
Flatulence	4%	5%
Colitis	4%	4%
Gastritis	2%	3%
Tooth Dz	2%	2%
Rectal Dz	2%	2%
Heme and Lymphatic System	9%	10%
Ecchymosis	4%	5%
Anemia	2%	3%
Musculoskeletal System	51%	52%
Arthraglia	22%	24%
Joint Dz	6%	7%
Myalgia	6%	7%
Pain Bone	5%	5%
Cramps Leg	3%	4%
Bursitis	3%	3%
Tendon Dz	3%	3%
Nervous System	31%	34%
Dizziness	6%	7%
Depression	6%	7%
Insomnia	5%	5%
Anxiety	3%	5%
Neuralgia	4%	4%
Vertigo	3%	4%
Hypertonia	2%	2%
Parasthesia	2%	2%
Respiratory System	37%	36%
Pharyngitis	5%	6%
Rhinitis	5%	6%
Dyspnea	3%	4%
Pneumonia	3%	3%
Lung Dz	3%	3%
Skin	27%	29%
Rash	7%	8%
Pruritis	2%	3%
Carcinoma	2%	2%
Herpes Zoster	2%	2%
Special Senses	22%	24%
Cataract	5%	6%
Conjunctivitis	3%	3%
Otitis Med	3%	3%
Urogenital System	25%	27%
UTI	10%	11%
Cystitis	4%	4%

Abdominal pain and anxiety were the only two Aes where the comparison between placebo and Ris was associated with a p-value < 0.05.

Phase III CIO

Body as a Whole	61%	62%
Pain Back	9%	18%
Headache	9%	12%
Pain Abd	8%	10%

Pain	8%	9%
Pain Chest	5%	6%
Asthenia	3%	5%
Pain Neck	4%	5%
Edema Face	1%	3%
Cardiovascular System	21%	22%
Syncope	1%	2%
Digestive System	47%	47%
Nausea	9%	12%
Diarrhea	7%	10%
Dry Mouth	2%	4%
Periodontal Abscess	1%	3%
Vomiting	2%	3%
GI Dz	0%	3%
Anorexia	2%	2%
Flatulence	2%	2%
Mouth Ulcer	2%	2%
Metabolic and Nutritional System	21%	23%
Peripheral Edema	8%	12%
Edema	1%	3%
Increased Weight	2%	3%
Musculoskeletal System	51%	52%
Arthralgia	15%	25%
Arthritis	4%	6%
Arthrosis	4%	5%
Cramps Legs	2%	3%
Nervous System	28%	27%
Depression	8%	9%
Insomnia	4%	5%
Hyperesthesia	1%	2%
Neuralgia	1%	2%
Respiratory System	29%	36%
Asthma	7%	8%
Bronchitis	5%	6%
Dyspnea	4%	5%
Pharyngitis	4%	4%
Pneumonia	2%	4%
Sinusitis	4%	4%
Epistaxis	1%	3%
Skin	27%	25%
Pruritus	2%	4%
Ulcer	2%	2%
Special Senses	19%	21%
Vision Abnormal	2%	4%
Urogenital System	19%	21%
UTI	4%	10%

Back pain and arthralgia were the only two Aes where the comparison between placebo and Ris was associated with a p-value < 0.05.

Special Safety Considerations

In this section more detailed analyses of gastrointestinal, cardiovascular and cancer adverse events.

Gastrointestinal Adverse Events

Combined Database

Upper gastrointestinal (UGI) adverse events were defined using the following preferred terms (COSTART descriptions): abdominal pain, chest pain substernal, duodenal ulcer, duodenal ulcer hemorrhage, duodenal ulcer perforation, duodenal ulcer with hemorrhage and perforation, duodenitis, dyspepsia, dysphagia, esophageal hemorrhage, esophageal ulcer, esophagitis, gastritis, gastrointestinal disorder, gastrointestinal hemorrhage, hematemesis, hemorrhagic gastritis, melena, peptic ulcer, peptic ulcer hemorrhage, peptic ulcer with hemorrhage and perforation, perforated peptic ulcer, perforated stomach ulcer, reactivated duodenal ulcer, reactivated peptic ulcer, stomach ulcer, stomach ulcer hemorrhage, stomach ulcer reactivated, and stomach ulcer with hemorrhage and perforation. Additional gastrointestinal adverse events of clinical relevance are nausea, vomiting, nausea and vomiting, and esophageal stenosis.

These preferred COSTART terms seem to be extensive and it is unlikely that any significant GI adverse events related to the study drug would be excluded from these analyses.

The overall incidence of UGI Aes was 24% for placebo-treated subjects and 26% for the Ris 5.0 mg-treated patients. The following table provides the GI adverse events that were recorded with a greater frequency in the Ris 5.0-mg group vs. the placebo group.

[illegible]	[illegible]	[illegible]
Abdominal Pain	9.5%	11.8%
Gastritis	2.4%	2.6%
GI Hemorrhage	0.6%	1.2%
Dysphasia	0.9%	1.1%
Duodenitis	0.1%	0.6%
Chest Pain Substernal	0.3%	0.5%
Peptic Ulcer	0.1%	0.3%
Melena	0.1%	0.2%
Nausea and Vomiting	0.2%	0.6%
Esophageal Stenosis	0.1%	0.3%

According to the sponsor, the distributions of the severity scores for the GI Aes (mild, moderate, severe) were not significantly different between the placebo and the Ris 5.0-mg groups.

Endoscopy

As part of the protocols, patients who were coded as having moderate to severe UGI Aes were asked to undergo endoscopy to evaluate the complaint in a more objective manner. Endoscopy was not required in these cases and the investigators were allowed to treat empirically prior to endoscopy.

A relatively small sample of subjects with moderate to severe UGI Aes underwent endoscopy. Approximately 21% of subjects in both the placebo and Ris 5.0-mg groups were evaluated directly by this method. In general, the most common finding at endoscopy was "normal" anatomy for both placebo and Ris 5.0-mg groups. At the three sites examined – esophagus, stomach, and duodenum – the Ris 5.0 mg group tended to have a slightly higher incidence of "inflammation" and "erosion or bleeding without ulceration," and a lower incidence of "ulceration," when compared with the placebo group.

Duration of therapy prior to endoscopy does not appear to be a probable explanation for the above findings. While 8 placebo patients and 12 Ris 5.0-mg patients underwent endoscopy during the first 90 days following initiation of therapy, for the remainder of the first year of treatment (divided into 90 day periods) an equal number of placebo and Ris 5.0 mg subjects were subjected to this GI procedure.

Also of note, 42% of placebo patients and 44% of Ris 5.0-mg subjects received empirical drug treatment for their upper GI complaint prior to endoscopy. These numbers argue against there being a difference in endoscopic findings due to a greater use of empirical drug treatment in the Ris group relative to the placebo group.

It is noteworthy that when the data for GI Aes was analyzed by age above or below 65 years, there was no apparent increase in the incidence of Aes relative to placebo for older vs. younger subjects.

Upper GI Adverse Events by Concomitant Use of NSAIDS and/or Aspirin-Containing Medications

To investigate whether the concomitant use of NSAIDS and/or aspirin-containing products increased the risk for GI Aes in patients taking risedronate the company analyzed the data by looking at regular users (take medication three or more days per week), nonregular users (less frequent use than regular users), and nonusers.

Approximately 9.5% of the subjects in the placebo and Ris 5.0-mg groups were categorized as regular users of NSAIDS. Whereas the absolute incidence of the more common GI Aes (abdominal pain, dyspepsia, gastritis) was higher in the regular users of NSAIDS for both the placebo and Ris 5.0 mg subjects compared with nonusers, the relative difference in incidence between active and placebo-treated subjects was not appreciably higher for regular users of NSAIDS.

A similar percentage of subjects – about 9-10% - were also categorized as regular users of aspirin-containing products. In general, compared with Ris 5.0 mg/aspirin-nonusers, the absolute incidence of GI Aes was not appreciably increased by the concomitant use of aspirin-containing drugs. In relative terms - that is, comparing rates between Ris and placebo within regular and nonregular user categories, the concomitant use of Ris 5.0 mg and aspirin also did not significantly increase the incidence of GI Aes. Of note, however, compared with the nonusers,

there was an increase in the relative incidence of esophagitis in the regular users of aspirin taking Ris 5.0 mg compared with placebo. For the nonusers, 19 (1.9%) placebo vs. 14 (1.5%) Ris 5.0 mg subjects were coded for esophagitis, whereas for regular users of aspirin, 2 (1.3%) placebo compared with 5 (2.9%) Ris 5.0 mg subjects were diagnosed with esophagitis.

It is not surprising that subjects who were taking H_2-blockers or proton pump inhibitors during the studies or who had GI-related disorders at baseline also reported a greater incidence of GI Aes during treatment with Ris 5.0 mg and placebo when compared to subjects not taking these concomitant medications or to subjects without GI disease at baseline.

Phase III CIO Studies

Twenty percent of placebo patients and 21% of Ris 5.0-mg subjects had an UGI AE during the two phase III CIO studies. The following table provides the specific Aes that were reported by a greater number of Ris 5.0-mg subjects compared with placebo subjects.

Abdominal Pain	8.2%	10.3%
Gastrointestinal Disorder	0%	2.9%
Esophagitis	0.6%	1.7%
Duodenitis	0%	1.1%
GI Hemorrhage	0%	0.6%
Nausea	9.4%	12.1%
Vomiting	1.8%	3.4%
Nausea and Vomiting	0%	0.6%

Although not impressive, there is some evidence for a slightly greater risk for some UGI Aes associated with Ris 5.0-mg use compared with placebo. The absolute risk for the more serious Aes (esophagitis, GI hemorrhage, etc.) is low however.

Overall, the majority of the Aes were reported as mild; yet, compared with no cases in placebo, there were 2 cases of severe esophagitis, 1 case of severe duodenitis, and 1 case of severe dysphasia in the Ris 5.0-mg group.

Endoscopy

A total of 17 (3.3%) subjects (3.5% of placebo and 3.4% of Ris 5.0 mg) underwent endoscopy to investigate suspicious clinical symptoms or signs. Most of the examinations were reported as normal. This was true for both treatment groups. There were no significant differences between groups in the percentage of reports of inflammation, erosion, or ulceration at the three sites examined: esophagus, stomach, and duodenum.

Overall, endoscopic examinations were conducted earlier in the Ris 5.0-mg group than the placebo group. Sixty-seven percent of placebo subjects and 50% of the Ris 5.0-mg subjects received empirical treatment prior to endoscopy. It's unknown if this may have influenced the findings at endoscopy; if anything, however, this would bias against the drug.

Age greater than 65 years did not appear to substantially alter the pattern of GI AE reporting.

Upper GI Adverse Events by Concomitant Use of NSAIDS and/or Aspirin-Containing Medications

What stands out in the analysis of the incidence of UGI Aes with concomitant use of NSAIDS or aspirin is the higher rate of abdominal pain reported by Ris 5.0 –mg-treated patients vs. placebo-treated patients. As a point of reference, in nonusers of NSAIDS or aspirin, the difference in the incidence of abdominal pain between placebo and Ris 5.0-mg groups was 1.5% in favor of placebo. In contrast, for users of NSAIDS the difference was 5.7% in favor of Ris 5.0 mg; and for users of aspirin the difference was 14.5% in favor of Ris 5.0 mg. The number of patients taking NSAIDS was relatively small, and smaller yet for aspirin users; therefore, these rates need to be interpreted cautiously.

The majority of patients who developed abdominal pain did not receive any specific intervention and only 2 patients (both placebo + aspirin users) withdrew because of this specific AE.

Unexpectedly, there was no evidence that risedronate-treated patients taking both NSAIDS and aspirin had an increased risk for symptomatic GI Aes, including abdominal pain. Again though, the small number of patients using both NSAIDS and aspirin make estimates of risk unreliable.

There did not appear to be a significant difference in the incidence of upper GI Aes between the placebo and Ris 5.0 mg groups when the data were analyzed by mean or median dose of steroid used.

Cancer

Phase III Combined and CIO Databases

The total number of cancers reported in patients treated with placebo, Ris 2.5 mg, and Ris 5.0 mg were similar (143, 150, and 133, respectively)[RR = 1.2 ——— for Ris 2.5 vs. placebo and RR = 0.9 ——— for Ris 5.0 mg vs. placebo]. There were however two imbalances noted. Fewer cases of GI cancer and more cases of lung cancer were reported in risedronate- vs. placebo-treated subjects. Details are provided below.

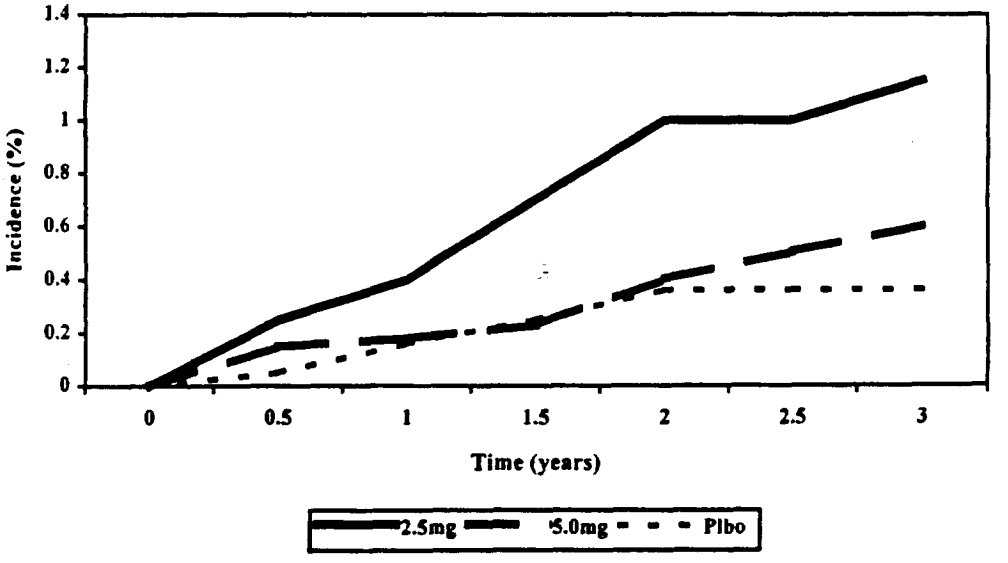
Lung Cancer (see consult from the Division of Oncology Drug Products)

During the initial review of the oncology adverse events, an imbalance in the number of lung cancer cases reported from the PMO and CIO studies was noted between the placebo and the risedronate groups. This was an unexpected finding, and in isolation meant little. In an attempt to gain a better perspective on these initial findings, the company was asked to provide, if available, additional placebo-controlled data. They responded by submitting recently unblinded results from two large hip fracture studies: RHE and RHN. In these studies over 9000 elderly women were randomized in equal fashion to placebo, Ris 2.5 mg, or Ris 5.0 mg once daily for 3 years. Completion rates were similar for all groups. In these data an imbalance in the rates of lung cancer was observed between the placebo and Ris 2.5-mg groups. No imbalance occurred between the placebo and Ris 5.0-mg groups. Although no dose response effect was noted, these findings were not completely reassuring and did not absolve risedronate from concern (see table and Kaplan-Meier plot below).

Study			
RVN	1	5	3
RVE	1	1	2
RON	0	1	1
ROE	0	2	1
RBL	0	0	1
RPE*	0	0	1
RCP	0	0	1
RCT	0	2	0
RHE	2	7	4
RHN	8	17	6
Total	13/10488 pyrs	36/9163 pyrs	20/10525 pyrs
Relative Risk	1	3.2	1.5

*Tx groups were ERT + Plo and ERT + Ris 5.0 mg

Cumulative Incidence of Lung Cancer
All Risedronate Phase 3 Studies



Log-rank p-values:
p<0.001 2.5mg vs. placebo
P=0.30 5.0mg vs. placebo

By way of further investigation, lung cancer data for 3 other bisphosphonates were evaluated. Formal statistics aside, two drugs were associated with a small to modest excess risk (RR~1.5) for lung cancer when compared with placebo, while the third was not .

Several issues should be kept in mind when evaluating the cancer findings from the risedronate trials (and the data for the other bisphosphonates). First, the studies were not designed to evaluate the risk of cancer with drug use and therefore no systematic screening for disease was done. Furthermore, a large number of patients dropped out of the trials and lacked follow-up, and a significant number of patients diagnosed with lung cancer lacked a confirmatory pathological

diagnosis. That these data are analyzed in a post-hoc manner further complicates their interpretation.

This being said, if one accepts that there is an association between the use of risedronate (or any other bisphosphonate) and an increased risk of being diagnosed with lung cancer, then the nature of this association is either due to chance, is causal, or due to bias.

When viewed in isolation, the data for each individual drug are of questionable concern. When viewed in aggregate [risedronate (2 hip fracture studies) + data from 3 other bisphosphonates] however, the relative risk for lung cancer in the drug vs. placebo-treated subjects is about 1.4. And depending on ones statistical approach, the p-values range from 0.06 to 0.15 for this association.

Given the relatively short-term exposure to drug in these trials, a causal association between risedronate and lung cancer would represent enhanced growth of pre-existing tumors, not tumor initiation. Aside from the consistency of the finding with other bisphosphonates, there is little to no reason to believe that risedronate is a tumor promoter. The drug is poorly absorbed (<1-2%), and animal data indicate that lung concentrations of the drug are extremely low, particularly in comparison with bone and small intestine. Matters are further complicated by the larger risk seen with the 2.5-mg dose of risedronate relative to the 5.0-mg dose. If risedronate were stimulating the growth of pre-existing tumors, at a minimum, one would expect the risks for lung cancer to be comparable for the two risedronate doses. Unfortunately, there are no animal data from appropriate models to refute or support the notion that risedronate may act as a promoter of lung cancer.

The randomization of large number of subjects within placebo-controlled studies makes it extremely unlikely that confounding and most forms of bias played any role in the lung cancer findings. Detection bias is a theoretical possibility, but no reasonable hypothesis as to how this might be operating has been generated. Here too, the greater incidence of lung cancer in the Ris 2.5-mg group compared with the 5.0 mg group makes no sense.

Gastrointestinal Cancer

As shown in the table and Kaplan-Meier figure below, there were fewer cases of GI cancer (in large part rectal, followed by pancreatic cancer) diagnosed and reported for patients in the Ris 2.5 mg and the Ris 5.0-mg groups compared with the placebo group. Like the lung cancer data, most of the cases of GI cancer arose in the two hip fracture studies; this is not surprising given that these are the largest studies with the oldest subjects. Unlike the lung cancer findings, however, both doses of risedronate were associated with a lower risk for being diagnosed with GI cancer when compared with the placebo rate.

Study			
RVN	9	1	5
RVE	2	3	3
RON	0	0	0
ROE	0	0	0
RBL	1	0	0
RPE*	0	NA	1
RCP	0	0	1
RCT	0	0	0
RHE	16	8	8

RHN	13	12	9
Total	41/10488 pyrs	24/9163 pyrs	27/10525 pyrs
Relative Risk	1	0.67	0.66

When placebo-controlled data for another bisphosphonate were analyzed, the relative risk for being diagnosed with GI cancer was also modestly lower (RR=0.61) for the drug group relative to the placebo group.

It is important to re-emphasize that, for the reasons cited above regarding evaluation of the lung cancer data, one must interpret the GI cancer data cautiously.

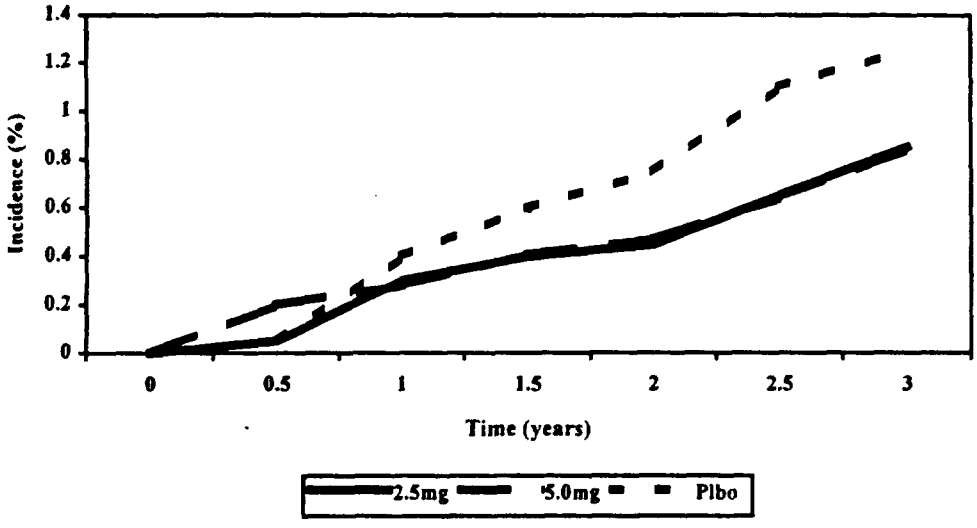
Here too, if one accepts that the use of risedronate (or any bisphosphonate) is associated with a lower risk of being diagnosed with GI cancer, then the nature of the association is either due to chance, is causal, or due to bias.

An imbalance in the rates of GI cancer between risedronate (2.5mg) and placebo first came to attention from review of the eight PMO and CIO trials. Given that a similar imbalance was subsequently seen in the risedronate hip fracture studies and in a dataset from another bisphosphonate, it's less likely that the association between risedronate and a lower risk for a GI cancer is due to chance.

In contrast to the cumulative incidence curves for lung cancer, the curves for GI cancer are more consistent with drug-induced inhibition of GI tumor growth or spread. The lines depicting the GI cancer event rates in the drug groups do not diverge from the placebo line immediately, as the 2.5 mg group does for lung cancer, but after approximately 1.5 to 2 years of drug exposure. In addition, unlike the discrepant dose response effect observed for lung cancer, both risedronate doses are associated with a similar reduction in risk for GI cancer relative to placebo. These curves are not, however, solid proof that risedronate – through some unknown biological mechanism – slows the growth of tumors originating in the GI tract, and they simply support such a proposal. However, as with lung cancer, there is little to no biological plausibility for the observations.

A third explanation for the risedronate (bisphosphonate) GI cancer data remains bias. Given bisphosphonates' potential to irritate the GI tract, it is tempting to speculate that drug use led to an increased rate of endoscopic evaluations. There is no evidence from the available data on rates of colonoscopy and sigmoidoscopy that this was the case. More importantly, if this type of surveillance bias were occurring, it would increase the rate of cancer detection in the risedronate compared with the placebo-treated patients. Thus, as with the lung cancer findings, no tenable hypothesis to support detection bias as an explanation for the GI cancer data has emerged.

Cumulative Incidence of GI Cancers
All Risedronate Phase 3 Studies



Log-rank p-values
p=0.12 2.5mg vs. placebo
p=0.09 5.0mg vs. placebo

In the final analysis, we are left with some uncertainty regarding the precise magnitude and nature of the associations between risedronate (and other bisphosphonates) with lung and GI cancers. Chance seems a less likely explanation for these observations than detection bias or causality. It is important to keep in mind that the incidence rates for mortality (on study) and all cancers did not differ between the two doses of risedronate and placebo. Perhaps a risedronate mortality follow-up study would help put these data into better perspective.

Fractures Reported as Adverse Events

Phase III Combined Dataset

Clinical fractures, either traumatic or atraumatic, were reported as adverse events in the phase III PMO clinical studies. Clinical fractures were comprised of all nonvertebral fractures, as well as those vertebral fractures reported as adverse events by the investigator.

Overall, 12% of placebo patients reported a total of 270 nonvertebral fractures. This is in contrast to the 9% of Ris 5.0-mg subjects who were coded as having a total of 202 nonvertebral fractures. The table below provides the data on the most common nonvertebral fractures in the placebo and Ris 5.0-mg groups.

[illegible]				
	No. (%) of patients	No. of fractures	No. (%) of patients	No. of fractures
Radius	39 (2.2%)	41	22 (1.3%)	22
Ribs	32 (1.8%)	35	23 (1.3%)	24
Foot	25 (1.4%)	27	28 (1.6%)	29
Humerus	23 (1.3%)	23	7 (0.4%)	7

There were no significant site-specific imbalances in the number of fractures between active and placebo-treated patients. In fact, the rates for most sites were lower for the Ris 5.0-mg group compared with the placebo group.

Clinical Laboratory Evaluations

Phase III Combined Dataset

For the purposes of this review the clinical laboratory evaluations include the following variables:

Hematology – hemoglobin (Hb), hematocrit (Hct), platelets (Plt), and white blood cells (WBC)
Hepatobiliary – total bilirubin (total bili), albumin (alb), ALT, AST, GGT, and total alkaline phosphatase (alk phos)
Renal function – creatinine (crt)
Electrolytes and Glucose – Sodium (Na), potassium (K), chloride (Cl), bicarbonate, and glucose
Bone metabolism – calcium (Ca) and phosphorus (phos)

In general, there were no significant differences between the placebo and Ris 5.0-mg groups in the mean changes from baseline to endpoint in the clinical laboratory parameters.

The shift table data (i.e., normal to low or high to low, normal to high or low to high) are based on the upper and lower limits of normal for the respective lab parameter.

Shift table data followed by potentially clinically significant change data will be presented for each of the five major laboratory parameter categories outlined above. Where appropriate, additional safety data evaluations will be included after the shift and clinically significant change data are shown.

Hematology

Shift Data

The only parameters in which a greater percentage of Ris 5.0-mg subjects compared with placebo subjects shifted to abnormal values from baseline to endpoint were Hb and Hct. Two percent of placebo patients compared with 4% of Ris 5.0-mg patients shifted from normal or high at baseline to low values at endpoint for Hb. Similarly, 2% of placebo patients and 3% of Ris 5.0-mg subjects shifted from normal or high values at baseline to low values at endpoint for Hct.

Clinically Significant Changes

For the most part, there were few subjects in any group ($\leq$ 1.0%) who had hematology values significantly below or above normal at endpoint. For Hb, the only parameter of note, less than 1.0% of placebo patients and 1.0% of Ris 5.0 mg subjects had Hb values that were significantly low at endpoint.

Additional Data

Because a greater percentage of Ris 5.0 mg treated patients had low Hb values at endpoint compared with placebo-treated subjects, additional information is provided for cases of anemia reported as adverse events.

Of the 5226 patients in the combined studies, 135 patients (52 placebo, 28 Ris 2.5 mg, and 55 Ris 5.0 mg) had a total of 139 events of anemia. Ninety-two percent of these cases had an identifiable anemia treatment reported: iron or vitamin supplementation. Sixty-three percent of the placebo and Ris 5.0-mg cases were recorded as resolved by endpoint. The mean duration for the events reported as resolved was 171 days in the placebo group and 159 days in the Ris 5.0 mg group.

These figures do not raise concern about risedronate's effect on Hb levels.

Hepatobiliary

Shift Data

There were more subjects in the Ris 5.0-mg group (37) compared with those in the placebo group (17) who shifted from a normal or high albumin to a low albumin at endpoint. The clinical significance of this difference is unknown.

Clinically Significant Changes

There did not appear to be any significant differences between the active and placebo-control groups in the percentage of patients who developed potentially clinically significant changes in the hepatobiliary parameters.

In fact, more placebo compared with Ris 5.0 mg treated subjects had high or markedly high AST, ALT and/or GGT values at endpoint or on two or more occasions during the studies: 241 placebo vs. 213 Ris 5.0 mg. Thirty-seven percent of placebo patients and 34% of the Ris 5.0 mg subjects had all elevations resolved by endpoint.

Renal Function

Shift Data

There were no significant differences between groups in the percentage of patients with shifts from normal or low creatinine values at baseline to high values at Months 12, 24, and 36, or at endpoint. Roughly 2% or less of subjects had abnormally high values during the trials.

Clinically Significant Changes

At endpoint, there were 1.9% of Ris 5.0-mg subjects and 1.5% of placebo subjects who had creatinine values of potential clinical significance.

Electrolytes and Glucose

Shift Data

There were no significant differences between groups in the percentage of patients with shifts from normal or low electrolyte or glucose values at baseline to high values at Months 12, 24, and 36, or at endpoint. Similarly, there were no significant differences between groups in the percentage of patients with shifts from normal or high values at baseline to low values at Months 12, 24, and 36, or at endpoint.

Clinically Significant Changes

The percentage of patients with electrolyte values that were markedly abnormally high or low was small and generally comparable across the treatment groups. At endpoint both the placebo and Ris 5.0-mg groups had 7% of the subjects with abnormally high serum glucose values.

Additional Data

There were no significant differences between the placebo and Ris 5.0-mg groups for electrolyte or glucose-specific adverse events: diabetes mellitus, hyperglycemia, hyperkalemia, hyponatremia, etc.

Serum Calcium and Phosphorus

Shift Data

There were more Ris 5.0 mg compared with placebo subjects who had low serum calcium values at endpoint (and all other time points): 26/1559 vs. 14/1555, p=0.08. Likewise, more active- vs. placebo-treated subjects had low serum phosphorus values at endpoint: 8/1558 vs. 3/1555, p=0.2. A greater number of Ris 5.0 mg subjects also had abnormally high serum phosphorus values at endpoint when compared with placebo-treated patients: 15/1558 vs. 6/1555, p=0.08

Clinically Significant Changes

Four placebo subjects and one Ris 5.0 mg subject had markedly low calcium levels at endpoint.

Additional Data

There were four subjects with a "calcium disorder" in the Ris 5.0-mg group and none in the placebo group. Hypercalcemia, as an adverse event, was reported for 4 and 3 of the Ris 5.0 mg and placebo subjects, respectively.

No cases of clinically manifest hypocalcemia were reported for any subject.

Serum iPTH

Serum iPTH data were collected from a subset of patients in studies RVN (n=136 for placebo and n=135 for Ris 5.0 mg) and RVE (n=119 for placebo and n=107 for Ris 5.0 mg); the changes from baseline to Months 12 and 36 are provided here. Additionally, data on the correlation between the changes in iPTH with the changes in forearm BMD are presented.

In study RVN, compared with baseline values, both groups had mean increases in iPTH at Month 12 and Month 36, although the increases were larger in the Ris 5.0-mg group compared with the placebo group. At Month 12, the 14% mean difference between the groups was statistically significant at p=0.03. At Month 36, the 9% mean difference was not statistically significant (p=0.5). In the 112 subjects in the Ris 5.0 mg group that had baseline and Month 12 midshaft radius BMD measurements, there was no correlation between the change in iPTH with the change in midshaft radius BMD (r= -0.1; p=0.3)

In study RVE, compared with baseline values, both groups had mean increases in iPTH at Months 12 and 36, with the increase in the Ris 5.0 mg group being significantly greater at Month

12 (18%; p=0.03), but not at Month 36 (8%; p=0.5). In the 66 Ris 5.0 mg subjects that had baseline and Month 12 midshaft radius BMD measurements, there was no correlation between the change in iPTH with the change in midshaft radius BMD (r=0.09; p=0.5).

These limited data suggest that treatment with risedronate (5 mg per day) increases the odds of developing increased levels of serum iPTH. These elevations do not, however, appear to be related to adverse effects on cortical bone.

Vital signs

There were small changes in the mean values for pulse rate and systolic and diastolic blood pressure in the placebo, Ris 2.5 mg, and Ris 5.0 mg groups. There did not appear to be any significant differences between the placebo and risedronate groups.

Urinalyses

Shift Data

There were no significant differences between groups in the percentage of patients with abnormal shifts in urine parameters.

VII. Clinical Studies

The Treatment of Postmenopausal Osteoporosis

7.1 Study RVN

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate in the Treatment of Postmenopausal Women with Established Osteoporosis-Related Vertebral Deformities

The first patient was enrolled 12/03/1993 and the final patient's last observation was 01/19/1998

7.1.2 Objective: To determine the efficacy of risedronate in reducing vertebral fracture incidence (and rate) in osteoporotic postmenopausal women.

7.1.3 Design: This was a randomized, double-blind, multi-center (110 sites in North America) 4-year study in postmenopausal women with osteoporosis. Subjects were randomized to one of three groups: placebo, Ris 2.5 mg daily, or Ris 5.0 mg daily. Following 3 years of active therapy, patients were followed for an additional one year off study drug (data from the 3 years of active therapy are provided here; the one-year follow-up data will be submitted at a latter date). All patients received 1 gram of elemental calcium equivalent per day for the 4-year period. During the study the sponsor, [redacted] terminated the 2.5 mg arm. Patients were instructed to take study drug "once daily with a large amount of water (8 oz.). Take on an empty stomach 30 to 60 minutes before breakfast. Take only with water. Do not lie down for one hour after taking the tablet. Take two calcium tablets daily with lunch or evening meal." All patients who withdrew prior to completing 3 years were requested to return to the study center at the time of their scheduled Month 36 visit.

7.1.4 Patient Population: Female patients at least 5 years postmenopausal and $\leq$ 85 years of age were enrolled in the study. Patients had to have had either 1) two or more vertebral fractures (T4-L4) or 2) had one vertebral fracture, combined with a low spinal BMD ($\leq$ 0.83 g/cm^2 by [redacted] or $\leq$ 0.94 g/cm^2 by [redacted] Some of the exclusion criteria included: history of hyperparathyroidism, hyperthyroidism, or osteomalacia within 1 year of enrollment, any condition that might interfere with evaluation of the spinal x-rays,
Any use of the following medications within 3 months of starting study drug or any use of the following medications for more than 1 month within 6 months prior to study entry:
- Oral or parenteral glucocorticoids (5 mg prednisone or equivalent/day),
- Anabolic steroids,
- Estrogen or estrogen-related drugs, e.g., tamoxifen, raloxifene, or tibolone (oral, skin patch). Low-dose vaginal estrogen (17 b-estradiol 0.2 mg/day; estropipate 1.5 mg/day) was allowed, and
- Progestogen;

· Any use of the following medications within 1 month of starting study drug or any use of the following medications for more than 1 month within 6 months prior to study entry:
- Calcitonin,
- Vitamin D supplements (>500 IU per day),
- Calcitriol (>1.5 mg/week), and
- Depot injection >10,000 IU Vitamin D in the previous 9 months;

· Any use of the following medications within 6 months of starting study drug or any use of the following medications for more than 14 days within 1 year prior to enrollment:
- Any bisphosphonate,

- Fluoride (10 mg/day), and
– Subcutaneous estrogen implant

7.1.5 Endpoints: Lateral thoracic and lumbar spinal x-rays were taken annually throughout the study. Bone mineral density (Dexa) of the spine and proximal femur was measured at baseline and then at Months 24 and 36. Standing height by stadiometry was measured at baseline and Months 24 and 36. In a subset of patients, densitometry of the spine, proximal femur, and midshaft and distal radius was obtained at Months 6, 12, 18, 24, 30, and 36. Also in a subset, iPTH levels were measured at baseline and Months 1, 3, 6, 12, and 36. Some patients also underwent bone biopsies at baseline and at Month 36.

7.1.5 a Baseline and Postbaseline Screening of Spinal Radiographs

Baseline Radiographs
A radiographic screening process was implemented for this study to ensure that quality spinal radiographs were obtained and that the appropriate patients were enrolled into the protocol. Lateral and AP radiographs of the thoracic and lumbar spine (T4 to L4) were obtained at the study centers according to guidelines outlined in the protocol. Anterior-posterior radiographs were taken at pretreatment only. Pretreatment films were sent either to [redacted] for determination of patient eligibility. If the radiographs were of acceptable quality, the films were evaluated to determine if the spine was of sufficient health to allow for subsequent assessments and morphometry (6 point measurement). The following criteria was used for this evaluation:
A: Absence of multi-level, advanced Scheuermann's disease;
B: Absence of multi-level, congenital or acquired fusion;
C: Absence of multi-level advanced hyperostosis or ankylosing spondylitis;
D: Absence of advanced degenerative remodeling and osteophytosis; and
E: Scoliosis or obliquity greater than 15-20° as seen from the AP view.

If the baseline screening films met all of the requirements above, an evaluation of the number of prevalent vertebral deformities was made (T4-L4). Using the following criteria:
A: Anterior to posterior or middle to posterior height ratios of 0.8 or less (as described in Section 3.15.1.2); and
B: For a crush deformity, a height reduction of 20% or greater as compared to neighboring vertebra (i.e., Hpi:Hpi-1 or Hpi:Hpi+1 0.8).

At this screening phase, the determination of prevalent deformities (fracture) was primarily made via a visual basis. A visual assessment was made first, and obvious fracture deformities were counted. If there were equivocal deformities, these were measured with a finely calibrated ruler or caliper and ratios of the anterior and middle vertebral body heights to posterior vertebral body height were determined. If the ratio was 0.8 or less, the level was counted as a vertebral deformity. Deformities were not graded during the screening process. The results of the deformity evaluation at baseline (number of prevalent deformities, if any) was faxed to the Clinical Sites within 48-72 hours of receipt of films at the Radiographic Screening Centers. These deformities were used only for the purpose of patient enrollment and stratification.

If the films satisfied the qualifying criteria for patient enrollment, the radiographs were electronically digitized at the Regional Screening Center and sent on optical disc to the [redacted]

The consistency of the Regional Radiographic Screening Centers selected for the risedronate Phase III clinical trials was tested in a cross-calibration study. A set of radiographs from 28 patients (AP and lateral thoracic and lumbar spine) was evaluated for prevalent fracture by an experienced radiologist "Gold Standard" and the radiologists from the screening centers. There was good overall agreement between the centers (kappa = 0.81) for the presence of a fracture.

Postbaseline Radiographs
The Regional Radiographic Screening Centers also evaluated the lateral spine films for radiographic quality at Months 12, 24, and 36. If the radiographs were of sufficient quality, they were digitized and sent to the [redacted] for processing. If the films were of insufficient quality, a repeat was requested.

7.1.5 bVertebral Body Height
Vertebral body heights were defined as follows:

Ha, the distance between the intersections of the line describing the vertebral contour running through the anterior vertebral margin and the lines through the superior and inferior endplates;
Hp, the distance between the intersections of the line running through the posterior vertebral margin and the lines through the superior and inferior endplates; and
Hm, the distance between the superior and inferior endplates in the mid-plane between the anterior and posterior margin.

Vertebral Body Height Ratios
Vertebral body height ratios were defined as follows:

Ha:Hp, the ratio of Ha over Hp as defined above;
Hm:Hp, the ratio of Hm over Hp as defined above;
Hpi: Hpi-1, the ratio of Hp over Hp of the cranially situated vertebral body; and
Hpi: Hpi+1, the ratio of Hp over Hp of the caudally situated vertebral body.

7.1.5 c Prevalent and Incident Vertebral Deformity (Fracture) Determination
The [redacted] processed all electronic spinal images for this study. Upon receipt of the optical discs from the Regional Screening Center, the images were checked for optical integrity and completeness. Morphometry point placements were performed by trained technicians on all measurable vertebral bodies and then verified by qualified radiologists. Height coordinates were sent to P&G personnel. Vertebral heights were calculated by P&G personnel from the points (x, y coordinates) and potential prevalent and incident deformities identified using the prescribed algorithms. These evaluations were all performed by personnel blinded to treatment assignment throughout the evaluation period.

Quantitative Morphometry (Baseline)
The algorithm for identifying prevalent deformities [fracture(s)] was the Eastell Trimming Method. A vertebral body was considered to be deformed at baseline (prevalent fracture), if any of the height ratios (Ha/Ha, Hm/Hp, Hpi/Hpi-1 or Hpi/Hpi+1) fell below 3 standard deviations of the mean for the normal (undeformed) population. If the height measurements for the vertebral body above (Hpi-1) or below (Hpi+1) were missing and the Hpi/Hpi-1 or Hpi/Hpi+1 criterion could not be evaluated, the next vertebra above (Hpi-2) or below (Hpi+2) was used in the denominator to determine the ratio. Within each vertebral level, cut-off values were computed for

each type of prevalent deformity (wedge, endplate, and crush) based on height ratios. The algorithm was performed for each vertebral height ratio separately. The actual trimming method consisted of the following algorithm. For a given value, the algorithm began by removing all observed values more than 1.5 times the interquartile range above the 75th percentile or below the 25th percentile. After removing these observations the percentiles and interquartile range were recalculated for the remaining sample and the process was repeated. This entire process was continued until no more observations qualified for removal. The mean and standard deviation of the final trimmed sample were then used as estimates of the mean and standard deviation of undeformed vertebrae for the given response. The minimum cut-off value for defining a potential deformity in terms of prevalence, was 3 standard deviations below the mean of the trimmed sample (ratios that are smaller than the cut-off value indicated a prevalent deformity).

Quantitative Morphometry (Postbaseline)
In a vertebra judged normal at baseline, based on the Eastell Trimming Method, a potential incident vertebral deformity was defined as a greater than or equal to 15% reduction in any one of the three measured vertebral heights (Ha, Hm, or Hp), measured between the baseline radiograph and the radiographs acquired at the subsequent visits. In a vertebra already judged deformed at baseline, based on the Eastell Trimming Method, a potential incident vertebral deformity (fracture) was defined as greater than or equal to 4 mm reduction in vertebral height (Ha, Hm, or Hp) measured between the baseline radiograph and radiographs acquired at subsequent visits.

Semiquantitative Assessment: Prevalent and Incident Deformities (Fractures)
In addition to quantitative morphometry, all electronic images of spinal radiographs were assessed for potential prevalent and incident deformities (fractures) using the Genant Scoring method. A grade or score of 0 was normal, Grade 0.5 was uncertain or questionable (less than 20% reduction in anterior, middle, and/or posterior height), Grade 1 indicated a mild deformity with approximately 20% to 25% reduction in anterior, middle, and/or posterior height, Grade 2 indicated a moderate deformity with approximately 25% to 40% reduction in anterior, middle, and/or posterior height, and Grade 3 indicated a severe deformity with greater than a 40% reduction in anterior, middle, and/or posterior height. Digitized images were sent on optical disc from the [redacted] for assessment by an expert radiologist. All radiographs for a patient were assessed at the same time and in temporal order. All evaluable vertebral levels were scored. A prevalent deformity was identified when a vertebral level had a semiquantitative score greater than or equal to 1.0 at baseline. An incident vertebral deformity was scored when there was at least an increase of 1.0 in the semiquantitative assessment score from baseline or an increase of 0.5 if the baseline was scored as 0.5. Scoring of vertebral deformities was done electronically on a dedicated workstation.

Adjudication of Discrepancies
Discrepancies between the quantitative and semiquantitative assessments for prevalent and incident vertebral deformities (fractures) were adjudicated by an expert radiologist at the [redacted]. A different radiologist performed the adjudication than the one who performed the semiquantitative assessment. During adjudication, all visits for a patient were reviewed. For vertebral levels needing adjudication, the radiologist assigned a yes (positive for deformity), no (negative for deformity), or cannot assess score. A dedicated workstation was used for this process. Software consistency checks were utilized to prevent incongruous scoring (i.e., a deformity scored at a certain visit did not go away at a subsequent visit). Vertebrae identified as deformed at baseline (prevalent deformities) or during the study (incident fractures) by both quantitative morphometry and semiquantitative assessment plus the fractures identified by adjudication constitute the final dataset for evaluations. Over the

course of the trial, no more than one incident vertebral deformity was counted per vertebral level in each patient.

7.1.5 d Bone Densitometry

Only [redacted] DXA instruments were used in this study. All DXA scans (patient and phantom data) were acquired according to procedures established by the central analysis and quality assurance facility [redacted] Patient scans of the AP lumbar spine (L1 to L4), proximal femur (femoral neck and trochanter), and radius (distal and midshaft [1/3]) were analyzed centrally at [redacted]. Dual Energy X-ray Absorptiometry phantom data were analyzed by [redacted] for consistent instrument performance throughout the study. If necessary, [redacted] generated longitudinal BMD correction factors were applied to patient data to compensate for instrument variations. Based on anthropomorphic spine phantom data, the DXA instrumentation at 24 clinical sites in this study required longitudinal correction factors to compensate for drifts or shifts in BMD measurements. In addition, 8 sites had instrument upgrades during the study (Appendix 1.2, DXA Interim QC Report). At Site 3945, no cross-calibration data were acquired between the old and new instruments. For 6 of the remaining 7 sites, cross-calibration correction factors were derived from phantom or human measurements.

7.1.5 e Bone Biopsy

In a subset of patients, bone biopsies were obtained at the ilium. Biopsies were taken after double labeling. In patients who had a previous biopsy, the sample was taken from the iliac crest opposite to the most recent biopsy and away from any previous biopsy site. The specimens were shipped to [redacted] and subsequently forwarded to [redacted], for processing, sectioning, and measurement. Stained and unstained bone sections were measured using transmitted and fluorescent light microscopy to derive static and dynamic parameters.

7.1.6 Statistical Analyses:

Two patient populations were defined in the protocol: 1) Intent-to-treat (ITT) population is defined as all patients who were randomized to one of the treatment groups and who received at least one dose of study medication and 2) evaluable (EV) population is defined as the patients who are included in the ITT population who were not protocol violators according to the inclusion/exclusion criteria and who took at least 80% of study drug. Data were analyzed by stratum: 1) patients with only one vertebral deformity and low BMD of the LS at baseline and 2) patients with two or more vertebral deformities at baseline.

All statistical analyses for treatment comparison were conducted at the 0.05 significance level, two-sided. Interactions were tested at the 0.05 level. For time-to-event variables (vertebral fracture incidence, osteoporosis-related fracture incidence, hip and wrist fractures, and discontinuation), Kaplan-Meier estimates are provided using visit dates rather than radiograph dates.

The primary efficacy analysis was based on incident vertebral fractures (new and worsening) diagnosed during the 3-year study. The adjudication process (previously described) identified incident vertebral fractures. Time to fracture was defined as the scheduled 3-monthly visit closest to the date of the radiograph, rather than the date of the radiograph.

Patients who did not have a baseline and at least one postbaseline radiograph during the

3-year treatment period and patients with an unknown incident fracture status were excluded from vertebral fracture analyses. The proportion of patients who sustained at least one incident vertebral fracture, (either a new fracture in a previously undeformed vertebrae, or a worsening fracture in a previously deformed vertebrae) at each time point during the study was determined based on life table methodology (time-to-first incident fracture). Vertebral fractures that were caused by severe trauma (e.g., car accidents, falls from greater than standing height) were excluded from analysis. For vertebral fractures, patients who did not have an event were censored at the visit of their last evaluable radiograph during the 3-year treatment period.
For the analysis of incident vertebral fractures, the placebo and 5-mg risedronate groups were compared based on time-to-first diagnosed incident vertebral fracture (new and worsening) using the stratified log-rank test with pooled centers as a stratification factor. A Cox proportional hazards regression model with treatment group and pooled center as covariates and stratified by stratum was utilized to estimate the relative risk of vertebral fracture incidence for patients receiving 5 mg risedronate relative to placebo patients and the corresponding 95% confidence interval (CI).

The treatment-by-center interaction was assessed using a Cox proportional hazards regression model including terms for treatment, pooled center, and treatment-by-pooled center interaction, stratified by stratum. The treatment-by-stratum interaction was assessed using a Cox proportional hazards regression model including terms for treatment, stratum, and treatment-by-stratum interaction. The validity of the proportional hazards assumption was qualitatively assessed using a plot of the log of the negative log of the estimated time-to-fracture distribution.

The estimates of the incidence of vertebral fractures up to and including specific time points (Months 12, 24, and 36) during the study were calculated for each of the three treatment groups using Kaplan-Meier estimates of the survival function. In addition, supporting analyses comparing the 5-mg treatment group to placebo over one and two years were performed.

The above analyses were performed on the ITT population, the EV patient population, and the adjudicated patient population.

In order to assess the possible subgroup differences in response to therapy, estimates of the incidence of vertebral deformities over 3 years were summarized using descriptive statistics for each of the following subgroups within the ITT population: race (Caucasian vs. non-Caucasian), age (<65 years vs. 65 years), smoking status (non-smokers vs. smokers), years since last menstrual period (≤15 years, >15 years), previous osteoporosis therapy (previous therapy vs. no therapy), and stratum, sBMD of the lumbar spine at baseline (equivalent to T-score ≤-2.5, T-score >-2.5), and BMD of the femoral neck (T-score ≤-2.5, T-score >-2.5). For each subgroup, additional estimates of incidence were calculated for the first year.

The impact of covariates (BMD at baseline, the number of prevalent spinal deformities, years since last menstrual period, smoking history (yes/no), and race: Caucasian/non-Caucasian) on incident vertebral deformities (new and worsening) was assessed for the ITT population using a Cox proportional hazards regression model including terms for treatment, pooled centers, the covariates of interest, and treatment-by-covariate interaction(s), stratified by stratum. If a significant treatment-by-covariate interaction was observed in the ITT analysis of incident vertebral deformities (new and worsening), then the interaction was included in this model.

7.1.6 a Height

Two sets of analyses were performed for height. One for the ITT population, and the other for those ITT patients with at least one vertebral deformity during the study. Height was measured in triplicate for each patient. If any of the three measurements differed by 4 millimeters or more from the closest of the other two, the height measurement was repeated twice. The average of the three or five measurements at each time point was used to calculate percent change and actual change from baseline.

Actual change from baseline in height was expressed as follows:
(Ht - H0), where
Ht = height at visit Month t (i.e., Months 12, 24, 36, and endpoint); and
H0 = height at baseline.
Percent change from baseline was calculated as follows:
[(Ht - H0)/H0] x 100%, where
Ht = Height at visit Month t (i.e., Months 12, 24, 36, and endpoint); and
H0 = Height at baseline.

Since the actual change in height following treatment may be affected by the magnitude of the baseline value, the change from baseline at each visit was analyzed using a three-way ANCOVA model, which included treatment group, pooled center, and stratum as factors and baseline value of height as the covariate. The percent change from baseline was analyzed using a three way ANOVA model, including treatment group, pooled center, and stratum as factors. Only the placebo and 5-mg risedronate groups were used in these analyses.

7.1.7 Results

7.1.7 a Patient Disposition (see figure below): A total of 2458 subjects were randomized (1:1:1) to either placebo, Ris 2.5 mg, or Ris 5.0 mg per day. Eight hundred twenty and 821 subjects were randomized to placebo and Ris 5.0 mg, respectively. Most of the subjects in both groups were from stratum 2 (two or more baseline vertebral deformities). Of these patients, 815 and 813 placebo and Ris 5.0-mg subjects, respectively, received at least one dose of study drug. Seventy-eight percent of placebo and 81% of Ris 5.0-mg subjects completed one year of the study. Fifty-five percent of placebo and 60% of Ris 5.0-mg subjects completed the 36-month study. Approximately 17% of subjects in both groups discontinued from the study because of an adverse event. There were slightly greater percentages of Ris 5.0 mg subjects compared with placebo subjects who discontinued for the following GI adverse events: nausea, dyspepsia, and colitis. About 14% of the subjects discontinued because of "voluntary withdrawal." In general, there were no large differences between the two groups in the percentage of patients discontinuing for any reason.

Of some interest, 20% of placebo patients with at least one incident vertebral fracture compared with 11% of Ris 5.0-mg subjects discontinued from the study. The sponsor claims that this "greatly diminished the apparent treatment effect in completed patients."

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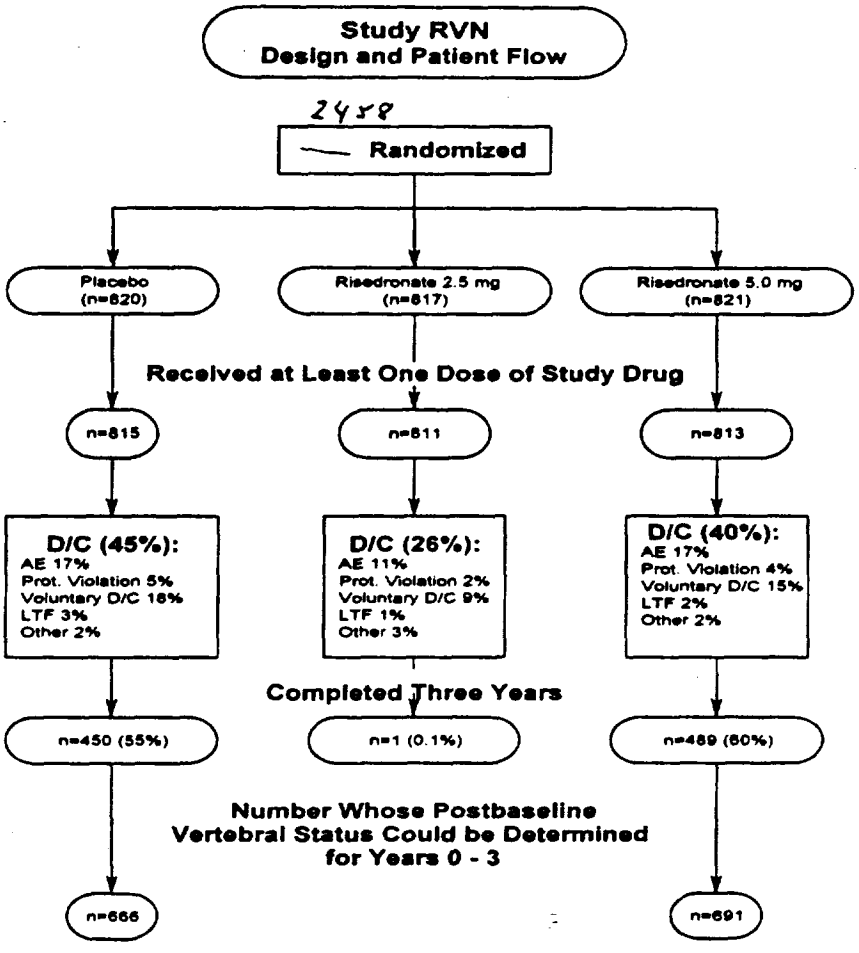


7.1.7 b Baseline Demographics: The two groups were well matched at baseline. The mean age was 69 years, the mean number of years since menopause was 24 years, 95% of the patients were Caucasian, 81% of the subjects were from stratum 2, 50% never smoked, and 43% never used alcohol. The mean LS T-score at baseline was –2.4. The baseline BMD measurements at the other skeletal sites were similar between groups and within each stratum. It is worth noting that although patients in stratum 1 had to have only 1 prevalent vertebral fracture plus low BMD and stratum 2 patients had to have at least 2 prevalent vertebral deformities at baseline, the mean LS BMD was lower in stratum 1 than stratum 2: 776 vs. 849 mg/cm^2. The mean levels of serum vitamin D, calcium, and iPTH were comparable between the two groups at baseline. Eighty percent of all patients did not receive any osteoporosis medication during the year preceding the trial. Of those that did receive therapy, similar percentages of patients in the placebo and Ris 5.0-mg groups received conjugated estrogens (6%), etidronic acid (5.9%), calcitonin (3.5%), and sodium fluoride (1.2%). There did not appear to be any significant differences between groups in the percentages of patients who took specific concomitant medications during the trial.

Compliance with study drug (not calcium) was calculated as 92% both treatment groups.

A total of 242 placebo and 209 Ris 5.0 mg subjects were excluded from the EV population. The reasons for these exclusion were non-compliant with study drug (13%), baseline radiograph not in

window (5.8%), and markedly abnormal labs (5.3%). There were no significant differences between the two groups in the percentages of patients falling into these 3 categories.

A total of 815 and 813 patients in the placebo and Ris 5.0-mg groups, respectively, comprised the ITT population. A total of 589 placebo and 601 Ris 5.0-mg subjects were included in the adjudicated patient subgroup for vertebral fracture analysis. The adjudicated patient population was composed of those patients in the ITT population who had either two or more adjudicated vertebral fractures at baseline or had one adjudicated fracture and low lumbar spine BMD at baseline. Following adjudication, the patients were restratified and patients without prevalent fractures were excluded from this population.

7.1.7 c Primary Efficacy Endpoint Outcome

Time to First Vertebral Fracture (Month 0-36, ITT)

As shown in the table below, subjects treated with Ris 5.0 mg daily had a lower vertebral fracture incidence compared with placebo-treated patients throughout the 3-year observation period. There was a 33% reduction in risk for new or worsening vertebral fractures in the Ris 5.0 mg subjects compared with the placebo subjects (p=0.02). The absolute reduction in risk was 5% in favor of Ris 5.0 mg. Similar results, in terms of the magnitude of the reduction in relative risks, were obtained in analyses of the EV and adjudicated populations.

CUMULATIVE VERTEBRAL FRACTURE INCIDENCE (NEW OR WORSENING							
Duration	N	Pt-yrs	# Pts with Incident Fx	%	RR	95% CI	p-value
			Year 0-1				
Plo	646	632	46	7.2			
Ris 5.0 mg	663	648	26	3.9	0.51	0.31, 0.84	0.009
			Year 0-2				
Plo	663	1184	77	12.8			
Ris 5.0 mg	689	1212	49	8.0			0.004
			Year 0-3				
Plo	666	1645	103	18.5			
Ris 5.0 mg	691	1710	77	13.9	0.67	0.50, 0.91	0.02

In an analysis of patients that completed the 3-year study, there was a non-significant 10% reduction in relative risk for new or worsening vertebral fractures in the Ris 5.0 mg group compared with the placebo group (p=0.6). The sponsor claims that this finding is due to the fact that, for patients who withdrew from the study prior to Month 36, 19% of placebo vs. 10% of Ris 5.0-mg subjects had vertebral fractures. This seems logical.

As expected, the small but evident benefit of risedronate, was only seen in the stratum 2 subjects: those with at least two or more prevalent vertebral deformities at baseline. Patients in stratum 1 (one vertebral deformity and low BMD) did not receive any benefit from risedronate relative to placebo treatment when treated over a 3-year period.

Another way to express these data is as follows: In the ITT population, 81% of the placebo subjects and 86% of the Ris 5.0 mg subjects did not suffer a new vertebral fracture during the 3-year study.

Change in Height

Median changes in height are reported because the data were not normally distributed. In the roughly 50-60% of patients that had baseline and follow-up height measurements at Months 24

and 36, there was a median reduction of –0.150 cm in the placebo group and a –0.080 cm change in the Ris 5.0 mg group after 2 years of treatment (p=0.03). At Month 36 the placebo group had a median reduction in height of –0.300 cm and the Ris 5.0 mg group had a –0.200 cm reduction (p=0.1). In a LOCF analysis, the median reduction in height at Endpoint in the placebo group was –0.270 cm and –0.140 cm in the Ris 5.0 mg group (p=0.004).

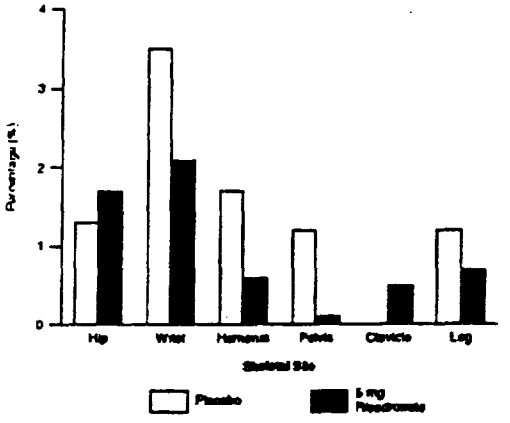
7.1.7 d Non-Vertebral Osteoporosis-Related Fractures

Fractures falling into this category included: hip, wrist, humerus, pelvis, clavicle, and leg. As shown in the following table, there was a small, but statistically significant reduction in the incidence of the above mentioned non-vertebral fractures in the Ris 5.0 mg group vs. the placebo group after 3 years of treatment.

CUMULATIVE NON-VERTEBRAL FRACTURE INCIDENCE							
Duration	N	Pt-yrs	# Pts with Fx	%	RR	95% CI	p-value
			Year 0-1				
Plo	815	732	25	3.4			
Ris 5.0 mg	812	739	15	2.0	0.59	0.31, 1.12	1.0
			Year 0-2				
Plo	815	1337	37	5.4			
Ris 5.0 mg	812	1353	24	3.5			0.08
			Year 0-3				
Plo	815	1832	52	8.4			
Ris 5.0 mg	812	1878	33	5.2	0.61	0.40, 0.94	0.02

Similar results were obtained in the analysis of the EV population. It is important to note that while the relative risk for non-vertebral fracture was decreased by approximately 40% in the Ris 5.0 mg group compared with the placebo group, the absolute risk reduction was about 3% after 3 years of treatment.

A lower incidence of fractures in the Ris 5.0 mg vs. placebo was noted at most skeletal sites, except hip and clavicle. The figure below provides the actual incidence rates by skeletal site.



Regarding all non-vertebral fractures reported as adverse events (this includes all skeletal sites), 105 (13%) placebo patients compared with 84 (10%) of Ris 5.0 mg subjects had such fractures reported.