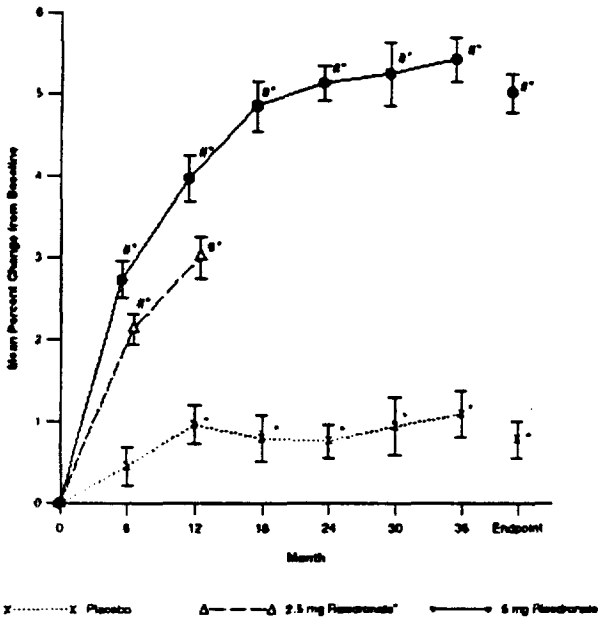
### 7.1.7 e Percent Change in LS BMD

As shown in the figure below, in the ITT dataset, the mean percent change in LS BMD increased throughout the study in both groups. At Month 36, the placebo group had a mean increase from baseline in LS BMD of 1.1% and the Ris 5.0 mg group had a mean increase of 5.4% ($p<0.001$).

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Similar results for the mean percent changes in BMD between placebo and Ris 5.0-mg subjects were observed at the femoral neck and trochanter.

In the subset of patients (roughly 200 patients per group) who had BMD measurements of the distal radius, both groups had reduction from baseline to Month 36 and Endpoint. The placebo group had a mean change of –1.8% and the Ris 5.0 mg group had a mean change of –0.7% ($p=0.08$).

There was a positive effect of risedronate relative to placebo treatment on cortical bone mass in a subset of patients who had measurement of the midshaft radius BMD. By Month 36, the placebo group had a mean percent change from baseline of –1.4% whereas the Ris 5.0 mg group had a mean percent change of 0.2% ($p<0.001$).

### 7.1.7 f Markers of Bone Metabolism

In the small subset of patients (approx. 150 – 200 per group) who had measurements of bone markers, the median levels of osteocalcin decreased in both groups during the study such that the reduction was significantly greater in the Ris 5.0-mg group compared with the placebo group throughout the study. From baseline to Endpoint, the median levels of dPyr/Cr increased slightly in the placebo group and, as expected, decreased in the Ris 5.0-mg group.

### 7.1.8 Safety Review

Because a comprehensive (and more accurate) review of risedronate's safety profile is provided in the Integrated Summary of Safety, herein I will focus on deaths, serious adverse events, withdrawals due to adverse events, GI-related adverse events, and the effects of treatment on serum levels of iPTH, calcium, and phosphorus, and bone histomorphometry.

Exposure to and compliance with study drug was comparable between the placebo and Ris 5.0-mg groups.

**Deaths:** The numbers of deaths were comparable between the two groups. A total of 16 placebo patients and 15 Ris 5.0 mg subjects died during the study and 6 placebo and 5 Ris 5.0 mg subjects died post-study. There were no apparent imbalances between the groups for the causes of death.

**Serious Aes**: Twenty-seven percent of placebo patients and 29% of Ris 5.0-mg patients reportedly had a serious adverse event. The most commonly reported event was traumatic bone fracture: 36 placebo patients and 25 Ris 5.0-mg patients. The other events were evenly balanced between the two groups.

**Withdrawal Due to Aes**: Sixteen percent of placebo patients and 17% of Ris 5.0-mg patients withdrew from the study because of an adverse event. A slightly higher number of Ris 5.0-mg patients vs. placebo patients withdrew because of abdominal pain (11 vs. 9) and nausea (12 vs. 7). Eight placebo and 2 Ris 5.0 mg subjects withdrew because of an atraumatic bone fracture.

**Upper GI Aes:** Twenty-seven percent of placebo and 30% of Ris 5.0-mg subjects had at least one UGI AE. For some of the events, (i.e., dyspepsia, abdominal pain, gastritis, duodenitis, GI hemorrhage, esophageal stenosis) the incidence in the Ris 5.0 mg group was slightly higher than that in the placebo group. Yet, for some other events such as esophagitis, stomach ulcer hemorrhage) the incidence was slightly higher in the placebo group compared with the Ris 5.0-mg group.

There was some suggestion that the concomitant use of risedronate with NSAIDs, but not aspirin, increased the risk for an UGI AE. For NSAID non-users, the incidence of UGI Aes was identical for the placebo and Ris 5.0-mg groups (23%); however, for NSAID users, the incidence of UGI Aes was 29% in the placebo group and 34% in the Ris 5.0-mg group. Most of this difference was due to reporting of abdominal pain, dyspepsia, gastritis, gastrointestinal disorder, and gastrointestinal hemorrhage.

**iPTH:** In the subset of patients who had measurements of iPTH, there was evidence that the levels increased during the study to a greater degree in the Ris 5.0 mg group compared with the placebo group. This difference was 14% at Month 12 ($p=0.01$) and 10% at Month 36 ($p=0.1$). However, there was no significant correlation ($r=0.10;p=0.3$) between the percent change from baseline to Month 12 in midshaft radius BMD vs. level of iPTH in the 5.0 mg Ris group, whereas there was a weak inverse correlation ($r= -0.23;p=0.01$) in the placebo group. Unfortunately, midshaft radius BMD was not measured past Month 12.

**Serum Calcium and Phosphorus:** There were no significant differences between the two groups for the mean changes in levels of serum calcium or phosphorus. However, it appeared that a greater percentage of Ris 5.0-mg subjects relative to placebo subjects developed low calcium levels during the study. Outlier values for serum calcium and phosphorus are discussed in the ISS.

**Bone Histomorphometry**: There were 31 paired bone biopsy samples from both the placebo and Ris 5.0-mg groups. Significantly fewer subjects had evaluable baseline and Month 36 data for each specific parameters evaluated. The following table provides the data on the antiresorptive and bone formation effects of Ris 5.0 mg in comparison with placebo treatment.

| SELECTED BONE HISTOMORPHOMETRIC INDICES FOR PAIRED BIOPSIES | | |
|---|---|---|
| Index | Plo | Ris 5.0 mg |
| | Bone resorption | |
| Final Erosion Depth (um) | | |
| N | 21 | 21 |
| Baseline | 44.9 | 45.6 |
| Month 36 | 50.3 | 44.0 |
| Mean Change | 5.4* | -1.6 |
| | Bone Formation | |
| Mineralization Surface | | |
| N | 21 | 23 |
| Baseline | 0.0815 | 0.0672 |
| Month 36 | 0.0607 | 0.0206 |
| Mean Change | -0.0208 | -0.0466* |
| | Bone Remodeling | |
| BMU-Balance (um) | | |
| N | 21 | 21 |
| Baseline | -5.95 | -4.15 |
| Month 36 | -8.70 | -2.59 |
| Mean Change | -2.75 | -1.56 |
| Activation Frequency ($yr^{-1}$) | | |
| N | 19 | 12 |
| Baseline | 0.433 | 0.392 |
| Month 36 | 0.322 | 0.173 |
| Mean Change | -0.112 | -0.218* |

*p<0.05 within-group, one-sample t-test

These data are consistent with risedronate antiresorptive effect. It's reported that no cases of osteomalacia were noted in any of the risedronate-treated patients.

### 7.1.9 Sponsor's Conclusions

The clinical results of Study RVN008993 demonstrate that daily oral administration of 5 mg risedronate is safe and effective in treating patients with established postmenopausal osteoporosis. The results clearly demonstrate a statistically significant and clinical meaningful reduction in fracture risk supported by a significant increase in bone mineral density for patients receiving 5 mg risedronate compared to placebo patients.

### 7.1.10 Medical Officer's Conclusions

In this 3-year study of postmenopausal women with osteoporosis (defined by low BMD and/or prevalent vertebral fractures), 5 mg per day of risedronate increased LS, femoral neck, and femoral trochanter BMD by approximately 4%, 3%, and 4%, respectively when compared with women treated with calcium and vitamin D alone. The change in LS BMD was associated with a modestly favorable effect on the risk for vertebral fracture: relative risk reduction slightly greater than 30% and absolute risk reduction equal to 5%. Most of this benefit was observed in women with two or more prevalent vertebral fractures at baseline.

No significant safety concerns emerged from this study. Some GI-related adverse events were reported by a slightly higher percentage of risedronate-treated subjects compared with placebo-

treated patients. These included dyspepsia, abdominal pain, gastritis, duodenitis, hemorrhage, and esophageal stenosis. More risedronate-treated subjects also discontinued from the study because of abdominal pain and nausea.

## 7.2. Study RVE

### 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 03/04/1994 and the last patient's last observation was on 03/28/1998.

**7.2.2 Objective:** The primary objective of this study was to examine the efficacy of risedronate in reducing vertebral deformity incidence (and rate) in osteoporotic postmenopausal women.

**7.2.3 Design:** This was a randomized, double-blind, multi-center (80 centers in Europe) 3-year study in postmenopausal women with osteoporosis. Subjects were randomized to one of three groups: placebo, Ris 2.5 mg, or Ris 5.0 mg daily. All patients received 1 gram of elemental calcium equivalent per day. About 35% of subjects in each group had low baseline plasma vitamin D levels (<40 nmol/L); these subjects received supplemental vitamin D during the trial. 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." Patients who withdrew during the first two years for any reason were requested to return to the study center at the time of their scheduled Month 24 visit. All patients in their third year who withdrew prior to completing three years were requested to return to the study center at the time of their scheduled Month 36 visit.

**7.2.4 Patient Population:** Female patients at least 5 years postmenopausal and $\leq$ 85 years of age were enrolled in the study. Patients also had to have two or more vertebral deformities at baseline. 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

**7.2.5 Endpoints:** Lateral 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, and 36.

**7.2.5 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] at the [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 [redacted] 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 [redacted] 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.

**7.2.5 b Vertebral 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.

**7.2.5 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 75$^{th}$ percentile or below the 25$^{th}$ 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 (Genant HK, et al, 1993). 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.

**7.2.5 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 17 clinical sites in this study required longitudinal correction factors to compensate for drifts or shifts in BMD measurements. In addition, 5 sites required correction factors due to instrument upgrades to another model by the same manufacturer during the study .

**7.2.6 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.

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 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.

**7.2.6 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.

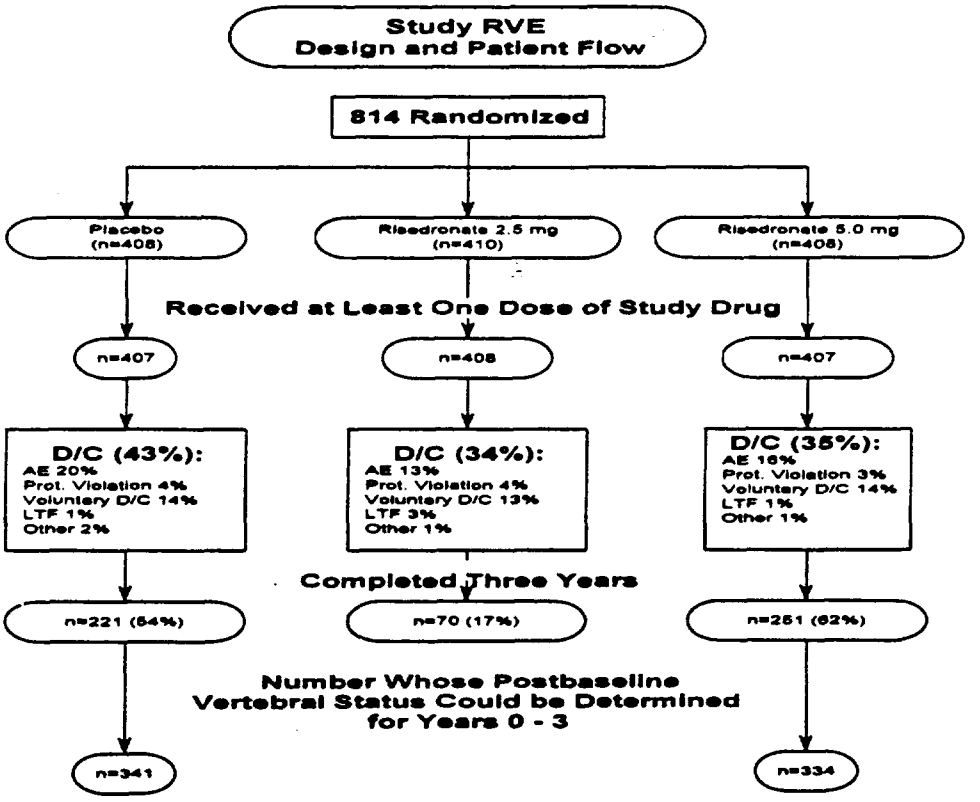
Actual change from baseline in height was expressed as follows:
(Ht - H0), where
Ht = height at visit Month t (i.e., Months 12, 24, 36, and endpoint); and
H0 = height at baseline.
Percent change from baseline was calculated as follows:
[(Ht - H0)/H0] x 100%, where
Ht = Height at visit Month t (i.e.,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

### 7.2.7 Results

**7.2.7 a Patient Disposition (see figure below):** A total of 1226 patients were enrolled into the 3 groups: 408 to placebo, 410 to Ris 2.5 mg, and 408 to Ris 5.0 mg. Eighty-two percent of subjects in each group completed one year of the study. Only 54% of placebo subjects and 62% of Ris 5.0 mg subjects completed 3 years of treatment (the 2.5 mg dose was discontinued per protocol amendment). Adverse event was the most common reason for early discontinuation: 20% in placebo, 13% in Ris 2.5 mg, and 16% in Ris 5.0 mg. Of the 460 patients who discontinued early, follow-up data were collected for 23% subjects.




**7.2.7 b Baseline Demographics:** The placebo and Ris 5.0-mg groups were well matched at baseline with no statistically significant imbalances between groups. The mean age of the subjects was 71 years with 81% of women 65 years of age or older. Nearly all of the women were Caucasian. About 18% were current smokers and 45% current alcohol users. The mean baseline LS BMDs were comparable between groups: 787 vs. 776 mg/cm$^2$, placebo vs. Ris 5.0 mg. The

overall mean T-score for the LS was –2.761 with about 60% of subjects having a T-score at or below –2.5. Of note, only 31% of subjects had values for LS T-score due to a high proportion of patients with prevalent vertebral fractures in the LS or with LS unsuitable for densitometry. The average BMD values at the other skeletal sites were comparable between the two groups. Ninety-one percent of subjects in each group had at least 2 prevalent vertebral fractures.

Compliance with study drug for the two groups was calculated to be 91%.

A total of 121 (30%) of placebo patients and 118 (29%) of Ris 5.0 mg subjects were excluded from the EV population. Thirteen percent of subjects were excluded because of noncompliance with study drug; about 8% for having a baseline radiograph outside of the defined window; roughly 3% for excessive vitamin D supplementation; and about 3% for markedly abnormal lab values.

A total of 407 placebo patients and 407 Ris 5.0-mg subjects comprised the ITT population.

### 7.2.7 c Primary Efficacy Endpoint Outcomes

**Time to First Vertebral Fracture (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 study. There was a 46% reduction in risk for new or worsening vertebral fractures in the Ris 5.0 mg group compared with the placebo group ($p<0.001$). The absolute reduction in risk was 12% in favor of Ris 5.0 mg. Similar results were obtained in the 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 | 328 | 324 | 51 | 15.3 | | | |
| Ris 5.0 mg | 321 | 317 | 27 | 8.2 | 0.5 | 0.30, 0.82 | 0.008 |
| | | | Year 0-2 | | | | |
| Plo | 340 | 611 | 90 | 28.3 | | | |
| Ris 5.0 mg | 331 | 613 | 44 | 13.9 | | | <0.001 |
| | | | Year 0-3 | | | | |
| Plo | 341 | 847 | 103 | 34.0 | | | |
| Ris 5.0 mg | 334 | 865 | 63 | 21.8 | 0.54 | 0.39, 0.75 | <0.001 |

In an analysis of patients that completed the 3-year study, there was a 41% reduction in relative risk in the Ris 5.0 mg group compared with the placebo group ($p=0.03$).

In all predefined subgroups (i.e., age < 65, previous osteoporosis therapy, LS T-score $\leq$ -2.5) benefit was evident in the Ris 5.0 mg group relative to the placebo group.

In the ITT population, about 66% of placebo patients and 78% of Ris 5.0 mg patients did not suffer a new or worsening vertebral deformity during the course of the 3-year study.

### 7.2.7 d Change in Height

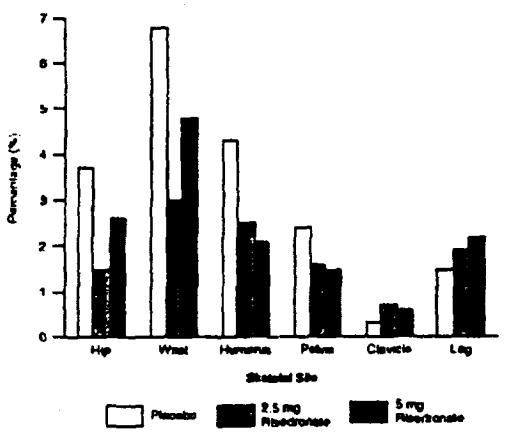
Because the data were not normally distributed, non-parametric analyses were performed and median values are presented. In the roughly 55 – 70% of patients that had height measurements at Months 24 and 36, there was a median reduction of –0.44 cm in the placebo group and –0.23 cm change in the Ris 5.0 mg group at Month 24 ($p<0.001$). At Month 36, the placebo group had a

median reduction in height of –0.68 cm and the Ris 5.0 mg group a –0.50 cm change from baseline (p=0.16). In a LOCF analysis, the median reduction in height at Endpoint in the placebo group was –0.57 cm and –0.37 cm in the Ris 5.0 mg group (p=0.005).

### 7.2.7 e Non-Vertebral Osteoporosis-Related Fractures

Fractures falling into this category included hip, wrist, humerus, pelvis, clavicle, and leg. Although there were small, nonsignificant reductions in the risk for nonvertebral fractures in the Ris 5.0 mg group relative to the placebo group during the first two years, the cumulative risk during Years 1-3 was reduced by 33%; p=0.06.

As noted in the figure below, a lower incidence of fractures in the Ris 5.0-mg group vs. the placebo group was noted at all skeletal sites except clavicle and leg.








Regarding all non-vertebral fractures reported as adverse events, 68 (17%) placebo patients and 56 (14%) of the Ris 5.0-mg subjects had such fractures reported as adverse events.

### 7.2.7 f Percent Change in LS BMD

In the 134 placebo and 158 Ris 5.0 mg subjects who had LS BMD measurements at baseline and Month 36, there was a mean percent change of 1.3% in the placebo group and a 7.1% increase in the Ris 5.0 mg group (p<0.001).

At the femoral neck and trochanter skeletal sites, the placebo group had reductions of about 1.0% in BMD at Month 36, whereas the Ris 5.0-mg group had increases of 2% and 5%, respectively at these sites. The differences between drug and placebo-treated groups were statistically significant.

In the roughly one-fourth of the randomized patients who had a Month 36 BMD measurement of the distal radius, there was a mean percent change of –3.5% in the placebo group and a –0.4% decrease in the Ris 5.0 mg group (p=0.002).

### 7.2.7 g Markers of Bone Metabolism

In the subset of patients (approx. 115 per group) who had measurements of bone markers at baseline and Month 36, the median levels of osteocalcin decreased in both groups, but the decrease was significantly greater in the Ris 5.0 mg group relative to the placebo group (-24.2% vs. –46.5%, placebo vs. Ris 5.0 mg; $p<0.001$). As expected, the median levels of dPyr/Cr decreased in the Ris 5.0-mg group to a greater extent than in the placebo group (-6.0 vs. –19.3%, placebo vs. Ris 5.0 mg; $p=0.04$).

**7.2.8 Safety Review**

Because a comprehensive (and more accurate) review of risedronate's safety profile is provided in the Integrated Summary of Safety, herein I will focus on deaths, serious adverse events, withdrawals due to adverse events, GI-related adverse events, and the effects of treatment on serum levels of calcium, and phosphorus.

Exposure to and compliance with study drug was comparable between the placebo and Ris 5.0-mg groups.

**Deaths:** There were fewer deaths in the Ris 2.5 mg and 5.0 mg groups compared with placebo: 10 (2.5%), 11 (2.7%), and 17 (4.2%), respectively.

**Serious Adverse Events:** There were 135 (33%) of the placebo, 124 (30%) of the Ris 2.5 mg, and 151 (37%) of the Ris 5.0 mg subjects reporting SAEs. Much of the difference in rates of SAEs between the placebo and Ris 5.0-mg groups was due to reports of colitis. Five Ris 5.0-mg subjects and none of the placebo subjects reported this AE. Of note, more placebo patients relative to Ris 5.0 mg subjects reported traumatic and atraumatic bone fractures as SAEs: 38 vs. 29, respectively.

**Withdrawals Due to Adverse Events**: Eighty-one (20%) of the placebo patients and 63 (16%) of the Ris 5.0 mg subjects withdrew from the study because of an adverse event.

**Upper GI Adverse Events**: A total of 104 (26%) of placebo patients and 109 (27%) of the Ris 5.0 mg subjects had at least one reported upper GI AE. Abdominal pain was reported with greatest frequency in the Ris 5.0 mg-group: 12% vs. 8%, Ris vs. placebo, respectively. While some events were reported more frequently in the Ris group, others were reported more frequently in the placebo group – this leading to the similarity in the overall incidence of upper GI Aes in the two groups. In all groups, most of the upper GI Aes were reported as mild.

The incidence of upper GI Aes, regardless of treatment with risedronate, was greater for users of NSAIDs or aspirin compared with non-users. In users of NSAIDs or aspirin, treatment with risedronate did not appreciably change the incidence of reported cases of upper GI Aes. Abdominal pain was reported by more risedronate + NSAID or + aspirin subjects than non-users of risedronate.

**Serum Calcium and Phosphorus:** The mean changes in serum calcium and phosphorus were similar in the Ris 5.0 mg and placebo groups. There was some evidence, however, that treatment with Ris 5.0 mg is associated with a greater risk for the development of low serum calcium and phosphorus levels compared with placebo treatment. Outlier values for these two serum parameters are discussed in the ISS.

**7.2.9 Sponsor's Conclusions**

The clinical results of study RVE demonstrate that 5.0-mg oral risedronate treatment is safe and effective in patients with established postmenopausal osteoporosis. These results clearly demonstrate a statistically significant and clinically meaningful reduction in fracture risk supported by a significant increase in bone mineral density in patients receiving 5 mg risedronate compared to placebo patients.

**7.2.7.10 Medical Officer's Conclusions**

In this 3-year study of postmenopausal women with osteoporosis (defined by two or more prevalent vertebral fractures), 5 mg per day of risedronate increased LS, femoral neck, and femoral trochanter BMD by about 6%, 3%, and 6% respectively, when compared with women treated with calcium (and some with vitamin D) alone. The change in LS BMD was associated with a modestly favorable effect on the risk for vertebral fracture: relative risk reduction of 46% and an absolute risk reduction of 12%.

Thirty-seven percent of Ris 5.0 mg-treated women vs. 33% of placebo-treated subjects reported at least one serious adverse event. This difference was due, in part, to more cases of colitis in the risedronate group (5 vs. 0). And as reported in previously reviewed studies, more risedronate-treated subjects reported abdominal pain (12%) compared with placebo patients (8%).

**The Prevention of Postmenopausal Osteoporosis**

**7.3 Study RBL**

**A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate in the Prevention of Postmenopausal Bone Loss**

The first patient was enrolled 09/29/1994 and the last patient's last observation was 04/17/1997.

**7.3.2 Objective**: To determine whether risedronate is effective in preventing loss of lumbar spine and proximal femoral BMD in early postmenopausal women.

**7.3.3 Design:** This was a double-blind, randomized, parallel-group, placebo-controlled, eleven-center, 24-month study conducted in Australia. Patients were randomized to one of three groups: placebo, Ris 2.5-mg, or Ris 5.0-mg daily. All subjects received 1 gram of elemental calcium per day. 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." Patients were also instructed not to take their calcium with the study drug. Patients who discontinued from the study early were requested to return to the study center at the time of their scheduled Month 24 visit.

Patient Population: Female patients who were between 6 and 36 months postmenopausal and had a serum FSH level $\geq$ 50 mU/mL and an estradiol level $\leq$ 20 pg/mL were enrolled into the study. Subjects had to have a LS BMD > 0.76 g/cm$^2$ ⌒ or > 0.87 g/cm$^2$ ⌒. Patients were excluded for the following reasons: history of hyperparathyroidism, hyperthyroidism, or osteomalacia within 1 year of enrollment, or 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

**7.3.4 Endpoints:** Densitometry of the lumbar spine and femur were obtained in duplicate at baseline and Month 24 as well as Months 3, 6, 12, and 18. Lateral spine radiographs were obtained at baseline and Month 24. Bone markers were evaluated at baseline and Months 1, 3, 6,

and 24. Levels of FSH and estradiol were measured at baseline and Months 6, 12, and 18. Standard safety laboratory evaluations were obtained at baseline and Months 6, 12, and 24. DXA of the midshaft (1/3) and distal radius were performed at baseline only. No subsequent scans at this site were required; however, a significant amount of data were collected at Months 3, 6, and 12.

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 the [redacted]. DXA phantom data were analyzed by the [redacted] for consistent instrument performance throughout the study. If necessary, the [redacted] generated longitudinal BMD correction factors for patient data to compensate for instrument variations. The instrument quality control analysis based on phantom data identified three sites that needed longitudinal correction due to detector drifts or failures. No longitudinal corrections were applied at the remaining clinical sites as instrument deviations were either not significant or attributed to technical errors.

**7.3.5 Statistical Analyses:** Two patient populations were identified prospectively. 1). Randomized population: all patients who were randomized to placebo or risedronate, and took at least one dose of study drug. This was also identified as the intent-to-treat (ITT) population; and 2). Evaluable patient population (EV): those in the ITT population who were not protocol violators as specified in the inclusion/exclusion criteria and who took at least 80% of study drug. In addition, only visits that occurred within ± 3 weeks of the scheduled visit date were included.

The primary effectiveness parameter was percent change from baseline in BMD of the lumbar spine at Month 24. In calculating percent change from baseline to each visit, only patients who had values at baseline and the specified visit were included. To ensure comparability of spinal BMD measurements, DXA measurements of vertebrae that were deformed as verified by radiographic assessment during the study (at baseline or during the study), as well as vertebrae that had at least one visit with a missing DXA measurement, were not included in the calculation of spinal BMD for a given patient. That is, only vertebrae that were undeformed at baseline, remained undeformed, and had non-missing DXA measurements throughout the study were included in the calculation of spinal BMD at each visit. However, if DXA measurements for all vertebral levels were missing for a specific visit, the DXA measurements from other visits were still used in the calculation of spinal BMD for those visits. Vertebrae with unknown deformity status due to missing radiographs were also excluded from the calculation. In addition, at visits where duplicate DXA measurements were taken (i.e., at Months 0 and 24), the average of the two DXA measurements was used in the analysis. Duplicate BMD measurements (where available) were averaged first at each vertebral level and then averaged over nondeformed/non-missing lumbar vertebrae for each patient.

At each time point, percent change from baseline in lumbar spine BMD was summarized for investigators combined, and for each investigator using descriptive statistics. Summary graphs of mean percent change from baseline are also provided. Within each treatment group, percent change from baseline to each visit in the lumbar spine BMD measurements were evaluated using a one-sample t-test together with corresponding 95% CIs.

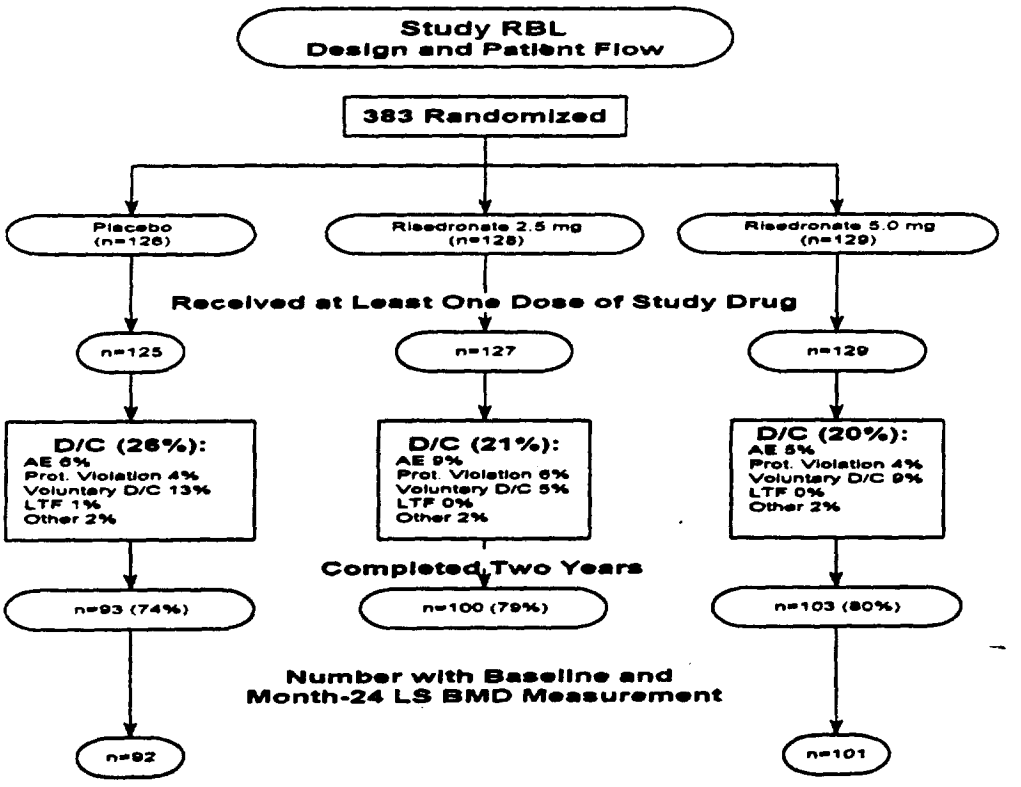
A two-way analysis of covariance (ANCOVA) model with treatment group and investigator as factors and years since menopause as a covariate was used to evaluate overall treatment effect and pairwise treatment differences of percent change from baseline in lumbar spine BMD at each

visit. Pairwise treatment differences against placebo (for the primary analysis at Month 24) were claimed as statistically significant if a) the overall treatment effect was found to be statistically significant, and b) a specific treatment vs. placebo test was found to be statistically significant. Although the main treatment comparison was based on the Month 24 data, this parameter was also analyzed at Months 3, 6, 12, 18, and endpoint.

A preliminary test for treatment-by-investigator and treatment-by-years since menopause interactions was performed on percent change from baseline at Month 24 only, to avoid multiple testing. Centers that enrolled fewer than two patients in at least one treatment group were pooled in testing the interactions. Interaction terms were assessed at the 0.100 significance level and dropped from the initial ANCOVA model if the test for significance resulted in a p-value > 0.100. In the event that a significant interaction was detected (p-value 0.100), the results for each investigator and/or years since menopause were examined for potential sources of interactions. The reduced ANCOVA model without the interaction terms was used as the primary model to test for treatment differences.

### 7.3.6 Results

**7.3.6 a Patient Disposition (see figure below):** Three hundred eighty-one patients were randomized and received study drug: 125 to placebo, 127 to Ris 2.5 mg, and 129 to Ris 5.0 mg. A similar percentage of patients completed the 24-month study (about 77% in each group). Voluntary withdrawal was the most common reason in the placebo and Ris 5.0 mg groups, followed by adverse events. More placebo subjects compared with Ris 5.0 mg subjects withdrew because of an adverse event (6% vs. 5%, respectively). In general, there were no significant differences between the placebo and Ris 5.0-mg groups in the percentages of patients discontinuing for any reason.



**7.3.6 b Baseline Demographics:** Aside from smoking status, the groups were well matched for baseline characteristics. Eighteen percent of placebo patients and 9% of Ris 5.0-mg subjects were current smokers. This is unlikely to have significantly affected the study results. The mean age of the participants was 53 years, 98% were Caucasian, and 19% had prevalent vertebral deformities. Twenty-two percent of subjects in the placebo and Ris 5.0 mg groups had low baseline levels of 25(OH)VitD3. The mean (standardized) LS BMD was 1076.9 mg/cm$^2$. The mean LS T-scores were –0.432 and –0.362 for the placebo and Ris 5.0-mg subjects, respectively. The BMD values for the other relevant skeletal sites were comparable between the placebo and Ris 5.0-mg groups.

The use of concomitant medications was not meaningfully different between the two groups

Compliance with study drug was calculated as 93% for both the placebo and Ris 5.0-mg groups.

The ITT population consisted of 125 placebo and 129 Ris 5.0 mg subjects. The sponsor further defined a subgroup of the ITT based on women whose last menstrual period was within 6 to 36 months of starting study drug. This subset consisted of 99 placebo and 108 Ris 5.0 mg subjects.

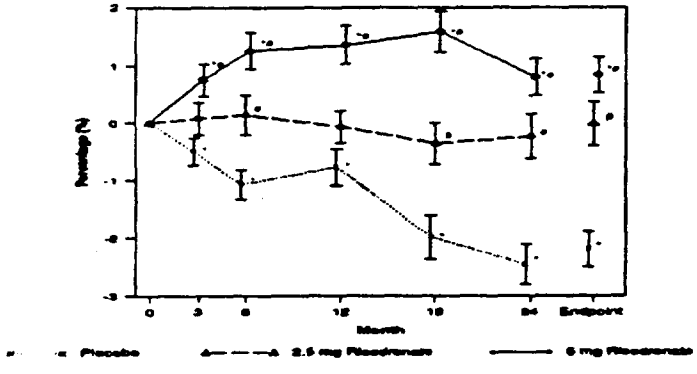
A total of 108 placebo and 112 Ris 5.0-mg subjects were included in the EV subgroup for LS BMD evaluations. Exclusion from the ITT dataset was due to 1) having had a BMD measurement taken outside the scheduled visit data by ± 3 weeks, 2) markedly abnormal labs, 3) non-compliant with study drug, or 4) FSH < 50 mu/ml and/or estradiol > 20 pg/ml.

**7.3.6 c Primary Efficacy Endpoint Outcome**

**Percent Change in LS Bone Mineral Density**

As shown in the table and figure below, there was a steady increase in the LS BMD over the course of the 2-year study in the Ris 5.0-mg group and a steady decrease in the placebo group. At Month 24, the difference between the Ris 5.0 mg and the placebo groups was 4.5% ($p<0.001$).

| MEAN PERCENT CHANGE IN LS BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 24 | Endpoint |
| Placebo | 1.09 g/cm$^2$ (n=102) | -2.48% (n=92) | -2.54% (n=103) |
| Ris 5.0 mg | 1.09 g/cm$^2$ (n=127) | 1.98% (n=101) | 1.89% (n=113) |
| Between group p-value | ----- | <0.001 | <0.001 |



Of some interest, in a subgroup analysis of smokers vs. nonsmokers, the difference in the change from baseline to Month 24 in LS BMD between the Ris 5.0 mg and placebo smokers (current or previous) was 5.6% and for nonsmokers 3.9%; both were statistically significant at $p<0.001$.

**Percent Change in Femoral Neck Bone Mineral Density**

As shown in the table below, in the placebo group, the BMD at the femoral neck progressively decreased over the 24-month trial period. Contrarily, in the Ris 5.0-mg group, there was a steady increase up to the Month 18-time period where a decline then ensued. The difference between the two groups in the change in femoral neck BMD from baseline to Month 24 was just over 3.0% in favor of Ris 5.0 mg ($p<0.001$).

| MEAN PERCENT CHANGE IN FEMORAL NECK BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 24 | Endpoint |
| Placebo | 0.890 g/cm$^2$ (n=122) | -2.46% (n=91) | -2.20% (n=115) |
| Ris 5.0 mg | 0.870 g/cm$^2$ (n=125) | 0.78% (n=103) | 0.83% (n=122) |
| Between group p-value | ---- | <0.001 | <0.001 |

In subgroup analyses (race, < median age, years since menopause, smoking status, LS T-score), the differences between the placebo and Ris 5.0 mg groups in the change in femoral neck BMD from baseline to Month 24 were fairly consistent and ranged from about 3.0 to 4.0% in favor of Ris.

**Percent Change in Femoral Trochanter Bone Mineral Density**

The changes in femoral trochanter BMD were similar to those noted for the femoral neck. In the placebo group there was a steady decline over the 2-year period, and a progressive increase was noted in the Ris 5.0-mg group. The increase in the Ris 5.0-mg group peaked at Month 18 and then declined slightly. The table below provides the changes in femoral trochanter BMD from baseline to Month 24 and Endpoint.

| MEAN PERCENT CHANGE IN FEMORAL TROCHANTER BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 24 | Endpoint |
| Placebo | 0.768 g/cm$^2$ (n=122) | -1.88% (n=91) | -1.96% (n=115) |
| Ris 5.0 mg | 0.754 g/cm$^2$ (n=125) | 2.46% (n=103) | 2.31% (n=122) |
| Between group p-value | ---- | <0.001 | <0.001 |

The results from the subgroup analyses were consistent with the overall analysis. The largest treatment effect was noted in the subgroup of patients with a baseline LS T-score of < -1. Here the difference between the two groups was 6.7% in favor of Ris 5.0 mg.

**Percent Change in Distal Radius Bone Mineral Density** (only measured at baseline and Month 12)

In both the placebo and Ris 5.0-mg groups, BMD at the distal radius progressively declined during the first year of the study. The mean percent change from baseline to Month 12 was –1.71% in the placebo group and –1.29% in the Ris 5.0 mg group (p=ns).

The analyses of the changes in LS, femoral neck, and femoral trochanter BMD in the EV populations were consistent with the ITT population analyses.

### 7.3.6 d Responder Analyses

In these analyses, a responder was defined as a patient who showed no decrease from baseline in BMD at Endpoint. As expected, there were significantly more patients in the Ris 5.0 mg group compared with the placebo group who were reported as responders. For the LS, 20% of placebo patients and 76% of Ris 5.0-mg subjects were responders ($p<0.001$). For the femoral neck, 28% of placebo patients and 59% of Ris 5.0-mg subjects were responders ($p<0.001$). And for femoral trochanter, 33% of placebo patients and 66% of Ris 5.0-mg subjects were responders ($p<0.001$).

### 7.3.6 e Vertebral Fractures

In the group of patients with known deformity status for all vertebral levels, 8/83 placebo subjects, 5/89 Ris 2.5 mg subjects, and 7/91 Ris 5.0 mg subjects had incident vertebral deformities at Month 24. These differences among groups were not statistically significant.

### 7.3.6 f Non-Vertebral Fractures

All in all, there were few patients with one or more non-vertebral fractures: 4.8% of placebo patients, 2.4% of Ris 2.5-mg subjects, and 3.9% of Ris 5.0-mg subjects. For any skeletal site, there were no more than two patients in a treatment group that sustained a fracture.

### 7.3.7 Safety Review

Because a comprehensive (and more accurate) review of risedronate's safety profile is provided in the Integrated Summary of Safety, herein I will focus on deaths, serious adverse events, withdrawals due to adverse events, GI-related adverse events, and the effects of treatment on serum levels of calcium and phosphorus.

Exposure to and compliance with study drug were comparable between the placebo and Ris 5.0-mg groups.

**Deaths:** Two patients, both in the Ris 2.5 mg group and both Caucasians in their late 50s, died during the study. One patient died in her sleep and no autopsy was performed to determine the cause of death. The second patient died of adenocarcinoma of unknown origin, possibly lung or pancreas.

**Serious Adverse Events:** The number and percentage of adverse events were similar in the treatment groups. The most common events were skin carcinoma (1.6%, 3.1%, and 1.6% in the placebo, Ris 2.5 mg, and Ris 5.0 mg groups, respectively) and traumatic bone fracture (0.8%, 0%, and 2.3% in the placebo, Ris 2.5 mg, and Ris 5.0 mg groups, respectively).

**Discontinuations Due to Adverse Events**: Overall, 26% of Ris 2.5-mg subjects, 18% of placebo subjects, and 12% of Ris 5.0-mg subjects discontinued due to an adverse event. Very few subjects discontinued due to a particular adverse event. There was one case of esophagitis reported in each dosing group.

**Upper GI Adverse Events:** Moderate to severe upper GI Aes were reported by 4.8% of placebo patients, 7.9% of Ris 2.5 mg subjects, and 10.1% of Ris 5.0 mg subjects. The only upper GI AE that was reported by a larger percentage of Ris 2.5 and 5.0 mg subjects compared with placebo was abdominal pain: 4.8% of placebo, 7.1% of Ris 2.5 mg, and 7.0% of Ris 5.0 mg subjects.

**Serum Calcium and Phosphorus:** The mean levels of serum calcium and phosphorus were comparable between the groups throughout the study. However, in general, a greater percentage of Ris 5.0-mg subjects compared with placebo subjects developed above normal serum calcium values during the study. Similarly, a greater percentage of Ris 5.0-mg subjects vs. placebo subjects developed abnormally low serum phosphorus levels during the study.

### 7.3 8 Sponsor's Conclusions

Based on the results of this study, it can be concluded that:

· There was a consistent dose response observed across all efficacy parameters assessed throughout this study with a better treatment response in the 5-mg risedronate group. These results are supported by subgroup analyses and the responder analysis.

· The subgroup analyses indicated that cortical bone BMD at the femoral neck was maintained only in the 5-mg risedronate group for the women with less than 2 years of menopause. This observation was confirmed by the midshaft (1/3) radius data.

· Overall, when compared to placebo, the magnitude of the response observed in the 5-mg risedronate group was similar to the one observed with estrogens .

· The safety data were comparable across treatment groups. Only a slight increase in GI AEs was observed in the 5-mg risedronate group.

In conclusion, the 5-mg risedronate dose should be recommended to prevent bone loss in postmenopausal women.

### 7.3.9 Medical Officer's Conclusions

The results of this study indicate that, on average, 5.0 mg per day of risedronate increase BMD at the lumbar spine, femoral neck, and femoral trochanter by 3-5% relative to placebo in early postmenopausal women.

Confirming data from previous trials with risedronate, more actively treated women complained of abdominal pain than did those given placebo. Most cases were mild to moderate and did not lead to withdrawal from the study.

## 7.4 Study RPE

**A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Compare the Efficacy and Safety of Risedronate Plus Estrogen Versus Estrogen Only in the Prevention of Bone Loss in Postmenopausal Women**

The first patient enrolled 08/31/1994 and the last patient's last observation was 06/05/1995.

**7.4.2 Objective:** To determine whether once daily combination therapy of 0.625 mg estrogen plus 5 mg risedronate (RisEst) is superior to once-daily 0.625 mg estrogen plus placebo (EstPlo) in improving BMD of the lumbar spine in postmenopausal women.

**7.4 3 Design:** This was a randomized, double-blind, multi-center (25 sites in North America), parallel-group, placebo-controlled 12-18 month study. Subjects were randomized to one of two groups: Ris 5.0 mg + placebo once daily and Ris 5.0 mg + 0.625 mg estrogen once daily. All subjects received 1 gram of elemental calcium. 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." Estrogen and calcium were to be taken with lunch or the evening meal. All patients who dropped out before the completion of the 1-year treatment period were requested to return to the study center at the time of their scheduled Month 12 visit.

In August of 1995 an amendment to shorten the study from 24 to 12 or 18 months was implemented. All previously scheduled study procedures at month 24 were brought forward for application at Month 12 or Month 18. The duration of the treatment phase was reduced to 12 months from 24 months for patients who had not completed their 12-month visit by August 1995. The duration of treatment was reduced to 18 months for patients who were beyond their scheduled Month 12 visit as of August 1995.

**7.4.4 Patient Population:** Female patients who had their last menstrual period at least 12 months before starting the study were eligible. Some of the exclusion criteria included:

- Had received systemic estrogen therapy for > 1 month within the past 12 months.
- Had a history of hyperparathyroidism, hyperthyroidism, or osteomalacia within 1 year prior to enrollment.
- Use of the following medications within 3 months of starting study drug or for more than 1 month within the last 6 months prior to starting study drug: > 400 ug/day of inhaled beclomethasone or equivalent, oral or parenteral glucocorticoids, anabolic steroids, calcitonin, vitamin D supplements (>500 IU per day), and calcitriol.
- Use of the following medications for more than 14 days within 1 year prior to starting study drug: any bisphosphonate, fluoride (≥ 10 mg per day).
- An abnormal mammogram that suggested malignancy.

**7.4.5 Endpoints:** In addition to the standard safety measurements, a lateral spine radiograph was obtained at baseline and Months 12 and/or 18. Markers of bone metabolism were measured at baseline and Months 3, 12, and 18. DXA of the lumbar spine, proximal femur, and radius (distal and midshaft) were taken at baseline (duplicate) and Months 6, 12 (duplicate) or 18. Bone biopsies were taken at baseline and Months 12 or 18.

**7.4.5 a 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 the [redacted] DXA phantom data were analyzed by the [redacted] for consistent instrument performance throughout the study. If necessary, the [redacted] generated longitudinal BMD correction factors for patient data to compensate for instrument variations. The instrument quality control analysis for this study identified six clinical sites with instrument deviations. In all cases, the deviations were either small, rectified or due to a technical error and, therefore, no instrument correction fractures were needed in the study.

**7.4.5 b Spinal Radiograph**

Anterior-Posterior (AP) and lateral thoracic and lumbar spinal radiographs (T4 to L4) were obtained at the study sites according to guidelines outlined in the protocol. Pretreatment films were sent to a central radiographic screening facility for determination of patient eligibility for lumbar spine BMD measurement. The screening facility also evaluated the films for radiographic quality at baseline and any post-baseline measurement. Lateral thoracic and lumbar spine radiographs were obtained for prevalent and incident vertebral deformity determination. Radiographs eligible for vertebral deformity analysis, as determined by the [redacted], were electronically digitized and sent on optical disc to the [redacted]. Morphometry point placements were performed by trained technicians and verified by qualified radiologists. Vertebral heights were calculated by P&G personnel from the points and potential deformities identified using morphometry. Visual verification of incident deformities as determined by morphometric analysis were performed by qualified radiologists from [redacted]

**7.4.5 c Bone Biopsy**

Bone biopsies were obtained at the ilium in a subset of patients. 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 light and fluorescent microscopy to derive static and dynamic parameters.

**7.4.6 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. In addition, only visits which occurred within $\pm$ 3 weeks of the scheduled visit date were included.

The two treatment groups were compared at baseline with respect to age, race, weight, height, postmenopausal stratum (< 5 years vs. > 5 years), years since menopause, smoking status, status of alcohol consumption, selected serum chemistry, bone turnover markers, T-score of the lumbar spine, BMD of the femoral trochanter, distal and midshaft (1/3) radius by manufacturer, and standardized BMD (sBMD) of the lumbar spine, and femoral neck.

Comparability of treatment groups was assessed using a two-way analysis of variance (ANOVA) including treatment and investigator as factors for continuous variables and using the Cochran-Mantel-Haenszel test (general association version) stratified by investigator for categorical variables. The comparisons were based on all the patients who were randomized to treatment.

The primary effectiveness parameter was percent change from baseline in BMD of the lumbar spine at Month 12. In calculating percent change from baseline to each visit, only patients who had values at baseline and the visit were included. The calculation of percent change from baseline was based on corrected (i.e., not standardized or normalized) BMD values.

To ensure comparability of spinal BMD measurements, DXA measurements of deformed vertebrae (at baseline or during the study), as well as vertebrae that had at least one visit with missing DXA measurements, were not included in the calculation of spinal BMD for a given patient. That is, only vertebrae that were undeformed at baseline, remained undeformed, and had nonmissing DXA measurements throughout the study were included in the calculation of the spinal BMD at each visit. However, if DXA measurements for all vertebral levels were missing for a specific visit, the DXA measurements from other visits were still used in the calculation of spinal BMD for those visits. Vertebrae with unknown deformity status due to missing radiographs were also excluded from the calculation. In addition, at visits where duplicate DXA measurements were taken (i.e., at Months 0 and 12), the average of the two DXA measurements were used in the analysis. Duplicate BMD measurements were averaged first at each vertebral level and then averaged over nondeformed/nonmissing lumbar vertebrae for each patient.

At each time point, percent change from baseline in lumbar spine BMD was summarized for centers combined, and for each center using descriptive statistics. Summary graphs of mean percent change from baseline for all centers combined were also provided. Within each treatment group, percent change from baseline in lumbar spine BMD were evaluated at each visit using a one-sample t-test, together with a corresponding 95% CI.

A three-way analysis of variance (ANOVA) model with treatment group, investigator, and stratum (< 5 years or > 5 years postmenopausal) as factors was used to compare the two treatments with respect to percent change from baseline in lumbar spine BMD at each visit. Although the primary treatment comparison was based on the data at Month 12, this parameter was also analyzed at Month 6 and endpoint. This analysis was not performed at Month 18 because of the small number of patients involved.

A preliminary test for treatment-by-investigator and treatment-by-stratum interactions was performed on percent change from baseline at Month 12 only, to avoid multiple testing. Data from investigators who enrolled fewer than two patients in at least one treatment group were pooled in testing the interactions. In the event that a significant interaction was detected (p-value < 0.10), the results for each investigator and/or stratum were examined for potential sources of interactions. Results from the ANOVA model without the interaction term were used as the primary model to test for treatment difference, to obtain 95% confidence interval and the results are described in the text of this report.

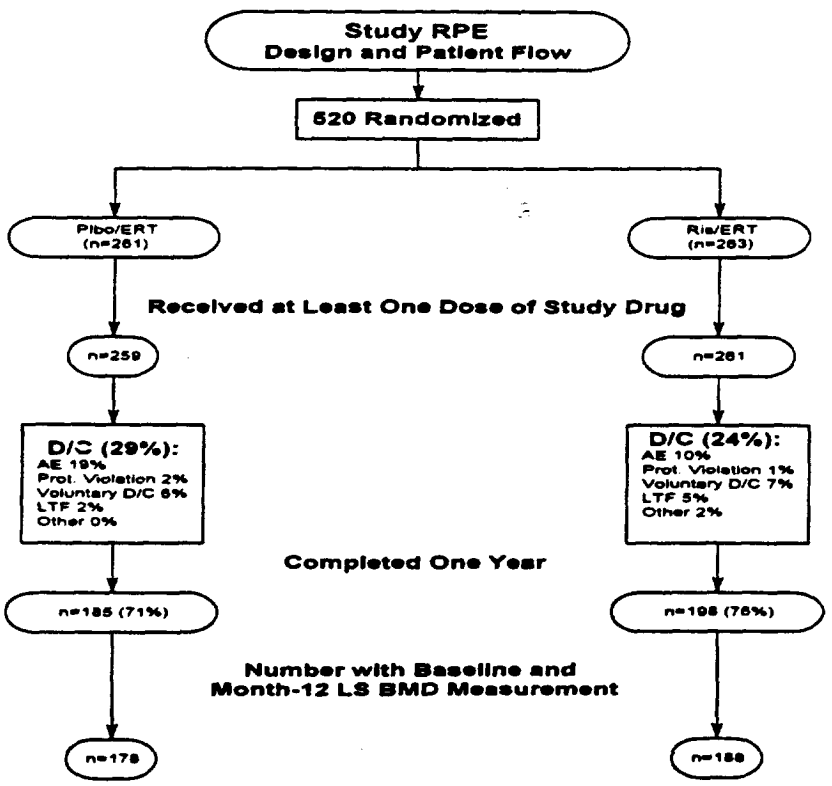
The residuals from the ANOVA model were checked for normality using the Shapiro-Wilk statistic and by visual inspection of the relevant normal probability plot (Q-Q plot of the residuals). Levene's test was used to test the homoscedasticity assumption. If the assumptions of normality and homoscedasticity were not tenable, the ANOVA model was to be

supplemented by appropriate nonparametric tests. Again, the conclusion regarding the assumption were based on the endpoint analysis. Results from nonparametric analysis are described in the text of this report only if they are inconsistent with the results of parametric analysis.

Percent change from baseline to Month 12 in BMD of the lumbar spine was summarized and analyzed using descriptive statistics for each of the subgroups defined by age (< 65 years vs. > 65 years), race (Caucasian vs. non-Caucasian), postmenopausal stratum (< 5 years vs. > 5 years), and Provera use (users vs. non-users).

### 7.4.7 Results

**7.4.7 a Patient Disposition (see figure below):** A total of 261 patients were randomized to EstPlo and 263 to RisEst. Seventy-six percent of patients in each group were from stratum II (> 5 years postmenopausal). Of patients randomized, 259 of the EstPlo and 261 of the RisEst subjects received at least one dose of study drug. Seventy-one percent of the EstPlo and 76% of the RisEst subjects completed one year of treatment. Only 3.5% and 2.3% of the EstPlo and RisEst subjects, respectively, completed 18 months of treatment. The vast majority, 19% in EstPlo and 10% in RisEst, discontinued early from the study because of an adverse event. The next most common reason – about 6% of subjects – discontinued under the category of voluntary withdrawal.



**7.4.7 b Baseline Demographics:** The groups were well matched for baseline characteristics. The mean age was 59-60 years, 91% were Caucasian, 76% were at least 5 years postmenopausal, 15% were current smokers, 57% were current users of alcohol, and 28% of the patients had at least one prevalent vertebral deformity at baseline. While the mean serum vitamin D levels were comparable between the groups at baseline (68 nmol/L), about 14% of the women had levels below normal. The mean LS T-scores were –1.35 and –1.162 for the EstPlo and RisEst groups, respectively. Approximately 61% of the women had T-scores < -1. The mean LS BMD values were similar in the two groups (963 and 979 mg/cm$^2$). The BMD values for the other skeletal sites were comparable between the two groups

Compliance with study drug was calculated to be over 90% for both groups.

A total of 256 EstPlo patients and 259 RisEst patients were included in the ITT population for lumbar spine. And a total of 236 EstPlo patients and 242 RisEst patients were included in the EV population for lumbar spine. In order for a lumbar spine BMD measurement to be included in the ITT analysis, the patient had to have had their BMD measurement obtained within 8 weeks of the scheduled visit data and both baseline and post-baseline spinal radiographs had to be available.

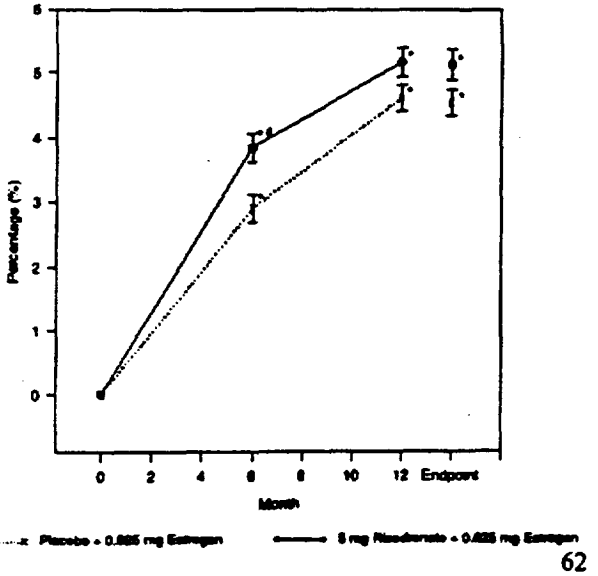
**7.4.7 c Primary Efficacy Endpoint Outcome**

**Percent Change in Lumbar Spine BMD**

As shown in the table and figure below, both groups had increases in LS BMD from baseline to Months 6 and 12. The increase in the RisEst group was statistically significantly greater than that in the EstPlo group at Month 6 but not Month 12 or Endpoint. Regardless of statistical significance, it should be noted that the absolute difference between groups at Month 6 (and Month 12) was small.

| MEAN PERCENT CHANGE IN LUMBAR SPINE BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 12 | Endpoint |
| Estrogen/Placebo | 0.945 g/cm$^2$ (n=256) | 4.6% (n=178)• | 4.5% (n=183)• |
| Ris5.0 mg/Estrogen | 0.959 g/cm$^2$ (n=259) | 5.2% (n=188)• | 5.1% (n=192)• |
| Between group p-value | ----- | 0.11 | 0.06 |

Significantly different from baseline ($p<0.05$) based on one-sample t-test



In the subgroup analyses, although the mean percent changes from baseline to Month 12 were slightly greater in the RisEst group compared with the EstPlo group, the differences were not statistically significant.

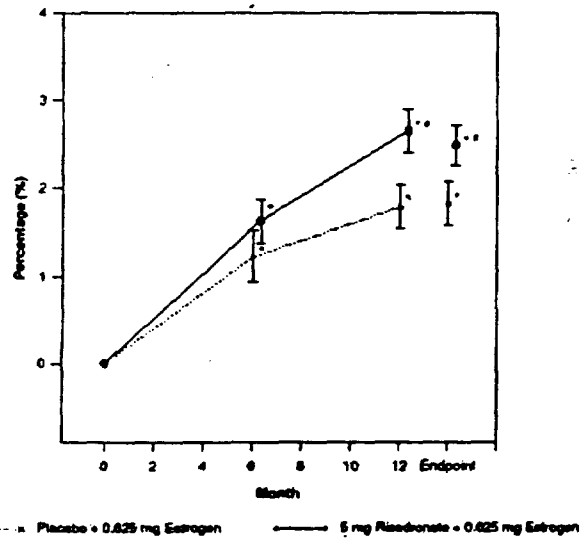
In the analysis of EV patients, the difference between the groups for the mean percent change in LS BMD from baseline to Month 12 was 0.70% in favor of RisEst (p=0.4).

**Mean Percent Change in Femoral Neck BMD**

As shown in the table and figure below, the use of risedronate with estrogen compared with estrogen with placebo resulted in slightly greater gains in femoral neck BMD over the course of one year.

| MEAN PERCENT CHANGE IN FEMORAL NECK BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 12 | Endpoint |
| Estrogen/Placebo | 0.752 g/cm$^2$ (n=258) | 1.8% (n=177)• | 1.8% (n=183)• |
| Ris5.0 mg/Estrogen | 0.763 g/cm$^2$ (n=260) | 2.7% (n=191)• | 2.5% (n=214)• |
| Between group p-value | ---- | 0.02 | 0.04 |

Significantly different from baseline (p<0.05) based on one-sample t-test



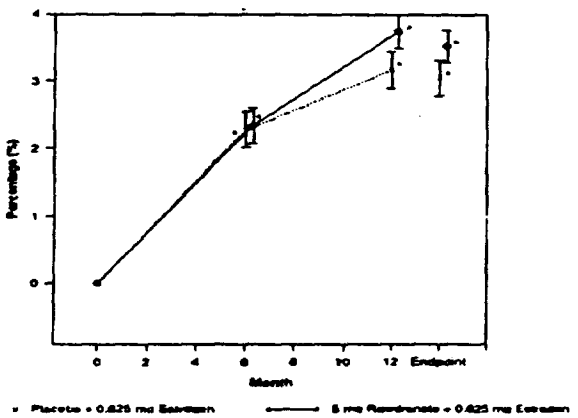

**Mean Percent Change in Femoral Trochanter BMD**

As shown below, both groups had increases from baseline in femoral trochanter BMD. These increases were quantitatively similar.

| MEAN PERCENT CHANGE IN FEMORAL TROCHANTER BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 12 | Endpoint |
| Estrogen/Placebo | 0.654 g/cm$^2$ (n=258) | 3.2% (n=177)• | 3.1% (n=183)• |
| Ris5.0 mg/Estrogen | 0.665 g/cm$^2$ (n=260) | 3.7% (n=191)• | 3.5% (n=214)• |

| MEAN PERCENT CHANGE IN FEMORAL TROCHANTER BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 12 | Endpoint |
| Between group p-value | — | 0.1 | 0.2 |

•Significantly different from baseline ($p<0.05$) based on one-sample t-test





**Mean Percent Change in Distal Radius BMD**

Although both groups had small increases (1.6% at Month 12) in distal radius BMD, the difference between groups was not statistically significant.

**Mean Percent Change in Midshaft Radius BMD**

As shown in the table and figure below, the RisEst group had a greater increase in cortical bone BMD at Month 12 than did the EstPlo group.

| MEAN PERCENT CHANGE IN MIDSHAFT RADIUS BMD (ITT) | | | |
|---|---|---|---|
| Treatment Group | Baseline BMD | Month 12 | Endpoint |
| Estrogen/Placebo | 0.684 g/cm$^2$ (n=257) | 0.37% (n=182)• | 0.47% (n=201)• |
| Ris5.0 mg/Estrogen | 0.682 g/cm$^2$ (n=258) | 0.70% (n=186)• | 0.63% (n=212)• |
| Between group p-value | — | 0.04 | 0.3 |

•Significantly different from baseline ($p<0.05$) based on one-sample t-test

**7.4.7 d Incident Vertebral Deformities:** The number of incident vertebral deformities in this study was small and the rates were not statistically significantly different between the two groups.

**7.4.7 e Non-Vertebral Fractures:** There were a total of 7 patients with fractures in the EstPlo group and 2 in the RisEst group. The two fractures in the RisEst group were both of the toe.

**7.4.8 Safety Review**

As mentioned previously, the review of safety data for this study will focus on deaths, serious adverse events, event leading to discontinuation, upper GI adverse events, bone histomorphometry, and serum calcium and phosphorus levels.

**Deaths**: Four patients in the EstPlo group and one subject in the RisEst group died during the time the study was being conducted. The patient in the RisEst group died of a myocardial infarction.

**Serious Adverse Events:** Nine percent of the EstPlo subjects reported 28 serious Aes and 5% of the RisEst subjects reported 16 serious Aes. Most of the events were reported under Cardiovascular System: 12 events in EstPlo and 1 in RisEst. Three RisEst patients and 1 EstPlo patient developed cholelithiasis during the trial.

**Withdrawals Due to Adverse Events**: Most of the Aes leading to withdrawal from the study were reported in the EstPlo arm. There were 23 patients in the EstPlo group and 9 in the RisEst group who withdrew because of an urogenital AE. Ten EstPlo and 2 RisEst patients dropped from the study because of vaginal hemorrhage, for example.

**Upper GI Adverse Events**: In general, the incidence of reported upper GI adverse events were similar between the two groups. Dyspepsia was reported by more EstPlo than RisEst patients, whereas, more RisEst patients reported "GI disorder" and gastritis. Additionally, there did not appear to be a significant difference between groups in the incidence of upper GI Aes for those subjects taking NSAIDs or aspirin.

**Serum Calcium** More RisEst patients than EstPlo patients went from a normal baseline serum calcium level to a low level at some point during the trial. One RisEst patient developed a markedly decreased serum calcium level at the Month 12 evaluation. There appeared to be a slightly greater percentage of RisEst patients compared with EstPlo patients who went from a normal baseline GGT or AST to an elevated level during the trial.

**Markers of Bone Metabolism:** Both groups had reductions from baseline throughout the study in serum levels of osteocalcin. By Month 3 the reductions were statistically significantly greater for the RisEst group compared with the EstPlo group. At Endpoint, the median percent reduction from baseline was –70% in the EstPlo group and –76% in the RisEst group ($p=0.01$). Both groups also had significant reductions from baseline in levels of N-telopeptide/Cr throughout the study. At Endpoint, the EstPlo group had a median percent reduction of 59% and the RisEst group had a median percent reduction of –70% ($p<0.001$).

**Bone Histomorphometry**: A total of 84 biopsies were obtained from 71 patients. Fifty-four biopsies were obtained at baseline and 30 at the end of the study. Paired biopsy data were obtained on a small sample of patients at baseline and Month 12. In the analyses of the paired biopsy data, some differences between groups in some parameters were noted; however, the small sample sizes and large standard error rates preclude one from making accurate assessments of the findings. Nevertheless, the marked reduction in activation frequency in the RisEst group does raise the issue of over-suppression of bone turnover. Of note, no cases of marrow fibrosis or osteomalacia were noted in any of the Month 12 biopsies.

| SELECTED BONE HISTOMORPHOMETRIC INDICES FOR PAIRED BIOPSIES | | |
|---|---|---|
| Index | EstPlo | RisEst |
| | Bone Resorption | |
| Final Erosion Depth (um) | | |
| N | 12 | 13 |
| Baseline | 44 | 44 |
| Month 12 | 39 | 42 |
| Mean % Change | -16%• | 2.0% |

| SELECTED BONE HISTOMORPHOMETRIC INDICES FOR PAIRED BIOPSIES | | |
|---|---|---|
| | Bone Formation | |
| Mineralization Surface | | |
| N | 12 | 12 |
| Baseline | 0.05 | 0.07 |
| Month 12 | 0.03 | 0.02 |
| Mean Change | -29% | -72% |
| | Bone Remodeling | |
| BMU-Balance (um) | | |
| N | 12 | 13 |
| Baseline | -3.6 | -2.8 |
| Month 12 | -1.9 | -4.0 |
| Mean % Change | 88% | -97% |
| Activation Frequency ($yr^{-1}$) | | |
| N | 8 | 9 |
| Baseline | 0.26 | 0.32 |
| Month 36 | 0.19 | 0.14 |
| Mean Change | -17% | -62%• |

•Significantly different from baseline at $p \leq 0.05$

### 7.4.9 Sponsor's Conclusions

Based on the results of this 12-month study, it can be concluded that:

· There was no significant difference in the primary endpoint between treatment groups in mean percent change from baseline in lumbar spine BMD at 12 months. Postmenopausal women treated with risedronate plus estrogen had statistically significant increases in BMD in the femoral neck and midshaft (1/3) radius (cortical bone sites) compared to the placebo/estrogen group.

· In combination with estrogen therapy, there were no adverse drug interactions between risedronate and estrogen, and the combination therapy is safe and generally well tolerated.

· Bone biopsies did not reveal any detrimental effects at tissue or BMU level for the combined risedronate plus estrogen therapy.

· There was no over suppression of bone turnover in the risedronate plus estrogen treatment, compared to the estrogen alone treatment based on the analysis of bone turnover markers.

· In estrogen-treated women, risedronate could be a safe and effective adjunct therapy (in increasing BMD) to the estrogen alone therapeutic regimen.

### 7.4.10 Medical Officer's Conclusions

The addition of 5 mg per day of risedronate to standard ERT for up to one year led to small improvements in BMD at most skeletal sites measured. It is unclear if the differential effects of the two drug regimens on BMD would increase with continued treatment.

In short, the results from this one-year study do not support or dissuade from the combined use of risedronate and estrogen for the prevention of postmenopausal osteoporosis.

**The Prevention and Treatment of Corticosteroid-Induced Osteoporosis**

Of greatest relevance to this review, the company performed two phase III studies in patients receiving corticosteroid therapy. Trial RCP was a randomized, double-blind, placebo-controlled study of patients receiving ≥ 7.5 mg prednisone equivalent for ≤ 3 months. This was considered a CIO prevention study. The second study, a treatment protocol, was RCT. This trial was a randomized, double-blind, placebo-controlled study of patients receiving ≥ 7.5 mg prednisone equivalent for ≥ 6 months. A review of these two studies follows.

**7.5 Study RCP**

**A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate in the Prevention of Corticosteriod-Induced Osteoporosis**

Enrollment started 4/25/1994 and the last subject's last observation was 12/11/1996.

**7.5.2 Primary Objective:** The primary objective of this study was to determine the efficacy of risedronate vs. placebo in maintaining or increasing lumber spine (LS) BMD in patients initiating high-dose glucocorticosteroid therapy within 3 months of study entry.

**7.5.3 Design:** This was a 12-month, double-blind, placebo-controlled, randomized, parallel-group, multicenter study conducted in North America. Subjects were randomized to one of three groups: placebo, Ris 2.5 mg QD, or Ris 5.0 mg QD. The cellulose-film-coated risedronate tablet formulation was used in this trial. Patients were instructed to take the study drug with a large amount of water (8 oz) on an empty stomach 30 to 60 minutes before breakfast and not to lie down for 1 hour after taking the tablet. All subjects received 500 mg of elemental calcium per day (OsCal), which was to be taken at a different time from the study drug. Subjects who dropped out of the study during the first 9 months of treatment were asked to return to the study center at the time of their scheduled Month 12 visit. Patients who dropped out at any other time had their Month 12 evaluation at the time of dropout. Patients who dropped out of the study because of an adverse event (AE) were to be followed until the event resolved. Investigators graded the severity of Aes as mild (normal activities unaffected), moderate (normal activities impaired), and severe (unable to perform normal activities). Moderate to severe upper GI Aes were to be recorded separately from other Aes. An endoscopy was requested at the earliest possible time for all patients who developed a moderate to severe complaint of any of the following upper GI symptoms: heartburn, mid-sternal pain, esophageal burning, epigastric pain, pain when swallowing, or difficulty swallowing. A moderate to severe complaint of upper GI disturbances was defined as any complaint listed above in which frequent (>3 times/day) episodes lasted longer than an hour per episode, required prescription or frequent (>3 times/week) over-the-counter medicinal intervention, resulted in impairment of normal activities, or resulted in incapacitation and/or hospitalization.

**7.5.4 Study Population:** The study population consisted of men and women aged 18-85 years who had been receiving at least 7.5 mg of prednisone or equivalent for ≤ 3 months prior to study entry. Patients had to have one of the following diagnoses for their steroid treatment: rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), polymyositis, temporal arteritis, systemic lupus erythematosis (SLE), chronic interstitial lung disease, asthma, chronic obstructive pulmonary disease (COPD), skin disease (i.e., pemphigoid), or vasculitis. Some of the exclusion criteria included: history of sarcoidosis, history of hyperparathyroidism, hyperthyroidism, or

osteomalacia within 1 year prior to enrollment. Use of anabolic steroids, estrogen or estrogen-related drugs, or progestogen within 3 months of starting the study or any use for more than one month within 6 months prior to starting study drug. Use of calcitonin, vitamin D supplements (>500 IU/day), or calcitriol within 1 month of starting study drug or any use for more than 1 month within 6 months prior to starting study drug. Use of any bisphosphonate, fluoride (≥ 10 mg per day), or subcutaneous estrogen implant within 6 months of starting study drug or any use for more than 14 days within 1 year prior to study start. Received any treatment with glucocorticosteroids within the last year prior to current therapy by any route of administration with the exception of intra-articular steroids, topical hydrocortisone, or < 400 ug/day of inhaled beclomethasone or budesonide. Patients were excluded during the study if they were deemed noncompliant: took less than 60% of study drug during first 3 months.

**7.5.5 Major Endpoints:** In addition to the standard evaluations (i.e., physical exams, clinical chemistries), DEXA evaluations ——————;) of the LS and proximal femur (femoral neck and trochanter) were performed in duplicate at baseline and at Month 6 and 12. A lateral spine x-ray was obtained at baseline and Month 12. A DEXA of the distal and midshaft radius was only obtained at baseline. Urine calcium excretion was obtained at baseline and Months 1, 3, 6, 9, and 12. Markers of bone turnover, bone specific alk phos, osteocalcin, and urinary collagen crosslinks, were obtained at baseline and Months 1, 3, 6, and 12. In a subset of subject, bone biopsies were obtained at baseline and Month 12. All non-vertebral fractures from any anatomical site were recorded at all post-baseline visits.

Bone biopsy samples were collected on a subset of patients at baseline and at Month 12 or at time of dropout if patient took study drug for > 3 months. Samples were reviewed from a safety perspective to assess overall bone quality and to identify any adverse changes in bone dynamics. All assessments were conducted in a blinded manner.

Samples were reviewed histologically for structural information, including overall architecture, accumulation of unmineralized bone, and deposition of woven or non-lamellar bone. Samples were also assessed histomorphometrically for data on trabecular architecture, the rate of bone turnover, bone formation, mineralization kinetics, and completed wall thickness.

Prevalent and incident vertebral body deformities were defined as follows A vertebral body was considered to be deformed at baseline if any of the vertebral height ratios fell below 3 standard deviations of the mean for the study population, as determined by the Eastell Trimming Method. Quantitative morphometry was used to identify potential incident deformities. A vertebral body that was not deformed at baseline sustained an incident deformity at a subsequent visit if the reduction from baseline in any one of the measured vertebral heights was ≥ 15%. For a vertebra judged deformed at baseline, an incident deformity was defined as a height reduction ≥ 4 mm in any vertebral height measured between the baseline and subsequent follow-up radiographs. Vertebrae identified as potential incident deformities by quantitative morphometry were visually assessed by a qualified radiologist to verify incident deformities. The final data defining the incident vertebral deformities were comprised of the verified vertebral deformities.

**7.5.6 Statistical Analyses**

The company has defined two patient populations for analyses: 1) Intent-to-treat (ITT) –all patients who were randomized and received at least one dose of study drug; 2) Evaluable population (EV) – those in the ITT population who were not protocol violators, who took at least 80% of study drug, and received at least 7.5 mg prednisone equivalent mean oral daily dose of

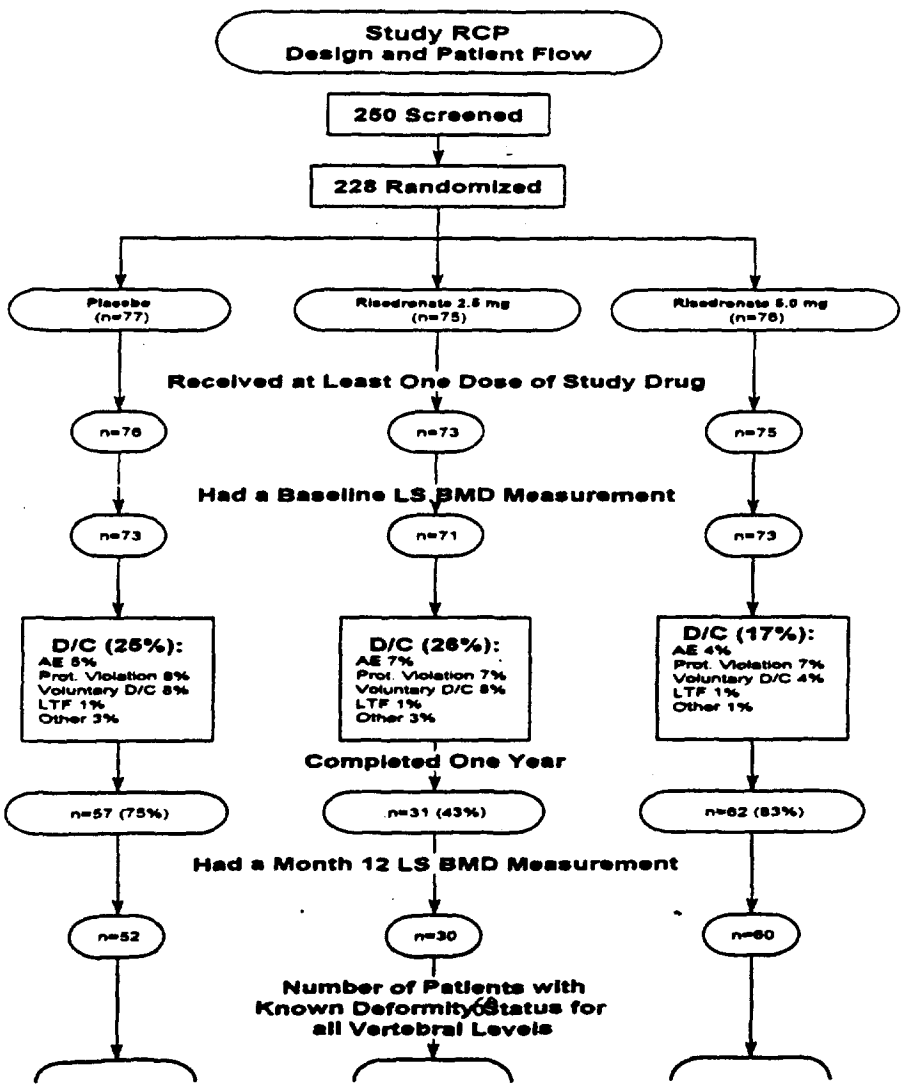
glucocorticosteroid therapy for at least 3 months and at least 2.5 mg for the subsequent 9 months of the treatment period.

For the primary endpoint – percent change in BMD – a three-way ANOVA model with treatment group, investigator, and stratum (males, premenopausal females, and postmenopausal females) as factors were used to evaluate the difference among the Ris 5.0 and placebo groups. Additional analyses were conducted using an ANCOVA model including treatment group, investigator, and stratum as main effects, and mean dose and duration of previous glucocorticosteroid treatment, and mean concomitant glucocorticosteroid dose as covariates. Changes in BMD were also evaluated in the following subgroups: age $\geq$ 65 years, Caucasian, stratum, primary condition for steroid treatment, duration of pre-study steroid treatment, mean daily dose of concomitant steroid therapy, and baseline BMD.

### 7.5.7 Results

### 7.5.7 a Patient Disposition (see diagram below)

A total of 153 patients were randomized to placebo (n=77) and Ris 5.0 mg (n=76). All but one subject in each group received at least one dose of study drug. A total of 57 subjects (75%) in the placebo group and 62 (83%) patients in the Ris 5.0-mg group completed the 12-month study. Of the patients that did not complete the 12-month intervention, 5% of placebo and 4% of Ris 5.0 mg subjects discontinued because of adverse events. A similar percentage of patients in each group discontinued early because of protocol violations, voluntary withdrawal, or loss to follow-up.



### 7.5.7 b Baseline Demographics and Concomitant Medications

The placebo and Ris 5.0-mg groups were fairly well matched at baseline. The mean age of the subjects in the placebo group was 57 year vs. 62 years in the Ris 5.0 mg group (p=0.02). The majority of the patients (60%) in each group were ≥ 65 years of age. About 65% of the patients in each group were female (47% of these were postmenopausal) and nearly all (90%) were Caucasian. There were more current smokers in the placebo group (30%) compared with the Ris 5.0-mg group (12%). This difference was of borderline statistical significance (p=0.07). The percentage of current alcohol users was similar in the two groups (35%). Twenty-nine percent of placebo subjects and 36% of Ris 5.0 mg subjects were determined to have prevalent vertebral deformities at baseline (p=0.2).

The mean LS T scores for the placebo and Ris 5.0 mg groups were –0.71 and –0.38, respectively (p=0.07). Roughly 60% of the patients in each group had LS T scores ≥ -1.0. The BMD values at the other sites were comparable between the two groups. For all three stratums (males, premenopausal, and postmenopausal women), the sex-specific LS T scores were lower in the placebo vs. the Ris 5.0-mg group; however, the differences were not statistically significant.

The majority of patients (approx. 38%) in each group were being treated with steroids because of rheumatoid arthritis (RA). Twenty-five percent of placebo subjects and 33% of Ris 5.0-mg subjects had diagnoses of polymyalgia rheumatica (PMR). Systemic lupus erythematosus (SLE) (14%) and temporal arteritis (TA) (7%) were the next most frequent steroid-requiring diagnoses, followed by very few subjects with vasculitis, asthma, COPD, polymyositis, and dermatomyositis.

The table below provides the type, dose, and duration of steroid used by the two treatment groups prior to study entry.

| DURATION AND DOSE OF PRIOR STEROID USE PRIOR TO [illegible] | | |
|---|---|---|
| Treatment | [illegible] | [illegible] |
| Dexamethasone | 0 | 1 |
| Methylprednisolone | 2 | 6 |
| Prednisolone | 11 | 16 |
| Prednisone | 68 | 59 |
| **Duration** | | |
| Unknown | 1 | 1 |
| ≤ 1 Month | 28 | 21 |
| > 1-2 Months | 26 | 27 |
| > 2-3 Months | 18 | 23 |
| > 3 Months | 4 | 4 |
| Mean (months) | 1.7 | 1.9 |
| **Daily Dose (prednisone equivalent)** | | |
| < 7.5 mg | 2 | 5 |
| ≥ 7.5 mg | 74 | 70 |
| Mean (mg) | 22 | 20 |
| Median (mg) | 14 | 15 |
| Min. Max (mg) | 0.8, 60 | 2.0, 68 |

The groups were well matched at baseline for previous use of steroids. Most of the patients had been taking steroids for 2 months or less. In the next table appears the duration and dose of steroids taken during the trial.

| | | |
|---|---|---|
| Prednisone | 65 | 60 |
| Methylprednisolone | 1 | 6 |
| Prednisolone | 15 | 16 |
| Dexamethasone | 0 | 1 |
| **Duration** | | |
| 0-3 Months | 8 | 7 |
| > 3-6 | 4 | 5 |
| > 6-9 | 5 | 1 |
| > 9-12 | 31 | 30 |
| > 12 | 28 | 32 |
| Mean (months) | 10 | 11 |
| **Daily Dose (prednisone equivalent)** | | |
| < 3.75mg | 4 | 2 |
| ≥ 3.75 mg | 72 | 73 |
| Mean (mg) | 11 | 11 |
| Median (mg) | 9 | 9 |
| Min, Max (mg) | 1.6, 40 | 1.6, 66 |

Like the exposure prior to study enrollment, both groups had similar dose and duration exposures to steroids during the study. The mean duration of exposure to the mean dose of prednisone or its equivalent (11 mg), was 10 months.

In general, the number of patients who took any concomitant medication during the trial was similar between the two groups.

It is perhaps reassuring that the measured compliance with study drug was 93% for the placebo group and 94% for the Ris 5.0 mg group.

### 7.5.7 c Primary Efficacy Outcome

Lumbar Spine BMD - The ITT population for the LS BMD consisted of 73 placebo and 73 Ris 5.0 mg subjects at baseline. The EV population for LS BMD consisted of 60 placebo and 60 Ris 5.0 mg subjects at baseline.

The table below provides the mean percent change in BMD from baseline to Month 12 and Endpoint for both the ITT and EV populations.

| | | | | |
|---|---|---|---|---|
| | Plo | Ris 5.0 mg | Plo | Ris 5.0 mg |
| Baseline BMD (g/cm$^2$) | 1.020 | 1.035 | 1.025 | 1.048 |
| %Change at Month 12 | -2.83%* | 0.59% | -2.93%* | 1.62%* |
| %Change at Endpoint | -2.75%* | 0.43% | -2.51%* | 1.06%* |
| Between group p-value | <0.001 | | <0.001 | |
| *Within group p-value ≤ 0.05 | | | | |

In the ITT analysis, the decrease in BMD in the placebo group accounts for the significance between the two groups at Month 12.

In an analysis which included all subjects with a baseline LS BMD measurement and a Month 12 measurement (this included 3 additional patients excluded from the above ITT analysis), the mean percent changes in LS BMD from baseline to Month 12 were –2.8% in the placebo group and 0.6% in the Ris 5.0 mg group (p<0.001).

In the ITT analysis, for the subgroup of males and postmenopausal women, the differences between active and placebo treatment in percent changes in LS BMD after 12 months of treatment were statistically significant and comparable to those in the overall population. In premenopausal women, however, the difference between active and placebo treatment was about 2% (p=0.2).

In analyses of demographic subgroups (race, age, mean daily dose of steroid, baseline BMD, disease category), the mean differences between placebo and Ris 5.0 mg groups in the percent change in LS BMD after 12 months of therapy ranged from ——— These differences were all nominally statistically significant, except for the disease category of RA. Here the p-value was of borderline significance - p=0.08.

**7.5.7 d Secondary Efficacy Outcomes**

**Femoral Neck BMD** - At the femoral neck, the results were similar to those at the LS. For the ITT population, the mean difference between placebo and Ris 5.0 mg groups at month 12 was 4% (p<0.001). This difference was mainly due to the significant decrease in BMD in the placebo group, with more or less of maintenance in BMD in the active-treatment group.

Much like that observed at the LS, the two strata that benefited the most from active therapy were males and postmenopausal women. The mean difference between the placebo and active therapy groups in the mean percent change in femoral neck BMD at Month 12 was only 0.5% in the premenopausal women (p=0.9). This contrasts with a difference of 5.1% (p=0.01) and 3.6% (p=0.03) in the male and postmenopausal female populations, respectively.

Similar results were obtained in the EV analyses.

**Femoral Trochanter BMD** – The placebo group had a mean percent decrease in femoral trochanter BMD of 3.1% at Month 12, whereas the active therapy group had a mean percent increase of 1.4% (p<0.001).

Only the male and postmenopausal women in the Ris 5.0-mg group had statistically significant changes in BMD when compared with placebo. Perhaps due to a younger age, the premenopausal women in the placebo group had a slight increase in mean BMD at month 12. In contrast, the placebo subjects in the male and postmenopausal groups had significant decreases in BMD at Month 12.

Similar results were obtained in the EV analyses.

**Distal Radius BMD** – Due to a protocol amendment, only 26 patients had distal radius BMD measurements at Month 12. Although there was a 2.8% difference in percent change from baseline between the placebo and 5.0 mg groups, this difference was not statistically significant (p=0.2).

**Mid-Shaft Radius BMD** – From baseline to Month 12 there was a small reduction in mid-shaft radius BMD in the placebo group and a small increase in the Ris 5.0 mg group. The difference, measured in just 52 patients, was not statistically significant.

### 7.5.7 e Markers of Bone Metabolism

**Osteocalcin** – The baseline values for osteocalcin were comparable in the placebo and Ris 5.0-mg groups. At Month 12, the placebo group had a mean percent increase of 56% compared to a 15% increase in the Ris 5.0 mg group (p=0.06). The stratum of postmenopausal women who had a mean increase of 129% drove the increase in the placebo group (Ris 5.0 mg group had a –0.8% decrease from baseline). A similar pattern was observed for bone specific alkaline phosphatase.

**Deoxypiridinoline/creatinine (dPyr/Cr)** – The baseline values for dPyr/Cr were comparable in the placebo and Ris 5.0-mg groups. At Month 12, there was a nonsignificant increase of 10% in the placebo group and a nonsignificant decrease of 13% in the Ris 5.0 mg group, such that the difference between the two was not statistically significant (p=0.4).

### 7.5.8 Safety Review

A comprehensive review of the safety data can be found in the ISS.

In the following review, data from the Ris 2.5mg group will be included where appropriate. It should be kept in mind that the Ris 2.5-mg group was discontinued from the study early, as per protocol amendment.

**Deaths** - Five patients died during the study. A placebo patient died from "lung disease". Two Ris 2.5 mg subjects died: one patient who had received study drug from June 9, 1995 until December 13, 1995 was diagnosed with AML on July 11, 1996; the second patient was a 31-year-old female with a history of SLE. This patient took study drug from October 13, 1994 until February 7, 1995. On February 8, 1995 the patient is recorded as suffering a pulmonary embolism which caused her death. Two Ris 5.0-mg subjects also died: an 81-year-old Hispanic female took risedronate from April 15, 1995 until September 23, 1995. The patient was hospitalized on September 25, 1995 for a presumed kidney infection. She stopped her study drug two days prior. On December 7, 1996 the patient died from septicemia. She had not been on study drug since September 1995. The second patient, a 64-year-old male began study drug on November 17, 1994. His last day of treatment was listed as March 8, 1995. On March 15, 1995 the patient underwent surgery for adenocarcinoma of the GE junction. On July 17, 1996, the patient died from an unknown cause.

**Serious Adverse Events** – In general, there were few subjects in each group that reported serious adverse events. In the GI system, one risedronate-treated patient had a GI carcinoma and one patient had esophagitis. In contrast, there was one placebo patient and no Ris subjects for each of the following Aes: cholecystitis, colitis, diarrhea, and pancreatitis.

**Discontinuations Due to Adverse Events** – Four placebo, 5 Ris 2.5 mg, and 3 Ris 5.0 mg subjects discontinued due to Aes. Of note, one of the Ris 2.5-mg dropouts was due to gastritis and one of the Ris 5.0-mg dropouts was because of abnormal LFTs.

**Upper GI Adverse Events** – Abdominal pain was reported by 5% of placebo, 8% of Ris 2.5mg, and 8% of Ris 5.0 mg subjects. Dyspepsia, on the other hand, was reported by a larger percentage of placebo patients (9% vs. 7%, vs. 4%, respectively). Although the percentage of mild and

moderate Aes reported by the three groups were similar, more active-treatment subjects had severe UGI Aes compared with placebo.

**Overall Incidence of Adverse Events** - see pages 12-14.

**Non-Vertebral Fractures** – The following table delineates the number of patients, by skeletal site, with non-vertebral fractures.

| Fracture Site | Plo (n=94) | Ris 2.5 mg (n=92) | Ris 5.0 mg (n=99) |
|---|---|---|---|
| Ankle | 1 | 0 | 0 |
| Hip | 1 | 1 | 1 |
| Pubis | 1 | 0 | 0 |
| Ribs | 1 | 1 | 0 |
| Sacrum | 0 | 0 | 1 |
| Toes | 0 | 0 | 1 |
| Wrist | 0 | 1 | 0 |
| Total | 4 (#Fx=5) | 3 (#Fx=4) | 3 (#Fx=3) |

**Vertebral Deformities** – There were 57 placebo and 61 Ris 5.0 mg subjects with evaluable radiographs at Month 12. Of these, there were 51 subjects in the placebo group and 51 in the Ris 5.0-mg group with known deformity status for all vertebral levels. Here there were 33 incident deformities in the placebo group vs.1 in the Ris 5.0-mg group. This difference was significant at $p<0.001$.

**Bone Histomorphometry**

At the completion of the study there were few subjects who had paired biopsy specimens for analysis. Only 4 placebo and 11 Ris 5.0 mg subjects had semi-complete data at Month 12. Because of the inadequate numbers, the sponsor did not perform statistical analyses of the data. Of the biopsies obtained, one specimen from a placebo subject showed marrow hyperplasia at Month 12. There were no reports of marrow fibrosis or osteomalacia.

**Vital Signs**

There were very small, non-clinically significant changes in blood pressure and pulse in the placebo and Ris 5.0-mg groups during the course of the study. Body weight did not change appreciably in any of the treatment groups.

Hematology – There were no clinically relevant differences between the placebo and Ris 5.0 mg groups in the mean changes from baseline to Month 12 or Endpoint for any of the hematology parameters.

Electrolytes and Glucose – There did not appear to be any meaningful differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint for any of the electrolytes and glucose.

Liver Function Tests – There were no clinically significant differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint for any of the LFT parameters. Of note, a 74-year-old female in the Ris 5.0-mg group developed markedly

elevated levels of ALT, AST, and GGT (3620) during the study. She had a positive re-challenge to the study drug.

Serum Calcium and Phosphorus – There were no clinically significant differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint for serum calcium and phosphorus.

24-Hour Urinary Calcium – The mean values for 24-hour urinary calcium decreased by –1.2 mmol in the placebo group at Month 12 compared with –0.9 mmol in the Ris 5.0 mg group.

Serum iPTH – In the roughly 100 patients who had measurements of iPTH, the mean percent difference between the Ris 5.0 mg and placebo groups was 22% greater in the Ris group (p=0.3). In the 20 Ris 5.0 mg patients who had measurements of their midshaft radius BMD, there was no meaningful correlation between the percent change from baseline to Month 12 in iPTH with the change in midshaft radius BMD (r=0.1; p=0.6).

Serum Creatinine – The mean change from baseline to Month 12 in creatinine was 1.0 umol/L in the placebo group and 4.2 umol/L in the Ris 5.0-mg group. Two placebo patients and 6 Ris 5.0 mg subjects developed above normal values for serum creatinine during the trial. Fifty percent of the subjects in each group had resolution of the abnormality at endpoint. The highest values noted was 150.3 umol/L. A placebo male and a Ris 5.0-mg male both had this degree of elevation.

### 7.5.9 Sponsor's Conclusions

In conclusion, risedronate 5 mg daily for 12 months significantly prevented bone loss in patients initiating high doses of glucocorticosteroid treatment and was well tolerated. Although a smaller number of patients in the 2.5-mg risedronate group completed the study, the results suggest that the 5-mg dose was more effective in preventing bone loss. Prevention of bone loss with risedronate therapy was associated with a substantial reduction in vertebral deformity incidence and vertebral deformity rate.

### 7.5.10 Medical Officer's Conclusions

The results of this one-year study suggest that, in patients recently initiating glucocorticoid treatment, 5 mg per day of risedronate plus supplemental calcium helps maintain bone mineral density at the lumbar spine, femoral neck, and femoral trochanter when compared with calcium treatment alone. Postmenopausal women and men appeared to benefit the most from the risedronate therapy; whereas premenopausal women had smaller relative gains in bone mineral density following active-drug treatment.

In the subgroup of patients in which vertebral deformity status was known for all vertebral levels, there was a marked reduction in the incidence of deformities in the group treated with 5 mg per day of risedronate vs. those treated with placebo (supplemental calcium). Importantly, there were no significant differences between the placebo and risedronate 5 mg groups in the number of patients (or # of fractures) with non-vertebral fractures.

Mean levels of serum iPTH increased to a greater extent in the risedronate 5 mg group compared with the placebo group following one year of treatment. Yet, in a subgroup of patients with midshaft radius BMD measurements, there was no correlation between the change in iPTH with the change in midshaft radius BMD.

Of note, as documented by a positive re-challenge, one patient had drug-induced hepatic transaminasemia.

## 7.6 Study RCT

### A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate in the Treatment of Corticosteriod-Induced Osteoporosis

Enrollment started 8/11/1994 and the last subject's last observation was 10/7/1996.

**7.6.2 Primary Objective:** The primary objective of this study was to determine the efficacy of risedronate vs. placebo in maintaining or increasing lumbar spine BMD in patients receiving high-dose oral glucocorticosteroid therapy for ≥ 6 months prior to study entry.

**7.6 3 Design:** This was a 12-month, double-blind, placebo-controlled, randomized, parallel-group, multicenter study conducted in the Europe. Subjects were randomized to one of three groups: placebo, Ris 2.5 mg QD, or Ris 5.0 mg QD. The cellulose-film-coated risedronate tablet formulation was used in this trial. Patients were instructed to take the study drug with a large amount of water (8 oz) on an empty stomach 30 to 60 minutes before breakfast and not to lie down for 1 hour after taking the tablet. Patients were also instructed to take 400 IU of vitamin D every day and 1 gram of calcium per day. The calcium was to be taken with lunch or the evening meal, at a different time from the study drug. Subjects who dropped out of the study during the first 9 months of treatment were asked to return to the study center at the time of their scheduled Month 12 visit. Patients who dropped out at any other time had their Month 12 evaluation at the time of dropout.

An endoscopy was requested at the earliest possible time for all patients who developed a moderate to severe complaint of any of the following upper GI symptoms: heartburn, mid-sternal pain, esophageal burning, epigastric pain, pain when swallowing, or difficulty swallowing. A moderate to severe complaint of upper GI disturbances was defined as any complaint listed above in which frequent (>3 times/day) episodes lasted longer than an hour per episode, required prescription or frequent (>3 times/week) over-the-counter medicinal intervention, resulted in impairment of normal activities, or resulted in incapacitation and/or hospitalization.

**7.6.4 Study Population:** The study population consisted of men and women aged 18-85 years who had been receiving at least 7.5 mg of prednisone or equivalent for ≥ 6 months prior to study entry. Patients had to have one of the following diagnoses for their steroid treatment: rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), polymyositis, temporal arteritis, systemic lupus erythematosis (SLE), chronic interstitial lung disease, asthma, chronic obstructive pulmonary disease (COPD), skin disease (i.e., pemphigoid), or vasculitis. Some of the exclusion criteria included: history of sarcoidosis, history of hyperparathyroidism, hyperthyroidism, or osteomalacia within 1 year prior to enrollment. Use of anabolic steroids, estrogen or estrogen-related drugs, or progestogen within 3 months of starting the study or any use for more than one month within 6 months prior to starting study drug. Use of calcitonin, vitamin D supplements (>500 IU/day), or calcitriol (> 1.5 ug/week) within 1 month of starting study drug or any use for more than 1 month within 6 months prior to starting study drug. Use of any bisphosphonate, fluoride (≥ 10 mg per day), subcutaneous estrogen implant, or deflazacort within 6 months of starting study drug or any use for more than 14 days within 1 year prior to study start. Received an injection of ≥ 10,000 IU of vitamin D within 1 year prior to enrollment. Patients with more

than 2 fractured lumbar vertebrae (L1-L4). Patients could have been excluded from further study if during the study they were deemed noncompliant (took less than 60% of study drug during the first 3 months), were treated with any other bisphosphonate, anabolic steroid, vitamin D supplement (>500 IU/day), calcitriol (>1.5ug/week), or estrogen.

**7.6.5 Major Endpoints**: In addition to the standard evaluations (i.e., physical exams, clinical chemistries), DEXA evaluations ——————— of the LS and proximal femur (femoral neck and trochanter) were performed at baseline and at Months 6 and 12. The average of two baseline and Month 12 DEXA measurements was used in statistical computations. A lateral spine x-ray was obtained at baseline and Month 12. Urinary calcium excretion was measured at baseline and Months 1,3,6,9, and 12. Markers of bone metabolism were measured at baseline and Months 1, 3, 6, and 12. Plasma levels of vitamin D were measured at Month 6.

Prevalent and incident vertebral body deformities were defined as follows. A vertebral body was considered to be deformed at baseline if any of the vertebral height ratios fell below 3 standard deviations of the mean for the study population, as determined by the Eastell Trimming Method. Quantitative morphometry was used to identify potential incident deformities. A vertebral body that was not deformed at baseline sustained an incident deformity at a subsequent visit if the reduction from baseline in any one of the measured vertebral heights was $\geq$ 15%. For a vertebra judged deformed at baseline, an incident deformity was defined as a height reduction $\geq$ 4 mm in any vertebral height measured between the baseline and subsequent follow-up radiographs. Vertebrae identified as potential incident deformities by quantitative morphometry were visually assessed by a qualified radiologist to verify incident deformities. The final data defining the incident vertebral deformities were comprised of the verified vertebral deformities.

**7.6.6 Statistical Analyses:** The sponsor has defined two patient populations: 1) Intent-to-treat (ITT) – all patients who were randomized to placebo or risedronate and took at least one dose of study medication, and 2) Evaluable population (EV) - those in the ITT population who were not protocol violators, who took at least 80% of study drug, and received at least 5.0 mg prednisone equivalent mean oral daily dose of glucocorticosteroid therapy for at least one year after enrolling in the study. In addition, only visits which occurred within $\pm$ 3 weeks of the scheduled visit dates were included.

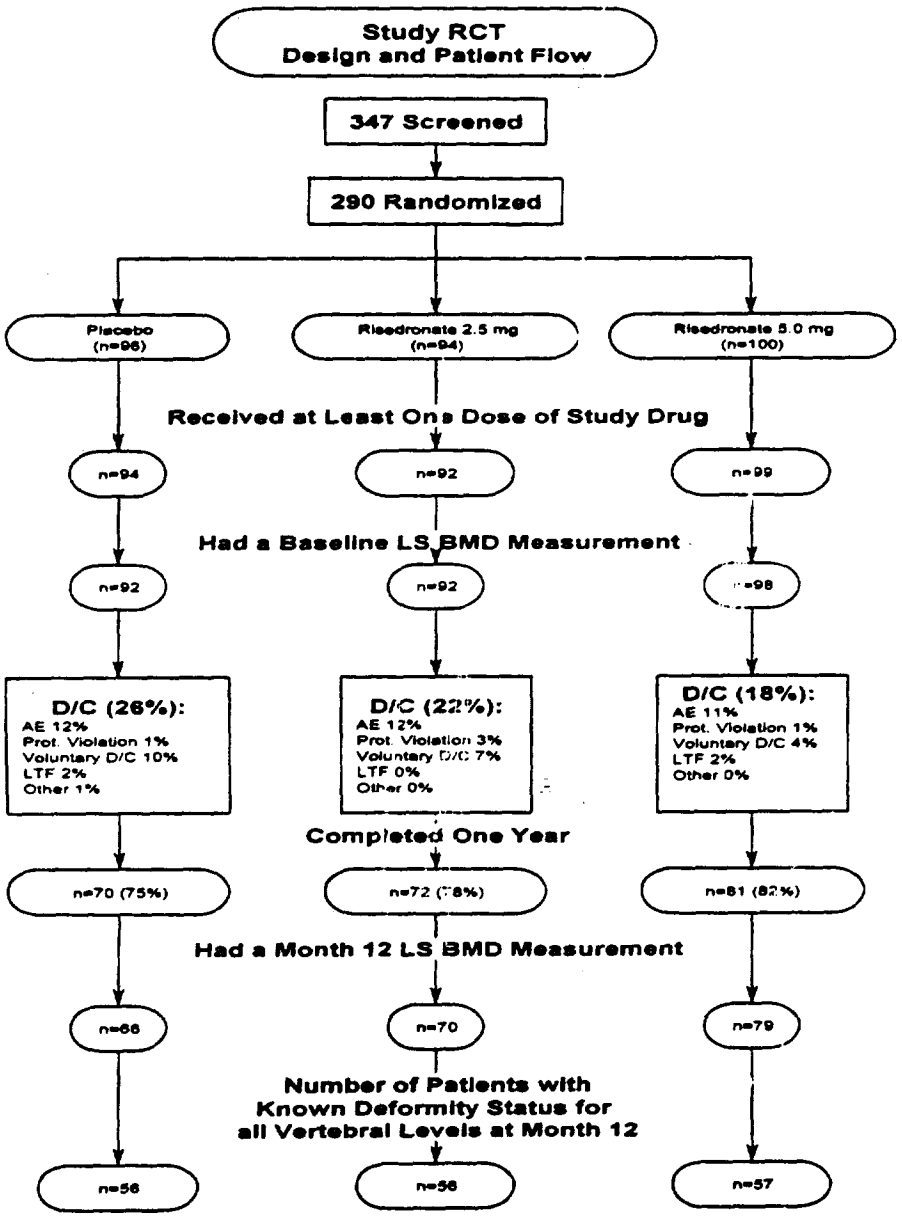
For the primary endpoint – percent change in BMD – a three-way ANOVA model with treatment group, investigator, and stratum (males, premenopausal females, and postmenopausal females) as factors were used to evaluate the difference among the two Ris and placebo groups. Additional analyses were conducted using an ANCOVA model including treatment group, investigator, and stratum as main effects, and mean dose and duration of previous glucocorticosteroid treatment, and mean concomitant glucocorticosteroid dose as covariates. Changes in BMD were also evaluated in the following subgroups: age $\geq$ 65 years, Caucasian, stratum, primary condition for steroid treatment, duration of pre-study steroid treatment, mean daily dose of concomitant steroid therapy, and baseline BMD.

**7.6.7 Results**

**7.6.7 a Patient Disposition (see diagram below)**

A total of 285 patients were randomized and received study drug: 96 to placebo, 94 to Ris 2.5 mg, and 100 to Ris 5.0 mg. A total of 94 placebo, 92 Ris 2.5-mg, and 99 Ris 5.0-mg subjects received at least one dose of study drug. Seventy (75%) of the placebo patients, 72 (78%) of the Ris 2.5mg patients, and 81 (82%) of the Ris 5.0 mg subjects completed the 12 month treatment period. The

most common reason for early withdrawal was adverse events: about 12% of patients from each group. Voluntary withdrawal was the next most common reason for early discontinuation.




### 7.6.7 b Baseline Demographics and Concomitant Medications

The placebo and Ris 5.0-mg groups were well matched at baseline with no statistically significant differences between them. The mean age was 58 years, 63% of the patients were female (55% postmenopausal), and 97% were Caucasian. About 23% of the patients in each group were current smokers and 49% of the placebo subjects and 39% of the Ris 5.0-mg subjects were current consumers of alcohol. Approximately 36% of the patients had prevalent vertebral

deformities. Importantly, the largest stratum was postmenopausal women: about 53 in the placebo and Ris 5.0 mg groups. There were only 7 premenopausal women in the placebo group and 9 in the Ris 5.0-mg group.

The mean LS BMD values were not significantly different between the placebo and Ris 5.0 mg groups (931 vs. 943 mg/c$^2$, respectively). The mean sex-specific T-scores were not significantly different between groups: -1.72 and -1.73 for the placebo and Ris 5.0 mg groups, respectively. A third of the patients in each group were osteoporotic at baseline based on T-scores below 2.5. Thirty-nine percent of placebo and 27% of Ris 5.0 mg subjects were osteopenic: T-scores of $\geq$ -2.5 $\leq$ -1. This difference was not statistically significant. At all other skeletal sites measured, the mean BMD values were similar between the placebo and Ris 5.0-mg groups.

Within the three stratums, the baseline LS BMDs were not statistically significantly different between the placebo and Ris 5.0-mg groups.

The majority of the patients were taking corticosteroids because of RA (~42%), followed by asthma (19%), PMR (12%), TA (6%), and vasculitis (3.5%). Very few patients had a history of COPD, polymyositis, pemphigoid, etc.

The following table provides the type, dose, and duration of steroid used by the two groups prior to study entry.

| DURATION OF STEROID TREATMENT PRIOR TO STUDY ENTRY | | |
|---|---|---|
| Steroid | Placebo | Ris 5.0 mg |
| Beclomethasone | 1 | 1 |
| Methylprednisolone | 4 | 4 |
| Prednisolone | 75 | 76 |
| Prednisone | 20 | 23 |
| **Duration** | | |
| Unknown | 1 | 1 |
| < 6 Months | 2 | 4 |
| > 6-9 Months | 11 | 5 |
| > 9-12 Months | 4 | 7 |
| > 12 Months | 78 | 83 |
| Mean (months) | 62 | 57 |
| **Daily Dose (prednisone equivalent)** | | |
| < 7.5 mg | 22 | 23 |
| $\geq$ 7.5 mg | 73 | 76 |
| Mean (mg) | 15 | 15 |
| Median (mg) | | |
| Min. Max (mg) | 0.6, 80 | 0.3, 67 |

Six patients received less than 6 months of steroid treatment prior to the study; they were excluded from the EV analyses. The majority of patients received a daily dose of 7.5 mg of prednisone or its equivalent.

The following table provides data on the type, dose, and duration of steroid used by the two treatment groups during the trial.

| | | |
|---|---|---|
| Prednisone | 21 | 24 |
| Methylprednisolone | 3 | 3 |
| Prednisolone | 73 | 77 |
| Beclomethasone | 0 | 1 |
| **Duration** | | |
| 0-3 Months | 12 | 7 |
| > 3-6 | 5 | 5 |
| > 6-9 | 5 | 4 |
| > 9-12 | 34 | 39 |
| > 12 | 38 | 44 |
| Mean (months) | 10 | 11 |
| **Daily Dose (prednisone equivalent)** | | |
| < 5.0 mg | 3 | 3 |
| ≥ 5.0 mg | 91 | 96 |
| Mean (mg) | 13 | 15 |
| Median (mg) | 9 | 9 |
| Min, Max (mg) | 3.4, 103 | 3.6, 134 |

The 6 patients who took less than 5.0 mg of prednisone or its equivalent were excluded from the EV analyses. The majority of subjects in each group took 5mg or more of prednisone or its equivalent for at least 9 months.

In general, the number of patients who took any concomitant medication during the trial was similar between the two groups.

The recorded compliance with the study drugs was determined to be 90% for the placebo group and 93% for the Ris 5.0-mg group.

The baseline levels of serum iPTH and calcium were comparable between the two groups. Further, the plasma levels of 25(OH) vitamin $D_3$ were the same in the two groups at Month 6.

### 7.6.7 c Primary Efficacy Outcome

**Lumbar Spine BMD** – The ITT population for LS BMD consisted of 92 placebo and 98 Ris 5.0 mg subjects. The EV population consisted of 83 placebo and 83 Ris 5.0 mg subjects. The majority of patients excluded from the EV analyses were noncompliant with study drug.

In the table below, the mean percent changes in BMD from baseline to Month 12 and Endpoint are shown for the ITT and EV populations.

| | | | | |
|---|---|---|---|---|
| | Plo | Ris 5.0 mg | Plo | Ris 5.0 mg |
| Baseline BMD ($g/cm^2$) | 0.903 | 0.920 | 0.899 | 0.916 |
| %Change at Month 12 | 0.43 | 2.90* | 0.57 | 2.92* |
| %Change at Endpoint | 0.49 | 3.02* | 0.70 | 3.11* |
| Between group p-value | <0.001 | | <0.001 | |
| *Within group p-value ≤ 0.05 | | | | |

As shown in the table above, the mean LS BMD remained fairly stable over the one-year treatment period in the placebo group; whereas, in the Ris 5.0-mg group there was a significant increase from baseline to Month 12 in LS BMD.

In the three stratum: males, premenopausal women, and postmenopausal women, the least square mean differences between Ris 5.0 mg and placebo therapy in mean percent change in LS BMD at Month 12 were 5.1%, 2.5%, and 1.8%, respectively. The differences in the men between the Ris 5.0 mg and placebo groups were statistically significant at $p<0.05$, but not in the other two subgroups.

In analyses of demographic subgroups (race, age, mean daily dose of steroid, baseline BMD, disease category), the mean percent change in LS BMD from baseline to Month 12 was, in all cases, greater for the Ris 5.0 mg subgroups compared with the placebo subgroups. Some of the subgroups were rather small, thus making statistical comparisons of questionable worth. Nonetheless, in many cases, the differences in mean percent change in LS BMD between Ris 5.0 mg and placebo were statistically significant. It is worth noting that in the subgroup analyses based on baseline BMD (<median, ≥median) and baseline iPTH (<median, ≥median) the group with BMD values below the median and the group with iPTH values above the median had very large relative increases in LS BMD (least square mean differences of 3.87 and 3.60, respectively).

**7.6.7 d Secondary Efficacy Outcomes**

**Femoral Neck BMD** – In the ITT population, from baseline to Month 12 there was a statistically significant increase of 1.8% in femoral neck BMD in the Ris 5.0 mg group compared with a loss of 0.25% in the placebo group. The relative increase in the Ris group was statistically significant. This trend was observed in males and postmenopausal women, but not in premenopausal women. In the latter subgroup, the placebo group had a greater mean percent increase in BMD than did the Ris 5.0-mg group. The reason(s) for this finding are unclear; however, it should be kept in mind that this subgroup consisted of only 5 placebo and 8 Ris 5.0 mg subjects.

Similar results were obtained in the EV analysis.

**Femoral Trochanter BMD** – In the ITT population, the mean percent increase in BMD from baseline to Month 12 at his skeletal site was 1.0% in the placebo group and 2.4% in the Ris 5.0 mg group. This difference was statistically significant. Similar trends in BMD changes were noted in the three stratums.

There were no significant differences between placebo and Ris 5.0 mg treated patients in the mean percent increases in femoral trochanter BMD after one year of treatment in the EV analysis.

**Distal Radius BMD** – In the ITT population, both groups had mean percent reductions in BMD at this skeletal site. Although the reduction was greater in the placebo group than in the Ris 5.0-mg group, the difference was not statistically significant.

**Mid-Shaft Radius BMD** – In the ITT population there was a non-statistically significantly greater reduction from baseline to Month 12 in mid-shaft radius BMD in the Ris 5.0 mg group (-0.5%) compared with the placebo group (-0.3%).

### 7.6.7 e Markers of Bone Metabolism

Osteocalcin – Values for osteocalcin decreased in both groups from baseline to Month 12. However, the decease was significantly greater in the Ris 5.0 mg group vs. the placebo group (-50% vs. –8%, respectively). This greater reduction in drug vs. placebo-treated groups was consistent within each of the three stratums. (Levels of Alk Phos remained stable in the Ris 5.0-mg group and increased from baseline in the placebo group such that the difference was statistically significant).

Deoxypiridinoline/creatinine (dPyr/Cr) – The mean levels of dPyr/Cr increased from baseline to Month 12 in the placebo group and decreased in the Ris 5.0-mg group. The difference between the two was statistically significant.

### 7.6.8 Safety Review

A comprehensive review of the safety data can be found in the ISS.

In the following review, data from the Ris 2.5mg group will be included where appropriate. It should be kept in mind that the Ris 2.5-mg group was discontinued from the study early, as per protocol amendment.

**Deaths** – Twelve patients are recorded as having died during the study: 4 placebo, 6 Ris 2.5 mg, and 2 Ris 5.0 mg subjects. The cause of the deaths varied from leukemia to myocardial infarction and there was no evidence of any significant imbalances among the groups.

**Serious Adverse Events** – By and large, few patients reported serious adverse events in any of the body systems. Musculoskeletal was the category with the most Aes reported and the numbers were balanced among the three groups. Of note, there were no serious GI Aes reported.

**Discontinuation Due to Adverse Events** – In general, more placebo patients discontinued due to an AE than did active-treatment patients.

**Upper GI Adverse Events** – The most commonly reported upper GI Aes were dyspepsia (10% vs. 13%, placebo vs. Ris 5.0 mg), abdominal pain (11% vs. 13%), and GI disorder (0% vs. 4%). Further, the groups were well balanced for severity scores for the upper GI Aes.

**Overall Incidence of Adverse Events** – See page 12-14.

**Non-Vertebral Fractures** – The following table provides the number of patients, by skeletal site, with non-vertebral fractures.

| Fracture Site | Plo (n=94) | Ris 2.5 mg (n=92) | Ris 5.0 mg (n=99) |
|---|---|---|---|
| Clavicle | 2 | 0 | 0 |
| Fibula | 1 | 1 | 1 |
| Hip | 1 | 0 | 0 |
| Humerus | 1 | 1 | 2 |
| Malleolus | 0 | 1 | 0 |
| Ribs | 0 | 2 | 2 |
| Sternum | 0 | 0 | 1 |
| Tibia | 2 | 1 | 1 |
| Toes | 1 | 0 | 0 |

| Fracture Site | Plo (n=94) | Ris 2.5 mg (n=92) | Ris 5.0 mg (n=99) |
|---|---|---|---|
| Wrist | 0 | 2 | 0 |
| Total | 6 (#Fx=9) | 8 (#Fx=11) | 8 (#Fx=10) |

Some subjects had more than one site fractured

Combining the number of patients with non-vertebral fractures from the prevention and treatment studies, there were 10, 11, and, 11 subjects in the placebo, Ris 2.5 mg, and Ris 5.0-mg groups, respectively, with fractures at the various non-vertebral sites. There were a total of 14, 15, and 13 non-vertebral fractures among the placebo, Ris 2.5 mg, and Ris 5.0-mg subjects, respectively.

**Vertebral Deformities** – There were 69 placebo and 79 Ris 5.0 mg subjects with evaluable radiographs at Month 12. Of these, 56 placebo patients and 57 Ris 5.0-mg subjects had known deformity status for all vertebral levels. There were a total of 11 deformities in the placebo group and only 2 in the Ris 5.0-mg group at Month 12. This difference was significant at $p<0.001$.

**Vital Signs**

From baseline to Month 12 there were equivalent changes in vital signs for the three groups.

**Clinical Chemistries**

Hematology - There were no clinically relevant differences between the placebo and Ris 5.0 mg groups in the mean changes from baseline to Month 12 or Endpoint for any of the hematology parameters. Further, the percentage of patients who developed values outside the reference range were similar for treatment groups.

Electrolytes and Glucose - There did not appear to be any meaningful differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint for any of the electrolytes and glucose. The percentage of patients who developed values outside the reference range were similar for treatment groups.

Liver Function Tests – There were no clinically significant differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint for any of the LFT parameters. Further, the percentage of patients who developed values outside the reference range were similar for treatment groups.

24-Hour Urinary Calcium – There were no clinically significant differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint. Further, the percentage of patients who developed values outside the reference range were similar for treatment groups.

iPTH – In the 136 patients from the Ris 5.0 mg and placebo groups who had measurements of iPTH, there was a small, nonsignificant increase in the Ris 5.0 mg group compared with the placebo group at Month 12 (4.4%; $p=0.8$). The correlation between the change in iPTH with the change in midshaft radius BMD from baseline to Month 12 was non-significant ($r= -0.1$; $p=0.4$).

Serum Creatinine - There were no clinically significant differences between placebo and Ris 5.0 mg treatment groups for the mean changes from baseline to Month 12 or Endpoint. Furthermore, the percentage of patients who developed values outside the reference range were similar for treatment groups.

### 7.6.9 Sponsor's Conclusions

The clinically relevant endpoint of treatment of CIOP is a reduction in fractures. Increases in lumbar spine BMD of the magnitude seen in this study are thought to be associated with a reduction in vertebral deformity incidence and rate. The safety data in this study demonstrated a substantial reduction in vertebral deformities and are consistent with this hypothesis. The BMD, bone marker, and vertebral deformity dose response indicate that 5-mg risedronate daily is a more clinically useful dose than the 2.5-mg treatment. Furthermore, the 5-mg risedronate treatment was well tolerated with a good safety profile. Risedronate 5-mg daily for 12 months offers an effective and well tolerated treatment for CIOP.

### 7.6.10 Medical Officer's Conclusions

In this study of pre and postmenopausal women and men on long-term glucocorticoid therapy, treatment for one year with risedronate 5 mg per day (plus 1 gram of supplemental calcium and 400 IU of vitamin D), increased lumbar spine, femoral neck, and femoral trochanter BMD to a greater extent than treatment with calcium and vitamin D alone. There was no drug effect observed on the radius.

In the subgroup of patients in which vertebral deformity status was known for all vertebral levels, there was a statistically significant reduction in the incidence of deformities in the group treated with 5 mg per day of risedronate vs. those treated with placebo. The number of patients (and the # of fractures) with non-vertebral fractures was similar in the placebo and Ris 5.0 mg groups.

Like the prevention trial, there was a small relative increase in level of iPTH in the Ris 5.0-mg group after one year of treatment. This increase is not likely to be of clinical significance as there was no correlation between the change in midshaft radius BMD and the change in iPTH in a subgroup of patients evaluated at baseline and Month 12.

## VIII. 180-Day Safety Update

As agreed upon at a pre-NDA meeting, this safety update includes safety information from two recently completed hip fractures studies: RHN and RHE, study 1997007, an examination of esophageal transit disintegration and gastric emptying times, and study 1998013, an endoscopy protocol. No serious adverse events or deaths were reported in the two latter studies, and therefore, a review of the safety data from the hip studies alone follows.

Study RHN was conducted in North America and study RHE was conducted in Europe. The protocols for these studies were nearly identical and included a multicenter, randomized, double-blind, placebo-controlled design. These trials were 3 years in duration and in addition to a placebo group, they included risedronate 2.5 mg and 5.0 mg once daily arms. All women were over the age of 70 years (mean age =78 years) at baseline and were instructed to take a 1.0 gram elemental calcium supplement per day and for those women with low baseline vitamin D levels, a 500 IU per day supplement was provided.

A total of 9497 patients were randomized in these studies: 3184 to placebo, 3151 to Ris 2.5 mg, and 3162 to Ris 5.0 mg. Roughly 50% of the subjects completed the 3-year studies with similar drop out rates for the 3 treatment groups.

The death rates during the studies were similar: 4% for placebo, 4.2% for Ris 2.5 mg, and 3.6% for Ris 5.0 mg. During post-treatment follow-up there were 49 deaths in the placebo group, 44 in the Ris 2.5-mg group, and 58 in the Ris 5.0-mg group. There did not appear to be any meaningful imbalances in the percentages of deaths by body system for the 3 groups. Of some interest, during active and post-treatment, 1 placebo subject and 3 Ris 2.5 and 3 Ris 5.0-mg subjects were coded with GI hemorrhage as an adverse event associated with death.

The incidence rates for serious adverse events were comparable for each major body system across the 3 groups, with atraumatic bone fracture the most common: ~ 5.0%. As noted in the ISS, there was a lower incidence of GI carcinomas reported for the 2 risedronate groups (19 and 13) vs. the placebo group (27) and a larger number of lung cancer cases reported for the Ris 2.5 mg group (21) compared with placebo (10). The rates of total cancer were similar for the 3 groups.

In general agreement with the data reviewed in the ISS, there were no marked imbalances among the groups for GI-related adverse events in the 2 hip fracture studies. Abdominal pain was one of the most common events reported in the hip studies, but unlike the data from the postmenopausal and CIO databases, there was no increased incidence in the actively treated groups when compared with the placebo group.

It can be concluded that no new or significant safety issues have emerged from a preliminary review of studies RHE, RHN, 1997007, or 1998013.

## IX. Medical Officer's Summary of Efficacy and Safety of Risedronate for the Prevention and Treatment of Postmenopausal Osteoporosis

There is now convincing evidence that the bisphosphonates significantly increase bone mineral density in postmenopausal women, with and without established osteoporosis. In a small study of early postmenopausal women, cyclical etidronate therapy increased lumbar spine BMD by nearly 3% relative to placebo over a two-year period[1]. In a larger and longer-term study of early postmenopausal women, 5 mg per day of alendronate increased lumbar spine BMD by over 5% relative to placebo after 3 years of treatment[2]. Alendronate-treated women also had significant increases in radius BMD relative to placebo.

The data from study RBL indicate that 5-mg per day of risedronate in early postmenopausal women also increases lumbar spine BMD by a significant amount when compared with placebo. Treatment with risedronate also increased BMD of the femoral neck and trochanter by 3-4% relative to placebo.

Following initial favorable reports in the early 90s of cyclical etidronate in the treatment of postmenopausal osteoporosis, a subsequent 3-year study found that etidronate's fracture efficacy disappeared during the third year of blinded therapy[3-5]. These mixed reports with cyclical etidronate were followed by data in the mid-90s on the effects of oral alendronate on fracture risk in women with established postmenopausal osteoporosis. In 1995 the Alendronate Phase III Osteoporosis Treatment Study Group published a report in which is was concluded that "daily treatment with alendronate progressively increases the bone mass in the spine, hip, and total body and reduces the incidence of vertebral fractures, the progression of vertebral deformities, and height loss in postmenopausal women with osteoporosis[6]." Treatment with daily alendronate (all dose groups combined) for 3 years decreased the vertebral fracture incidence from 6.2% to 3.2%. In a second study of 36 months duration, 5 mg per day of alendronate for two years followed by 10 mg per day for one year decreased the incidence of morphometrically defined vertebral fractures from 15% to 8.0% and clinical vertebral fractures from 5.0% to 2.3%[7].

The two well-conducted studies in this NDA that examined risedronate's effect on vertebral fracture risk in women with postmenopausal osteoporosis are in agreement with the results reported for alendronate and indicate that risedronate is a modestly effective agent for the treatment of postmenopausal osteoporosis. On average, the absolute risk for vertebral fracture was decreased by 5-12% following 3 years of treatment with 5-mg daily of risedronate. It should be emphasized that the women at highest risk for vertebral fracture at baseline had the greatest benefit from drug treatment.

The principal established safety concerns for the bisphosphonates as a class include effects on bone quality, gastrointestinal tolerance, and mineral metabolism.

Higher doses of etidronate, but not pamidronate or alendronate, have been associated with osteomalacia[8]. There is no evidence from the bone biopsy data from risedronate that this bisphosphonate, at a dose of 5 mg per day, impairs mineralization or adversely affects bone quality.

There is convincing evidence that the bisphosphonates, particularly the amino compounds, are associated with an increased risk for symptomatic gastrointestinal adverse events such as esophagitis, abdominal pain, nausea, vomiting, diarrhea, and asymptomatic gastric mucosal injury

[redacted][3]. In the risedronate database, there were no statistically significant differences between active- and placebo-treated patients for the incidence of serious gastrointestinal adverse events or withdrawals due to gastrointestinal events. As expected, however, a number of GI adverse events were reported by more risedronate- than placebo-treated subjects. These included abdominal pain, gastritis, GI hemorrhage, esophagitis, nausea, and vomiting. The risk for abdominal pain appeared to be increased by the concomitant use of risedronate with a NSAID. It is reasonable to say that individuals who take risedronate will be at some increased risk for symptomatic GI events, some serious.

Due to their ability to inhibit bone resorption while not affecting apposition, bisphosphonates can trigger a cascade of events involving calcium, phosphorus, PTH, and vitamin D metabolism. The influx of calcium into bone that follows initiation of bisphosphonate treatment leads to hypocalcemia, hyperparathyroidism, and hypophosphatemia. These changes stimulate increased levels of 1,25-dihydroxy-vitamin $D_3$, which tends to increase the absorption and retention of calcium. The predicted net effect of these changes is transient hypocalcemia and hyperparathyroidism. Subjects treated with 5 mg per day of risedronate did indeed tend to have more episodes of mild (presumably asymptomatic) hypocalcemia and hypophosphatemia accompanied by slight elevations in PTH. None of these subjects required specific intervention for their altered laboratory values and there was no evidence that the altered PTH metabolism adversely affected cortical bone mineral density. The supplemental calcium, and in some cases vitamin D, that all patients were instructed to take during the studies probably helped keep the PTH-calcium-phosphorus-vitamin D axis in check.

Two unexpected observations were made during the review of the risedronate data: compared with placebo, risedronate-treated patients had a slightly higher incidence of lung cancer and a slightly lower incidence of GI cancer. These findings, in a general sense, were evident in other bisphosphonates as well. Although the evidence does not strongly support a causal role for risedronate (or other bisphosphonates) in the excess lung cancer cases, [redacted]

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