CENTER FOR DRUG EVALUATION AND RESEARCH

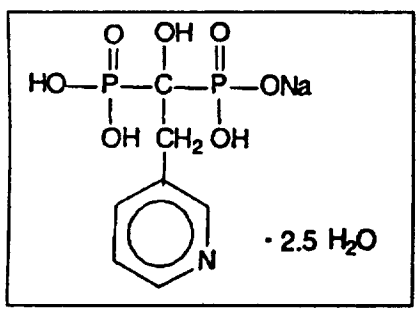
APPLICATION NUMBER: 20-835/S001-004

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS:

Reviewer Name:	Gemma A. Kuijpers, Ph.D.
Division Name:	Division of Metabolic and Endocrine Drug Products
HFD # :	510 (DMEDP)
Review Completion Date:	August 18, 1999
NDA NUMBER:	**20,835 (Efficacy Supplement SE1, S-001)**
Date of submission:	December 18, 1998
Information to sponsor:	Yes (x) No ( )
Sponsor (or agent):	Procter & Gamble Pharmaceuticals, Inc, Cincinnati, OH
Manufacturer for drug substance:	[redacted]
DRUG:	**Risedronate**
Proprietary name:	**ACTONEL**
Code Name:	NE-58095
Established name (USAN):	Risedronate Sodium
Chemical Name:	[1-hydroxy-2-(3-pyridinyl) ethylidene] bis [phosphonic acid] monosodium
Molecular Formula:	$C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$
Molecular Weight:	350.13 (hemi-pentahydrate)
Drug Class:	Bisphosphonate
Structure:	



CLINICAL INFORMATION

Indications:	Corticosteroid-induced osteoporosis
Clinical formulation:	Tablet
Strength:	5 mg
Route of administration:	Oral
Clinical protocol:	Phase III protocols
Relevant INDs/NDAs:	IND [redacted] (Risedronate) (Procter & Gamble Pharmaceuticals, [redacted] NDA 20,835 (Risedronate; Actonel[R]) for the indication Paget's disease (Procter & Gamble Pharmaceuticals); Approval date March 27, 1998
Recommendation Code:	AP

CARCINOGENICITY:

1. The initial evaluation of the carcinogenicity study in rats indicated a possible increase in malignant brain glioma in male and female rats, and benign thyroid c-cell adenomas in male rats. After further evaluation, considering historical data from the performing laboratory and the elimination of data from the high dose male rat group from statistical calculations (due to the determination that this dose had exceeded the MTD in male rats), the Executive Carcinogenicity Assessment Committee concluded that there were no significant tumor findings in male rats under the conditions of the rat carcinogenicity study. The team leader agrees with the e-CAC assessment.
2. In the statistical evaluation of the mouse carcinogenicity study, there were no positive dose-tumor related trends at any sites.
3. Under the conditions of the rat and mouse carcinogenicity bioassays, there was no evidence for a tumorigenic effect or Risedronate in either rats or mice.

REPRODUCTIVE TOXICOLOGY:

In the initial NDA submission, Risedronate was found to decrease fertility. However, since both males and females were treated in the study, it was not possible to determine if the effect was specific for males or females. In the current submission, the sponsor performed a fertility study in which male rats were treated for 30 days prior to mating. Dosing 10, 40 and 80 mg/kg for 30 days. Significant morbidity and mortality was noted in both mid and high dose groups. There were no apparent drug-related effects on sperm motility or morphology, plasma FSH, LH, testosterone or prolactin. There appeared to be no treatment-related effect on sperm parameters.

This study did not assess mating ability in male rats. Thus, while there appear to be no direct effects on sperm, an effect on mating behavior in males has not been ruled out. Neither has an effect in females been established that would account for the decreased fertility observed in the study submitted under the original NDA. The pharmacology reviewer concluded that labeling regarding effects on fertility should not be changed based on these findings. The team leader concurs with the reviewer. However, some recommendations to update the wording of this section have been recommended (see attachment to pharmacology review).

ICH recommends that 30 days is sufficient exposure in male rats for determination of fertility effects when there is an absence of effect in toxicology studies. However, testicular findings were noted in male rats after 13 weeks of treatment. Therefore, a longer exposure might be warranted and this study (at 30 days treatment) is not directly comparable to the previous study where males were treated for 60 days. Another approach to identify if there was a sex specific effect on fertility would be to treat only females in a fertility assessment study.

With the available data, one cannot make an assessment as to whether the fertility effect noted in the initial NDA review was male or female specific.

The data submitted in the nonclinical section of this supplement support the following conclusions, which may be reflected in the labeling:

1. Under the conditions of the mouse and rat carcinogenicity bioassays, there was no evidence for a tumorigenic effect or Risedronate in either rats or mice.
2. Bone quality studies in rats and minipigs indicate that the bone mineral density (BMD) can serve as a reasonable surrogate marker for bone strength for the postmenopausal indication.
3. There are no adequate animal models for corticosteroid-induced osteoporosis. Therefore, the issue of BMD changes reflecting bone quality was not addressed in nonclinical studies. Efficacy for corticosteroid osteoporosis must rely on human data.
4. In the dog fracture study at doses approximating human clinical exposure, there was no significant effect on bone healing. However, at doses approximately 10 times the proposed clinical dose, there was a delay in healing and a decrease in ultimate load and strength at the fracture site.
5. Some modifications are proposed to update the fertility section of the labeling. Based on the current data, it is not possible to ascribe whether the effect on fertility observed in the initial NDA submission (where both males and females were dosed during the fertility study) was due to effects on males, females or both.

An initial proposal from pharmacology for modifications to the labeling is attached to Dr. Kuijper's review.

The pharmacology team leader recommends that this supplement is approved (AP) from a pharm/tox standpoint. It is noted that there are no adequate animal models of corticosteroid-induced osteoporosis that would support any clinical claims. An efficacy determination for corticosteroid-induced osteoporosis must be made entirely based on clinical data.

/S/

8/10/99

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Hedin
Review Code: AP
Filename:

APPEARS THIS WAY
ON ORIGINAL

NDA 20-835 August 9, 1999

DRUG: Risedronate (ACTONEL)

PROPOSED NEW INDICATION IN SUPPLEMENT 001: Corticosteroid-induced osteoporosis

TEAM LEADER MEMO TO FILE REGARDING PRECLINICAL PHARMACOLOGY/TOXICOLOGY ISSUES FOR NDA 20-835 (Risedronate, ACTONEL) SUPPLEMENT 001

The following comments are based upon the primary pharmacology review of NDA-835/S-001:

Actonel was approved for treatment of Paget's Disease under the initial submission to NDA 20-835 (Approval date March 27, 1998). Several supplemental NDA submissions have been submitted under NDA 20-835 for new indications:

1. Corticosteroid-induced osteoporosis (S-001)
2. Treatment of postmenopausal osteoporosis (S-002)
3. Prevention of postmenopausal osteoporosis (S-003)

Most of the relevant nonclinical data were reviewed under the initial NDA submission. The current supplements provide the following additional information to cover osteoporosis and chronic use:

1. Bone efficacy and safety studies (including chronic bone quality studies)
2. Carcinogenicity study in rats
3. Carcinogenicity study in mice
4. Reproductive toxicity study in male rats (30 day administration)

SUMMARY OF KEY POINTS OF PRECLINICAL SUBMISSION:

BONE EFFICACY/SAFETY:

1. A number of bone safety/efficacy studies were submitted. These included studies in ovariectomized (OVX) rats with up to 52 weeks of exposure, OVX ferrets treated for 12 weeks, OVX minipigs treated up to 18 months and intact dogs treated up to 168 days. Overall, the nonclinical studies indicate that Risedronate did not have any significant adverse effect on bone quality. In general, the effect appeared to be most beneficial on the vertebrae. This indicates that the bone mineral density (BMD) can serve as a reasonable surrogate marker for bone strength for the postmenopausal indication.
2. There are no adequate animal models for corticosteroid-induced osteoporosis. Therefore, the issue of BMD changes reflecting bone quality was not addressed in nonclinical studies. Efficacy for corticosteroid osteoporosis must rely on human data.
3. It is interesting to note that in the dog fracture study (surgically created fracture of radius) at doses approximating human clinical exposure, there was no significant effect on bone healing. However, at doses approximately 10 times the proposed clinical dose, there was a delay in healing and a decrease in ultimate load and strength at the fracture site.

PHARMACOLOGY/TOXICOLOGY STUDIES REVIEWED FOR NDA 20,835 (SE1) S-001:

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APPEARS THIS WAY
ON ORIGINAL

BACKGROUND

An NDA Supplement (SE1) for risedronate (Actonel[R]) was submitted on December 18, 1998, by P&GP Pharmaceuticals. The supplement was divided in three parts (S-001, S-002, S-003) for the following three different indications:

1. Corticosteroid-induced osteoporosis (S-001)
2. Treatment of postmenopausal osteoporosis (S-002)
3. Prevention of postmenopausal osteoporosis (S-003)

Actonel[R] has previously been approved for the indication of Paget's disease (NDA 20,835; Submission Date March 31, 1997; Approval Date March 27, 1998). The Pharmacology/Toxicology Review of this NDA was completed on January 9, 1998, by D. Coleman, Ph.D., and G. Kuijpers, Ph.D. In the submission of the SE1 efficacy supplement to the NDA (indication: treatment and prevention of postmenopausal and corticosteroid-induced osteoporosis), the Sponsor submitted additional study reports on carcinogenicity studies in rat and mouse, bone efficacy and safety pharmacology studies, a male reproductive toxicity study, and various other additional preclinical toxicity studies.

The current review of NDA 20,835 (SE1), S-001 (corticosteroid-induced osteoporosis), includes a summary review of preclinical bone efficacy and safety studies, a full review of carcinogenicity studies, a review of the additional reprotoxicity study, an overall summary and evaluation, a recommendation, and a labeling review. The previous Pharmacology/Toxicology Review of the NDA for risedronate for the indication of Paget's disease (NDA 20,835; Review Date January 9, 1998) is on file for NDA #20,835, and contains the written reviews of all major toxicology studies. The recommendation given for NDA 20,835, S-001, in the current review is based on the study results submitted and reviewed for NDA 20,835, and the study results submitted for NDA 20,835 (SE1).

Pivotal clinical studies:

1. TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Study RVN008993: 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

Study RVE009093: 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

Study ROE009493: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate in the Treatment of Osteopenic Postmenopausal Women

Study RON009393: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study To Determine The Efficacy And Safety Of Risedronate In Treatment of Osteopenic Postmenopausal Women

2. PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

Study RBL004494: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate (NE-58095) in the Prevention of Postmenopausal Bone Loss

Study RPE002494: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Compare the Efficacy and Safety of Risedronate (NE-58095) Plus Estrogen Versus Estrogen Only in the Prevention of Bone Loss in Postmenopausal Women

3. CORTICOSTEROID-INDUCED OSTEOPOROSIS

Study RCT009893: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate (NE-58095) in the Treatment of Corticosteroid-Induced Osteoporosis (CIOP)

Study RCP009993: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate (NE-58095) in the Prevention of Corticosteroid-Induced Osteoporosis

PRECLINICAL PHARMACOLOGY STUDIES

1. IN VITRO EFFICACY/SAFETY

A. Bone
B. Bone cell cultures

2. IN VIVO EFFICACY/SAFETY

A. ovx animals (rats, ferrets, minipigs)
B. young growing rats
C. immobilized rats
Note: (A) and (B) have increased bone turnover, while (C) has reduced bone formation and uncoupled bone cell activity
D. intact dog fracture healing study

1. IN VITRO ACTIVITY AND MECHANISM OF ACTION

Effects of risedronate on bone resorption and on activity of bone cells were studied in vitro. Risedronate was a potent inhibitor of bone resorption in organ cultures. The results suggest that risedronate may inhibit the activity of mature osteoclasts, and possibly the formation of mature osteoclasts from hematopoietic precursors. Risedronate also inhibited osteoblast and osteoblast cell-like activity in vitro. In general this occurred at higher concentrations relative to those inhibiting osteoclast activity. The contributions of these effects to the decreases in bone formation and resorption seen in vivo have not been determined.

Risedronate, like other bisphosphonates, decreases activity and induces morphological changes including apoptosis in mature osteoclasts and osteoclast-like cells (In Vivo Studies F48, F49, F50, and F56). The data suggest that risedronate inhibits apoptosis in osteoclast-like cells as well as post-translational modification of certain types of proteins. Specifically, it inhibits post-translational prenylation with farnesyl and geranylgeranyl groups of intracellular proteins such as lamins, Ras and Rab6. The exact enzymes inhibited have not been determined. Sponsor speculates that decreased availability of lamin proteins could lead to altered assembly of the nuclear lamina, allowing endonucleolytic digestion of chromatin. Accumulation of non-prenylated GTP-binding proteins such as Ras could lead to intracellular acidification due to loss of Ras-dependent pH homeostasis.

The rank order of potency of several bisphosphonates for induction of apoptosis is the same as that for the anti-osteoclast, antiresorptive activity in vivo. This lends support to the hypothesis that inhibition of protein prenylation and the resulting disruption in cell activity or cell apoptosis are involved in the antiresorptive effect of bisphosphonates. Although overt osteoclast apoptosis is seen in vivo with high doses of risedronate (e.g., Study F56), it's uncertain whether apoptosis is required for antiresorptive activity. The fact that antiresorptive doses of risedronate typically do not reduce osteoclast numbers suggests that decreased osteoclast activity rather than complete loss of cell function may be sufficient for antiresorptive effects.

Prenyl synthesis and transfer is a common metabolic pathway. The fact that risedronate appears to act specifically on bone cells and in particular on osteoclasts is likely to be the results of the compound's specific localization to bone.

Summary of In Vitro Activity Studies		
Study	**Culture/Test System**	**Parameters**
F45	Fetal rat long bones; Fetal rat calvariae	bone resorption; osteoclast activity and development
F51	Fetal mouse radii; Fetal mouse metacarpals	bone resorption; osteoclast activity, development and recruitment

F57	Chick osteoclasts	bone resorption; osteoclast activity
F52	Rat osteosarcoma ROS 17/2.8 cells	osteoblast activity
F47	J774 mouse macrophages	osteoclast apoptosis
F46	J774 mouse macrophages	protein prenylation

2. EFFECTS RELATED TO PRIMARY ACTIVITY (IN VIVO)

Primary activity of risedronate relating to the therapeutic indication of postmenopausal osteoporosis is defined in the NDA as activity in animal models, with osteoclast-mediated bone resorption or bone loss as the primary end-point. The models used include young growing rats and ovariectomized animals (rats, ferrets and minipigs). These studies, together with a study in immobilized rats (in which there is uncoupling of bone remodeling) may or may not be relevant to the therapeutic indication of corticosteroid-induced osteoporosis. Study results on bone remodeling dynamics in intact dogs, and study results relating to bone safety and fracture healing in the dog, are also presented in the NDA as results related to the primary activity of risedronate.

Regulatory guidelines for preclinical evaluation of drugs for use in prevention or treatment of postmenopausal osteoporosis recommend two long-term studies, one in ovariectomized rats and one in a larger, non-rodent, bone remodeling species. The specific objective of these studies is to demonstrate that long-term administration of a test compound provides dose-related protection against ovariectomy/estrogen-depletion-induced loss of bone structure and strength, and has no detrimental effects on bone quality even at doses substantially higher (5x) than the equivalent of the proposed clinical dose.

The long-term studies carried out with risedronate in ovariectomized rats (Studies F48 and F49) and ovariectomized minipigs (a bone remodeling species; Study F56) were designed to address these concerns, and the study reports are provided in the NDA supplement. Although the results of the studies in ovariectomized animals are summarized below, the relevance of these studies for the indication of corticosteroid-induced osteoporosis is uncertain, since the mechanisms of bone loss due to estrogen-deficiency is entirely different from the one due to corticosteroid treatment. In estrogen-deficient states bone mass is decreased as a result of increased bone resorption, while in corticosteroid-treated individuals bone mass is decreased primarily as a result of reduced bone formation. Unfortunately, there are no good animal models for corticosteroid-induced osteoporosis.

In most of the described studies risedronate was administered daily by the oral route. In three studies (F25, F6, F54) it was administered on an intermittent or cyclical regimen. Intermittent dosing regimens were, for example, 2 days out of 7 days (or 2 day/7 day cycle) meaning that in a 7 day period drug was given for 2 consecutive days followed by 5 days without dosing (i.e., 2 days on, 5 days off). Depending upon the study design, the cycle was then repeated.

In Vivo Bone Efficacy

Risedronate showed potent, dose-dependent anti-osteoclast, antiresorptive activity in all the investigated models of osteoclast-mediated bone resorption and bone loss.

- The lowest effective dose varied among animal models and was dependent upon dosing duration. Risedronate inhibited osteoclast-mediated bone resorption with a lowest effective subcutaneous dose of 0.0015 mg/kg/day in growing rats and short-term ovariectomized rats (Studies F5, F6, F25). The lowest effective oral dose was in the range of 0.1 to 0.5 mg/kg/day, and was consistent with approximately 1% oral bioavailability (Studies F48, F49, F50, F54, F56).

- Risedronate could completely prevent the loss of bone mass, structure and strength induced by estrogen depletion (ovariectomy) and by mechanical unloading (limb immobilization)

(Studies F6, F25, F48, F49, F50, F53, F56). Risedronate prevented further ovariectomy-induced bone loss when initiation of treatment was delayed for up to 12 weeks post ovariectomy (Study F49). Risedronate maintained or improved the positive correlation between bone density and bone strength (Studies F48, F49, F50, F53, F56)

- Risedronate was effective when dosed daily or intermittently, though in intact dogs daily dosing was more effective than intermittent dosing at the same total, cumulative dose (Study F54).

- Risedronate suppressed bone turnover. The magnitude of suppression, and therefore the inhibition of osteoclast resorptive activity, appeared related to the initial bone resorption and turnover rates (for example, suppression was greater in ovariectomized animals than in intact dogs) (Studies F48, F49, F53, F56, F54).

- At dose levels producing significant antiresorptive effects, both short-term (28 days) (Study F50) and long-term (12-18 months) (Studies F48, F49, F56) administration of risedronate induced changes in osteoclast morphology indicative of altered cell activity (including increased cell size, increased number and altered morphology of nuclei, and cell apoptosis).

In Vivo Bone Safety

The results support risedronate's bone safety, and indicate that risedronate has no deleterious effects on bone quality, i.e., bone structure and bone strength.

- Risedronate did not impair mineralization (no osteoid accumulation or growth plate widening) and did not produce woven bone, at all doses tested (Studies F48, F49, F56). In the minipig vertebrae, after 18 months of treatment with risedronate, normal non-woven bone with lamellar structure was observed (Study F56).

- In the [redacted] rat model assay, using subcutaneous drug administration, there was no inhibition of mineralization (evidenced by lack of effect on growth plate width) even at the highest dose tested of 5.0 mg/kg/day. This dose is equivalent to an oral dose of approximately 500 mg/kg. As the lowest effective antiresorptive dose in this model is 0.0015 mg/kg/day, this gives an inhibition-of-mineralization - to - antiresorption therapeutic index of at least 3333 (Study F5).

- Risedronate had no deleterious effects on bone quality and significantly increased vertebral strength, at all doses tested (up to 2.5 mg/kg/day for 12 months in ovariectomized rats and 18 months in ovariectomized minipigs). Risedronate maintained the positive correlation between bone mass/density and strength (Studies F48, F49, F50, F53, F56).

- At an oral dose equivalent to 10 times the proposed osteoporosis clinical dose (1 mg/kg/day) risedronate caused a slight delay in the healing of a surgically created fracture of the right radius. In female dogs, this dose level also caused a decrease in ultimate load (N) and strength (N/mm^2) of the healed fracture site. However, at an oral dose equivalent to the proposed osteoporosis clinical dose (approximately 0.1 mg/kg/day), risedronate had no significant detrimental effect on fracture healing in the dog, including no effect on the biomechanical strength of the fracture site (Study F55).

Summary of In Vivo Primary Activity Studies Study							
Study	Model	Age at Start	Dose Duration	Dose Range (mg/kg/dose)	Dose Route	Dose Regimen	Parameters
Young growing rat							
F5	Young growing rat	24d	7d	0.00015-5.0	sc	daily	BMD;histo
Bone Loss Models							
F25	OVX rat	10wk	6wk	0.005-0.015	sc	1d/2wk	BMD; histo
F6	OVX rat	10wk	5, 10, 15wk	0.015	sc	1d/2wk	BMD
F48	OVX rat[A]	17-21 wk	52wk	0.01-2.5	oral	daily	BMD; histo; biomech; biomark
F49	OVX rat[B]	16-20wk	52wk	0.05-0.5	oral	daily	BMD; histo; biomech; biomark
F50	Immobilized rat	4mo	28d	0.1-1.0	oral	daily	BMD; histo; biomech
F53	OVX ferret	7mo	12wk	0.001-0.005	sc	daily	BMD; histo; biomech
F56	OVX minipig	18mo	18mo	0.05-2.5	oral	daily	BMD; histo; biomech; biomark
F54	Intact dog	18-21mo	168d	0.0625-3.5	oral	daily/ICT*	BMD; histo;
Fracture Healing							
F55	Dog	21-22mo	2, 4, 6mo	0.1-1.0	oral	daily	X-ray; histo; biomech

A Prevention model: Animals 17-21wk at ovariectomy; treatment initiated da after ovariectomy
B Treatment model: Animals 16-20wk at ovariectomy; treatment initiated 12 wk later
* ICT=intermittent dosing at 3.5 mg/kg/dose for 1d/28d (total dose 3.5 mg/kg over 28d), or at 0.5 mg/kg/dose for 7d/28d (total cumulative dose 2mg/kg over 28d), or at 0.44 mg/kg/dose for 2d/7d (total cumulative dose 3.5 mg/kg over 28d). Daily dosing of 0.0625, 0.125 or 0.25 mg/kg/day for 28d resulted in total doses of 1.75, 3.5 and 7.0 mg/kg over 28d.

Reviewers comments on long-term bone efficacy and safety studies in ovariectomized rats and mini-pigs

Sponsor measured BMD, bone histology and bone strength in long-term bone efficacy and safety studies in rats and minipigs. Study duration was 12 months in rats and 18 months in minipigs. Risedronate prevented the loss of bone mineral density (BMD) at various bone sites (vertebrae, tibia, femur). Risedronate also prevented the loss of bone strength resulting from estrogen deficiency in the vertebrae of both species. Risedronate generally maintained the positive correlation between bone mineral density (BMD) and biomechanical bone strength. In the rat, the correlation between BMD and bone strength in the vertebrae was stronger than in the femoral midshaft and particularly stronger than in the femoral neck.

Risedronate suppressed bone resorption mostly by suppressing the activation frequency of new Bone Remodeling Units (BRU's). Histologically, it was clearly seen that risedronate (partially) prevents the sparsity and decreased connectivity of the trabecular network that is seen in the ovariectomized, low-estrogen situation. However, risedronate also suppressed bone formation. It does this partly because of the reduced resorption (this is to be expected since the resorption and formation processes are coupled), but partly also by suppressing the formation of new bone in the individual BRU (results from rat and minipig studies). This may result in the finding that trabeculae in risedronate-treated bone are not thicker, but rather thinner than in the placebo and ovx controls.

The latter effect was statistically significant in the proximal tibia in rats and in the iliac crest in minipigs, but not significant in the vertebrae of either species. The exact reason for this finding is unclear. It may be that risedronate prevents trabecular perforation rather than trabecular thinning: once the bone is perforated no new bone can be build up at that site. The fact that with risedronate proximal tibia (rat) and iliac crest (minipig) trabeculae are thinner than with placebo treatment, indicates that the structure of risedronate-treated nonvertebral cancellous bone is different than normal bone. In conclusion, it seems that cancellous bone that is treated with risedronate, as compared to placebo, has more but not thicker trabeculae.

Taken together, the study results in ovariectomized animals suggest that cancellous bone that is treated with risedronate, as compared to placebo, has lower bone turnover, more and thinner trabeculae and, at least in vertebrae, increased strength. Cortical bone also tends to have increased BMD and increased strength.

The long term preclinical studies were designed to give us an idea about long term efficacy and safety. The studies predict that risedronate effectively increases vertebral bone mass and strength. The correlation between bone mass and strength was not as obvious at bone sites other than the vertebrae, i.e., femoral midshaft or femoral neck. However, this was the case in all experimental groups (intact, ovariectomized, and risedronate-treated ovariectomized). Therefore, there was no indication that risedronate specifically affected bone strength in an adverse manner. The other safety issue is the interference of the suppression of bone turnover with bone fracture healing. The results from the dog fracture healing study confirmed this.

3. EFFECTS OF COMBINATION WITH OTHER THERAPIES

It is likely that in treatment of both postmenopausal osteoporosis and corticosteroid-induced osteoporosis risedronate will be administered concomitantly with other therapies (such as estrogen and prednisone). Two studies were performed in ovariectomized rats to determine the interaction of estrogen with concomitant or consecutive risedronate. One study in intact dogs investigated the effect of prednisone on risedronate's ability to affect bone remodeling.

- Risedronate's antiresorptive effect was maintained when administered in combination with estrogen in ovariectomized animals (Studies F6, F25).

- Risedronate maintained or enhanced the bone effects of estrogen in ovariectomized rats (Studies F6, F25)

- Risedronate (0.1-0.5 mg/kg/day) suppressed bone remodeling (e.g. decreased bone formation rate and mineral apposition rate) in control dogs, and risedronate (0.1-2 mg/kg/day) suppressed bone remodeling in prednisone (2.5-5mg/day)-treated dogs (treatment duration up to 112 days). Prednisone alone did not significantly affect bone formation rate or mineral apposition rate. Although the effect of risedronate (0.5 mg/kg/day) in prednisone-treated dogs on bone formation rate was relatively less than in control dogs, the results indicated that risedronate was effective in combination with prednisone (Study F58). It should be noted that this study does not give any information on the effect of risedronate on corticosteroid-induced bone loss, since prednisone in this study did not reduce bone formation rate

CARCINOGENICITY STUDIES

MOUSE STUDY

GENERAL INFORMATION

Study Title: 80-week oral (gavage) carcinogenicity study in the mouse
Study Number: 995.09.00-ER (E1), Accession Nr. 45201
Volume Numbers: sNDA Vols. S1.036-s1.049
Test Facility: Procter & Gamble Pharmaceuticals Toxicol Laboratories, Ltd., England;
Toxicol Report Refs NEP/2/93 (Part 1) and NEP/2E/94 (Part 2)
Study Period: November 1990-June 1992
Date of Submission: 12-18-1998
GLP Compliance: Yes
QA Report: Yes
Dose-range-finding study: Study B1 (13 weeks) (43744): 0, 1, 3,2. 10, 32 mg/kg/day
Study B14 (20 weeks) (Nr. 43427): 0, 16, 24, 64 mg/kg/day

STUDY PROTOCOL AND METHODS

Study Type: Gavage
Species/strain: CD-1(Crl:CD-1) (ICR)BR VAF+
Number of animals: 60/sex/dose group
Age at start of study: 8-10 weeks
Weight at start of study: 20-37g (m), 19-31g (f)
Animal housing: Individual
Drug Lot/Batch number(s): NE-58095, Batch Nr. 12287-062C
Drug Purity: Samples taken before study start, in first month and every 3 months
thereafter. No results reported.
Drug Homogeneity: Not assessed
Drug Stability: 6 weeks
Vehicle employed: Deionized water

Doses:

PART 1

Group		Dose (mg/kg/day)	N/sex/group
1	Control	0	60
2	LD	1	60
3	MD	8	60
4	HD	32	60
5	Control	0	60

PART 2

Group		Dose (mg/kg/day)	N/sex/group
6	Control	0	60
7	LD	4	60
8	HD	16	60

Basis of Dose Selection: 13-week and 20-week toxicity studies
Relation to Clinical Use: Dose: 5 mg/day, equivalent to ca. 0.1/kg/day

CAC Concurrence: Carcinogenicity study doses were discussed and agreed upon with the Division (HFD-510),
Route of Administration: Oral (gavage)
Frequency of Drug Administration: Daily
Controls Employed: Dual control groups (Group #1 and #5)
Interim Sacrifices: Timing, #, function
Satellite PK or Special Study Group(s): None
Unscheduled Sacrifices or Deaths: See Results (Mortality)

STUDY RESULTS

PART 1 (NEP/2/93)

Groups and doses

Group		Dose (mg/kg/day)	N/sex/group
1	Control	0	60
2	LD	1	60
3	MD	8	60
4	HD	32	60
5	Control	0	60

Clinical Observations (Part 1)

Noisy respiration: Increased incidence in HD m (wks 5-36 and 42-80), and HD f (wks 3-60)
Piloerection: Increased incidence in HD m (wks 64-70), and HD f (wks 6-9 and 46-63)
Tail scabbing: Increased incidence in HD m (wks 61-80)

Mortality

Incidence of deaths: Markedly increased in HDm and HDf from week 6 on. Slightly decreased in LDm,f and MDm,f
Clinical signs prior to death: Hypoactivity, piloerection, noisy respiration
Survival data analysis: Significant, positive dose-mortality trend in both males and females

(see CDER Biometrics review)

Mortality over entire 80-week treatment period

	MALES					FEMALES				
GROUP	control 1	control 2	LD	MD	HD	control 1	control 2	LD	MD	HD
Group #	1m	5m	2m	3m	4m	1f	5f	2f	3f	4f
# animals found dead or euthanized (including terminal sacrifice period)	13/60	19/60	21/60	21/60	37/60	15/60	12/60	20/60	18/60	33/60
% of total # animals found dead or euthanized	22%	32%	35%	35%	62%	27%	20%	33%	30%	55%

Survival (%) at weeks 20, 40, 60, 80

	MALES					FEMALES				
GROUP	control 1	control 2	LD	MD	HD	control 1	control 2	LD	MD	HD
#	1m	5m	2m	3m	4m	1f	5f	2f	3f	4f
wk20	98	95	98	98	83	100	97	97	97	83
wk40	97	92	97	87	65	98	95	95	90	73
wk60	95	88	93	80	55	93	95	87	85	58
wk80	78	68	65	65	38	75	80	67	70	45

Note: Survival data analysis (CDER Biometrics) showed that the dose-mortality trend in male and female mice is statistically significant, i.e., mortality increased with dose in both male and female mice

Palpable masses: No evidence of drug-related effect

Body Weight

Body weight gain: Decreased in HDm (no BW gain in HDm after 80 wks, ie, at end of study)

Decreased in HDf (BW gain after 80 wks in HDf: 44% of control)

Body weight and body weight gain

		control1	control 2	LD	MD	HD
	BW at wk 80 (g)					
MALES		37	37	38	36	29*
FEMALES		33	33	33	33	28*
	BW gain wk 0-80 (g)					
MALES		7	8	10	8	0
FEMALES		9	9	9	9	4
	BW gain wk 0-80 (%)					
MALES		100	100	133	107	0%
FEMALES		100	100	100	100	44%

*significantly different from controls

Food Consumption

Food consumption: Reduced in HDm and HD f by ca. 10%

Food consumption/week (g/wk) reduced in HD from week 2 on

Food consumption

		contr 1	contr 2	LD	MD	HD		contr 1+2	LD	MD	HD
	total food consumed (g)						% of control				
MALES		1286	1290	1312	1261	1149		100	102	98	89
FEMALES		1223	1241	1234	1209	1106		100	100	98	89

Ophthalmoscopy:

Retinal hyper-reflectivity: Increased incidence in MDf, HDf at 80wks

FEMALES	control 1	control 2	LD	MD	HD
n examined	45	49	39	44	27
Incidence (n)	6	2	4	9	6
Incidence (%)	13	4	10	20	22

Hematology (at sacrifice):

White blood cell count: Decreased in HDm,f (non-significant)

Hematology

		control 1	control 2	LD	MD	HD
	WBC (10^3/ul)					
MALES		4.7	4.8	4.3	4.3	2.9 (n.s. ↓)
FEMALES		4.9	3.3	4.1	3.2	3.2 (n.s. ↓)

Clinical Chemistry: No data

Organ Weights:

Relative-to-body organ weights (%)

		control 1	control 2	LD	MD	HD
MALES	Body weight (g)	37	37	37	36	29*
	Brain	1.34	1.35	1.31	1.38	1.64*
	Testes	0.59	0.54	0.56	0.58	0.68*
	Adrenals	13.2	12.6	13	14.4	22.4*
FEMALES	Body weight (g)	32	32	32	32	28*
	Brain	1.57	1.58	1.57	1.55	1.71*
	Ovaries	63	55	55	74	40 (n.s.↓)
	Adrenals	27.8	27.6	25	28.6	30.3

*significantly different from controls

Note:
Weight change was more than expected on basis of body weight change alone in:
Adrenals (m): increase; Ovaries (f): decrease

Gross Pathology

Gross pathology findings at sacrifice (Incidence, n)

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
mg/kg/day		ctrl	ctrl	1	8	32		ctrl	ctrl	1	8	32
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*13*	*19*	*11*	*11*	*37*		*15*	*12*	*10*	*18*	*33*
N terminal		*47*	*41*	*39*	*39*	*23*		*45*	*48*	*40*	*42*	*27*
Adrenal glands	small	14	17	10	10	2		0	0	0	3	0
Cecum	distension	0	4	3	12	18		2	1	5	5	12
Colon	distension	1	5	3	13	17		1	1	4	5	13
Duodenum	distension	2	3	4	15	18		3	1	6	6	9
Ileum	distension	0	5	5	16	22		3	2	6	6	15
Jejunum	distension	2	5	6	16	25		2	3	8	6	16
Penis	abnormal color/shape	1	3	1	1	7						
Prostate	small	1	1	3	2	6		-	-	-	-	-
Seminal vesicle	small	0	1	2	1	7		-	-	-	-	-
	enlarged	26	27	31	16	5		-	-	-	-	-
Spleen	small	19	18	10	18	30		3	3	4	4	13
	enlarged	7	5	8	3	1		14	8	13	13	5
Stomach	distension	0	2	0	8	12		1	1	1	7	9
Tail	tip absent	4	0	5	5	10		0	0	0	0	0
Thymus	enlarged	3	0	3	0	0		14	7	10	13	3
Urethra	plug	29	27	25	26	13		0	0	0	0	0
Urinary bladder	distension	10	15	15	14	3		2	0	3	1	1

Histopathology

Neoplastic histopathology findings at sacrifice (Incidence, n)

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
mg/kg/day		ctrl	ctrl	1	8	32		ctrl	ctrl	1	8	32
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*13*	*19*	*11*	*11*	*37*		*15*	*12*	*10*	*18*	*33*
N terminal		*47*	*41*	*39*	*39*	*23*		*45*	*48*	*40*	*42*	*27*
Cervix	Histiocytic sarcoma	-	-	-	-	-		0	0	0	2	1
Axillary lymph nodes	Malignant lymphoma	1	0	1	0	0		1	0	4	3	0
Kidney	Malignant lymphoma	1	0	1	0	0		3	3	7	4	1
Mesenteric lymph node	Malignant lymphoma	1	2	2	0	2		4	2	11	7	2
Sciatic nerve	Malignant lymphoma	1	0	0	0	0		1	0	0	2	0
Submand lymph nodes	Malignant lymphoma	1	0	2	0	2		3	1	8	6	1
Thymus	Malignant lymphoma	1	2	1	0	2		5	4	10	10	3
Harderian gland	adenoma	2	2	3	3	1		3	0	1	0	0
	carcinoma	0	0	0	0	0		1	0	0	0	0
Lungs	adenoma	16	10	9	8	11		5	8	1	8	5

Non-neoplastic histopathology findings at sacrifice (Incidence, n)

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
mg/kg/day		ctrl	ctrl	1	8	32		ctrl	ctrl	1	8	32
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*28*	*34*	*35*	*42*	*45*		*42*	*50*	*36*	*40*	*46*
N terminal		*32*	*26*	*25*	*18*	*15*		*18*	*10*	*34*	*20*	*14*
Adrenal[a]	spindle cell hyperplasia	15	11	11	12	8		45	54	43	48	27
Bone (femur)[a]	epiphyses open	0	1	10	45	60		2	3	18	58	59
	trabecular thickening[a]	0	1	0	1	39		0	1	1	34	54
Bone (sternum)[a]	epiphyses open	5	9	22	56	57		12	18	44	56	59
	trabecular thickening[a]	0	1	0	2	16		0	1	3	28	42
Bone marrow[a]	hyperplasia	7	9	4	0	1		8	9	13	1	4
Cecum[b]	distension	0	0	0	6	1		0	0	0	1	5
Colon[b]	distension	2	4	2	9	7		1	0	1	2	13
Duodenum[b]	distension	0	0	0	3	3		0	0	0	1	3
	villous atrophy	0	0	0	0	4		0	0	0	0	0
Ear, middle[a]	inflammation	2	3	0	2	20		4	0	1	4	8
	mucopurulent exudate	0	1	0	0	5		0	0	0	0	0
Esophagus[a]	distension	0	0	0	2	3		0	1	0	1	1
Ileum[b]	distension	0	0	0	5	7		0	0	0	3	9
	villous atrophy	0	0	0	0	5		0	0	0	0	0
Jejunum[b]	distension	0	0	0	6	9		0	1	0	3	6
	villous atrophy	1	0	0	0	4		0	0	0	0	0

Joints, stifle[a]	chronic arthritis	20	25	29	17	8		18	24	18	10	6
Lacrimal glands[a]	lymphocytic infiltration	26	31	23	26	11		24	26	23	14	8
Liver[a]	focal necrosis	0	1	1	2	8		7	5	0	6	4
Lung[a]	bronchiolitis	0	0	0	0	1		0	0	0	0	2
	bronchopneumonia	1	1	1	1	1		0	0	0	0	5
Nasal cavity[a]	olfactory degeneration*	0	5	2	43	53		0	0	0	22	49
	mucopurulent exudate*	0	3	1	8	51		1	0	3	12	34
Rectum[b]	distension	1	2	0	1	5		1	1	0	0	5
Seminal vesicles[b]	colloid depletion	0	0	1	0	10		-	-	-	-	-
	increased colloid	10	15	20	8	6		-	-	-	-	-
Spleen[a]	lymphoid depletion	2	2	1	7	13		0	1	0	4	3
Tail	necrosis	0/7	0/3	2/9	0/12	10/17		2/17	6/20	2/14	3/14	5/19
Trachea[a]	inflammation	1	0	0	0	6		0	0	0	1	5
	chronic inflammation	0	0	0	2	3		1	4	0	2	2
	fibrosis	0	0	1	4	8		0	1	0	0	4
	ulceration	0	0	0	0	0		0	0	0	0	1
Thymus[a]	lymphoid depletion	0	1	0	5	6		1	0	2	3	10
	no thymic tissue	1	2	1	1	8		0	1	2	1	2
Urinary bladder[b]	eosinophilic plug	14	10	10	11	1		0	0	0	0	0
	distension	6	7	7	6	1		1	0	0	0	0
Uterus[a]	cystic endometrial hyperplasia	-	-	-	-	-		46	47	43	44	27

* degree of effect dose-related (grade: minimal/moderate/marked)
[a] N examined = 56-60
[b] N examined = 49-60

Reviewers Comments:

- There were no obvious dose-related increases in tumor incidence at any site.
- An excess of malignant lymphomas at various sites appeared to occur in the low dose females. The lymphoma incidence in the three female dose groups was usually: LDf>MDf>HDf.
- It is not clear whether there was any drug related effect on tumor latency at any site.
- There was an increased incidence of distension throughout the entire GI tract in MD, HD males and in LD,MD,HD females
- Open epiphyses were seen in all drug-treated and trabecular thickening was seen in MD and HD
- There was a dose-related increase in the incidence and degree of olfactory degeneration (flattening of columnar epithelium) and of mucopurulent exudate in the nasal passage, in MD and HD groups.
- Inflammation and/or chronic inflammation, fibrosis or ulceration of the trachea were seen in some MD and HD animals.
- An increased incidence of lung bronchiolitis and pneumonia was seen in HD females.
- Liver necrosis of varying degrees occurred in some HD males
- In spleen and thymus, there was an increased incidence of lymphoid depletion in MD and HD (m,f)
- Colloid depletion of the seminal vesicles was seen in HD males.
- There were no obvious relationship of tumor findings to non-neoplastic findings.

STATISTICAL ANALYSIS OF TUMOR FINDINGS

SPONSOR'S ANALYSIS

Incidence of tumors and other lesions were compared among dose groups, taking into account any differences in survival. The statistical methodology was as described by Peto (1980). Neoplastic and non-neoplastic conditions were considered to be incidental, unless classified as possible cause of death when they were considered fatal. Trend analyses were carried out of tumor incidences, survival, and "factor contributory to death" or "predominant pathology". Where incidences were low enough, exact tests were also conducted.

Results of Sponsor's analysis.

There were no significant treatment-group or dose-level variations in tumor incidence at any site. A treatment- and dose-relationship was observed for upper respiratory disease as a factor contributing to death. Upper respiratory disease was also the predominant pathology in part of the high dose males and females.

Sponsor's conclusion. The Sponsor concluded that "the oral administration of the test article NE-58095 at dose levels of 32, 8 and 1 mg/kg/day for 80 weeks had no tumorigenic effect."

CDER REVIEWERS STATISTICAL ANALYSIS

Note: For Review see *APPENDIX (Attachment 1)*

Result

According to the CDER Biometrics Review, there was no statistically significant dose-tumor positive linear trend for any tumor, either in male or female mice.

Reviewers conclusions

Risedronate was not carcinogenic in male or female mice.

Toxicokinetics: No data

STUDY RESULTS

PART 2 (NEP/2E/94)

Groups and doses

Group		Dose (mg/kg/day)	N/sex/group
6	Control	0	60
7	LD	4	60
8	HD	16	60

Clinical Observations

Noisy respiration: Increased incidence in HD m (wks 5-36 and 42-80), and HD f (wks 3-60)

Piloerection: Increased incidence in HD m (wks 64-70), and HD f (wks 6-9 and 46-63)

Tail scabbing: Increased incidence in HD m (wks 61-80)

Mortality

Incidence of deaths: Increased in LD m,f and HDm,f from week 6 on.

Clinical signs prior to death: Hypoactivity, piloerection, noisy respiration

Survival data analysis: Significant, positive dose-mortality trend in both males and females (CDER

STAT review, p.17, p.19)

Mortality in mice over entire 80-week treatment period

	MALES			FEMALES		
GROUP	control	LD	HD	control	LD	HD
Group #	6m	7m	8m	6f	7f	8f
# animals found dead or euthanized (incl terminal sacrifice period)	7/60	12/60	31/60	8/60	21/60	28/60
% of total # animals	12	20	52	13	35	47

Survival (%) at weeks 20, 40, 60, 80

	MALES			FEMALES		
GROUP	control	LD	HD	control	LD	HD
#	6m	7m	8m	6f	7f	8f
wk20	98	98	80	95	92	68
wk40	98	93	72	93	83	62
wk60	93	88	60	93	80	57
wk80	88	80	48	87	65	53

Palpable masses: No evidence of drug-related effect

Body Weight

Body weight gain: Decreased in HDm (BWG after 80 wks in HDm: 50% of control)
Decreased in HDf (BWG after 80 wks in HDf: 78% of control)

Body weight and body weight gain

		control	LD	HD
	BW at wk 80 (g)			
MALES		38	39	36*
FEMALES		35	34	32
	BW gain wk 0-80 (g)			
MALES		8	8	4*
FEMALES		9	8	7*
	BW gain wk 0-80 (%)			

MALES		100	100	50
FEMALES		100	89	78

*significantly different from controls

Food Consumption

Food consumption: Reduced in HDm and HD f by ca. 10%
Food consumption/week (g/wk) reduced in HD from week 1 on

Food consumption

	control	LD	HD		control	LD	HD
total food consumed (g)				% of control			
MALES	1237	1225	1144		100	99	92.5
FEMALES	1254	1236	1126		100	98.6	89.8

Ophthalmoscopy:

No remarkable findings

Hematology (at sacrifice):

White blood cell count: Decreased in LDm,f and HDm,f

Hematology

		control	LD	HD
WBC (10^3/ul				
	MALES	6.3	5.1*	4.7*
	FEMALES	5.3	4.6*	3.3*

Clinical Chemistry: No data (!)

Organ Weights

Relative-to-body organ weights (%)

		control	LD	HD
MALES	Body weight (g)	38	38	35*
	Brain	1.33	1.32	1.41*
	Kidneys	2.28	2.25	2.1*
FEMALES	Body weight (g)	34	33	32*
	Brain	1.52	1.55	1.62*

Gross Pathology

Gross pathology findings at sacrifice (Incidence, n)

		MALES				FEMALES		
Group #		6	7	8		6	7	8
		ctrl	LD	HD		ctrl	LD	HD
mg/kg/day		0	4	16		0	1	8
N examined		60	60	60		60	60	60
N preterminal		*7*	*12*	*31*		*8*	*21*	*28*
N terminal		*53*	*38*	*29*		*52*	*39*	*32*
Cecum	distension	0	6	20		2	7	20
Colon	distension	0	6	16		2	4	18
Duodenum	distension	0	6	20		2	6	19
Ileum	distension	0	6	23		2	8	21
Jejunum	distension	0	6	24		2	10	19
Seminal vesicle	enlarged	21	23	12		-	-	-
Spleen	small					4	2	19
Stomach	distension	0	5	16		1	7	12

Histopathology

Neoplastic histopathology findings at sacrifice (Incidence, n)

		MALES				FEMALES		
Group #		6	7	8		6	7	8
		ctrl	LD	HD		ctrl	LD	HD
mg/kg/day		0	4	16		0	4	16
N examined		60	60	60		60	60	60
N preterminal		*7*	*12*	*31*		*8*	*21*	*28*
N terminal		*53*	*38*	*29*		*52*	*39*	*32*
Axillary lymph nodes	malignant lymphoma	0	0	0		3	0	0
Harderian gland	adenoma	4	0	5		4	3	1
Kidney	malignant lymphoma	0	1	0		7	3	1
Lungs	adenoma	21	15	11		10	9	7
	carcinoma	4	1	3		2	2	0
Mesenteric lymph node	malignant lymphoma	1	1	0		6	6	5
Sciatic nerve	malignant lymphoma	0	0	0		2	0	0
Submand lymph nodes	malignant lymphoma	1	0	1		9	4	4
Thymus	malignant lymphoma	1	3	2		14	10	7

Non-neoplastic histopathology findings at sacrifice (Incidence, n)

		MALES				FEMALES		
Group #		6	7	8		6	7	8
		ctrl	LD	HD		ctrl	LD	HD
mg/kg/day		0	4	16		0	4	16
N examined		60	60	60		60	60	60
N preterminal		*7*	*12*	*31*		*8*	*21*	*28*
N terminal		*53*	*38*	*29*		*52*	*39*	*32*
Adrenal[a]	spindle cell hyperplasia	21	16	11		52	47	30
Bone (femur)[a]	epiphyses open	0	25	59		2	57	60
	trabecular thickening[a]	0	2	23		0	25	44
Bone (sternum)[a]	epiphyses open	1	47	55		3	54	60
	trabecular thickening[a]	0	0	12		0	23	28
Cecum[b]	distension	0	0	2		0	1	7
Duodenum[b]	distension	0	3	8		0	4	12
Ear, middle[a]	inflammation	1	3	8		0	2	2
	mucopurulent exudate	0	0	2		0	1	0
Ileum[b]	distension	0	3	17		1	5	17
Jejunum[b]	distension	0	4	18		0	5	15
Joints, stifle[a]	chronic arthritis	33	30	21		26	23	11
Lacrimal glands[a]	Chronic inflammation	32	34	23		39	21	15
Mammary gland	Acinar development	-	-	-		18	11	4
Nasal cavity[a]	olfactory	2	17	54		1	15	54

	degeneration*							
	mucopurulent exudate*	2	5	29		4	2	24
Spleen[a]	Lymphoid depletion	1	2	20		1	5	17
	Preterminals	0	2	19		1	3	17
	Terminals	1	0	1		0	2	0
Stomach (glandular mucosa)[b]	Atrophy	2	4	10		0	1	2
	hyperplasia	24	21	8		28	24	20
Thymus[a]	lymphoid depletion	0	7	20		1	5	19
	Preterminals	0	6	19		1	5	19
	Terminals	0	1	1		0	0	0

* degree of effect dose-related (grade: minimal/moderate/marked)
[a] N examined = 56-60
[b] N examined = 49-60

Comments:

- There were no obvious dose-related increases in tumor incidence at any site.
- An excess of malignant lymphomas at various sites appeared to occur in the low dose females. The lymphoma incidence in the three female dose groups was usually: LDf>MDf>HDf.
- There were no obvious relationship of tumor findings to non-neoplastic findings;
- It is not clear whether there was any drug related effect on tumor latency at any site.

STATISTICAL ANALYSIS OF TUMOR FINDINGS

SPONSOR'S ANALYSIS

Incidence of tumors and other lesions were compared among dose groups, taking into account any differences in survival. The statistical methodology was as described by Peto (1980). Neoplastic and non-neoplastic conditions were considered to be incidental, unless classified as possible cause of death when they were considered fatal. Trend analyses were carried out of tumor incidences, survival, and "factor contributory to death" or "predominant pathology". Where incidences were low enough, exact tests were also conducted.

Results of Sponsor's analysis.

There were no significant treatment-group or dose-level variations in tumor incidence at any site. A treatment- and dose-relationship was observed for upper respiratory disease as a factor contributing to death. Misdosing was also a dose-related factor contributing to detah in some HD animals.

Sponsor's conclusion. The Sponsor concluded that "the oral administration of the test article NE-58095 at dose levels of 32, 8 and 1 mg/kg/day for 80 weeks had no tumorigenic effect."

CDER REVIEWERS STATISTICAL ANALYSIS

Note: For Review see APPENDIX

Result

According to the CDER Statistical Review, there was no statistically significant dose-tumor positive linear trend for any tumor, either in male or female mice.

Reviewers conclusions

Risedronate was not carcinogenic in a 80-week bioassay in mice at doses up to 32 mg/kg/day

Toxicokinetics: No data

OVERALL INTERPRETATION AND EVALUATION MOUSE CARCINOGENICITY STUDY (PART 1 and PART 2)

Adequacy of the carcinogenicity studies and appropriateness of the test model
In the male and female high dose groups (32 mg/kg/day) in Part 1 of the study, survival reached 38% and 45%, respectively, at the end of the study. At 16 mg/kg/day, in Part 2 of the study, survival reached 48% and 53%, for males and females respectively. Control survival was ca. 80% (average; Part 1and Part 2). For this review, CDER's Statistical Reviewer carried out statistical analyses of the data from all male and all female dose groups. Note that the statistical tests were survival-adjusted. The duration of treatment (80 weeks) was appropriate.

Dose selection consistency with the carcinogenicity study dose selection guidance
Part 1 of the mouse carcinogenicity study was based on results of a 13-week mouse oral toxicity study (doses 0, 1, 3, 10, 32 mg/kg/day; Study B1). No significant toxicity was observed at any dose. Increased trabecular bone was seen at all doses. A carcinogenicity study (Part 1) was initiated with doses 0, 0, 1, 8, 32 mg/kg/day. A second dose-ranging study (doses 0, 16, 24, 64 mg/kg/day; Study B14) was initiated to confirm the appropriateness of the dose selection of Part 1. Within 20 weeks all dose groups developed clinical signs, GI distension and reduced body weight gain and food consumption. Since the dose range study suggested that 24 mg/kg/day exceeded the MTD, it was agreed with the Division (10/9/91) that there would be an additional Part 2 of the study using doses of 0, 4, 16 mg/kg/day,
The results of Part 1 and Part 2 of the mouse carcinogenicity study (doses 0,0,1,8,32 mg/kg/day and 0,4,16 mg/kg/day), as described in this review, show that survival and body weight gain were reduced at doses of 16 and 32 mg/kg/day. GI and nasal toxicity was observed at doses of 8 mg/kg/day and above. These results suggest that the MTD was somewhere between 8 and 16 mg/kg/day. Thus, the combination of Part 1 and Part 2 of the study (doses 0, 1, 4, 8, 16, 32 mg/kg/day) was appropriate to generate valid tumorigenicity data.

Appropriateness of route of administration, bioavailability and pharmacodynamics
The intended clinical route of administration is oral, by capsule. Thus, the route of administration in the animals (oral gavage) was appropriate. Bioavailability of bisphosphonates is generally very low (1%-3%), and absorption is strongly suppressed by food. This has been observed in both animals and humans. Pharmacokinetic studies with risedronate have been carried out in rats and dogs, and in humans. Absorption is rapid (T_{max} ca. 1h), and ca. 60% of an absorbed dose distributes to bone. Drug bound to bone is released very slowly ($T_{1/2}$ in rats > 1 year). Soft tissue levels are usually very low, and not detectable by 72h after the last dose. Plasma protein binding is 98%, 37%, and 24% in rats, dogs and humans. Excretion is mainly renal. Systemic metabolism has not been observed with current methodologies. However, two metabolites have been detected in urine samples in the dog, 1-oxo-2-(3-pyridinyl)ethylphosphonic acid (keto) and 2-pyridyl acetic acid (3-PAA). Sponsor suggests that degradation of parent drug to these two breakdown products occurs in the urinary bladder.
The pharmacological action of the bisphosphonates such as risedronate is an inhibition of bone resorption. In intact growing animals, this can cause trabecular bone thickening and open epiphyses, as observed in the current study in all dose groups.

Evaluation of Tumor Findings: Weight of Evidence
There were no positive dose-tumor related trends at any site, according to both Sponsor's and CDER Biometrics' statistical analysis, in either Part 1 or Part 2 of the study.
In Part 1 of the study, in female mice, the incidence of malignant lymphoma at various sites appeared to be increased particularly at the low dose of 1 mg/kg/day, and also at the mid dose of 8 mg/kg/day, but not at 32 mg/kg/day. In Part 2 of the study, however, at doses of 4 and 16 mg/kg/day, the incidence of these lymphomas in females was generally lower than in the control groups. The significance of these anomalous results is unclear.

Body weight gain in HD males and females was reduced by 100% and 56% (Part 1) and by 50% and 22% (Part 2), respectively. This reduction was most likely due to decreased food consumption. The reduction may have been a confounding effect in the study, causing tumor incidence in HD groups to be lower then expected as a result of drug-related events. However, drug-related toxicity in the MD (Part 1) and HD (Part 1 and Part 2) groups may have led to larger-then-expected tumor incidences.

The relative exposures of the mice as compared to the exposure to be expected in humans is not known. On the basis of dose per m^2 surface area the animal doses were the following multiples of the 5 mg human dose:

Estimated human dose multiples for the proposed therapeutic dose (5 mg/day)

Dose	Human dose multiple, based on mg/m^2 comparison
1 mkd	0.83x
4 mkd	3.3x
8 mkd	6.7x
16 mkd	13.3x
32 mkd	27x

Risedronate is a bisphosphonate which is structurally and pharmacologically related to other bisphosphonates such as alendronate, pamidronate, etidronate, tiludronate, ——— ——— The other bisphosphonate that has been tested for carcinogenicity so far is alendronate (Fosamax^R). In female mice, in a 92-week study, a statistically significant increase in adenomas of the Harderian gland of the eye was observed (ctrl-ctrl-LD-MD-HD: 0-1-1-2-6*). This type of tumor did not appear in the current studies with risedronate.

There was no clear evidence of genotoxicity of risedronate in previously completed genotoxicity studies.

In the placebo-controlled clinical trials with risedronate that have been reported to the NDA osteoporosis supplement, at doses of 2.5 mg/day and 5 mg/day, an increased incidence of lung cancer has been detected mainly in the 2.5 mg/day dose group. The finding was statistically significant. However, since there was no obvious dose-response, the clinical importance of this finding is unclear at this point.

Lung neoplasms were not seen in the current mouse carcinogenicity study.

Conclusion

The results of the 80-week mouse carcinogenicity study suggest that risedronate is not carcinogenic in male or female mice.

NDA 20,835 (Suppl. 1,2,3)
Mouse carcinogenicity study (Part 2)

Histopathology Inventory

Sponsor Study # 995.09.00-ER (E1)		
Species: Mouse	Pathology	Organ weight
Adrenals	X	X
Aorta	X	
Bone marrow (femur)	X	
Bone (femur)	X	
Bone (sternum)	X	
Brain	X	X
Cecum	X	
Colon	X	
Duodenum	X	
Ears	X	
Epididymides	X	
Esophagus	X	
Eyes	X	
Fallopian tube		
Gall bladder	X	
Gross lesions		
Harderian gland	X	
Heart	X	X
Hyphophysis		
Ileum	X	
Injection site		
Jejunum	X	
Kidneys	X	X
Lacrimal gland, exorbital	X	
Larynx		
Liver	X	X
Lungs with bronchi	X	
Lymph nodes, cervical		
Lymph nodes, submandibular	X	
Lymph nodes, mesenteric	X	
Mammary Gland	X	
Nasal cavities	X	
Optic nerves	X	
Ovaries	X	X
Pancreas	X	
Parathyroids	X	
Pharynx		
Pituitary	X	
Preputial gland	X	
Prostate	X	X
Rectum	X	
Salivary gland	X	
Sciatic nerve	X	
Seminal vesicles	X	
Skeletal muscle	X	
Skin	X	
Spinal cord	X	
Spleen	X	X
Stifle joint	X	
Stomach	X	
Teeth (incisor)		
Testes	X	X

Thymus	X	
Thyroid	X	
Tongue	X	
Tonsils		
Trachea	X	
Ureter		
Urethra		
Urinary bladder	X	
Uterus	X	
Vagina	X	
Zymbal glands	X	

ATTACHMENT

Sponsor's neoplasm incidence summary tables (Part 1 and Part 2)

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Name of Sponsor/Company: Procter & Gamble Pharmaceuticals Name of Finished Product: Name of Active Ingredient: risedronate sodium	EU only: Ref to Part III.E page 1/25 Location of Full Report in the Submission <Vs1.036/p5> to <Vs1.048/p334>	(For National Authority Use Only)

Oncogenic/Carcinogenic Potential - Study Data

Study Title:	80 Week Oral (Gavage) Carcinogenicity Study in the Mouse (Part 1 - NEP/2/93)		
Report Date:	17-Jun-96	*Study No.* 996.09.00-ER [45201]	*Study Period:* Nov-90 to Jun-92
Species/Strain:	Mouse (Crl:CD-1(ICR)BR)	*Lot No.:*	12287-062C
Number of Animals:	600	*Duration of Study:*	80 weeks
Administration Route:	oral (gavage) fasted 4 hr prior to dosing to 2 hr post-dosing		
Treatment of Controls: Deionized water 10 mL/kg/day, po	*Age (at study initiation):* approx 8 to 9 weeks *Body Weight (at study initiation):* 19 - 37 grams *Treatment Days Per Week:* 7		
Combination with Chronic Toxicity Study?	☐ Yes ☒ No		

Treatment Group			(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)			0		1		8		32		0	
Sex (M/F)			M	F	M	F	M	F	M	F	M	F
Total Number of Animals	At Study Initiation		60	60	60	60	60	60	60	60	60	60
	Evaluated		60	60	60	60	60	60	60	60	60	60
Premature Necropsy	Scheduled Int. Sacr.		0	0	0	0	0	0	0	0	0	0
	Died/Sacr. In Extremis	Total	13	15	21	20	21	18	37	33	19	12
		Eval.	13	15	21	20	21	18	37	33	19	12
Terminal Sacrifice			47	45	39	40	39	42	23	27	41	48

Non-tumor Important Findings:

Expected treatment related non-neoplastic changes were seen in the bone at all dose levels including dose related increase in incidence of open epiphyses. There were also changes in the respiratory tract (nasal turbinates, middle ear, trachea and lungs) which were treatment- and dose-related. However, these were considered to be related to reflux of the dose following gavage, rather than a direct toxic effect of the test article.

In the 32 mg/kg dose group, a significant increase in deaths was seen with marked excess of deaths early in the study. Thickening of the metaphyseal trabeculae was seen. Also seen were an increase in RBC counts and a reduction in body weight gain, food consumption, ovary weights and WBC counts. Atrophy of the intestinal mucosal villi seen in some males at this dose was considered to be associated with the reduced food consumption and body weight gain and not to a direct effect of the test article. Increased incidence of piloerection, noisy respiration, stomach and intestinal distention, small spleen, small prostate, small seminal vesicles, abnormal colored and shaped penis, tail tip absent, degeneration of the olfactory epithelium, presence of a muco-purulent exudate, inflammatory changes in the middle ear and minor degenerative and inflammatory change in the trachea were seen at this dose. Females showed retinal hyper-reflectivity and decreased incidence of enlarged thymus and reduced incidence of bronchopneumonia and bronchiolitis. There were also reduced incidences of enlarged spleen, abnormal colored Harderian glands, enlarged or abnormally shaped seminal vesicles, distended urinary bladders, urethral plugs, ovarian and uterine cysts, distended uterus and small adrenal glands.

At the 8 mg/kg/day dose, there was a slight increase in number of deaths. There was an increased incidence of stomach and intestinal distention and thickening of the metaphyseal trabeculae. Females showed retinal hyper-reflectivity.

Variations in the incidence of a range of minor changes which are common in aging mice were seen in the spleen, thymus, bone marrow, stifle joints and lacrimal glands of both sexes, in the liver, seminal vesicles, urinary bladder, urethra, penis, tail and pinnae of males, and in the adrenals and uterus of females. None of these changes was considered to be of toxicological significance. All the other non-neoplastic changes observed and recognized as those which occur commonly in aging mice, showed no clear relationship to treatment and were not considered to be significant.

Histology performed according to ——— for Guidance: ☒ Yes ☐ No

Study conducted by the applicant: ☐ Yes ☒ No

If "no", indicate the name and address of the institute that conducted the study:

Name: [redacted]

Address: [redacted]

Study in compliance with GLP: ☒ Yes ☐ No

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Name of Sponsor/Company: Procter & Gamble Pharmaceuticals Name of Finished Product: Name of Active Ingredient: risedronate sodium	EU only: Ref to Part III.E page 2/25 Location of Full Report in the Submission <Vs1.036/p5> to <Vs1.049/p334>	(For National Authority Use Only)

Oncogenic/Carcinogenic Potential - Tumor Data

Study Title: 80 Week Oral (Gavage) Carcinogenicity Study in the Mouse (Part 1 - NEP/2/93)

Report Date: 17-Jun-96 | *Study No.* 995.09.00-ER (45201) | *Study Period:* Nov-90 to Jun-92

No. of tumors in all animals which were evaluated (without consideration of the causes and relevance) see below

Biometrical Evaluation ☒ *Yes* ☐ *No*

Treatment Group		*Frequency According to Dose and Sex (n)*									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		8		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60	60	60	60	60
Organ	Identification of the Tumor										
Adrenals	M Granulocytic leukemia		2	1							
	B Adreno-cort adenoma									2	
	B Phaeochromocytoma	1							1		1
	M Malignant lymphoma		1		2		1				
	M Histiocytic sarcoma	1									1
	B Spindle cell tumor										1
Aorta	M Granulocytic leukemia		1								
	M Malignant lymphoma		1		1		1		1		
Axillary Lymph Nodes	M Granulocytic leukemia		2	1							
	M Hemangiosarcoma									1	
	M Malignant lymphoma	1	1	1	4		3				
	M Histiocytic sarcoma	1	1	3						1	1
Bone Marrow	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	1	1	4		3				4
	M Histiocytic sarcoma	1	1	2						1	1
Brain	M Granulocytic leukemia			1							
	M Malignant lymphoma										1
Cecum	M Malignant lymphoma	1			1						
	M Histiocytic sarcoma			1	1						
	M Granulocytic leukemia		1								
	B Leiomyoma						1				
Cervix	B Leiomyoma		1				1		1		
	M Histiocytic sarcoma						2		1		
Colon	M Malignant lymphoma	1			1						
	M Histiocytic sarcoma	1									
Deep Cervical Lymph N.	M Histiocytic sarcoma			1							
	M Granulocytic leukemia		1								
	M Malignant lymphoma				1						
Duodenum	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1									
	M Histiocytic sarcoma	1		2							
Ear: external	B Fibroma	1									
	M Malignant lymphoma				1						
Ear: internal	M Granulocytic leukemia			1							

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		8		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60	60	60	60	60
Organ	Identification of the Tumor										
Ear: middle	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1		1	2		1				
Epididymides	M Granulocytic leukemia			1							
	M Malignant lymphoma	1									
	M Histiocytic sarcoma			1							
Esophagus	M Granulocytic leukemia			1							
	M Malignant lymphoma						1				
Eyes	M Granulocytic leukemia		1	1							
Forelimbs	M Hemangiosarcoma									1	
Gall Bladder	M Granulocytic leukemia		1	1							
	M Malignant lymphoma		1		4		1		1		
Harderian Glands	M Granulocytic leukemia		2	1							
	B Harderian adenoma	2	3	3	1	3		1		2	
	M Malignant lymphoma		1				1				
	M Histiocytic sarcoma	1		2							
	M Harderian carcinoma		1								
Heart	M Granulocytic leukemia		2								
	M Malignant lymphoma				3		1		1		
	M Histiocytic sarcoma				1						
Hepatic Lymph N.	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	1	1	6		2				
	M Histiocytic sarcoma	1	2	2						1	1
Hindlimbs	M Osteosarcoma					1					
Ileum	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1									
	M Histiocytic sarcoma			1							
Iliac Lymph Nodes	M Histiocytic sarcoma				1						
Inguinal Lymph Nodes	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	1		4		1				
	M Histiocytic sarcoma		1	2						1	1
Jejunum	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1									
	M Histiocytic sarcoma			3							

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		8		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60	60	60	60	60
Organ	Identification of the Tumor										
Kidneys	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	3	1	7		4		1		3
	M Histiocytic sarcoma	2	2	3							1
	B Renal adenoma			1							
Lacrimal Glands	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	2	2	4						1
	M Histiocytic sarcoma	1		2							1
Liver	M Granulocytic leukemia		2	1							
	B Hemangioma			1							
	B Cholangioma		1								
	M Hemangiosarcoma										1
	M Malignant lymphoma	1	2		9		4	1	2		2
	B Hepatocellular adenoma	2		5				1		1	
	M Hepatocellular carcinoma	1									
	M Histiocytic sarcoma	2	2	4	1		1		1	1	2
Lungs	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	2	3	2	7		3		1	1	1
	B Pulmonary adenoma	16	5	9	1	8	8	11	5	10	8
	M Histiocytic sarcoma	2	2	4	1				1		1
	M Pulmonary carcinoma			1	2	2	1	1	1	1	2
Mammary Gland (cranial)	M Granulocytic leukemia		1	1							
	M Malignant lymphoma		1	1	1		1				
	M Histiocytic sarcoma										1
Mediastinal Lymph N.	M Histiocytic sarcoma	1	2								
	M Granulocytic leukemia		1								
	M Malignant lymphoma		2		5		1				
Mesenteric Lymph Node	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	4	2	11		7	2	2	2	2
	M Histiocytic sarcoma	2	3	4	1					1	1
Nasal Turbinates	M Granulocytic leukemia			1							
	M Malignant lymphoma	1									
Oesophagus; see Esophagus											
Optic Nerves	M Malignant lymphoma		1		1						1

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		5		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60	60	60	60	60
Organ	Identification of the Tumor										
Ovaries	M Granulocytic leukemia		2								
	M Malignant lymphoma		1		6		1		1		
	B Luteoma		1		5		2				3
	B Tubular adenoma										1
	B Ovarian cystadenoma		6		1		3		1		1
	M Histiocytic sarcoma				1				1		1
	B Thecoma				1						
	B Sertoli cell tumor				1						
Pancreas	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1	2	1	6		2		1		2
	B Islet cell adenoma	1								2	
	M Histiocytic sarcoma	2	2	3	1						1
Pancreatic Lymph N.	M Histiocytic sarcoma		1	1							
	M Malignant lymphoma		1								1
Parathyroid	M Malignant lymphoma			1							
	M Granulocytic leukemia		1					1			
	B Interstitial cell tumor										
Para-aortic Lymph N.	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	3	1	5		2		1		
	M Histiocytic sarcoma	2	1	3					1	1	1
Pituitary	M Granulocytic leukemia		2	1							1
	M Malignant lymphoma							1			
	B Pituitary adenoma		1								
Popliteal Lymph Node	M Histiocytic sarcoma			1							
	M Malignant lymphoma				2		1				
Preputial Glands	M Granulocytic leukemia		1	1							
	M Malignant lymphoma		1	1	2		1				1
	M Histiocytic sarcoma										
	M Squamous carcinoma	1									
Prostate	M Granulocytic leukemia			1							
	M Malignant lymphoma	1									
	M Histiocytic sarcoma	1		1							

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		6		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated											
Organ	Identification of the Tumor										
Rectum	M Histiocytic sarcoma	1		2							
	M Granulocytic leukemia		1								
	M Malignant lymphoma		1								
Renal Lymph Nodes	M Granulocytic leukemia		2				2		1		
	M Malignant lymphoma	1	2	1	6					1	1
	M Histiocytic sarcoma	2	1	3							
Salivary Gland	M Granulocytic leukemia		2	1							2
	M Malignant lymphoma	1	4	1	6		2		1		1
	M Histiocytic sarcoma	1	1	3							
Sciatic Nerve	M Granulocytic leukemia		1	1							
	M Malignant lymphoma	1	1				2				
Seminal Vesicles	M Granulocytic leukemia			1							
	M Malignant lymphoma			1							
	M Histiocytic sarcoma	1		2							
Skeletal Muscle	M Granulocytic leukemia		1	1							
	M Malignant lymphoma		1		1		1				1
	M Histiocytic sarcoma			2					1		
	M Undiff sarcoma										
Skin	M Granulocytic leukemia		1	1							
	M Malignant lymphoma		1				1				
Skin-Abnormal at PM	M Granulocytic leukemia			1							
	M Malignant lymphoma		1	1							
Spinal Cord	M Granulocytic leukemia				3		1		1		1
	M Malignant lymphoma	1									1
	M Histiocytic sarcoma		1								
Spleen	M Granulocytic leukemia		2	1			7	1	2	1	1
	M Malignant lymphoma	1	5	2	9					1	1
	M Histiocytic sarcoma	2	2	3	1						
	M Malignant lymphoma				1						
Sternum	M Granulocytic leukemia		1	1							
Stifle Joints	M Granulocytic leukemia		2	1							
Stomach	M Malignant lymphoma	1	2	1	3						
	M Histiocytic sarcoma	1		1			1				
	M Squamous carcinoma										

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Pisadronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		8		32		0	
Sex (M/F)		M	F	M	F	M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated											
Organ	Identification of the Tumor										
Subcutaneous Mass	M Hemangiosarcoma									1	
	M Malignant lymphoma				2						
	M Mammary carcinoma				1						
	M Undiff sarcoma								1		
Subcutaneous Tissue	M Hemangiosarcoma									1	
	M Osteosarcoma					1					
Submandibular Lymph N.	M Granulocytic leukemia		2	1							1
	M Malignant lymphoma	1	3	2	8		6	2	1	1	1
	M Histiocytic sarcoma	2	2	4						1	
Testes	B Interstitial cell tumor	2				1			1		
Thoracic Cavity	M Malignant lymphoma	1									
Thoracic Mass	B Hemangioma				1						
Thymic Lymph Nodes	M Granulocytic leukemia		2	1							
	M Malignant lymphoma				2		2			1	1
	M Histiocytic sarcoma	1		5							
Thymus	M Granulocytic leukemia		2	1							
	M Malignant lymphoma	1	5	1	10		10	2	3	2	4
	M Histiocytic sarcoma	1	2	3	1						1
Thyroid Glands	M Malignant lymphoma		1	1	2		1				
	M Granulocytic leukemia		1								
	B Follicular adenoma	1			1				1		1
	M Follicular carcinoma									1	
Tongue	M Granulocytic leukemia		2								
	M Malignant lymphoma		1								
	M Histiocytic sarcoma		1								
Trachea	M Granulocytic leukemia		1	1							
	M Histiocytic sarcoma	1					1				
	M Malignant lymphoma										
Ureters	M Malignant lymphoma		1	1	2						1
Urinary Bladder	M Malignant lymphoma		2	2	6		2			1	1
	M Histiocytic sarcoma	1	1	2							
	M Granulocytic leukemia		1								

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Treatment Group		Frequency According to Dose and Sex (n)									
		(1) Control		(2) Risedronate		(3) Risedronate		(4) Risedronate		(5) Control	
Dosage (mg/kg/day, po)		0		1		8		32		0	
Sex (M/F)		M 80	F 80	M 80	F 80	M 80	F 80	M 80	F 80	M 80	F 80
Number of Test Animals		60	60	60	60	60	60	60	60	60	60
Number of Animals Evaluated											
Organ	Identification of the Tumor										
Uterus	B Fibroma								1		1
	B Hemangioma		2								
	M Hemangiosarcoma				1						
	B Leiomyoma						1		2		1
	M Leiomyosarcoma		1		2						2
	M Malignant lymphoma		1		4		1		1		
	M Histiocytic sarcoma		1		2		2		1		2
	M Endometrial carcinoma		1								
	M Malignant lymphoma		2		2		1				
	M Malignant lymphoma		2								1
Vagina	M Histiocytic sarcoma										
	M Squamous carcinoma				1						
Vulva	M Granulocytic leukemia		2	1							
Zymbal's Gland	M Malignant lymphoma	1	1	1			1				
	M Histiocytic sarcoma	1									

Conclusions: There was no increase in the incidence of neoplasia, nor alteration in the time of tumor onset and no induction of rare tumors with risedronate treatment. Under the conditions of this study, risedronate was not carcinogenic in male or female mice.

Explanations: M = malignant tumors B = benign tumors

TSS114

S: E1

Tabulated Study Summary

Name of Sponsor/Company: Procter & Gamble Pharmaceuticals Name of Finished Product: Name of Active Ingredient: risedronate sodium	EU only: Ref to Part III.E page 9/25 Location of Full Report in the Submission <Vs1.036/p5> to <Vs1.049/p334>	(For National Authority Use Only)

Oncogenic/Carcinogenic Potential - Study Data

Study Title:	80 Week Oral (Gavage) Carcinogenicity Study in the Mouse (Part 2 - NEP/2E/94)		
Report Date:	17-Jun-96	*Study No.* 995.09.00-ER (45201)	*Study Period:* Nov-91 to Jun-93
Species/Strain:	Mouse (Crl:CD-1(ICR)BR)	*Lot No.:*	12287-062C
Number of Animals:	360	*Duration of Study:*	80 weeks
Administration Route:	oral (gavage) fasted 4 hr prior to dosing to 2 hr post-dosing		
Treatment of Controls: Deionized water 10 mL/kg/day po	*Age (at study initiation):*	approx 9 to 10 weeks	
	Body Weight (at study initiation):	21-38 grams	
	Treatment Days Per Week:	7	

Combination with Chronic Toxicity Study? ☐ Yes ☒ No

Treatment Group			(6) Control		(7) Risedronate		(8) Risedronate	
Dosage (mg/kg/day, po)			0		4		16	
Sex (M/F)			M	F	M	F	M	F
Total Number of Animals	At Study Initiation		60	60	60	60	60	60
	Evaluated		60	60	60	60	60	60
Premature Necropsy	Scheduled Int. Secr.		0	0	0	0	0	0
	Died/Sacr. or Extremis	Total	7	8	12	21	31	28
		Eval.	7	8	12	21	31	28
Terminal Sacrifice			53	52	48	39	29	32

Non-tumor Important Findings:
There were no clinical signs noted that were clearly related to administration of the test article. Ophthalmic examination did not reveal any treatment-related effects. Treatment-related non-neoplastic changes were seen in the bone at both dose levels including thickening of the metaphyseal trabeculae and open epiphyses. There were also changes in the upper respiratory tract, including degeneration of the olfactory epithelium and a purulent exudate in the nasal passages and middle ear. Although these changes were apparently treatment-and dose-related, they were considered to be related to reflux of the dose following gavage, rather than a direct toxic effect of the test article. Upper respiratory tract disease characterized by these changes, was a factor contributing to the death of a significant proportion of animals in the 16 mg/kg/day dose group.

In the 16 mg/kg dose group, a significant increase in deaths was seen with marked excess of deaths early in the study. Also seen were decreases in body weight gain, food consumption and white blood cell count and decreased incidence of abnormal-colored Harderian glands. All organ weight changes could be attributed to the growth retardation observed. An increased incidence of distention of the intestinal tract was observed. This was not considered to be a direct toxic effect of the test article but instead, probably due to the reduced food consumption. Males showed a reduced incidence of enlarged seminal vesicles, kidney cysts and abnormally-shaped kidneys. Females showed an increased incidence of small spleen and a decreased incidence of ovarian and uterine cysts, distended uterus, and abnormally shaped cervix.

At the 4 mg/kg/day dose, an increase in deaths was seen for males and females but was significant only for females. Also seen were decreases in white blood cell count, increased incidence of distention of the stomach and intestinal tract and decreased incidence of abnormal-colored Harderian glands.

Histology performed according to ——— for Guidance: ☒ Yes ☐ No

Study conducted by the applicant: ☐ Yes ☒ No

If "no", indicate the name and address of the institute that conducted the study:
Name:
Address:

Study in compliance with GLP: ☒ Yes ☐ No

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S: E1

Treatment Group		Frequency According to Dose and Sex (n)					
		(6) Control		(7) Risedronate		(8) Risedronate	
Dosage (mg/kg/day, po)		0		4		16	
Sex (M/F)		M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60
Organ	Identification of the Tumor						
Abdominal Fat	M Histiocytic sarcoma				1		
Adrenals	B Adreno-cort adenoma						2
	B Phaeochromocytoma		1				
	M Malignant lymphoma		3		1		
	M Histiocytic sarcoma				1		
Aorta	M Malignant lymphoma		2				
	M Histiocytic sarcoma				1		
Axillary Lymph Nodes	M Malignant lymphoma		3				
	M Histiocytic sarcoma				1		
Bone Marrow	M Granulocytic leukemia					1	
	M Malignant lymphoma		3		2		
	M Histiocytic sarcoma		1		2	1	
Cervix	M Malignant lymphoma		1				
	M Histiocytic sarcoma				3		
Deep Cervical Lymph N.	M Malignant lymphoma		3				
Ear: external	B Fibroma			1			
	M Malignant lymphoma		1				
Ear: internal	M Malignant lymphoma		1				
Ear: middle	M Malignant lymphoma		2				
Epididymides	M Malignant lymphoma	1					
Esophagus	M Malignant lymphoma		1				
	M Histiocytic sarcoma				1		
Eyes	M Histiocytic sarcoma				1		
Harderian Glands	B Harderian adenoma	4	4		3	5	1
	M Malignant lymphoma		2				
	M Histiocytic sarcoma		1				
Heart	M Malignant lymphoma		2				
	M Histiocytic sarcoma				2		
Hepatic Lymph Nodes	M Malignant lymphoma		3		1		1
	M Histiocytic sarcoma		1		1	1	
Ileum	M Adenocarcinoma		1				
Inguinal Lymph Nodes	B Hemangioma		1				
	M Malignant lymphoma		3				
Jejunum	M Malignant lymphoma				1		

S: E1 TSS114

Treatment Group		Frequency According to Dose and Sex (n)					
		(6) Control		(7) Risedronate		(8) Risedronate	
Dosage (mg/kg/day, po)		0		4		16	
Sex (M/F)		M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60
Organ	Identification of the Tumor						
Kidneys	M Malignant lymphoma		7	1	3		1
	M Histiocytic sarcoma			1	1		
	B Renal adenoma	1					
Lacrimal Glands	M Granulocytic leukemia					1	
	M Malignant lymphoma		4		1		
	M Histiocytic sarcoma				1		
Lip	B Squamous papilloma		1				
Liver	M Granulocytic leukemia					1	
	B Hemangioma			1			
	B Cholangioma			1			
	M Hemangiosarcoma			1		1	
	M Malignant lymphoma	1	5	1	3		1
	B Hepatocellular adenoma	8		6		2	1
	M Hepatocellular carcinoma	1		3		1	
	M Histiocytic sarcoma		1	1	2	1	
Lungs	M Malignant lymphoma		5	1	1		
	B Pulmonary adenoma	21	10	15	9	11	7
	M Histiocytic sarcoma		1		2	1	
	M Pulmonary carcinoma	4	2	1	2	3	
Mammary Gland	M Malignant lymphoma		1				
	M Histiocytic sarcoma				1		
Mediastinal Lymph Nodes	M Malignant lymphoma		2		1		
Mesenteric Lymph Node	M Granulocytic leukemia					1	
	M Malignant lymphoma	1	6	1	6		5
	M Histiocytic sarcoma		1	1	1	1	
Nasal Turbinates	M Malignant lymphoma		1				
	M Neurofibrosarcoma	1					
Oesophagus; see Esophagus							
Optic Nerves	M Malignant lymphoma		2				
Ovaries	B Hemangioma				1		
	M Malignant lymphoma		4		2		1
	B Luteoma		2		2		
	B Ovarian cystadenoma		2		2		2
	M Histiocytic sarcoma		1		3		
S: E1						TSS114	

Treatment Group		Frequency According to Dose and Sex (n)					
		(6) Control		(7) Risedronate		(8) Risedronate	
Dosage (mg/kg/day, po)		0		4		16	
Sex (M/F)		M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60
Organ	Identification of the Tumor						
Pancreas	M Malignant lymphoma		4		1		
	M Histiocytic sarcoma				1		
Pancreatic Lymph Node	M Histiocytic sarcoma					1	
	M Malignant lymphoma		1				
Para-aortic Lymph Node	M Malignant lymphoma		4		1		
Parathyroid	M Malignant lymphoma		1				
Pituitary	M Malignant lymphoma		2				
	B Pituitary adenoma		1				
Popliteal Lymph Node	M Malignant lymphoma		3				
Preputial Glands	M Malignant lymphoma		2				
Renal Lymph Nodes	M Malignant lymphoma		3		1		
Salivary Gland	M Malignant lymphoma		7		1		
	M Histiocytic sarcoma				1		
Sciatic Nerve	M Histiocytic sarcoma				1		
	M Malignant lymphoma		2				
Skeletal Muscle	M Malignant lymphoma		2				
	M Histiocytic sarcoma		1				
Skin	M Histiocytic sarcoma				1		
	M Malignant lymphoma		1				
Skin-Abnormal at PM	M Histiocytic sarcoma				1		
Spinal Cord	M Malignant lymphoma		2				
Spleen	M Hemangiosarcoma		1				
	M Granulocytic leukemia					1	
	M Malignant lymphoma	1	8	1	4		2
	M Histiocytic sarcoma			1		2	
Sternum	M Osteosarcoma	1					
Stifle Joints	M Malignant lymphoma		1				
	M Histiocytic sarcoma				1		
Stomach	M Granulocytic leukemia					1	
	M Malignant lymphoma		1				
	M Histiocytic sarcoma				1		
Subcutaneous Mass	M Histiocytic sarcoma				1		
	M Mammary carcinosarcoma		1				
S: E1						TSS114	

Treatment Group		Frequency According to Dose and Sex (n)					
		(6) Control		(7) Risedronate		(8) Risedronate	
Dosage (mg/kg/day, po)		0		4		16	
Sex (M/F)		M	F	M	F	M	F
Number of Test Animals		60	60	60	60	60	60
Number of Animals Evaluated		60	60	60	60	60	60
Organ	Identification of the Tumor						
Submandibular Lymph N.	M Granulocytic leukemia					1	
	M Malignant lymphoma	1	9		4	1	4
	M Histiocytic sarcoma		1		1	2	
Testes	B Interstitial cell tumor	1					
	B Hemangioma			1			
Thymic Lymph Nodes	M Malignant lymphoma		2				
	M Histiocytic sarcoma				1		
Thymus	M Malignant lymphoma	1	14	3	10	2	7
	M Histiocytic sarcoma		1		2	1	
Thyroid Glands	M Malignant lymphoma		1				
	M Histiocytic sarcoma				1		
Trachea	M Histiocytic sarcoma				1		
Ureters	M Malignant lymphoma				1		
Urinary Bladder	M Malignant lymphoma		4		1		
	M Histiocytic sarcoma				1		
Uterus	B Leiomyoma		1				1
	M Malignant lymphoma		2		1		
	M Histiocytic sarcoma		3		2		3
Vagina	M Malignant lymphoma		1				
Zymbal's Gland	M Malignant lymphoma		1				

Conclusions: There was no increase in the incidence of neoplasia, nor alteration in the time of tumor onset and no induction of rare tumors with risedronate treatment. Under the conditions of this study, risedronate was not carcinogenic in male or female mice.

Explanations: M = malignant tumors B = benign tumors

S: E1 TSS114

RAT STUDY

GENERAL INFORMATION

Study Title: An oral carcinogenicity study of NE-58095 in the albino rat
Study Number: 995.09.00-BS (E3), Accession Nr. 46202, [redacted] Project Nr. 83815
Volume Numbers: sNDA Vols. S1.050-S1.058
Test Facility: [redacted]
Study Period: January 1995-January 1997 (total of 92-104 weeks) (Day 0-726)
Date of Submission: 12-18-1998
GLP Compliance: Yes
QA Report: Yes
Dose-range-finding study: Study B4 (13 weeks) [redacted] Nr. 85775): 0, 4, 8, 16, 32, 64 mg/kg/day
Study B16 (52 weeks) [redacted] Nr. 83815): 0, 0.1, 0.6, 4 mg/kg/day

STUDY PROTOCOL AND METHODS

Study Type: Gavage
Species/strain: Sprague-Dawley Crl:CD^{R} (SD) BR [redacted]
Number of animals: 60/sex/dose group (Group 1,2,3,4,5) (Main study group)
10/sex/group (Group 3,4,5) for toxicokinetic analysis (Satellite subgroup)
Age at start of study: Appr. 42 days
Weight at start of study: Main study 130-197g (m), 115-160g (f), Satellite study 126-191g (m), 125-155 (f)
Animal housing: Individual
Drug Lot/Batch number(s): NE-58095, Lot no. 13427-070B
Drug Purity: Samples of test article solutions taken in Weeks 1, 4, 12, 26, 52, 79, 104. Samples assayed by P&GP.
Drug Homogeneity: Not assessed
Drug Stability: Not assessed in this study
Vehicle employed: Deionized water

Doses

Group		Dose (mg/kg/day)	N/sex/group
1	Control	0	60
2	control	0	60
3	LD	4	60
4	MD	10	60
5	HD	24	60

Basis of Dose Selection: 13-week and 52-week toxicity studies
Relation to Clinical Use: Doses: 2.5 or 5 mg/day, equivalent to circa 0.05 and 0.1 g/kg/day
CAC Concurrence: Carcinogenicity study doses were discussed and agreed upon with the Division (HFD-510). [redacted]
Route of Administration: Oral (gavage) 10 ml/kg/day
Frequency of Drug Administration: Daily
Dosing in relation to feed: Animals fasted ≥4h before, and ≥2h after dosing
Controls Employed: Dual vehicle control groups (Group #1 and #2)
Interim Sacrifices: None
Satellite TK Study Groups: 10/sex/group (Groups 3,4,5) for toxicokinetics, for 78 weeks

Unscheduled Sacrifices or Deaths: See Results (Mortality)

Toxicokinetics Blood samples (h): 0.5, 1, 2, 4, 24h postdosing
Blood samples (days): 1, 25, 179, 361, 543 days
Assay: Risedronate, by [redacted]

Statistics

Sponsor's evaluation of mortality and tumors was done using the PROC CHRONIC program. For tumors in males, the initial analysis was done without data from Group 5 (prematurely terminated group). Then a supplementary analysis of male data was performed including data from Group 5.

All lesions previously analyzed using PROC CHRONIC were also re-analyzed using the Exact trend (permutation) test from the StatXact-3 software whenever the following 2 conditions were satisfied: (A) The total number of tumor bearing animals was smaller than 10, and (B) The number of tumor bearing animals in Group 4 or in Group 5 was greater than the number of tumor bearing animals in each of the control groups.

CDER statistical methods: See CDER Biometrics Review

STUDY RESULTS

Groups and doses

Group		Dose (mg/kg/day)	N/sex/group
1	Control	0	60
2	Control	0	60
3	LD	4	60
4	MD	10	60
5	HD	24	60

Clinical Signs

Abdominal distension: Increased incidence in HDm,f that died

Abnormal respiratory sounds: Increased incidence in MDm,f and HDm,f throughout study

Decreased activity, backbone prominent, cold to touch, dehydration, reduced feces, fur staining, hunched posture, pallor, thinness, weakness, broken or eroded teeth: Increased incidence in HDm,f throughout study

Mortality

Incidence of deaths: (Sponsor's analysis) Significant increase in mortality in males (dose-related trend), and significant increase in MDm and HDm vs. combined m controls).
Slight but significant decrease in LDf.

Premature termination Group 5: Mortality in males reached 75% (45 animals) by Week 93, therefore all remaining Group 5 animals were terminally euthanized in Week 93 (per protocol).

Clinical signs prior to death: Abdominal distension, abnormal respiration, decreased activity, broken/eroded teeth

Survival data analysis: Significant, positive dose-mortality trend in both males and females (see CDER STAT review)

Mortality in rats over entire treatment period

	MALES					FEMALES				
GROUP	control 1	control 2	LD	MD	HD	control 1	control 2	LD	MD	HD
Group #	1m	2m	3m	4m	5m*	1f	2f	3f	4f	5f
Number of animals found dead or euthanized in study (including terminal sacrifice period)	28/60	34/60	35/60	41/60	45*/60*	42/60	50/60	35/60	40/60	46/60
% of total	45%	55%	57%	70%	75*%*	70%	83%	58%	67%	77%

* Mortality reached 75% (45 animals) by Week 93, therefore all remaining Group 5 animals were terminally euthanized in Week 93 (per protocol).

Possible cause of death

	MALES					FEMALES				
GROUP	control 1	control 2	LD	MD	HD	control 1	control 2	LD	MD	HD
Group #	1m	2m	3m	4m	5m*	1f	2f	3f	4f	5f
Number of animals found dead or euthanized for cause:										
Neoplastic	19	21	13	25	4	40	45	32	33	9
Non-neoplastic	5	5	22	7	9	0	3	0	3	4
Undetermined	4	8	15	9	32	2	2	3	4	33

* Mortality reached 75% (45 animals) by Week 93, therefore all remaining Group 5 animals were terminally euthanized in Week 93 (per protocol).

Body Weight

Body weight and BW gain: Decreased in HDm,f (from Week 6, Week13)

Body weight (g) on Day 363 and Day 726 (Day 643,Group 5m) (g, mean values)

			control1	control 2	LD	MD	HD
		BW (g)					
MALES	Day 363		752	739	710*	664*	537*
	Day 726 (Group 5: Day 643)		765 (Day 643: 804g)	792 (Day 643: 821g)	749	756	(556)
FEMALES	Day 363		432	439	414	405	309*
	Day 726		504	535	492	474	342*

* significantly different from control

Body weight (%) on Day 363 and Day 726 (Day 643,Group 5m) (g, mean values)

			control1	control 2	LD	MD	HD
		BW (%)					
MALES	Day 363		100	100	95%	89%	72%
	Day 726 (Group 5: Day 643)		100	100	96%	97%	(68%)
FEMALES	Day 363		100	100	95%	93%	71%
	Day 726		100	100	95%	91%	66%

* significantly different from control

Body weight gain (g) from Day -1 to Day 363, or from Day-1 to Day 726 (Day 643,Group 5m) (g, mean values)

			control1	control 2	LD	MD	HD
		BW gain (g)					
MALES	Day-1 - Day 363		579	568	538*	496*	363*
	Day-1 - Day 726 (Group 5: Day -1 - Day 643)		591	622	581	585	(383)
FEMALES	Day-1 - Day 363		298	303	280	269	175*
	Day-1 - Day 726		371	402	359	337	206*

* significantly different from control

Body weight gain (%) from Day -1 to Day 363, or from Day-1 to Day 726 (Day 643,Group 5m) (% of combined controls, mean values)

			control1	control 2	LD	MD	HD
		BW gain (%)					
MALES	Day-1 - Day 363		100	100	94*	86*	63*
	Day-1 - Day 726 (Group 5: Day -1 - Day 643)		100	100	96	96	(63)
FEMALES	Day-1 - Day 363		100	100	93	89	58*
	Day-1 - Day 726		100	100	93	87	53*

* significantly different from control

Food Consumption

Weekly food consumption: Reduced in HDm and HDf from Week 3 or 4
Reduced in MDm and MDf in most weeks througout study
Occasionally reduced in LDm throughout study

Ophthalmoscopy:

Bilateral congestion of ocular vessels: Observed in HDf @104 weeks (incidence 4/14)

Hematology (at sacrifice):

Lymphocyte count%: Decreased in HDm
Segmented neutrophil count%: Increased in HDm,f (non-significant)
Platelet count: Decreased in HDm (non-significant)

Hematology at Week 52

		control 1	control 2	LD	MD	HD
Lymphocyte count (%)						
	MALES	77.9	73.1	73.8	66.5	65.4*
	FEMALES	72	71.2	71.7	75.3	63.8
Segm neutrophil count (%)						
	MALES	17.4	23.8	20.6	26.5	29.6*
	FEMALES	24.0	21.4	23.1	20.4	30.9
Platelet count						
	MALES	978	929	843	850	804
	FEMALES	891	888	778	770	650*

*significantly different from control (Group 1)

Hematology at Week 104

		control 1	control 2	LD	MD	HD	HD (Week 93) (ie, $t_{sacrifice}$)
Lymphocyte count (%)							
	MALES	53.9	50	46*	56.4	-	57.7
	FEMALES	53.6	48.6	54.2	53.9	49.6	-
Segm neutrophil count (%)							
	MALES	40.4	44.4	48.7*	39.4	-	34.3
	FEMALES	41	45.2	41.4	41.5	46.2	-
Platelet count							
	MALES	1011	1124	850*	795*	-	803
	FEMALES	844	891	723*	722*	693*	-

*significantly different from control (Group 1)

Clinical Chemistry: No data

Organ Weights: No data

Gross Pathology:

Gross pathology findings at sacrifice

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
		ctr 1	ctr 2	LD	MD	HD		ctr 1	ctr 2	LD	MD	HD
mg/kg/day		0	0	4	10	24		0	0	4	10	24
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*28*	*34*	*35*	*42*	*45*		*42*	*50*	*36*	*40*	*46*
N terminal		*32*	*26*	*25*	*18*	*15*		*18*	*10*	*34*	*20*	*14*
Carcass	emaciation	0	1	2	1	18		2	2	1	4	21
Cecum	dilatation	1	0	1	0	19		1	1	0	2	14
Colon	dilatation	0	0	1	0	5		0	0	0	0	2
Digesta	discoloration	1	3	5	5	6		1	2	2	5	3
Duodenum	dilatation	0	0	1	0	14		0	0	0	1	10
Esophagus	perforation	0	0	1	3	2		0	0	0	2	2
	dilatation	0	0	0	0	3		0	0	0	0	3
Ileum	dilatation	0	0	1	2	28		0	1	0	1	19
Jejunum	dilatation	0	0	1	1	27		0	0	0	1	19
Lung	spongy	0	0	0	0	2		0	0	0	0	4
	depression	0	1	0	3	5		0	1	0	1	2
	nodule	1	1	1	0	2		0	0	1	2	1
Prostate	small	1	2	1	0	9		-	-	-	-	-
Seminal vesicle	small	2	2	1	2	7		-	-	-	-	-
Spleen	small	0	0	0	0	11		2	2	2	0	11
Stomach	dilatation	0	0	1	0	12		0	0	0	2	13
	area dark	9	7	8	9	13		3	5	6	6	12
Thymus	small	4	4	6	5	21		7	5	11	6	24
Urinary bladder	dilatation	2	2	6	5	3		0	0	1	2	0
Tooth	one not found	0	0	0	0	4		0	0	0	0	0

Histopathology

Neoplastic histopathology findings at sacrifice

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
		ctr 1	ctr 2	LD	MD	HD*		ctr 1	ctr 2	LD	MD	HD
mg/kg/day		0	0	4	10	24		0	0	4	10	24
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*28*	*34*	*35*	*42*	*(45)**		*42*	*50*	*36*	*40*	*46*
N terminal		*32*	*26*	*25*	*18*	*(15)**		*18*	*10*	*34*	*20*	*14*
Brain	Glioma (M)	0	2	0	4	(0)*		0	0	0	0	2
Thyroid	C-cell adenoma (B)	1	3	4	7	(3)*		5	2	8	6	1
Pituitary	Carcinoma, pars distalis (M)	1	1	0	2	(0)*		7	4	1	2	1

	adenoma, pars dist (B)	38	35	35	31	(14)*		47	52	53	46	12
Subcut. tissue	fibroma (B)	0	4	1	4	(0)*		2	0	0	1	1

* HD males did not complete the study (termination of n=15 remaining in Week 93). Therefore, data from HD males have questionable significance.

Incidence/ Time of diagnosis of brain and thyroid tumors

			MALES						FEMALES				
	Group #		1	2	3	4	5		1	2	3	4	5
			ctr 1	ctr 2	LD	MD	HD		ctr 1	ctr 2	LD	MD	HD
	mg/kg/day		0	0	4	10	24		0	0	4	10	24
Brain	Incidence	Glioma (M)	0	2	0	4	0		0	0	0	0	2
	Incidence in preterminals			2/34 (5.9%)		3/42 (7.1%)							1/46 (2.2%)
	Incidence in terminals			0/26 (0%)		1/18 (5.6%)							1/14 (7.1%)
	week of diagnosis			*75* 100**		*82* 101* 102* 105*							*45* 104*
Thyroid**	Incidence	C-cell adenoma (B)	1	3	4	7	3		5	2	8	6	1
	week of diagnosis		*92*	*92 104 104*	*53 92 104 104*	*79 92 92 104 104 104 104*							

* Fatal tumor (all but 2 brain gliomas were fatal)
**All thyroid tumors were incidental

Non-neoplastic histopathology findings at sacrifice

		MALES						FEMALES				
Group #		1	2	3	4	5		1	2	3	4	5
		ctr 1	ctr 2	LD	MD	HD		ctr 1	ctr 2	LD	MD	HD
mg/kg/day		0	0	4	10	24		0	0	4	10	24
N examined		60	60	60	60	60		60	60	60	60	60
N preterminal		*28*	*34*	*35*	*42*	*45*		*42*	*50*	*36*	*40*	*46*
N terminal		*32*	*26*	*25*	*18*	*15*		*18*	*10*	*34*	*20*	*14*
Bone (femur)	hypertrophy (primary spongiosa)	0	0	60	60	59		0	0	60	60	60
Bone (sternum)	hypertrophy (primary spongiosa)	0	0	59	60	60		0	0	60	60	60
Brain	vacuolation	0	0	0	0	2		0	0	0	1	1
Cecum	hemorrhage	0	0	2	4	3		0	0	1	0	1
	typhlitis	1	4	4	2	4		1	1	2	6	6
Colon	colitis	0	0	1	0	1		0	0	1	1	0
Esophagus	perforation	0	0	0	2	0		0	0	0	1	0
	esophagitis	0	0	0	0	2		0	0	0	1	0
	hemorrhage	0	0	0	1	1		0	1	0	0	1
Ileum	hemorrhage	0	0	1	1	3		0	0	1	0	1
	ileitis	0	0	0	0	2		0	0	0	0	2
Jejunum	hemorrhage	0	0	2	1	1		0	0	0	0	1
Kidney	pyelonephritis	0	0	0	0	3		0	0	0	4	0

Liver	hematopoiesis, extramedullary	1	2	2	1	0		2	2	1	10	2
Lung	granuloma	3	1	2	1	22		0	2	3	3	14
	histiocytosis	3	4	5	13	15		3	4	9	13	15
	hemorrhage	1	2	1	8	6		3	1	3	1	5
	edema	0	0	0	5	4		1	0	0	0	1
	bronchiectasis	0	0	0	0	5		0	0	0	0	0
	atelectasis	0	0	0	0	3		0	0	0	0	1
	bronchopneumonia	0	1	0	0	6		1	1	1	1	4
	emphysema	0	0	0	0	2		0	1	0	0	1
	pneumonia, interstitial	0	0	1	1	3		0	0	0	1	2
Lymph node	hemorrhage	2/21	0/36	4/20	2/20	4/12		3/39	3/35	2/30	3/26	0/8
Nasal cavity	new bone formation	0	0	59	60	60		0	0	60	60	60
	rhinitis	8	5	29	45	59		2	3	54	53	58
Pituitary	hyperplasia, pars distalis	13	10	12	3	6		6	2	5	6	10
Spleen	increased hematopoiesis, extramedullary	11	13	24	23	7		11	11	26	32	14
	congestion	0	0	1	0	0		0	0	0	0	3
	lymphoid atrophy	0	0	0	0	2		1	1	0	0	3
Stomach	gastritis	4	7	11	10	8		3	8	11	8	2
	hemorrhage	2	0	0	2	4		0	0	0	0	2
Testis	atrophy, tubular epithelium	15	13	13	13	24		-	-	-	-	-
Trachea	tracheitis	1	0	0	0	7		0	0	0	0	6
Spinal cord	necrosis	0	0	0	2	1		0	0	2	0	0
Thyroid	C-cell hyperplasia	5	4	6	3	1		5	2	7	9	2
Tooth	atrophy	3	7	3	14	42		5	5	7	18	31

Reviewers comment: Neoplastic and non-neoplastic findings:

- There appeared to be a drug-related increase in tumor incidence in brain (malignant glioma, males and females), and thyroid gland (benign c-cell adenoma, males), in the dose groups that completed the study.
- In brain there was a possibly related increased incidence of vacuolation (males and females).
- In the thyroid, C-cell hyperplasia was seen in all groups, but the incidence was not dose-related in males, and not clearly dose-related in females.

STATISTICAL ANALYSIS OF TUMOR FINDINGS

SPONSOR'S ANALYSIS

First analysis. The first analysis was done using the PROC CHRONIC program. The initial analysis with this program excluded data from Group 5 males which were terminated early. The analysis was done for the "unshortened" experimental period from Day 0-Day726 (Wk1-Wk104). An additional analysis including the data from Group 5 males was then carried out, for the "shortened" experimental period from Day0-Day644. The significance of linear dose-related increases in tumor occurrence was assessed with the trend test across dose levels, followed by pairwise comparisons of each treatment group against the control(s).

The results are shown in Table A below.

Table A: Summary from Proc Chronic analysis.

Sex	Organ / Tissue	Lesion Type	Experimental Period	Tumor classification	Number of Tumor-Bearing Animals / Sample Size				P-VALUE	
					control group(s)	group 3	group 4	group 5	Heterogeneity test	Trend test
♂	Brain	malignant glioma	unshort	F=fatal	2	0	3			
				I=incidental	0	0	1			
				Pooled=F+I	2 / 120	0 / 60	4 B / 60		-	-
			short	F=fatal	1	0	1	0		
				I=incidental	1	0	3 A	0	-	
				Pooled=F+I	2 / 120	0 / 60	4 A / 60	0 / 60	*	
	Pituitary	malignant carcinoma pars distalis	unshort	F=fatal	0	0	2 B		-	-
				I=incidental	2	0	0			
				Pooled=F+I	2 / 119	0 / 60	2 / 60			
	Subcutaneous tissue	benign fibroma	unshort	F=fatal	0	0	1			
				I=incidental	0	1	3 C		-	-
				Pooled=F+I	0 / 60	1 / 60	4 C / 60		*	-
	Thyroid	benign c-cell adenoma	unshort	F=fatal						
				I=incidental	4 / 120	4 / 60	7 B / 60		-	-
				Pooled=F+I						
			short	F=fatal						
				I=incidental	4 / 120	4 / 60	7 B / 60	3 / 60	-	-
				Pooled=F+I						
♀	Brain	malignant glioma	unshort	F=fatal	0	0	0	1		
				I=incidental	0	0	0	1		
				Pooled=F+I	0 / 119	0 / 60	0 / 60	2 A / 60	*	-

P-value for the heterogeneity test and the trend test: * : $0.01 < P \leq 0.05$, ** : $0.001 < P \leq 0.01$

Sign ficantly higher tumor occurrence rate than the one in Groups 1 and 2 combined: A $0.01 < P \leq 0.05$, B $0.001 < P \leq 0.01$

Significantly higher tumor occurrence rate than the one in Group 1: C $0.001 < P \leq 0.01$

Results of Sponsor's first analysis. According to the first analysis, using a trend test for the unshortened period (i.e. excluding Group 5), significant increases in tumor incidence (number of tumor-bearing animals/sample size) were found (data from pooled fatal and incidental tumors) for:

- Brain malignant glioma in male rats
- Subcutaneous tissue benign fibroma in male rats (when analysis done with control group 1)
- Thyroid benign c-cell adenoma in male rats
- Brain malignant glioma in female rats

Second analysis. Since the incidence of tumors with significant results was rather low (<7/60), Sponsor also conducted an exact trend test with StatXact software. This test was done only if (A) the total number of tumor bearing animals was smaller than 10, and (B) the number of tumor bearing animals in Group 4 or 5 was greater than the number of tumor bearing animals in each of the control groups

Results of Sponsor's second analysis. According to the second analysis, using an exact trend test, significant increases in tumor incidence were found for:

- brain malignant glioma in male rats (p=0.0163).

- brain malignant glioma in female rats (p=0.0285).

Sponsor's conclusion. The Sponsor, although these statistically significant increases in tumor incidence were described in the study report, concluded in the report summary (p.2 of the Study Report), that "***based on the results of this study, oral administration of NE-58095 (risedronate) to rats, for a period of 93 weeks in high dose males and for a period of 104 weeks in all other treated groups and in high dose females, did not produce any evidence of tumorigenicity at dosages of 24 mg/kg/day or lower***".

This final conclusion was preceded by a discussion opening with the statement *that "the tumors showing statistically significant increase occur spontaneously in Sprague-Dawley rats and the variations were viewed as incidental"*.

- For the subcutaneous fibromas the significant finding was dismissed because it was only seen when compared with Control Group 1;
- The increased incidence of thyroid adenomas in the MD male group was considered unrelated to treatment because " *adenomas were not accompanied by an increase of other proliferative changes (e.g. hyperplasia), and the increase was not noted in female rats*";
- The increased brain gliomas in MD males and HD females (6.7% and 3.3%, respectively) were considered unrelated to administration of the test article because " *the Sprague-Dawley rat has shown wide variations in the incidence of brain tumors in untreated controls, and one of the Performing Laboratories' in-house control groups had a similar 6% incidence in brain gliomas*".

However, historical control values provided in response to a request from this Reviewer (Submission June 1, 1999) indicated a maximal incidence of brain gliomas of 4/100 (4%) and not 6%. This 4% occurrence was seen in a female control group (Study E). Historical control values are provided below.

HISTORICAL CONTROL VALUES

Tumor incidence: Historical control values provided by Sponsor

MALES

Study	A	B	C	D	E	Total	Percentage (%)		Risedronate Study
Number of animals examined	60	55	120	120	100	455	ave rage	range	60/dose group
									dose groups: c1 - c2 - LD - MD (- HD)
Brain glioma (malignant)									
Incidence (# of animals)	0	1	0	2	2	5			0 - 2 - 0 - 4 (- 0)
Incidence (%)	0%	1.8%	0%	1.7%	2%	-	1.1%		0 - 3.3 - 0 - 6.7 (- 0%)
Thyroid C-cell adenoma (benign)									
Incidence (# of animals)	3	0	8	3	15	29			1 - 3 - 4 - 7 (- 3)
Incidence (%)	5%	0%	6.7%	2.5%	15%	-	5.8%		1.7 - 5 - 6.7 - 11.7 (- 5%)

FEMALES

Study	A	B	C	D	E	Total	Percentage (%)		Risedronate Study
Number of animals examined	60	55	120	120	100	455	ave rage	range	60/dose group
									dose groups: c1 - c2 - LD - MD - HD
Brain glioma (malignant)									
Incidence (# of animals)	0	0	1	0	4	5			0 - 0 - 0 - 0 - 2
Incidence (%)	0%	0%	0.8%	0%	4%	-	1.0%		0 - 0 - 0 - 0 - 3.3%

Reviewers' Conclusions:

- On the basis of the Sponsors tumor data analysis, disregarding the data from the HD male group, statistically significant increases in tumor incidence were found for malignant brain glioma in male rats, malignant brain glioma in female rats, and benign thyroid c-cell adenoma in male rats.
- Consideration of historical control values shows that the MD male incidence of brain glioma (6.7%) lies outside the range of historical control values [redacted]. Thus, the increased incidence of brain glioma in MD animals (2x concurrent control incidence (second control group), 3.4x maximal historical control incidence) indicates that this may be a significant effect.
- The incidence of brain glioma in HD female rats (n= 2/60, 3.3%) was within the range of historical control values [redacted]. The incidence of thyroid c-cell adenoma in MD male rats (n= 7/60, 11.7%) was also within the range of historical control values [redacted] Thus, the biological significance of the increased incidences of these two tumor types is not evident.

CDER STATISTICAL REVIEW:

Main analysis

Note: For Review see APPENDIX (Attachment 1)

Result

According to the CDER Statistical Review, a statistically significant dose-tumor positive linear trend was found for malignant brain glioma in female rats (trend test, p=0.0029). Since the concurrent control incidence is 0/120 (0%), i.e., ≤1%, this tumor is classified as a rare tumor and the cut-off P-value for this tumor is 0.025. Historical control values, however, did not confirm that this is a rare tumor (incidence range: [redacted] in five female historical control groups and [redacted] in five male historical control groups, and incidence of 3.3% in one concurrent male control group).

Additional analyses

Note: For Review see APPENDIX (Attachments 2 and 3)

Two additional analysis were carried out at the request of this Reviewer:

(A1) Tumor data analysis, ie, trend test, for male rats with high-dose group excluded. This request was made because the surviving 25% of animals in the HD group were terminated in Week 93.

Results

The asymptotic P-value for malignant brain glioma in the male rat groups was 0.009, which is >0.005, the cut-off P-value for common tumors. Consideration of historical control values (average 1.1%) confirms that this tumor does not qualify as a rare tumor.

The exact P-value for benign thyroid c-cell adenoma in the male rat groups was 0.007, which is >0.005, the cut-off P-value for common tumors.

Thus, the analysis showed that, with the exclusion of the high dose male group, the dose-tumor positive linear trend in male rats was not statistically significant for any listed tumor.

(A2) Tumor data analysis, ie, pairwise comparisons, for the following tumors:
brain glioma in male rats: controls vs. MD
brain glioma in female rats: controls vs. HD
thyroid c-cell adenoma in male rats: controls vs. LD, and controls vs. MD

Results

Tumor incidence and P-values for pairwise comparisons

		males	females
Tumor incidence			
brain glioma	ctr1-ctr2-LD-MD-HD	0-2-0-4	0-0-0-0-2
thyroid c-cell adenoma	ctr1-ctr2-LD-MD	1-3-4-7	
P-values			
brain glioma	controls vs. MD	0.038	
	controls vs. HD		0.097
thyroid C-cell adenoma	controls vs. LD	0.286	
	controls vs. MD	**0.009**	

For pairwise comparison, the cut-off P-value for common tumors (spontaneous incidence >1%) is 0.01, and for rare tumors it is 0.005. However, interpretation of these P-values was not attempted by Statistical Reviewer because of multiple testing on the same data set.

Reviewer's Conclusions

- On the basis of CDER's tumor data analysis, a statistically significant dose-tumor positive linear trend is found for malignant brain glioma in female rats (trend test, p=0.0029).
- The dose-tumor positive linear trend in male rats, when the data from the high dose male group were excluded, was not statistically significant for any listed tumor, including brain glioma and thyroid c-cell adenoma.
- Pairwise comparison of dose groups suggested a significant increase in the incidence of thyroid c-cell adenoma in MD male rats (pairwise comparison, p=0.009, <0.01). The increased incidence in the MD group (n=7/60, 11.7%), however, was within the range of historical control values →

Toxicokinetics

Results on T_{max}, AUC and C_{max}

APPENDIX NO. 14

Table 1. Mean T_{max} (% coefficient of variation) values on study days 1, 25, 179, 361, and 543 for rats given once-daily risedronate doses of 4, 10, and 24 mg/kg for 543 days.

Sex	Dose (mg/kg)	T_{max} (hr) Study Day 1	25	179	361	543
Female	4	0.67 (42)	0.50 (1.3)	0.66 (76)	0.44 (44)	0.75 (38)
Male	4	0.50 (0)	0.70 (99)	1.0 (108)	0.56 (35)	0.56 (29)
Combined	4	0.58 (36)	0.60 (58)	0.83 (101)	0.51 (34)	0.64 (37)
Female	10	0.87 (28)	0.50 (1.7)	0.50 (1.3)	0.50 (1.6)	0.52 (3.3)
Male	10	0.51 (4.1)	0.50 (2.4)	0.80 (35)	0.55 (30)	0.50 (0)
Combined	10	0.66 (38)	0.50 (2.0)	0.65 (28)	0.53 (25)	0.51 (3.0)
Female	24	0.53 (16)	0.60 (35)	0.65 (37)	0.51 (3.0)	0.66 (35)
Male	24	0.50 (0)	0.55 (29)	0.65 (37)	0.72 (70)	0.67 (39)
Combined	24	0.51 (10)	0.58 (32)	0.65 (36)	0.58 (65)	0.66 (35)

Table 2. Mean AUC (% coefficient of variation) values on study days 1, 25, 179, 361, and 543 for rats given once-daily risedronate doses of 4, 10, and 24 mg/kg for 543 days.

Sex	Dose (mg/kg)	AUC (ng•hr/ml) Study Day 1	25	179	361	543
Female	4	24.5 (135)	96.1 (78)	149.4 (62)	310.2 (73)	150.7 (62)
Male	4	21.0 (78)	65.8 (103)	112.5 (119)	139.3 (72)	192.3 (70)
Combined	4	22.8 (112)	80.9 (88)	130.0 (88)	196.3 (85)	176.7 (68)
Female	10	58.0 (31)	315.0 (25)	954.9 (66)	830.1 (132)	1040 (89)
Male	10	52.0 (52)	256.9 (124)	836.7 (97)	1060 (107)	937.9 (99)
Combined	10	70.0 (46)	290.0 (101)	895.8 (89)	973.8 (111)	981.6 (91)
Female	24	231.5 (198)	3850 (47)	9138 (52)	14320 (68)	6840 (71)
Male	24	96.8 (44)	3101 (33)	4432 (82)	6168 (90)	4557 (94)
Combined	24	164.2 (198)	3503 (69)	6785 (70)	7227 (77)	5611 (81)

Table 3. Mean C_{max} (% coefficient of variation) values on study days 1, 25, 179, 361, and 543 for rats given once-daily risedronate doses of 4, 10, and 24 mg/kg for 543 days.

Sex	Dose (mg/kg)	C_{max} (ng/ml) Study Day 1	25	179	361	543
Female	4	13.4 (108)	57.7 (85)	72.0 (121)	78.3 (137)	55.1 (89)
Male	4	10.7 (48)	39.9 (160)	28.7 (179)	45.2 (133)	64.0 (102)
Combined	4	11.9 (86)	48.8 (115)	50.4 (145)	58.8 (139)	60.1 (95)
Female	10	27.2 (28.1)	223.0 (109)	462.4 (95)	385.6 (141)	409.3 (110)
Male	10	28.7 (45)	213.3 (147)	334.3 (97)	460.7 (121)	364.2 (92)
Combined	10	28.1 (41)	218.4 (124)	398.3 (96)	432.5 (124)	385.2 (99)
Female	24	221.8 (207)	2252 (63)	2981 (56)	2825 (58)	2960 (95)
Male	24	45.3 (34)	1875 (83)	1517 (76)	1727 (100)	1827 (89)
Combined	24	118.0 (250)	2063 (71)	2249 (71)	2066 (87)	2432 (95)

Comments:

- Absorption is rapid (T_{max} < 1h)
- Steady state in serum levels reached between Day 25 (1 mo) and Day 179 (6 mo)
- AUC and C_{max} usually higher in females than in males
- Systemic accumulation (AUC_{ss}/AUC_{Day1}): 6x (4mkd) - 40x (24mkd)
- Dose-dependence: 6-fold increase in dose (4 to 24 mkd) gives 40-fold and 30-to-50-fold increase in C_{max} and AUC

Human dose multiples:

Estimated human dose multiples for the maximum proposed therapeutic dose (5 mg/day)

Dose	Gender	Animal AUC averaged for days 179, 361 and 543 (ng.h/ml)	MULTIPLES: Human dose multiple, based on AUC comparison*	Human dose multiple, corrected for species differences in protein binding**	Human dose multiple, based on mg/m² comparison
4 mkd	females	203	33	0.87	
	males	148	24	0.63	
	combined	168	28	0.74	8x
10 mkd	females	942	155	4.1	
	males	945	156	4.1	
	combined	951	157	4.1	20x
24 mkd	females	10099	1667	44	
	males	5052	834	22	
	combined	6608	1090	29	48x

* Values are based on animal AUC data averaged for days 179, 361 and 543. AUC values are of total parent drug concentrations. There is no evidence for systemic metabolism. Estimated human steady-state AUC is 6.06 ng*h/ml. (range ca. ———). Human data are from postmenopausal women receiving 5mg oral dose daily for approximately 6 months.

** Protein binding: rats 98%, dogs 37%, humans 24%

Tables 8 & 9 display the descriptive statistics of cumulative vertebral fracture incidence over three years by subgroup.

Table 8 Descriptive Statistics of Vertebral Fracture Incidence by Subgroup - RVN

	Placebo				5 mg Risedronate			
Subgroup	n	Patient Years	Pts with Event	%[a]	n	Patient Years	Pts with Event	%[a]
Age								
<65	186	467	19	**12.2%**	221	549	15	**8.5%**
≥65	480	1177	84	**20.9%**	470	1161	62	**16.5%**
Years since menopausal								
≤15 Years	147	378	14	**10.6%**	160	415	11	**8.0%**
>15 Years	518	1264	89	**20.9%**	531	1295	66	**15.9%**
Stratum[b]								
Stratum 1	129	324	11	**9.7%**	130	323	9	**8.8%**
Stratum 2	537	1321	92	**20.6%**	561	1386	68	**15.1%**
Previous OP therapy								
No	545	1349	80	**17.4%**	543	1336	54	**12.6%**
Yes	121	296	23	**23.2%**	148	374	23	**18.8%**
Smoking History								
User	327	781	54	**19.9%**	349	836	43	**15.5%**
Nonuser	339	863	49	**17.1%**	342	874	34	**12.3%**
Lumbar Spine T-Score								
≤-2.5	350	865	57	**19.7%**	347	851	45	**16.4%**
>-2.5	270	670	25	**11.1%**	284	712	12	**5.2%**
Femoral Spine T-Score								
≤-2.5	363	899	81	**25.9%**	399	997	55	**16.8%**
>-2.5	280	691	17	**7.4%**	269	660	18	**8.9%**

[a] Cumulative proportion of patients with incident vertebral fractures based on the Kaplan-Meier estimate of the survival function.

[b] stratum 1=one vertebral fracture + low spinal BMD, stratum 2= ≥2 vertebral fractures at baseline.

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Table 9 Descriptive Statistics of Vertebral Fracture Incidence by Subgroup - RVE

Subgroup	Placebo				5 mg Risedronate			
	n	Patient Years	Pts with Event	%[a]	n	Patient Years	Pts with Event	%[a]
Age								
<65	71	185	13	20.2%	66	182	10	16.1%
≥65	270	662	90	37.8%	268	683	53	23.5%
Stratum[b]								
Stratum 1	51	128	14	31.6%	55	153	4	8.0%
Stratum 2	290	718	89	34.4%	279	712	59	24.8%
Previous OP therapy								
Yes	132	326	45	38.1%	132	350	26	22.7%
No	209	521	58	31.4%	202	515	37	21.2%
Smoking History								
User	125	298	35	33.3%	128	315	30	27.7%
Nonuser	216	549	68	34.5%	206	550	33	18.4%
Lumbar Spine T-Score								
≤-2.5	142	349	33	26.9%	141	370	28	22.8%
>2.5	75	187	14	20.8%	63	169	5	8.8%
Not evaluable	124	311	56	50.0%	130	327	30	27.7%
Femoral Neck T-Score								
≤-2.5	203	502	70	38.7%	204	526	51	28.5%
>2.5	123	309	27	24.6%	114	304	11	11.2%

[a] Cumulative proportion of patients with incident vertebral fractures based on the Kaplan-Meier estimate of the survival function.

[b] years since last menstrual period Stratum 1, ≤15 years, Stratum 2, >15 years

In Study RVN, the difference of vertebral fracture incidence between the placebo group and the 5 mg risedronate group was greater in Stratum 2 (20.6% vs. 15.1%) than in Stratum 1 (9.7% vs. 8.8%). For years since last menstrual period, the treatment effect was greater in patients with > 15 years since menopausal (20.9% vs. 15.9%) than patients with ≤ 15 years since menopausal (10.6 vs. 8.0).

Secondary Efficacy Variables

Spinal Fracture Index (Genant) and Spine Deformity Index (Minne)

The mean change from baseline to endpoint (LOCF) for both Genant's Spinal Fracture Index and Minne's Spine Deformity Index by treatment for the ITT population is displayed in Tables 8 and 9. In Study RVN, the difference in change from baseline at endpoint for Genant's Spinal Fracture Index was statistically significant and the Minne's Spine Deformity Index was not statistically significant between 5 mg group and the placebo group (Table 10). In Study RVE, both the indexes were statistically significant in favor of the 5 mg risedronate (Table 11).

Table 10 Change From Baseline in Genant's Spinal Fracture Index and Minne's Spine Deformity Index by Visit Intent-to-Treat Study RVN

Index	Placebo		2.5 risedronate		5 mg risedronate		p-value*
Spinal Fracture Index (Genant)							
Baseline (N)	814		808		810		
Mean (S.E.)	0.279	(0.0103)	0.332	(0.0119)	0.298	(0.0113)	
Endpoint ** (N)	679		--		698		
Mean Change (S.E.)	0.028	(0.0033)	--		0.018	(0.0024)	0.005
Spine Deformity Index (Minne)							
Baseline (N)	732		722		734		
Mean (S.E.)	1.027	(0.0542)	1.165	(0.0594)	1.165	(0.0617)	
Endpoint ** (N)	588		--		608		
Mean Change (S.E.)	0.166	(0.0322)	--		0.114	(0.0306)	0.15

* P-value for testing the difference between the 5-mg risedronate and placebo groups (ANCOVA).
** Endpoint is the last postbaseline measurement during the treatment period (i.e., through Month 36).

Table 11 Change From Baseline in Genant's Spinal Fracture Index and Minne's Spine Deformity Index by Visit Intent-to-Treat Study RVE

Index	Placebo	2.5 risedronate	5 mg risedronate	p-value
Spinal Fracture Index (Genant)				
Baseline (N)	404	407	406	
Mean (S.E.)	0.456 (0.0170)	0.45 (0.0160)	0.472 (0.0158)	
Endpoint (N)	347	343	346	<0.001
Mean Change (S.E.)	0.057 (0.0069)	0.027 (0.0044)	0.032 (0.0046)	
Spine Deformity Index (Minne)				
Baseline (N)	355	364	354	
Mean (S.E.)	2.298 (0.1124)	2.389 (0.1119)	2.607 (0.1176)	
Endpoint (N)	301	295	296	0.014
Mean Change (S.E.)	0.481 (0.0674)	0.231 (0.0675)	0.275 (0.0604)	

* P-value for testing the difference between the 5-mg risedronate and placebo groups (ANCOVA).
** Endpoint is the last postbaseline measurement during the treatment period (i.e., through Month 36).

Height

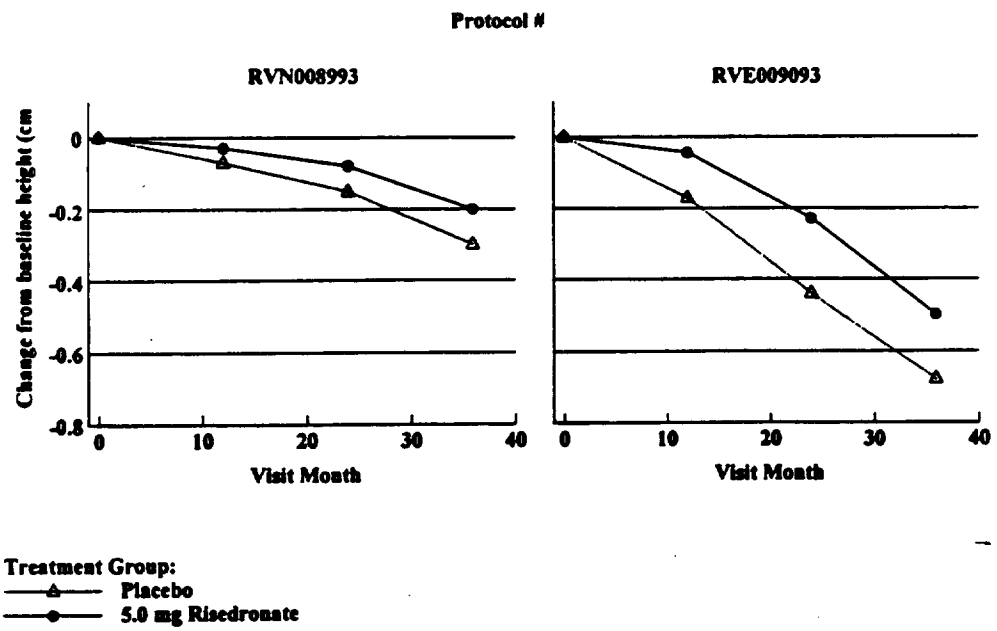
The sponsor used the nonparametric Kruskal-Wallis test for treatment effects since the data did not meet the assumptions of the ANOVA. The median change from baseline in height by treatment for the ITT population is displayed in Table 12. The endpoint analysis showed statistically significant difference between the 5 mg risedronate group and the placebo group for both Studies RVN & RVE. For the observed cases of the ITT population, it was not statistically significant between treatment groups for both of the studies (Table 13 & Figure 2).

Table 12 Change From Baseline in Height (cm) - Intent-to-Treat

		RVN				RVE			
		Placebo	2.5 mg	5.0 mg	p*	Placebo	2.5 mg	5.0 mg	p*
Baseline	N	807	805	804		405	405	406	
	Median	159.27	158.33	158.47		155.6	155.2	155.03	
Month 36	N	448	--	476		224	67	247	
	Median	-0.3	--	-0.2	0.139	-0.68	-0.7	-0.5	0.163
Endpoint	N	692	--	708		344	341	351	
	Median	-0.27	--	-0.14	0.004	-0.565	-0.24	-0.37	0.005

* P-value for testing the difference between the 5 mg-risedronate and placebo groups based on the Kruskal-Wallis test.

Figure 2 Median Change from Baseline over Time



Even with the robust non-parametric test, the observed cases and the endpoint analyses on the ITT population were not consistent in statistical significance. The sponsor also displayed the median rate of change in height per year on endpoint value, which is not a planned secondary efficacy analysis.

Non-vertebral Osteoporosis-Related Fracture Incidence

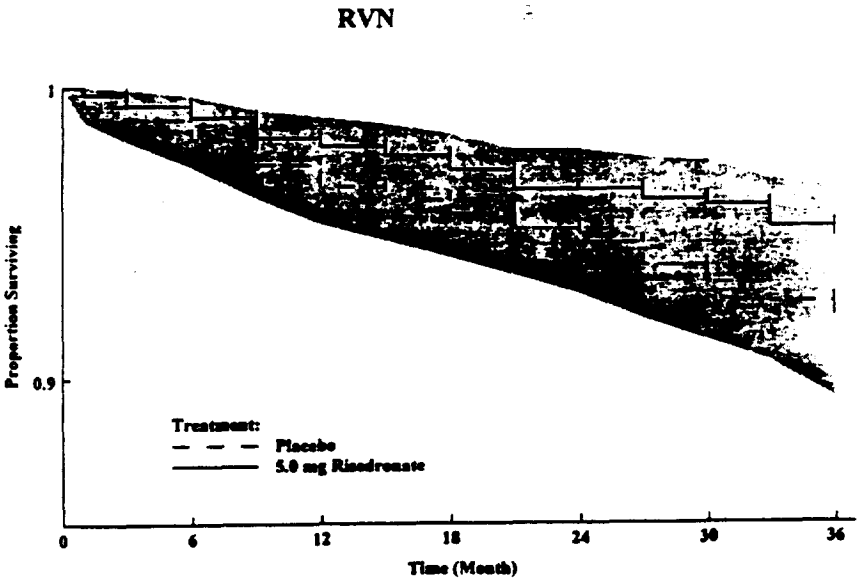
This category involved fractures from the anatomical sites of hip, wrist, humerus, pelvis, clavicle, and leg. For the 3-year duration, the p-values from the log rank test were 0.02 and 0.07 for studies RVN and RVE, respectively (Table 13 & Figure 3).

Table 13 Cumulative non-Vertebral Fracture Incidence

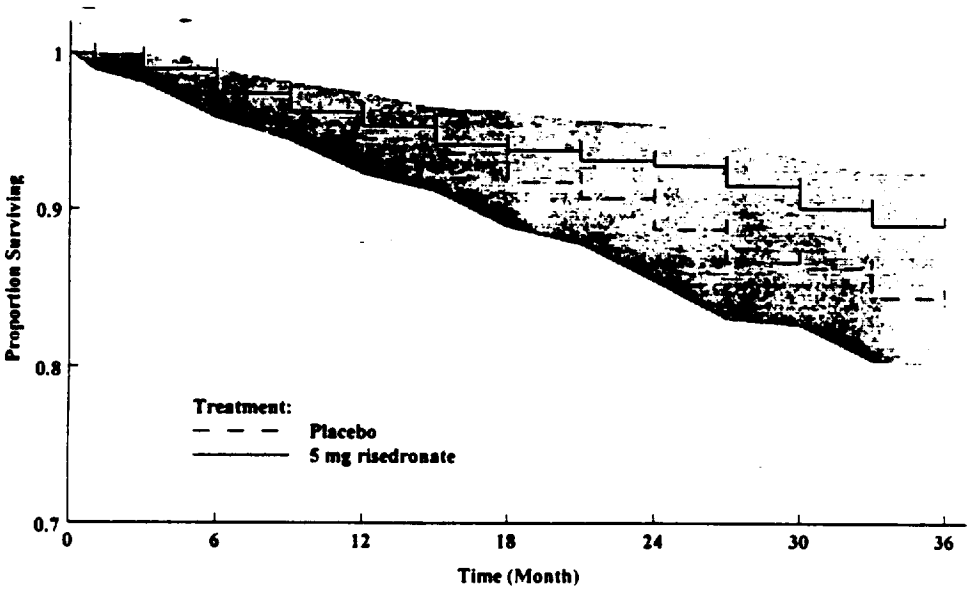
Study	RVN		RVE		
	Placebo	5.0 mg	Placebo	2.5 mg	5.0 mg
n[1]	815	812	406	408	406
Year 0-Year 3					
Patient Years+	1831.75	1877.92	944.58	861.58	963.50
Patients With First Fracture	**52**	**33**	**51**	34	**36**
Percentage[2]	**8.40**	**5.16**	**15.95**	10.59	**10.89**
p-value 5.0 mg vs. Placebo[3]		**0.020**			**0.071**

[1] Number of patients with baseline and at least one non-follow-up visit during the 3-year study.
[2] Based on the Kaplan-Meier estimate of the survival function.
[3] P-value from the log-rank test with pooled investigator group and stratum in the model

Figure 3 Time to First Non-Vertebral Osteoporosis-Related Fracture – ITT



RVE



Labeling Comments:

These comments pertain to the Treatment of Osteoporosis in Postmenopausal Women of the Clinical Studies section.

1. The protocol-specified primary efficacy variable for the study was vertebral fracture incidence (new and worsening) over 3 years of treatment. The label presented the **new** vertebral fractures. The sponsor mentioned that in Europe the Committee for Proprietary Medicinal Products (CPMP) issued a document entitled Note for Guidance on Involutional Osteoporosis in Women (March 1998) which recommended that "The primary variable should be based on patients with new axial or peripheral fractures (not worsening of previous fractures." However, the label should present the primary efficacy results as the pivotal information.

2. In addition to the 3 year results, the one year results were presented with p-values. The one-year new vertebral fracture incidence is not an efficacy variable mentioned in the protocol.

3. The number of patients should be displayed in the figures for the treatment groups.

4. The p values of the secondary efficacy variables should not be displayed.

Conclusion:

For the primary efficacy variable, new and worsening vertebral fracture, the two 3-year studies RVN and RVE showed statistically significant differences in time to the first vertebral deformity fracture in the intent-to-treat population. However, the ITT population included only ~80% of the randomized patients as only patients with known deformity status during the treatment period were in the calculation. At the end of the trial, the sponsor should make every effort to collect the information on deformity status for those patients who withdrew early so that the "ITT" population will be as close to the set of randomized patients as possible. Sensitivity analyses on different populations and utilizing non-time-to-event methodology were consistent with the ITT results. The percentages of vertebral incidence were 13.9% vs. 18.5% in RVN and 21.8% vs. 34.0% in RVE for the 5 mg risedronate-treated patients and placebo-treated patients, respectively. Therefore, it is concluded that 5 mg risedronate was statistically efficacious in the treatment of postmenopausal women with osteoporosis.

/S/

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Concur: Dr. Sahlroot /S/ 2/10/00

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cc:
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