CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020835

MEDICAL REVIEW(S)

March 16, 1998
Memorandum
To: the File NDA 20-835 Actonel Tablets (risedronate sodium)
From: Solomon Sobel M.D Director, Division of Metabolic and Endocrine Drug Products
Subject: Approval of NDA

This NDA is for a bisphosphanate of the pyridinyl class. The requested indication at this time is limited to that of treatment of Paget's Disease of bone.

There were no new issues which arose in respect to the basic requested indication (Paget's disease).
The sponsor had requested a Quality of Life indication in respect to pain attenuation. There was diminution of pain from baseline (information elicited in a multiple domain questionnaire in which pain decrease was the only area of improvement) in the risedronate group when compared to baseline. However, there was no statistical difference to the etidronate comparison group which also had experienced decrease of pain from baseline of a lesser degree. This,among other reasons, made the granting of an indication in respect to pain problematic. (The study was designed to demonstrate the superiority of risedronate to etidronate in Paget's disease. This,indeed, was demonstrated in respect to the decrease in the primary outcome variable of serum alkaline phosphatase (SAP) but not in respect to pain).

The pivotal clinical study was an actively controlled blinded randomized study in which risedronate was compared to etidronate, a bisphosphanate already approved for thew treatment of Paget's disease. There was no placebo control. The protocol stated that a positive result would be an outcome which would show that risedronate was superior to etidronate in the treatment of Paget's Disease . The primary endpoint was a reduction of serum alkaline phosphatase (SAP).

Risedronate was shown to be superior in regard to the primary efficacy variable (per centage of patients achieving a 75% reduction from baseline of SAP).
Statistical methodology: The null hypothesis of equal percentages in the risedronate and etidronate groups was tested against the alternative hypothesis of unequal mean per centages. The targeted alternative was a difference of 30% or greater in the per centage of patients who achieved a maximum response (i.e a reduction of 75% of baseline SAP).

A second (pivotal) study was an open, dose ranging study comparing the effects on SAP of daily doses of 10,20 and 30 mgm of risedronate. The study was not powered to show differences of SAP response between groups. All groups showed significant reductions from baseline SAP values.

There was also a non-significant trend of SAP response to rising doses of risedronate.
An analysis which used a reponse of 50% reduction in baseline SAP and the number of days required to achieve the 50% reduction gave support to the findings of the etidronate controlled study (the first mentioned of the pivotal studies.) In the 30mg group of the dose ranging study, 85% of patients achieved a reduction of 50% in SAP over the treatment and follow up period as compared to 93% in the etidronate controlled study. Also, the median time to response was 43 days as compared to 59 days in the etidronate controlled study. This shorter time to response in the dose ranging study may be partially attributed to the more frequent observations of AP levels resulting in a more accurate estimation.

The overall safety profile was comparable to etidronate.

Conclusion:
The approval of risedronate rests on 2 studies. Both studies demonstrated significant reductions in alkaline phosphatase.
One study was controlled by an active control (etidronate).
The other study which was controlled, to a degree, by dose response methodology showed a significant reduction from baseline SAP values in all dose groups. Because of the relatively small number of subjects in each group it was not possible to show statistical significance in the SAP response between groups.
However, the trend of response was evident.
Also, the 30 mg segment of this study supported the findings of the etidronate controlled study.
The Division judges that the evidence that the sponsor has presented for safety and efficacy of risedronate is adequate for the approval for the indication of the treatment of Paget's disease.

/S/
Solomon Sobel

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cc: Arch NDA 20-835
HFD-510
HFD-510/SSobel/GTrundle/RHedin

NDA 20835
27 February, 1998
Risedronate (Actonel)
Team Leader's Review on Approvable NDA
Proctor and Gamble

Risedronate is a **bisphosphonate.** The proposed indication is for Paget's Disease of bone. It is the fifth bisphosphonate to be approved for this indication, after etidronate, pamidronate, alendronate, and tiludronate. It is expected that application will also be made soon for post-menopausal osteoporosis.

Two **controlled trials** are submitted for efficacy in reducing Serum alkaline phosphatase in Paget's Disease of Bone. One of them (RPD001694) was randomized, double-blind and compared to etidronate. Although etidronate is approved for this same indication and sponsored by the same company, it was not intended as an active-control equivalency trial but was **to show superiority** of 30 mg/day risedronate to 400 mg/day etidronate.

To be eligible for entry into the study, patients **had serum alkaline phosphatase** (SAP) $\geq$ 2x ULN and skeletal pagetic lesions confirmed by xray or scintigraphy. 62 patients were randomized to receive risedronate and etidronate placebo and 61 patients to etidronate and risedronate placebo for the first 60 days. One patient assigned to risedronate received no drug and was not included in analyses. Etidronate and etidronate placebo were continued to 180 days, but risedronate and risedronate placebo were discontinued at 60 days. Observation of patients for efficacy continued to day 360, and then patients who chose to remain in the study were further observed for another 180 days to day 540.

Efficacy endpoints were Total SAP, bone specific SAP and QOL assessed by Short Form Health Survey, and the primary efficacy analysis was the percent of patients who achieved $\geq$75% decrease from baseline in SAP excess over normal. It was hypothesized that there would be a difference of between the two drugs.

56 and 57 patients **completed** the treatment period in the risedronate and etidronate groups, and 53 and 47 completed the follow-up. Four and five **discontinued** during treatment or follow-up **due to adverse events;** four and nine **discontinued voluntarily or were lost to follow-up.** Three patients were **excluded** from the ITT analyses because of taking or wishing to take other medications or due to blurred vision; they had no baseline data or did not take

study medication. Three other patients were excluded from the evaluable population because of taking tiludronate, prior colon or bladder cancer, or poor compliance. Baseline characteristics were similar across groups.

Twenty percent of patients (n=60) **achieved 75% reduction in SAP excess** in etidronate and 85% in risedronate groups in both treatment and follow-up periods. **Time to maximum response** was >360 days on etidronate and 67 days on risedronate. 51 and 12 patients obtained this reduction in risedronate and etidronate treatment periods and 51 and 14 in both treatment and follow-up periods. A 50% or greater increase in SAP from the nadir and SAP >2 x ULN was considered a relapse. There were no **relapses** during the treatment periods; altogether, 3.3% of risedronate and 15% of the etidronate group relapsed.

QOL assessment measured 8 health scales. Only the pain scale scores showed improvement, and the improvement was compared to baseline. There was no significant difference between etidronate and risedronate.

Safety assessment indicates more adverse events and more serious adverse events (15 vs 9) in risedronate patients. There were 19 vs 16 **upper GI events** in 12 vs 12 patients. 3 vs 2 of the upper GI events were moderate to severe. No gastritis is reported for etidronate and 1 for risedronate. Abdominal pain is reported 7 and 5 times, none of them severe. **Non-vertebral fractures** occurred in (4)6.6% of risedronate patients compared to (1)1.6% in etidronate patients. All but one in the right femur were attributed to trauma. There were some modest decreases in hemoglobin, phosphorus.

The **second trial** (88040) was a phase 2 study in 62 patients at 3 doses (17. 18, 15 patients at 10, 20, and 30mg) given for 28 days. Endpoint was at least a 30% reduction from baseline in SAP excess, and at least a 50% reduction in hydroxyproline. Also, residronate was considered effective if >50% of patients achieved at least a 30% decrease in SAP excess. Three of the 62 patients discontinued due to hepatic dysfunction during treatment (20mg), diagnosis of biclonal gammopathy (20mg), and ineligible (10mg). 9, 12, and 12 responded at 10, 20, and 30 mg; one relapsed at 10 mg. Mean days to maximum change 64, 75 and 78 for 10, 20, and 30 mg. No new safety concerns were determined.

There were several **uncontrolled trials**: 91007 tested three different dosage forms on pain and found inconsistent results; 90009 tested the time course of SAP and

hydroxyproline (HP) changes, 90003 tested time course of SAP and HP changes; 91000 tested bone turnover changes compared to markers and pain. The uncontrolled studies (about 330 patients in 4 studies) contribute very little to the evaluation of risedronate but are supportive. Doses were generally 30 mg and duration of treatment 84 days.

There is a slight and not significant difference in number of patients who suffered non-vertebral fractures in the controlled study 001694: 6.6 vs 1.6%. One 001694 patient had 2 traumatic fractures in one day. In the combined, controlled, and non-controlled studies, there were 10 fractures, counting 5 in the risedronate group in this study, one in the etidronate group and 4 in the uncontrolled studies. We have very little information on non-vertebral fractures in bisphosphonate-treated patients, in spite of the large FIT study using alendronate so we should note carefully the results obtained in all available studies.

The pain data derived from the QOL instrument and based on baseline comparison cannot be allowed in the package insert.

The information is meager, but it appears adequate to conclude that this drug is safe and effective for treatment of Paget's Disease of Bone.

Recommendation: Approval

/S/

Gloria Trobendle

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1. **Title and General Information**

1.1 Medical Officer's Review

1.1.1 **N.A.#** 20-835

1.1.2 **Submission Date:** March 31,1997.

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1.1.3 **Filing Date:** May 31,1997.

1.1.4 **Review Completed:** December 12, 1997

1.1.5 **DSI Inspection report (NAI) on Dr. Paul D. Miller's site (Protocol # RPD-001694) dated 6/27/97. Inspection report on Dr. Will G. Ryan's site submitted on 7/1/97.**

1.2 Drug Name:

1.2.1 Generic name: Risedronate sodium

1.2.2 Chemical name: [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium

1.2.3 Trade name: Actonel

1.3 Sponsor:

Procter and Gamble Pharmaceuticals
11450 Grooms Road
Cincinnati, Ohio 45242

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1.4 Pharmacologic Category:

Inhibits osteoclast-mediated bone resorption.

1.5 Proposed Indications and Usage:

"ACTONEL treatment is indicated for patients with Paget's disease of bone having alkaline phosphatase levels at least two times the upper limit of normal, or those nonresponsive to previous anti-pagetic therapy, or those who are symptomatic, or those at risk for future complications from their disease to:

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· **induce remission (normalization of serum alkaline phosphatase),**
· **reduce disease activity and/or,**
· **reduce associated pagetic pain."**

1.6 Dosage form and Route of ADMINISTRATION:

Supplied as 30-mg film-coated tablets for p.o. use.

1.7 NDA Drug Classification: 1 S

1.8 Important Related Drugs:

- Etidronate (1-hydroxyethylidene) bisphosphonate
- Alendronate (4-amino-1-hydroxybutylidene) bisphosphonate
- Pamidronate (3-amino-1-hydroxypropylidene) bisphosphonate
- Clodronate (dichloromethylene) bisphosphonate
- Tiludronate ([4-chlorophenyl)thio]-methylene) bisphosphonate

Except for clodronate, all of these bisphosphonates are approved for the treatment of Paget's disease of bone.

1.9 Related Reviews:

Chemistry
Pharmacology
Biopharmaceutics
Statistics

2. Table of Contents

3. Material reviewed

See Table 1 for information.

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Table 1. Material reviewed with volume numbers.

Topics	Volume Numbers
Overview and NDA Contents	1.001
Nonclinical Pharmacology and Toxicology	1.002, 1.008-1.010
Human pK and Bioavailability Summary	1.002, 1.0661.066-1.098
Clinical Data Section	
a. Clinical Pharmacology	1.102-1.115
b. Controlled Trials	1.116-1.133
c. Uncontrolled Trials	1.133-1.156
d.Integrated Summary of Efficacy Data	1.157
e. Integrated Summary of Safety Data	1.158
f. Benefits and Risk ratio	1.161
g. Clinical references	1.161
h. Statistical Overview	1.162-1.1.185
i.Case Report Tabulation	V1.118-1.186,

4. Chemistry/Manufacturing Controls

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See Chemistry review.

5. Animal Pharmacology/Toxicology

Oral administration of risedronate to rats, ferrets, minipigs, and dogs was shown to inhibit osteoclast-mediated bone resorption. These studies are summarized in table 2 (Sponsor's Table in V1.002/p70). The sponsor claims that the results from these studies

provided evidence in support of "risedronate's efficacy and bone safety at a dose equivalent to the Paget's clinical dose of 30 mg orally."

Table 2. Summary of primary studies in animal models.

Summary of Primary Activity Studies			
Study	Animal Model	# of Studies	Parameters
F1,F2,F4B,F5	Young growing rat	4	BMD; histomorphometry
F4A	TPTX rat	1	PTH-induced increase in serum calcium
F3AB, F6, F7AB, F8, F24-F26, F44	OVX rat	10	BMD; histomorphometry; biomechanics; trabecular connectivity;
F9	OVX ferret	1	BMD; histomorphometry; biomechanics
F15	OVX minipig	1	BMD; biomechanics
B16	Intact rats	1	Potential for spontaneous fractures
F10-F14 B17, B19	Intact dogs	6	BMD; histomorphometry; biomechanics; microfractures; spontaneous fractures
TPTX- hypoparathyroidectomized; OVX-ovariectomized; BMD-bone mineral density			

The lowest effective doses (LED, dependent upon duration of exposure) of risedronate for inhibition of osteoclast-mediated resorption are shown below:

Animal Models	Mode of Administration	LED
Growing rat &TPTX rat	S.C. Inj.	0.00015mg/kg/day*
OVX rat	S.C.Inj.	0.000015-0.0015 mg/kg/day**
OVX rat	Oral, gavage	0.008-0.5mg/kg/day‡

* These were short-term studies lasting for 4-7 days. ** In OVX rat studies, risedronate was administered cyclically over 2 weeks to 360 days. ‡ Drug was administered daily for 3-7 days and then no drug for 21 days over a total period of 84 days.

These studies primarily assessed the effects of short-term and long-term continuous or pulse dosing of risedronate on bone turnover, bone growth, and bone density. In OVX rat study, bone mass loss was "completely" prevented and the effect was sustained for "at least" 6 months after completion of risedronate treatment. The results of these studies are likely to be reviewed in depth by the Pharmacology reviewer.

Studies in Beagle dogs were directed to assess the effects of risedronate, daily or cyclic dosing on bone remodeling dynamics, bone densitometry, incidence of micro fractures, and **biomechanical strength**. Sponsor states that in intact rats (at a dose of 4 mg/kg/day for 1 year) and in dogs (at a dose of 2 mg/kg/day for 2 years), risedronate showed no evidence of impaired mineralization or spontaneous fractures (including micro fractures), and increased or maintained biomechanical strength. Comparing the lowest effective dose (0.0015 mg/kg/day) of risedronate for inhibition of resorption to the dose (4 mg/kg/day) at which no impairment of mineralization occurred, the therapeutic index was found to be >3000.

A number of secondary pharmacodynamic studies were also carried out in order to assess the effects of risedronate on tumor-induced hypercalcemia and osteolysis, and

arthritis (spontaneous, or induced by collagen or adjuvant). Summary of these secondary studies are presented in Table 3 (Sponsor's Table in V1.002/p71).

Table 3. Summary of secondary pharmacodynamic studies.

Summary of Studies on Secondary Activity						
Study	Animal	Model	Dose (mg/kg/dose)	Dose Route	Dose Duration	Dose Regimen
Tumor Models						
F19	Rat	Leydig cell tumor	0.0005-0.05	sc	5 days	daily
F17B F17A	Rat	PA-III tumor	0.0005-0.16 0.0005-5.0	sc oral	7, 11, 29 or 30 days 29, 30 or 35 days	daily daily
F20	Rat	Mammary adenocarcinoma	0.15	sc	1 mo	daily
Arthritis Models						
F16B	Mouse	Collagen-induced arthritis	9.9	oral	10 wk	daily
F19	Rat	Adjuvant arthritis	0.025	sc	19 days	daily
F22	Guinea pig	Spontaneous osteoarthritis	0.01	sc	6/12 mo	5 days/wk for 6 wk then 20 days off
F21	Guinea pig	Spontaneous osteoarthritis	0.15	sc	4/6 mo	daily for 2 wk; alternate days

Primarily, risedronate's anti-osteoclast (antiresorptive) action was evaluated for suppression of hypercalcemia and osteolysis in these animal models. Risedronate was reported to suppress tumor-induced hypercalcemia. In arthritis models, the effects of risedronate were equivocal.

Risedronate was tested in combination with some other bone-targeted agents such as estrogen, PTH, fluoride, and indomethacin in both intact and OVX rat studies lasting for 28 days to 15 weeks. Summary of these studies are presented in Table 4 (Sponsor's Table in V1.002/p72).

Table 4. Summary of risedronate studies.

Summary of Studies of Combination Therapies						
Study	Animal	Concomitant Therapy	Concomitant Drug Dose (mg or mg/kg)	Risedronate Dose (mg/kg/dose)		Dose Duration
R25	OVX rat	Estrogen	0.01 or 0.03 mg over 90 days	0.005-0.015	(1 d/2 wk)	6 wk
R24	OVX rat	Estrogen	0.01 or 0.03 mg over 90 days	0.005	(2 d/wk)	5 wk
R26	OVX rat	Estrogen	0.01 or 0.03 mg over 90 days	0.005	(2 d/wk)	12 wk
R5	OVX rat	Estrogen	0.03 mg over 90 days	0.015	(1 d/2 wk)	5 wk estrogen 5 or 10 wk RIS
F7A	OVX rat	PTH	0.09 mg/kg/day, 5 days/wk	0.005	(2 d/wk)	5, 10, 15 wk
R23	Intact rat	Fluoride	0.8 mg/kg/day for 28 days	0.015	(1 d/wk or 1 d/2 wk)	28 days
F19	Intact rat	Indomethacin	0.1 mg/kg/day	0.025	daily	19 days

Note that Study R5 is sequential and no concomitant administration of estrogen and risedronate.
All drugs were given subcutaneously except for fluoride, which was given in the drinking water.
Estrogen was given as slow release implant the released drug at rate of 0.01 or 0.03 mg over 90 days.

The drug was reported to maintain its antiresorptive/bone protective effect in OVX model when administered in combination with estrogen or PTH. In combination with indomethacin, risedronate was reported to exhibit an additive effect on paw edema/inflammation.

The safety of risedronate treatment in relation to neuromuscular, cardiovascular, GI, liver, and kidney function was also tested in a series of invivo and in few invitro experiments. At very high doses mg/kg/day), risedronate was reported to show antidiuretic effect, decreased blood coagulation time, and cardiac contractility. Clinical significance of these findings in the context of treating patients with Paget's disease of bone at the recommended dosage regimen is not clear. There were no significant adverse pharmacological effects on other organ systems tested.

Risedronate was reported to increase gastric acid secretion after oral administration (at a dose of 30 or 60 mg/kg), contrary to its no effect after intravenous dosing (3 mg/kg). The mechanism of this local action of risedronate was not determined.

Repeated dose tox. Studies (≤ 3 months):

Thirteen (8 with oral and 5 with i.v. administration) repeated doses studies were carried out in rats and dogs. In 7 of 13 studies, the no adverse effect levels (NOAEL) for the oral dosing were evaluated. The NOAEL values were reported to vary from study to study because of variations in doses levels. Beside skeletal tissue, liver, kidney, testes, and the stomach were "possibly" affected by subchronic administration of risedronate.

Liver: Risedronate at doses of 32 mg/kg/day or higher caused consistent increases in transaminase levels in 4- and 13-week studies. In 4-week dog study, there were changes in transaminase level, liver weight, and cellular necrosis at a dose of 8 mg/kg/day. In 13-week dog study, there was liver toxicity with secondary hepatoencephalopathy at a dose of 8 mg/kg. Sponsor states that this dose (8 mg/kg for 13 weeks) was equivalent to "34 times the expected steady-state exposure following a human dose of 30 mg" for Paget's disease of bone. No liver toxicity was reported at a dose of 4 mg/kg/day for 13 weeks.

Kidney: Slight polyuria with decreased specific gravity was reported to occur in rat study in a dose range of 0.8-8 mg/kg/day for 4 weeks. Mild renal cortical effect was reported in dog study at a dose of 8 mg/kg/day.

Testis: Both in rat and dog studies testicular toxicity was reported to occur at doses of 8 mg/kg/day or higher for 13 weeks. At these doses, drug-related deaths were reported in both species. Testicular toxicity was seen at doses "equivalent to systemic exposure times the expected steady-state exposure following a human dose of 30 mg (proposed Paget's dose)" In mice risedronate treatment showed no testicular lesions even at high dose (64 mg/kg/day for 20 weeks.

Stomach: The results were equivocal Gastric lesions were reported at a dose of 8 mg/kg/day for 4 weeks in rat study, but 13-week study showed no gastric lesions.

Intravenous Toxicity Studies

The results are summarized below:

Species	Risedronate Dose/ Duration	Reported Toxicity
Dog	1.5 mg/kg/day/14 days	Hepatic toxicity Spermatid maturation blockade Renal cortical necrosis
	0.3 mg/kg/day/14 days	Mild hepatotoxicity
	0.05 mg/kg/day/14 days	No adverse effects on liver

Rat	12.5 mg/kg/2 days	Gastric submucosal edema Renal tubular nephrosis

Repeated Dose Tox. Studies (> 3 Months)

Table 5 presents summary of these tox. Studies (Sponsor's Table in V1.002/p96).

Table 5. Summary of tox. Studies (> 3 months).

Summary of NOAELs From Studies >3 Months With Oral Risedronate

Study	Duration (weeks)	Species	NOAEL (mg/kg/day)	First Toxic Level (mg/kg/day) or: GI	Liver	Testes	Kidney
B14[b]	20	Mouse	ND	16	NTE	NTE	NTE
B15	26	Rat	90	16	32	NTE	NTE
B16[b]	52	Rat	4[a]	NTE	NTE	NTE	NTE
B18	52	Dog	4	8	8	8	8
B19	104	Dog	2[a]	NTE	NTE	NTE	NTE

[a] Highest dose tested was the NOAEL
[b] Non-tumor component of carcinogenicity studies included in this section for chronic toxicology data
[c] Listed in the reports as the 'no toxic effect level'
ND = not determined; this dose-ranging study was to verify that dosages selected for the tumor study were sufficient to induce some toxicity.
NOAEL = no observed adverse effect level
NTE = no toxic effect was observed at any dose level in this study.

These studies (2 rat, 1 mouse, and 2 dog) were carried out fo[illegible] weeks. In these studies, beside bone, the liver, the kidney, the testes, and the GI tract were reported to show toxicity due to chronic administration of risedronate. The results are summarized below:

Species	Risedronate Dose/ Duration	Toxicity
Dog	8 mg/kg/52-Wk*	Increased liver transaminase Liver lesions (hepatocellular degeneration, inflammation) Deaths
		Renal tubular necrosis, capsular cysts
		Testicular tubular degeneration
		Gastric erosion and ulceration
Rat	32 mg/kg/26-Wk 16 mg/kg/26-Wk**	Increased liver transaminase Gastric erosion and ulceration
Mouse	16 mg/kg/20-Wk	Gastric distension

* This dose was reported to be equivalent to 34 times the expected human exposure at a dose of 30 mg/day for Paget's disease of bone. ** Reported to be equivalent to 31 times

the human steady-state exposure at a dose of 30 mg/day for the proposed indication.

Reviewer's comments:

Both in rat and dog studies, risedronate was reported to cause histologic liver and kidney lesions at doses reported to be equivalent to times the expected human steady-state exposure at a dose of 30 mg/day for 2 months. Long-term (> 3 months) oral administration of risedronate in rats, dogs, and mice resulted in gastrointestinal distension, erosion and ulceration. The drug has also been shown to cause testicular adverse histological lesions that may interfere with fertility and reproductive performance. Clinical significance of these adverse events is not clear. In long-term clinical trials with approved bisphosphonates (e.g., etidronate and alendronate), hepatic or renal toxicities were not common events. Oral bisphosphonates are known to cause upper GI adverse events. Although it is unlikely to expect similar adverse events in short-term clinical trials, particular attention has been paid in reviewing clinical safety data for identifying adverse events related to liver, kidney, and testes in pagetic patients.

Toxicokinetic data:

Data from preclinical studies were compared to human pK data in terms multiples of human exposure (at the proposed dosage regimen for pagetic patients). Such a comparison provided an index of safety in humans. The results are summarized in Table 6 (Sponsor Table in V1.002/p100).

Table 6. Multiples of human AUC.

AUC in Animals Expressed as Multiples of Corresponding Human AUC					
Dose (mg/kg/d)	4-Week Study Rat G28	13- Week Study Rat G29	26-Week Study Rat G30	13-Week Study Dog G31	52-Week Study Dog G32
2	0.59	--	--	-	-
4	0.83	3.72	1.91	-	15.3
6	--	--	--	15.2	-
8	2.00	7.0	6.7	33.7	46
12	--	--	--	160	-
16	7.3	62	31.0	-	NS
32	56	652	207	-	NS
64	315	1210	--	-	-

-- = Dose level not used in this study; NS = no sample due to unscheduled deaths

Multiples of human exposure were calculated from AUC obtained on the terminal sampling day in nonclinical toxicity studies, expressed as a ratio to the estimated steady-state AUC from pharmacokinetic studies in humans receiving a 30 mg/kg oral dose (40.9 ng*hr/mL).

Human data were collected from studies involving normal male volunteers who received 30 mg oral dose of risedronate. At the NOAEL in rats, the multiples of exposure ranged from with a duration of dosing from 4 to 26 weeks. At the NOAEL in dogs (4-6 mg/kg), the multiple of exposure was about 15. At the "minimally toxic dose" (8 mg/kg), the relative exposure ranged from . In rats, the following adverse events were reported to occur with risedronate at doses of 32 and 64 mg/kg : deaths, broken/eroded incisors, abnormal respiratory sounds, lower body weights and food intake and "histopathological, hematological, clinical chemistry and organ weight changes." At the highest dose, gastritis, renal tubular necrosis, enteritis, testicular, thymus and prostate gland atrophy and enlargement of thyroid gland were reported. In 26-week rat study, risedronate at all doses caused " hypertrophy of the primary spongiosa of the femur and

sternum and new bone formation in the nasal cavity.." In dogs, risedronate at higher doses (8-32 mg/kg, oral cap.) Resulted in histopathological lesions of liver, testes, kidney, GI toxicity, and changes in clinical chemistry and hematological parameters.

Special Toxicity Studies

GI toxicity was the major focus in 6 of 9 studies (in rats and rabbits) for elucidation of mechanism(s) of risedronate-induced irritation. The effect of intra-articular injection of risedronate was studied in one dog study. The remaining special studies were carried out to investigate the occupational safety (for personnel involved in the manufacture of the).

The results of GI special tox. Studies showed: a) irritation of colonic mucosa from risedronate capsule administration, but not with solution; b) increased gastric acid secretion; and c) concomitant administration of risedronate with NSAID (indomethacin or naproxen) potentiation of gastric damage by drugs.

Repeated intra-articular injections of risedronate (5 injections of 2.5 mg over 2 weeks) resulted in non-septic inflammation and synovial necrosis of the joint.

Reproductive Toxicity Studies

These studies were carried out in rats and rabbits. The NOAELs for F_0 males and F_0 females were 3.2 and 7.1 mg/kg, respectively. Risedronate was not reported to be teratogenic in both rat and rabbit Segment II studies.

Genotoxicity

Sponsor states that the results of seven in vitro and invivo mutagenicity studies showed that risedronate was not genotoxic (see Pharmacology review for details).

Pharmacokinetic Studies

These pK (single and repeated-doses) studies were carried out in mice, rats and dogs. The overall results of these studies showed:

a) Approx. [redacted] of the drug is absorbed with T_{max} of about [redacted]

b) About 60% of absorbed dose is reported to be distributed to bone with low levels in soft tissues. About 90% of drug not bound to bone is excreted in urine in the first 8 hours after administration.

c) Approx. 40% of an absorbed dose is excreted in urine.

d) Half-life in bone (in rats) is > 1 year.

e) The drug is not metabolized and shows no evidence of cytochrome p-450 induction.

f) A steady-state level is achieved "by at least Day 14 in rats and dogs at doses < 8 mg/kg/day..with little or no systemic accumulation."

g) Drug shows a linear kinetics (in rats) at doses up to 8 mg/kg/day. At higher doses the drug shows non-linear kinetics.

6 Clinical Background

6.1 Relevant human experiences:

Published reports on therapeutic uses of risedronate in Paget's disease of bone are very few. Most of the references provided by the sponsor in this NDA are related to approved therapeutic regimens, such as etidronate, pamidronate, alendronate, and calcitonin.

The pharmacological basis for use of bisphosphonates in the treatment of Paget's disease of bone is well documented in the literature. For individual approved bisphosphonates see respective labeling. The relevant abstracts and full reports on clinical experience of risedronate are reviewed here.

A) Zegels et al. Biochemical evidence of antiresorptive effect of risedronate in established osteoporosis (Abstract). Osteoporosis Int. 6 (suppl.1): 249,1996.

Short-term (7-14 days) administration of risedronate (20 mg/day) was reported to cause significant decreases (from baseline) in urinary 2-hour pyridinoline/creatinine and deoxypyridinoline collagen cross links excretion in postmenopausal women over 84 days of trial. Risedronate was reported to be well tolerated in this small study. (**Comments:** Data presented in this abstract support antiresorptive action of risedronate in postmenopausal women with established osteoporosis).

B) McClung et al. Risedronate treatment of postmenopausal women with low bone mass: Preliminary data (Abstract). Osteoporosis Int. 6 (suppl. 1): 257, 1996.

In a large (n=648) multi center controlled prospective trial, oral risedronate was administered at doses of 2.5 or 5 mg/day to postmenopausal women with osteopenia (baseline BMD > 2 SD below peak). All patients received daily supplemental calcium of 1 g (elemental) during the study. The report presents preliminary 1-year data on spine, femoral neck, and femoral trochanter BMD. Preliminary data showed dose dependent increases in BMD of spine and hip. Spinal BMD increased by almost 4% over one year at a dose of 5 mg/day. At the same dose, femoral trochanter BMD increased by about 3.5% over 1-year period. (**Comments:** Risedronate, a third generation bisphosphonate is expected to increase BMD in women at risk of developing postmenopausal osteoporosis. The results tend to be similar to those obtained with alendronate sodium (an approved bisphosphonate for the prevention and treatment of postmenopausal osteoporosis).

C) Taquet et al, Three-year double-blind, placebo-controlled study of risedronate in postmenopausal osteoporosis (Abstract). Osteoporosis Int. 6 (suppl.1): 262, 1996.

Daily or cyclical (2 weeks on, 10 weeks off) administration of risedronate (2.5 mg/day) in postmenopausal women with established osteoporosis, resulted in increased spinal BMD in the active drug groups over a 2-year period. All patients were reported to receive daily supplement calcium of 1 g. Changes in femoral neck and trochanter BMD were equivocal. The results also indicated a trend in decreased incidence of vertebral

fractures. The report indicated no significant differences between different treatment groups with respect to incidence of adverse events.(**Comments:** Contrary to usual early morning dosing of bisphosphonate in empty stomach, risedronate was administered in this study 2 hours before bedtime with no food 2 hours before or after dosing).

D) Ryan and Bekker. Long term follow up in Paget's patients treated with risedronate. (Abstract). JBMR 10 (suppl.1): S502,1995.

A large group (n=162) patients with severe Paget's disease of bone (baseline serum alkaline phosphatase, SAP 3 times the upper limit of normal) received risedronate, 30 mg/day for 84 days. These patients were followed up for additional 112 days. Patients who were partial and/or nonresponders to first cycle of treatment received a second course of treatment. By the end of second cycle of treatment, 53% of patients were reported to achieve normalization of SAP and about 97% of patients showed a decrease in SAP of at least 30%. The results from one study center in which 21 patients were followed up after completion of treatment were also reported. In this center, 6 patients received only one cycle of treatment and 15 were given risedronate for the second time. In 10 of 21 patients (48%) SAP decreased to within normal limit by day 196 of the second cycle of treatment. Some patients were followed up for up to 19 months after completion of first cycle of treatment and 3 patients continued to show a decrease in SAP during the extended follow up period. (**Comments**: The report showed good biochemical improvement with risedronate treatment at a dose of 30 mg/day for 84 to 168 days in patients with severe Paget's disease of bone).

E) Langdahl et al. Histomorphometry from a three year risedronate bone loss prevention study. JBMR 10 suppl. 1): S199, 1995.

Iliac crest bone biopsy after double tetracycline labeling was performed at baseline and 1 year after risedronate treatment in a three-year controlled study involving early postmenopausal subjects. Patients were randomly assigned to receive placebo, risedronate 5 mg daily, or cyclically (2 weeks risedronate, 2 weeks placebo).The following histomorphometric parameters were evaluated for safety purpose) activation frequency ($year^{-1}$), ii) mineral apposition rate (μm/day), iii) mineralized surface (%),iv) osteoid thickness (μm), v)mineralization lag time (median, days), vi)erosion depth (μm), vii) wall thickness (μm), and viii) bone balance (μm). The primary efficacy endpoint of the study was change in spinal BMD from baseline at Month 24.

The results showed decreased activation frequency, mineralization surface, and osteoid thickness in risedronate groups at Year 1.Mineralization lag time increased in risedronate 5 mg (continuous group). Changes in erosion depth and wall thickness were minimal and inconsistent with respect to risedronate dosage regimens. Bone balance data showed negative values in all treatment groups at Year 1. Sponsor claims that one-year treatment (continuous or cyclical) showed no evidence of osteomalacia. (**Comments**: Although presented data showed no obvious evidence of osteomalacia, one cannot draw any conclusion about the long-term effect of risedronate. Since these patients need to be treated for indefinite period. The reviewer does not agree with the sponsor's conclusion that risedronate prevented worsening of the negative bone balance at the BMU level. This issue is relevant to long-term use of risedronate in osteopenic/osteoporotic patient population).

F) Ettinger et al. A pilot three-year study of risedronate in women with breast cancer and chemotherapy-induced menopause. JBMR 10 (suppl.1) S198, 1995.

In this controlled prospective trial, 38 patients with artificial menopause due to chemotherapy for breast cancer were randomized to receive placebo or risedronate 10 or 20 mg/day cyclically (2 weeks active drug, 10 weeks off) for one year (4 cycles of treatment).The primary efficacy endpoint of the study was the percent change in BMD of spine from baseline. Safety and tolerance of risedronate were also evaluated. About half of the patient population opted for a second year of treatment. The results showed variable increases in BMD (determined by QCT) at Year 1 and Year 2. There were no differences between placebo and risedronate groups with respect to incidence of serious adverse events and gastrointestinal adverse events.(Comments: Data from this controlled small study seem to provide some evidence of efficacy and safety of risedronate).

G) Delmas et al. Intermittent risedronate prevents bone loss in women with artificial menopause induced by chemotherapy of breast cancer. JBMR

Cyclical administration of risedronate (30 mg/day for 2 weeks, 10 weeks off) for 2 years resulted in slight increase in lumbar spine BMD compared to loss in BMD in the placebo group. At the femoral trochanter and Ward's triangle, BMD increased in the risedronate group. The drug was reported to be well tolerated by this patient population.

H) Smith et al. Bone marker changes in risedronate treated postmenopausal women (Abstract). JBMR 10 (suppl.1):S351, 1995.

In a small pilot study, early postmenopausal women (n=11) were given risedronate (p.o.) at a dose of 30 mg/day for 14 days. These subjects were followed up for up to 85 days. Bone formation markers such as bone specific alkaline phosphatase and procollagen C-terminal peptide (CICP) decreased (< 11%) after 2 weeks of treatment. Resorption markers, deoxypyridinoline, N-telopeptide, and C-telopeptide significantly decreased early on with risedronate treatment and remained suppressed up until Day 43. On Day 85, all resorption markers tended to return towards baseline and decreases were no longer significant. Only CICP was reported to remain depressed (-21%) at Day 85. (**Comments:** The effect of short-term risedronate therapy on bone formation markers is minimal in this pilot study and the clinical significance of this change is difficult to interpret,. Changes in bone resorption markers are similar to those reported in the literature with approved bisphosphonates for use in the management of postmenopausal osteoporosis. After about 10 weeks resorption markers returned to baseline).

I) Mortensen et al. Prevention of early postmenopausal bone loss by risedronate: A two year study (Abstract). JBMR 10 (suppl.1): S140,1995.

In this controlled study, early postmenopausal women (n=111) with normal bone mass were randomly assigned to receive placebo, or risedronate 5 mg/day continuously or 2 weeks on, 2 weeks placebo) for 24 months. Risedronate treatment prevented vertebral bone mass loss when given cyclically, but increased BMD about 2% in the risedronate continuous group at Month 24. The placebo group showed about 4% decrease in spinal BMD at the end of the study. Trochanteric BMD showed similar changes in three

treatment groups. There were no differences between three treatment groups with respect to incidence of serious adverse events, dropouts due to adverse events, and fractures.

J) Ward et al. Single dose risedronate (pyrydinyl-bisphosphonate) does not induce acute phase reaction in healthy subjects (Abstract). JBMR 11(suppl. 1): S346, 1996.

Both pamidronate and alendronate (amino-alkyl bisphosphonates) are known to cause acute phase reactions (APR), such as fever, myalgia, leukopenia, elevated-reactive protein, and decreased serum zinc levels. Sixty-one men and 6 women were randomly assigned to one of three doses of risedronate (2.5, 5.0, or 30 mg). The following parameters were monitored at 2,4,24 and 48 hours post dosing: oral temperature, WBC, lymphocytes and neutrophils, C-reactive protein, and serum zinc. Except for slight shift in WBC and differentials, the other parameters did not show any change suggesting acute phase reactions. Sponsor has concluded that unlike amino-bisphosphonates (e.g., alendronate and pamidronate), risedronate does not cause APR. (**Comments:** In the literature amino-bisphosphonates are reported to exhibit APR at a dose of 10 mg (i.v.). The mechanism for APR is not clear, but effects are dose-dependent, with maximum expression within 28-36 hours after i.v. dosing, and disappeared 2-3 days later despite continued treatment. The response has been shown to be due release of interleukin-1, by macrophages. IL-1 interacts with hepatocytes to induce synthesis of acute-phase proteins including C-reactive protein. It has been suggested that bisphosphonates which reside in bone induces IL-1 production through macrophage-derived osteoclasts. The APR to nonamino-bisphosphonates such as risedronate remains to be confirmed by large clinical trials).

K) Mitchell et al. The effect of dosing regimen on the pharmacokinetics of risedronate. (Abstract). JBMR 11 (suppl.1): S 347, 1996.

In normal healthy subjects, the rate and extent of absorption of risedronate (30 mg p.o.) were studied after its administration following four different dosing schedules: a) 4 hours before meal, b) 1 hour before breakfast, c) 0.5 hour before breakfast, and d) 2 hours after dinner. Except for after dinner group, subjects for all other groups were fasted for 10 hours prior to dosing. Serum and urine samples were collected over a period of 168 hours for monitoring the following pK parameters: area under the serum concentration-time curve (AUC), cumulative urinary excretion of risedronate (A_e) maximum serum concentration (C_{max}), and time C_{max} occurs (t_{max}). There were no differences in AUC and Ae between 2 hours after dinner group and 0.5 hour before breakfast group. One or four hours before meal dosing resulted in significantly higher extent of absorption of risedronate. Risedronate given 0.5 to 4 hours before a meal showed higher C_{max} values compared to 2 hours after dinner dosing. (**Comments**: In the proposed labeling, sponsor recommends that risedronate should be taken "at least 30 minutes before the first food or at least 2 hours after the last food of the day." The results of this study showed that C_{max} is about one-third of that achieved with 0.5 hour before breakfast dosing, 2.68 vs 0.97 ng/ml. The results indicate a possible interference with the absorption of drug due to the presence of residual food. Data from clinical pK and efficacy trials are likely to provide additional information on these dosing issues).

L) Kanis et al. Treatment of Paget's disease with new bisphosphonates. In: Paget's

Disease of Bone: Clinical Assessment, Present and Future Therapy, Proc.Sympos. On the Treatment of Paget's Disease of Bone, October 1989, New York. Ed. F.R. Singer and S. Wallach, Elsevier, New York, p. 112-134, 1991.

This report reviews the pharmacokinetc, pharmacodynamic, and clinical effects of new bisphosphonates including clodronate, tiludronate, alendronate, dimethylaminopropylidene bisphosphonate, aminohexane bisphosphonate, and aminobutane bisphosphonate.

Etidronate is the first bisphosphonate approved for the treatment of Paget's disease of bone. At the recommended dose (5 mg/kg/day for 3-6 months) etidronate was reported to show variable therapeutic response and at a higher dose (e.g., 20 mg/kg/day) it impaired mineralization. This led to great interest in developing a bisphosphonate drug with less effect than etidronate on mineralization of bone.

All bisphosphonates share the same chemical backbone structure, namely a P-C-P bond. Though the final common pathway of their pharmacological action is to inhibit osteoclast-mediated bone resorption, the precise cellular mechanism of action on bone turnover is not clear and seems to vary with different bisphosphonates. It is known that in experimental systems there are large differences between bisphosphonates with respect to inhibitory action on bone resorption. However, their effects on human remodeling of bone appear to be quite similar. Thus, for the treatment of Paget's disease of bone, various bisphosphonates share more of their similarities with respect to the pharmacokinetics and clinical effects than their differences in potency.

Similarities and differences in pharmacokinetics :

- Intestinal absorption of bisphosphonates varies between

- Because of their strong affinity for the bone, they disappear from the circulation rapidly.

- "They are thought not to be metabolized."

- In normal individuals, about 75% of absorbed drug is excreted in the urine unchanged and the rest is taken up by the bone.

- Skeletal uptake of bisphosphonates by the pagetic patients is highly variable, but seems to be dependent on blood flow and the rate of bone remodeling.

- In Paget's disease of bone, scintigraphy provides a sensitive method for examining the extent of skeletal involvement. Bisphosphonates are selectively taken up by the sites of disease activity.

- With a fixed dose of bisphosphonate, there is a possibility of overloading skeletal sites in patients with less extensive disease activity.

Effects on bone:

- Bisphosphonate-induced suppression of bone resorption can be measured by

monitoring changes in biochemical markers of bone resorption, studying bone histology and tracer kinetics.

- With intravenous administration of bisphosphonate, decrease in urinary excretion of hydroxyproline (OHPr) can be detected within days. Decrease in OHPr is dose-dependent with a half-time of several days.

- Response of serum alkaline ohosphatase (SAP) to bisphosphonate is quite similar to OHPr, but lags behind that of OHPr.

- Compared to calcitonin, the onset of decrease in OHPr level is relatively slow (several hours vs several days).Thus the major effect of bisphosphonates may be to inhibit recruitment of osteoclasts, rather than a direct inhibition of osteoclasts within the resorption pits.

- Since coupling of resorption and formation remains intact in Paget's disease of bone, inhibition of bone formation follows inhibition of resorption. This can be detected either by bone biopsy or by monitoring biochemical markers of bone turnover.

-Decrease in bone turnover due to bisphosphonate therapy is associated with decrease in blood flow to the bone. Histologically, woven bone structure reverts back to normal lamellar pattern as a result of treatment with bisphosphonate. Suppression of disease activity may result in radiographic and/or scintigraphic improvement of pagetic lesions with decrease in temperature over affected long bones.

- Secondary biochemical effects of bisphosphonate therapy in the early phase, include decrease in serum calcium (due to reduction in net efflux of from the bone) and rise in serum PTH level. Hypocalcemic condition is then corrected by increase synthesis of 1,25 $(OH)_2$ D_3 and increased intestinal absorption of calcium.

- These effects of bisphosphonates on calcium metabolism represent homeostatic responses to therapy rather than side effects.

APPEARS THIS WAY
ON ORIGINAL

Clodronate:

Clodronate has been investigated in several trials in varying doses from 400 mg to 3.2 g daily orally. Clodronate 1600 daily for 3 to 6 months appears to be "very effective regimen" for the treatment of Paget's disease of bone. Biochemical suppression (decreased urinary OHPr and SAP) of disease activity has been reported to be associated with improved bone scan and clinical benefits. Treatment with clodronate (1600 mg/day) for 1 month appears to suppress disease activity to the same extent as achieved after 3 to 6 months of treatment. The duration of treatment response may be shorter, particularly with i.v. administration of clodronate (300 mg daily for 5 days).

Side effects of clodronate include dose-dependent GI intolerance with oral administration and transient proteinuria after i.v. administration. The differences between clodronate and etidronate therapy in Paget's disease of bone are summarized in next table (Table 7).

Table 7. Comparison clodronate and etidronate treatment regimens in Paget's disease of bone.

Drug	Daily Dose Mg/kg(Dura-tion-Mo)	N=	Responders %	Normali-zation, %	Relap. Free %	
					1 Yr	2 Yr
Etidronate	5-10 (6)	24	71	65	61	15
	20 (1)	19	95	57	62	29
	20 (6)	41	95	59	51	20
Clodronate	800 (6)	18	89	69	66	37
	1600 (6)	45	100	60	90	60
	1600 (1)	20	90	44	64	27

Tiludronate, alendronate, dimethyl APD, and aminohexane bisphosphonate:

Tiludronate at doses of 200 to 400 mg/day seems to be less effective than clodronate in suppressing Paget's disease. The degree of efficacy seems to be similar to that of calcitonin. Amino bisphosphonates have been shown to have a higher potency in Paget's disease of bone. With respect to biochemical suppression of disease activity, the duration of remission appears to be less prolonged after short treatment. The duration of remission depends on the degree of suppression resulting from initial treatment. Patients who achieve normalization of SAP are likely to manifest longer periods of remission. Clodronate and amino bisphosphonates have been reported to cause marked suppression of disease process with prolonged treatment effects.

Clinical effects of treatment with bisphosphonates:

Pain

Pain relief appears to be achieved following treatment with bisphosphonates. In most studies, about 80% of patients treated with bisphosphonates are reported to experience improvement in bone pain. Improvement in bone pain may not be evident until several months after initiation of treatment. Probably relief in bone pain coincides with decrease in blood flow. This seems to indicate a vascular basis for pagetic bone pain. There are still some uncertainties about the role of osteoarthritis in the causation of bone pain in pagetic patients.

Bone quality, enlargement, and deformity

Paget's disease of bone results in formation of woven bone. Bisphosphonate therapy is associated with resumption of lamellar bone (normal bone) formation with adequate mineralization. Continued lamellar bone formation due to bisphosphonate therapy may cause gradual improvement "of bony enlargement and deformity." Pamidronate has been shown to improve radiographic improvements; reduction in bone size, widening of medullary cavity, improved corticomedullary differentiation, uniform cortical density, and

cessation of progress of the resorption front. Treatment with bisphosphonates has been shown to decrease in skull or facial volume and restoration of a more normal shape by sequential stereo photography.

Fracture:

There is no evidence that bisphosphonate therapy could change the natural history of fissure fractures in pagetic patients. However, there are some evidence in support of normal rates of fracture healing in pagetic patients.

Neurologic syndromes:

Effective treatment with bisphosphonates (clodronate data to support) may results in improvements in spinal neurological syndromes. The rate of neurological improvement is rapid, occurring within days or weeks after initiation of treatment.

Sarcoma

There is no evidence to indicate that bisphosphonate treatment alters the natural history "established sarcoma."

Cardiac output

With extensive involvement of skeletal system, cardiac output is markedly increased. A decrease in vascularity with bisphosphonate may lower the cardiac output.

The report summarizes the indications for bisphosphonates therapy in Paget's disease of bone:

Indications	**Evidence of Efficacy**
a. **Long-term suppression of disease activity**	
Neurologic syndromes	
Vascular steal	Yes, rapid improvement
Cord Compression	Yes, slow improvement
Root Compression	Yes, slow improvement
Deafness, tinnitus	Rarely improve
- **Skeletal deformity** (skull and wt. bearing)	Likely
- **Healing of fissure fractures**	Not likely
- **High-output cardiac failure**	Yes
- **Reduced risk of fractures**	Likely but unproven

b. **Short-term treatment**

Bone pain	
Before orthopedic surgery	
(To decrease bone vascularity)	Bone blood flow decreases
Fracture healing	No evidence
Sarcoma	No evidence

c. **Relapse** Yes

Comments: This review article dealt mostly with the clinical experiences about clodronate and etidronate in the treatment of Paget's disease of bone. Clodronate is not an approved drug for Paget's disease of bone in the U.S. Etidronate, pamidronate, alendronate, and tiludronate are all approved for this indication in the U.S.A. and their package inserts are fully informative with respect to their safety and efficacy in the treatment of Paget's disease of bone.

6.2 Information from related NDAs

INDs:

NDAs (all approved):

I. Etidronate disodium (Didronel) tablets (NDA 17-831- sponsored by P&G).

ii. Pamidronate disodium for injection (Aredia) (NDA 20-036- sponsored by Ciba-Geigy).

iii. Alendronate sodium (Fosamax) tablets (NDA 20-560- sponsored by Merck & CO, INC.).

iv. Tiludronate disodium (Skelid) tablets (NDA 20-707- sponsored by Sanofi Winthrop).

v. Salmon calcitonin (Calcimar) injection (NDA 17-497- sponsored by R-PR).

Package insert of each of these products contains relevant information regarding their use in the treatment of Paget's disease of bone.

6.3 Foreign experience

Sponsor states that risedronate has not been submitted or approved for marketing in any other country.

6.4 Human pharmacology and pharmacokinetics:

Pharmacology

Risedronate belongs to the class of geminal bisphosphonates with characteristic P-C-P bond. The P-C-P bond of all bisphosphonates is reported to be relatively stable to enzymatic hydrolysis. The side chains of the parent compound may be metabolized. Like other bisphosphonates, physicochemical effects of risedronate include binding to the surface of calcium phosphate by chemisorption, inhibition of precipitation of calcium phosphate, delaying the aggregation of apatite crystals into larger clusters, and inhibition of dissolution of these crystals. In rat assay method, risedronate has been reported to have antiresorptive activity 5,000 times higher than etidronate.

The mechanism of cell-mediated effects of bisphosphonates (including risedronate) is not clear, but seems to include effects on osteoclast differentiation, recruitment, and activity. The ability of bisphosphonates to inhibit bone formation varies widely between bisphosphonates. The results of preclinical studies in rats (4 mg/kg/day for 1 year)and dogs (2 mg/kg/day for 2 years) showed no evidence of impairment of mineralization and

biomechanical strength.

Risedronate is a cyclic geminal bisphosphonate with a nitrogen atom in the ring and has been shown to inhibit bone resorption. The ranking and relative potencies of various bisphosphonates as determined in rats are very similar to that in humans. Human pharmacology of bisphosphonates is well documented in the literature and it could be reasonably assumed that the overall human pharmacology profile of risedronate is similar to that of other approved drugs of this class of compounds.

The side effects of approved bisphosphonates (etidronate, pamidronate inj., alendronate, and tiludronate) in the treatment of Paget's disease of bone are well documented in the package insert of each drug. Gastrointestinal side effects (e.g., abdominal pain, diarrhea, nausea, vomiting, dysphagia, odynophagia, esophagitis) are common with oral formulation of bisphosphonates. Asymptomatic hypocalcemia and hyper-phosphatemia/hypophosphatemia may occur during treatment with bisphosphonates. Severe hypocalcemia has been reported to occur with concomitant administration of aminoglycoside and bisphosphonates. Acute-phase reactions (fever, lymphopenia and increased C-reactive protein) may occur with parenteral use of bisphosphonates and oral aminobisphosphonates. A few cases of leukemia were reported with clodronate therapy, but a direct causal relationship between clodronate and leukemia was not established. Acute renal failure has been reported with rapid intravenous injection of bisphosphonates (etidronate, clodronate, pamidronate). Rare hypersensitivity reactions and skin rashes to bisphosphonates have also been reported in some cases.

Clinical pharmacokinetics

Clinical pharmacokinetic studies included its metabolism, pK profile after single and multiple i.v. and oral dosing, and the influence of food, renal function impairment, aging, and gender differences. In early pK studies, kinetic properties were studied by collecting urine samples and there was no assay method available for the determination of serum or plasma levels. With the development of plasma or serum assay method, the recent pK studies utilized both urine and serum data. These studies will be reviewed critically by the Biopharm reviewer. This reviewer will only summarize the results and conclusions.

Metabolism [invitro studies using liver slices from the livers of humans, dogs, and rats #995.23.00-AE(44357)]- Sponsor states that no in vivo metabolism study was carried out in humans. When incubated with human urine over 24 hours, there was no degradation of risedronate observed. Similarly, invitro studies with liver slices, plasma, serum and fecal flora from humans showed no metabolism of risedronate.

In healthy subjects, after a single i.v. injection of risedronate. , of the dose was reported to be excreted in the urine within 24 hours and about 85% of the dose was recovered in the urine over 28 days. It appears that **about 14% of the administered dose was incorporated into bone.** With multiple i.v. dosing (0.25 mg/day-0.5 mg/day for 7 days), urinary excretion of risedronate

Oral bioavailability of risedronate was 0.65% with a T_{max} of approx 1 hour. The drug was absorbed from the entire upper gastrointestinal tract and the extent of absorption was not influenced by the rate of drug delivery. The rate and extent of absorption of risedronate

are similar after administration of a single dose (40 mg in 30 mL water) into the stomach, duodenum, and terminal ileum (Study #91013-995.86.51-0912).The C_{max} and AUC of risedronate increased proportionally from single oral doses of 2.5 to 30 mg. The terminal half-life was calculated to be 220 hours. Oral multiple dosing (up to 14 days) studies showed a 2-3-fold increase in the accumulation of the drug in the body (based on cumulative urinary excretion). At steady state, the mean AUC was estimated to be 40.9 ng.h/mL.

Influence of food (Study # RRF008593)

Phase II clinical trials were carried out with risedronate administered generally **2 hours after dinner and** Phase III studies were carried out with risedronate administration **0.5 to 1 hour before breakfast**. There were no significant differences between two dosing schedules (after dinner and 0.5 hour before breakfast) with respect to the extent of absorption (AUC, Ae). However, the rate of absorption (Cmax) was about 2-fold increased when risedronate was administered before breakfast. Both the rate and extent of absorption of risedronate increased (3.3 and 1.4-fold, respectively) when risedronate was administered 1 hour before breakfast compared to 2 hours after dinner. Administration of food 0.5 hour after administration of an oral dosage formulation of risedronate resulted in marked decrease in the absorption of risedronate as determined by the Ae (cumulative amount of drug excreted in urine). There was a 40% reduction in Ae of , and a decrease in the median Ae of risedronate. The results indicate greater risedronate-food interaction of due to delay in dissolution of the dosage form.

Influence of renal function (Study # RR1013294)

There was good correlation between renal function and clearance of risedronate. Renal clearance of risedronate was decreased by about 77% when creatine clearance decreased from . The sponsor suggests that in patients with severely impaired renal function (creatinine clearance < 20 mL/min), the dose of risedronate should be decreased by 50% or the interval between doses should be doubled.

Influence of age

The pK profile of risedronate in older (aged with normal renal function) and younger (aged) subjects was similar. Older subjects with "normal renal function" may not require dosage adjustment.

Influence of gender

There were no consistent significant differences between normal healthy men and women with respect to changes in kinetic parameters after administration of 30 mg of risedronate 4, 1, and 0.5 hour before a meal and 2 hours after dinner.

Plasma protein binding [Study # 995.69.00-AF (43965)]

Risedronate has been reported to be highly protein bound (93%) at a concentration of At a very high concentration, saturation of proteins (other than plasma albumin) may occur, resulting in nonlinearity in protein binding (Biopharm reviewer may have additional comments on this phenomenon).

Summary of plasma protein binding of risedronate:

Concentrations (μg/mL)	% risedronate Binding
0.01	93.7 ± 0.56
0.05	90.3 ± 3.01
0.25	95.0 ± 0.61
1.0	83.6 ± 4.46
10.0	67.6 ± 4.31

6.5 Background information (meetings and commitments)- Information provided under this subsection is copied from the NDA (vol. 1.162, p. 22).

"On 15 June 1994, Procter and Gamble informed the FDA that although they would remain the sponsor for would assume responsibility for all activities related to the conduct of the RPD-001694 clinical trial. Specifically, would perform specified clinical research activities in accordance with the transfer of obligations, such as ensuring adequacy of clinical sites and investigators, ensuring compliance with informed consent and the IRB approval processes, ensuring periodic on-site visits, reviewing, encoding, and computer entry of clinical data, and final report generation.

In a meeting with members of the Division of Metabolism and Endocrine Drug Products on 26 March 1996, the Division accepted serum alkaline phosphatase (AP) as the primary measure of efficacy in all Paget's disease clinical trials with risedronate. In addition, the Division accepted Procter and Gamble's phase II dose-comparison study (88040) and phase III active-control study (RPD-001694) as adequate and well-controlled investigations which can provide the primary basis of determining substantial evidence of effectiveness.

6.6 Proposed Direction for Use

" The recommended treatment regimen is 30 mg daily for 2 months.

Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse has occurred, or if treatment fails to normalize serum alkaline phosphatase. For retreatment, the dose and duration of therapy are the same as for initial treatment. There are no data available on more than one course of treatment.

ACTONEL should be taken at least 30 minutes before the first food or at least 2 hours after the last food of the day. In order to facilitate delivery to the stomach, patients should take ACTONEL while in an upright position with a full glass (6 to 8 oz) of plain water and should avoid lying down for 10 minutes after taking the medication. Patients with Paget's disease should receive supplemental calcium and vitamin D if dietary intake is inadequate (see PRECAUTIONS, General). Calcium may interfere with the absorption of ACTONEL and should be taken at different time of the day as with food. For patients with severe renal impairment (creatinine clearance < 20 mL/min), a dosage adjustment (dosing every other day) should be considered with appropriate clinical monitoring."

Reviewer's Comments:

7. Clinical Data Sources

7.1 Study Type and Design/Patient Enumeration, Demographics, Extent of Exposure

Table 8. Summary of study categories (pK, controlled and uncontrolled). (Sponsor's Table 1, vol.1.002, p 183)

Table 1

Study Categorization

Study No.	Dose Tolerance	Primary Pharmaco-dynamics	Special Studies	Pharmaco-kinetics	"Controlled Studies" Section of NDA	"Uncontrolled Studies" Section of NDA
87093	X*			X		
88020	X*			X		
90011	X*			X		
88082	X*			X		
88040	X				X*	
88008/11	X*					
90009		X				X*
91007		X				X*
92024			X*			

*Primary category for this study

Four studies (88008/11, 88040, 91007, and 90009) were carried out in patients with "biologically active" Paget's disease of bone. In these studies patients had SAP values ≥ 3 x times upper limit of normal (ULN). The remaining studies (mainly for pK) were carried out in normal volunteers.

Study 90009 had pagetic patients with marked increase in SAP (≥9 x ULN) and had failed to respond to previous pagetic treatment or experienced a relapse.

Table 9. Summary of patient enumeration, demographics, and duration of treatment.

Total number of subjects: 351

Male- 241
Female- 110

Age: years

Dose of risedronate :

Oral- 0.25-30 mg daily
I.V.- 0.1--0.5 mg

Duration of treatment: 1 to 84 days

Non-treatment follow-up period: 1-112 days

Duration of **retreatment** 28 to 84 days

Non-treatment follow-up period 1-112 days

Table 10. Summary of Phase II and Phase III trials (Sponsor's Table in vol.1.002/p228).

Panel 2
Select Design Characteristics of the Phase II/III Studies Included in the Paget's NDA

Study No. (Investigator)	Entry Criteria	No. of Patients/ Treatment	Age Range	Gender	Race	Frequency of Dosing	Duration of Drug Exposure
Controlled Studies							
RPD-001694 (Paul D. Miller, M.D.)	AP ≥ 2x ULN	61 / 400 mg Didronel® 62 / 30 mg Risedronate		85 Male 38 Female	Caucasian 113 Other 10	Daily	Risedronate 60 days Didronel® 180 days
88040 (Jacques P. Brown, M.D.)	AP ≥ 3x ULN	20 / 10 mg 21 / 20 mg 21 / 30 mg Risedronate		35 Male 27 Female	Caucasian 61 Other 1	Daily	28 days
Uncontrolled Studies							
91007 (Ethel S. Siris, M.D.)	AP ≥ 3x ULN	54/Capsules 53 /Tablets 55/Beads 30 mg Risedronate		102 Male 60 Female	Caucasian 150 Other 12	Daily	84 days
90009 (Frederick R. Singer, M.D.)	AP ≥ 9x ULN	13 / 30 mg Risedronate		8 Male 5 Female	Caucasian 8 Other 5	Daily	56 days
90003 (Ethel S. Siris, M.D.)	AP ≥ 3x ULN	73 / 20 mg Risedronate		45 Male 28 Female	Caucasian 72 Other 1	Daily	28, 56, or 84 days
91020 (David Hosking, M.D.)	AP ≥ 3x ULN	20 / 30 mg Risedronate		12 Male 8 Female	Caucasian 19 Other 1	Daily	84 days

AP = serum alkaline phosphatase.

This table includes additional controlled and uncontrolled trials (RPD-001694, 91007, and 91020) are not listed in Table 6. A total of 390 patients received risedronate 10, 20, or 30 mg daily) for 28,56, or 84 days. Fifty-eight patients were retreated (one course) for similar period of time (28-84 days). The study RPD-001694 was an active-controlled trial in which one of two groups received etidronate for 180 days.

Reviewer's comments: Sponsor has carried out adequate and well designed studies in support of demonstrating the efficacy and safety of risedronate for the treatment of Paget's disease of bone. At this time four bisphosphonates (pamidronate i.v. and oral etidronate, alendronate, tiludronate) are approved for the same indication. During the

process of development of risedronate, sponsor discussed the study design, endpoints, and results of these studies periodically with the Agency. **The primary efficacy endpoint of these studies was the "reduction in excess serum alkaline phosphatase at specified time points during the treatment period and the nontreatment follow-up period."** Sponsor states that the purpose of this adjustment was to combine SAP data from centers with different laboratory normal range.

7.2 Post-Marketing Experience

The drug has not been marketed in any other country.

7.3 Literature

Selected references cited in clinical section:

1.Adami et al : The acute phase response after bisphosphonate administration. Calcif. Tissue Int. 41: 326, 1987.

Acute-phase response (APR) characterized by transient, hyperpyrexia, lymphopenia, and a decrease in serum zinc level is known to occur in patients with infectious and inflammatory diseases. Intravenous administration of aminiobisphosphonates to patients with metabolic bone diseases (never been treated with bisphosphonate) were reported to induce APR with a concomitant rise in C-reactive protein. APR was maximally expressed within 28-36 hours of administration and lasted for 2-3 days despite continued bisphosphonate therapy. APR has been shown to be dose dependent and non-aminobisphosphonate like clodronate, was found to be devoid of APR even at very high dose (1 g per day i.v.). Desensitization phenomenon has been reported to occur following pretreatment with even non-aminobisphosphonates. This study examined the relationship between APR characteristics and bone resorption during bisphosphonate therapy in patients with metabolic bone diseases other than Paget's disease of bone. The results suggest an interaction between bisphosphonates and "macrophages-like" cells (macrophage-derived osteoclasts) in the skeleton that results in an increased release of IL-1 and APR.

2. Cantrill JA and Anderson DC: Treatment of Paget's disease of bone. Clin. Endocrinol. 32:507, 1990.

A review article on the therapeutic role of calcitonin and bisphosphonates has been discussed. The authors have concluded that calcitonin therapy is "expensive, inconvenient, produces an unacceptable incidence of side-effects and rarely produces the desired biochemical and clinical response."

With regard to bisphosphonates for the treatment of Paget's disease of bone, only etidronate (oral) was available for this indication at the time of this report and several other bisphosphonates were being investigated. Therapeutic effects of approved and investigational bisphosphonates (including i.v. pamidronate, APD) were discussed. In addition to clinical and biochemical improvement, APD treatment was reported to induce healing of lytic pagetic lesions (radiologically determined). APD was also reported to cause restoration of lamellar bone formation.

3. Reginster et al: The effect of nasal hCT on bone turnover in Paget's disease of bone-implications for the treatment of other metabolic bone diseases. Br. J. Rheumatol. 31(1): 35, 1992.

Long-term Intramuscular or s.c. administration of salmon calcitonin usually results in decreased activity. The suggested mechanisms for this decreased activity are: a) production of specific anti-sCT antibodies, and b) desensitization of sCT receptors. Patients who become resistant to sCT have reported to respond well to human calcitonin (hCT). The purpose of this study was to determine the biological effects of intranasal administration of hCT in a group of pagetic patients for 6 months.

In this open study, 30 patients (17 M and 13 F, aged 51-85 years) with moderate to severe Paget's disease of bone received 2 mg of synthetic hCT daily for 6 months. SAP and urinary OHPr/Cr ratio were reported to decrease significantly from the first month of treatment and at the end of 6 months SAP and urinary OHPr/Cr ratio were decreased by about 30% and 22%, respectively. Some patients failed to show any decrease in these biochemical parameters. After reaching the maximum decrease in 3-4 months no additional effect was noted with further treatment. Intra nasal hCT was reported to be well tolerated. (**Comments** - The overall biological effects of intranasal CT (salmon or human) in Paget's disease of bone are conflicting in the literature reports).

4. Siris et al: Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. JCEM 81(3): 961,1996.

The efficacy, safety, and tolerability of alendronate were compared with etidronate in a group of 89 patients with clinically active Paget's disease of bone. The study was randomized and double-blind. Baseline SAP was required to be at least 2 x the ULN if they were never treated with bisphosphonates or plicamycin; or at least 4 x the ULN if they had received such treatment in the past. Forty-two and 47 patients were randomly assigned to ALN (40 mg/day) and etidronate (400 mg/day) groups. All patients received calcium (450 mg as carbonate) containing vitamin D (400 IU) supplement. Treatment lasted for 6 months.

Baseline characteristics of patients of the two treatment groups were similar. The primary efficacy endpoint of the study was the percent change in SAP from baseline to Months 6. Additionally, the prevalence of responders (with normalization of SAP or $\geq$ 60% reduction in SAP), and the percent change in urinary OHPr were also evaluated. Improvement in pain score and radiologic improvement in skeletal lesions were noted in subsets of study population.

The results showed greater decreases in SAP in the ALN group compared to the etidronate group (79% vs 44%). Similarly U/OHPr decreased by 75% in the ALN group as opposed to 51% in the etidronate group ($p < 0.01$). About 63.4% of patients in the ALN group achieved normalization of SAP compared to 17% in the etidronate group. There were no significant differences between two treatment groups with respect to changes in pain or functional impairment scores. Radiologic improvement (based on scoring system) was reported in about 32.4% of ALN-treated patients compared to 26.5% of patients in the etidronate group. Worsening of osteolytic lesions was reported in about 8.8% of ALN-treated patients compared to 14.7% of patients in the etidronate

group.

The frequency of drug-related AS (including upper GI events) was similar in the two treatment groups. The upper GI AS included abdominal distension, abd. pain, acid regurgitation, dyspepsia, melena, and nausea. None of these AS was considered serious by the sponsor. One patient in the etidronate group was reported to develop osteomalacia (determined by bone biopsy). There was no qualitative histomorphometric abnormalities reported in the ALN group.

The overall results of this comparative trial showed ALN as a safe and effective treatment regimen for Paget's disease of bone with some advantage over etidronate.

Comments:. From the efficacy standpoint, treatment with ALN (compared with etidronate) achieved greater decreases in elevated levels of SAP and U/OHPr and with regard to percent of patients with normalization of SAP after therapy. With regard to safety, the frequency of drug-related AS was similar for two drugs. Both drugs are now approved for the treatment of Paget's disease of bone. In recent years the Agency approved pamidronate (i.v.), alendronate, and tiludronate for the treatment of Paget's disease of bone. Package insert of the individual product provides adequate information on the efficacy and safety of the drug for critical comparison.

8 Clinical Studies

CONTROLLED TRIALS

8.1 Sponsor's Trial # RPD-001694

8.1.1 *Objective/Rationale*

The primary objective of the study was to compare the efficacy of risedronate (30 mg/day) with that of etidronate (400 mg/day) in patients with Paget's disease of bone.

8.1.2 *Design*

A randomized, double-blind, active-controlled, multicenter study.

8.1.3 *Protocol*

8.1.3.1 *Population, procedure*

Male or female patients with Paget's disease of bone were recruited for the study, Table 11 summarizes treatment groups and study periods.

Table 11. Treatment groups and study periods (Sponsor's Table in vol.1.2.116, p. 33).

Panel 1 Treatment Groups and Study Periods of Study RPD-001694				
	Treatment Phase		Follow-up Period	
Group*	Days 1 - 60	Days 61 - 180	Days 181 - 360	Days 361 - 540
I (n = 62)	Risedronate 30 mg Didronel placebo	Didronel placebo	No study drug Follow-up	No study drug Extended follow-up
II (n = 61)	Didronel 400 mg Risedronate placebo	Didronel 400 mg	No study drug Follow-up	No study drug Extended follow-up
Data Included in This Report				Data to be supplemented
* Number of patients randomized.				

The first patient was enrolled in July 1994 and the last patient was reported to complete therapy in October 1995. Patients were initially followed up for 360 days (until April 1996) and thereafter for an extended period (up to Day 540). Patients were stratified according to past etidronate treatment.

During the course of the study protocol was revised to exclude patients who received etidronate within 6 months of initiation of test drug therapy.

Patients who met the following key inclusion criteria were enrolled into the study:

• SAP level $\geq$ 2 x the ULN range.

• Radiographically or scintigraphically confirmed skeletal pagetic lesions.

The important exclusion criteria included:

• Presence of clinically significant organic disease

• History of hyper or hypothyroid disease, or osteomalacia within one year prior to enrollment.

• Use of one of the following drugs within 3 months prior to initiation of test drug.:

- Anabolic steroids

- Oral or parenteral glucocorticoids

• Use of the following drugs within one month prior to starting the test drug:

- Calcitonin
-Vitamin D (>1000 units /day)
-Calcitriol > 1.5 µg/week)

• Use of one of the following within 6 months prior to initiation of test drug therapy:

- Any bisphosphonate
- Fluoride
-Plicamycin
-Gallium nitrate
-Parathyroid hormone

There were 12 centers and in each center, the patients were randomized into two treatment groups using a randomization code "with a block size of two within each stratum." This way a reasonable balance was achieved between two treatment groups.

Patients in Group I received one 30 mg risedronate tablet and one etidronate 400 mg placebo tablet on Days 1 to 60. Then one etidronate 400 mg placebo on Days 61 to 180. Patients in Group II received on risedronate placebo tablet and one 400 mg etidronate tablet on Days 1 to 60. Thereafter, one etidronate 400 mg daily from Day 61 to 160. During the entire follow-up period (Days 181-540 days) no study drug was administered.

Patients were instructed to take **risedronate tablet daily on empty stomach (30 to 60 minutes before breakfast) with 8 ounces of water and not to lie down for one hour after taking the tablet. Didronel tablet or placebo was taken on an empty stomach (2 hours before a meal) with water, coffee, tea, or juice.**

Compliance with dosing regimen was checked by the return of all unused tablets.

Patients on chronic concomitant medications were maintained on stable regimen. All concomitant medications were recorded on Case report Form (CRF).

A patient was considered as a dropout if one voluntarily withdrew from the study or violated exclusion criteria. Patients who were dropped from the study were not replaced.

8.1.3.2 Endpoints

For efficacy-

a. Total SAP
b. Bone specific SAP and urinary deoxypyridinoline /creatinine
c. Quality of life (QOL) assessment by the Short Form Health Survey (SF-36)

SAP and bone turnover markers will be determined at baseline and thereafter every month during the 6-month treatment period) and every 2 months during the follow-up phase (up to Month 12).

Bodily pain and Physical Functioning are parts of QOL assessment by SF-36.

Clinical AE assessment will be done every month during the course of the study including the follow-up period.

For safety-

a Incidence of clinical adverse events (AS). Adverse event is defined as any unexpected clinical experience (related or unrelated to the test drugs) occurring to a patients during therapy. Severity of AS will be graded by the investigator and the outcome to noted. Death, life-threatening, permanent disability, or an event that required hospitalization was to be considered as serious AE. An endoscopy was required (but not mandatory) if any of the following symptoms occurred:

- heartburn
- mid-sternal pain
- esophageal burning
- epigastric pain
- pain while swallowing (odynophagia)
- difficulty in swallowing (dysphagia)

b. Laboratory (hematology, serum and urine chemistries) evaluations:

Hematology: red blood cell count (RBC), hemoglobin, hematocrit, platelet count, white blood cell count (WBC), differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, metamyelocytes, myelocytes, blast cells, atypical lymphocytes)

Serum Chemistry: glucose, creatinine, calcium, phosphorus, total bilirubin, albumin, alkaline phosphatase, alanine aminotransferase (ALT, SGPT), aspartate transaminase (AST, SGOT), gamma glutamyl transpeptidase (GGTP), sodium, potassium, chloride, HCO_3, magnesium, pregnancy test (β-HCG), $25(OH)D_3$ (baseline only)

Urine Dipstick: protein, RBCs, WBCs. (If the dipstick was positive for these, the urine sample would undergo urine microscopy for an estimated count, per high power field (HPF), of RBCs and WBCs.)

All laboratory determinations were performed every month initially and thereafter, every 2 months during the follow-up phase of the study.

c. Slit-lamp eye examination at baseline and at Months 2 and 5.

Clinical adverse events and laboratory data were reviewed by an independent Safety Advisory Group (SAG) periodically, in order to provide an "objective view of the safety profile of risedronate on an ongoing basis."The members of SAG had no connection with the clinical trial.

8.1.3.3 Statistical considerations

Statistical analyses were performed for:

a. Comparing the demographic and baseline measurements of two treatment groups.

b. Efficacy analyses

c. Safety evaluations

In performing statistical analyses for efficacy, the following definitions were used (copied from NDA vol. 1.116, p.48):

Total serum AP excess: the difference between the measured level and the midpoint of the normal range for serum AP at baseline

· Maximum response: a reduction of 75% from baseline in serum AP excess

· No response (resistant): a reduction of < 10% from baseline in serum AP excess

· Maximum change: the greatest change (reduction or increase) between the baseline total serum AP level and the total serum AP level at any visit throughout Day 360

· Maximum reduction: the reduction from baseline in total serum AP level to the lowest total serum AP level achieved throughout Day 360 for patients who showed a reduction. In this study, some Didronel patients encountered an increase in serum AP. In order to have a meaningful time-to-event analysis, the term "maximum reduction" was used in addition to the "maximum change" as specified in the protocol

· Time to maximum reduction: the time between onset of treatment and the maximum reduction

Relapse: an increase of 50% or more in serum AP above the lowest level of total serum AP after a minimum response (³ 10% reduction) and total serum AP > 2 times the upper limit of the normal range any time prior to or on Day 360

· Time to relapse: the time between the lowest level of total serum AP and the first relapse

· Time to maximum response: the time between onset of treatment and the first time when maximum response is achieved (a reduction of ³ 75% from baseline in serum AP excess)

- Normalization: the total serum AP falls within the normal range
- Time to normalization: the time between onset of treatment and the first time when serum AP is normalized

Though all of these definitions were primarily related to SAP, definitions for max. reduction, time to max. reduction, normalization and time to normalization were also applied to skeletal AP (Ostase)

The last measurement prior to test drug administration was considered as the "baseline" value. Two "endpoints" were examined in the study

"Endpoint 1" was referred to the last measurement taken during the first 6 months of treatment and the "Endpoint 2" was referred to the last measurement during the entire study (regardless of the period it was in)

Example:

If a patient dropped out of the study at Day 120, measurements obtained at this point were used as Endpoint 1 and Endpoint 2 values. If the dropout occurred at day 360, measurements taken at this point was Endpoint 2 and Endpoint 1 values were those taken at Day 180.

For statistical analyses of data, the patient populations were divided into:

a. Randomized population- included all randomized patients irrespective of the fact that they received any test drug.

b. Intent-to-treat population: Included patients who had taken at least one dose of study medication, had at least one baseline and one postbaseline SAP determinations.

c. Safety population: Included patients who had taken at least one dose of study medication.

d. Evaluable patient population: Included patients I) who received at least 80% of the study medication during the first 180 days or until discontinuation from the study, ii) did not violate any inclusion or exclusion criteria; and iii) met all protocol visit schedules between Days 30 and 360 within ± 7 days. About of patients in either treatment group had one or more visits outside ± 7 days. Therefore, the window was extended to ± 14 days.

The Intent-to-treat was the primary target population for efficacy evaluation based on both primary and secondary endpoints.

Additionally, "endpoint" analysis was performed in order to study the effect of dropouts on the efficacy results. Both "endpoint 1" and "endpoint 2" values were used.

Routine statistical parameters were used in the final analyses of efficacy and

safety data **(see Statistical review for additional comments).**

For statistical analysis of primary efficacy endpoint (SAP), percent change from baseline relative to total SAP excess was calculated using the following equation:

Percent change from baseline relative to total serum AP excess = $[(V_i - V_b)/(V_b - M_b)]$ 100%, where:
V_i = value at visit I
V_b = value at baseline
M_b = midpoint of the normal range
$(V_b - M_b)$ = baseline AP excess

The primary efficacy parameter was the percent of patients who achieved ≥75% decrease (from baseline) in SAP excess (i.e., a maximum response). Treatment-by-covariates (age, sex, race, and smoking status) analysis was performed in order to study the impact of these covariates on the treatment effect. For each study center, the "number and percentage of patients"with maximum response were evaluated for each center. Treatment-by-investigator interaction was not performed, because of small number of patients at the majority of the centers.

With regard to statistical analyses of secondary efficacy measurements (serum skeletal alk. phosphatase, urinary DPYR, QOL), routine statistical methods were applied.

Analysis of safety data

All patients who entered into the study and received at least one dose of the test drug were included in the safety analysis. Routine statistical methods were applied in analyzing safety data that included extent of exposure and compliance, adverse events (AS), vital signs, physical examination results, and clinical laboratory parameters.

The following additions and/or deviations were made in statistical plans:

- for testing the treatment-by-investigator interaction, those investigators who had fewer than two patients in each treatment groups were pooled.

- From QOL questionnaire the changes in the intensity of bodily pain to test drugs was evaluated.

- Subgroup analysis based on previous (preentry) Didronel therapy and the extent of baseline elevation in the total SAP (X ULN).

- The number and % of patients with maximum response in total SAP were evaluated for each of the study center.

Sample size calculation

The null hypothesis of equal percentages of patients with maximum

response was tested against an alternate hypothesis. The alternate hypothesis was that there would a difference of between two groups with respect to percentages of patients with maximum response (40% risedronate vs 10% Didronel). With an estimated dropout rate of 20%, 60 patients per treatment group (48 completed/group) would provide 90% power for detection of above-mentioned difference between two groups at a significance level of 0.05. Statistical reviewer may have comments on sample size calculation method.

8.1.4 **Results**

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8.1.4.1 Patient Disposition, comparability

Patient disposition (accountability) is presented in Table 12.

Table 12. Summarizes patient disposition including discontinuations (Sponsor's Table in vol.1.116, p.59).

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Panel 5
Patient Accountability
Study RPS-003594

	400 mg Didronel n (%)	30 mg Risedronate n (%)
Randomized	61	62
Received Study Drug	61	61
Completed Treatment Period	57 (93.4)	56 (91.8)
Discontinued Treatment Period	4 (6.6)	5 (8.2)
Adverse Event	4 (6.6)	3 (4.9)
Voluntary Withdrawal	0	2 (3.3)
Completed Follow-up Period	47 (77.0)	53 (86.9)
Discontinued Follow-up Period	10 (16.4)	3 (4.9)
Adverse Event	1 (1.6)	1 (1.6)
Voluntary Withdrawal	8 (13.1)	2 (3.3)
Lost to Follow-Up	1 (1.6)	0

The number of patients who received study drug in each treatment group was used as the basis for the calculation of percentages (61 Didronel; 61 risedronate).
Corresponding data can be found in Table 7; Appendix 6.1, Listing 8.

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After enrollment, one patient in the risedronate group was withdrawn by the investigator for protocol violation. This patients took Florical (calcium carbonate and sodium fluoride). Of nine patients who discontinued during the course of the treatment period, seven were due to AS and 2 voluntarily withdrew from the study. During the follow-up period (Days 240-360), a total of 13 patients discontinued the study ;10 voluntarily withdrew, two due to AS, and 1 was lost to follow-up. Two patients were unblinded both in the Didronel group); because one was not responding to treatment and the other experienced AE (blurred vision).

Appendix 10 (vol. 1.124, pp. 1-12) provides narrative description of deaths, patient withdrawals due to AS and patients with serious AS. Review of individual cases showed no direct causal relationship between

deaths and AS and the test drugs. Few cases of upper GI AS were possibly related to the test drugs. Both risedronate and etidronate are known to cause upper GI complaints.

Reviewer's comments: Though slightly higher percentage of patients in the risedronate group was reported to discontinue treatment during the treatment period (8.2% vs 6.6), higher discontinuations were due to voluntary withdrawal rather than to AS. Two treatment groups did not show significant differences with respect to patient accountability.

Demographics and baseline characteristics

Table 13 summarizes the demographics.

Table 13 (Sponsor's Table in vol.1.116/p60) presents demographics of study population.

Panel 6

Demographics of the Study Population

Study RPD-001694

	400 mg Didronel (N = 61)	30 mg Risedronate (N = 62)	Overall (N = 123)	P-Value
Age (years)				
18-49	4 (6.6)	4 (6.5)	8 (6.5)	
50-64	15 (24.6)	24 (38.7)	39 (31.7)	
65-85	42 (68.9)	34 (54.8)	76 (61.8)	
N	61	62	123	
Mean (S.E.)	67.1 (1.1)	65.5 (1.3)	66.8 (0.9)	0.710
Median	68.0	66.5	68.0	
Minimum, Maximum				
Sex				
Male	40 (65.6)	45 (72.6)	85 (69.1)	0.400
Female	21 (34.4)	17 (27.4)	38 (30.9)	
Race				
Caucasian	57 (93.4)	56 (90.3)	113 (91.9)	0.717
Black	3 (4.9)	5 (8.1)	8 (6.5)	
Oriental/Asian	1 (1.6)	0 (0)	1 (0.8)	
Hispanic	0 (0)	1 (1.6)	1 (0.8)	
Weight (kg)				
N	59	61	120	
Mean (S.E.)	73.5 (1.6)	78.6 (2.1)	76.1 (1.4)	0.054
Median	73.6	77.5	75.5	
Minimum, Maximum				
Height (cm)				
N	59	61	120	
Mean (S.E.)	165.9 (1.2)	167.6 (1.2)	166.8 (0.9)	0.353
Median	167.3	168.7	168.1	
Minimum, Maximum				
Previous Didronel Uses				
Yes	37 (60.7)	37 (59.7)	74 (60.2)	N/A
No	24 (39.3)	25 (40.3)	49 (39.8)	
Previous Paget's Treatment				
Yes	45 (73.8)	43 (69.4)	88 (71.5)	0.587
No	16 (26.2)	19 (30.6)	35 (28.5)	

N/A = not applicable, expected to be equal by study design.
Corresponding data can be found in Table 2.1; Appendix 6.1, Listing 1.1.

There were no significant differences between the two treatment groups with respect to demographic characteristics. Table 14 presents baseline SAP and bone turnover markers of the two treatment groups.

Table 14 (Sponsor's Table in vol.1.116, p.61) shows baseline SAP and bone turnover marker values.

Panel 7

Serum Alkaline Phosphatase and Bone Turnover Marker Values at Baseline[a]

Study RPD-001694

Parameter	400 mg Didronel (N = 61)	30 mg Risedronate (N = 62)
Serum Alkaline Phosphatase (U/L)	496.2 ± 42.4	481.6 ± 49.2
Serum Alkaline Phosphatase Excess (U/L)	421.5 ± 42.5	407.4 ± 49.2
Skeletal Alkaline Phosphatase (Ostase) (µg/L)	151.2 ± 14.7	150.8 ± 22.0
Urinary Deoxypyridinoline/Creatinine (pmol/µmol)	60.0 ± 4.4	50.2 ± 5.3
Serum 25-hydroxy-vitamin D_3 (ng/mL)	25.6 ± 1.4	26.0 ± 1.1

[a] Values shown are mean ± S.E.
Corresponding data can be found in Table 4.

This panel provides the following information on the severity of pagetic bones of the study population:

a. Number of patients with mild to moderate pagetic lesions (SAP $\geq$ - < 3 x ULN)= 59 (22 Didronel, 37 Risedronate).

b. Number of patients with severe pagetic lesions (SAP $\geq$ 3 to < 7 x ULN)=49 (33 Didronel, 16 Risedronate).

c. Number of patients with markedly severe pagetic lesions (SAP > 7 x ULN)= 15 (6 Didronel, 9 Risedronate).

With regard to previous treatments for Paget's disease of bone within 10 years prior to study drugs, of patients in either treatment group had received previous Didronel therapy. In addition, about 10% of patients in both groups received previous Aredia (I.V.) therapy. There was no significant differences between the two treatment groups with respect to prior treatment with approved or other investigational drugs for Paget's disease of bone. Seventeen (12 in the Didronel group and 5 in the risedronate group) were reported to be nonresponders (< 30% reduction in SAP) to previous therapy, and 37 patients were considered as responders. Sponsor was unable to collect adequate information on response to previous treatment for the rest of patients. (**Comments:** Didronel group appears to include slightly more patients who were considered nonresponders to previous Didronel treatment. This minor difference in the distribution of patients in two treatment groups may have

some impact on the final outcome of the trial).

Concomitant medications

About 97% of patients in the two treatment groups received concomitant medications. The most common concomitant medications included analgesics, vitamins, anti-inflammatory and antirheumatic, antacids, antiflatulents and antiulcer drugs. The two treatment groups had similar distribution of patients with same concomitant medication(s).

Compliance:

The overall compliance to the dosing schedule (% of patients) was 97.8% for Didronel and 99.3% for the risedronate group.

Exposure to study drugs:

The cumulative dose of study drug (mg) is shown below:

	Didronel 400m/day	Risedronate 30 mg/day
Total number of Patients	61	61
Mean	69652.50	1810.30
S.E.	1614.97	38.00
Median	72000.00	1830.00
Minimum		
Maximum		

The cumulative dose of study drugs was close to actual values based on dosing schedules of the study protocol, i.e., Didronel for 6 months and risedronate for 2 months.

Protocol violations:.

Four patients (2 Didronel and 2 risedronate) were reported to violate exclusion/inclusion criteria of the study. Two patients in the Didronel group had history of malignancy of bladder or colon prior to entry into the study. Patients in the risedronate group took "prohibitive" drugs during the course of the study; one received Florical (sodium fluoride plus calcium) and the other received tiludronate (investigational).

8.1.4.2 Efficacy endpoint outcomes

Data sets

A total of 3 patients were excluded from the intent-to-treat (ITT) population and the evaluable-patient subset.

Reasons for exclusion:

Pt.# 15121821- Took Florical (calcium plus sod. Fluoride) and violated the study entry criteria. This patient was assigned to the risedronate group but was withdrawn prior to administration of drug.

Pt. # 33901810- Patient was assigned to Didronel group and received only one dose (400 mg) of it. Voluntarily withdrew from the study due to AE (blurred vision).

Pt. # 33901830- Sought treatment with other investigational antipagetic medication and discontinued the study voluntarily.

Of these three patients who were excluded from ITT analysis, 2 had no post baseline data and one did not take the study medication.

Number of patients for ITT analysis = 120. Sixty patients in each group.

Five additional patients were excluded from **evaluable-patients subset analysis:**

Pt. # 33901801 and Pt. # 10941801- Had history of prior colon or bladder cancer.

Pt. # 33911806- Received tiludronate during the study and was dropped from the study.

Pt. # 43461822 and Pt. # 14701823- The overall and cumulative (at Day 30) compliance was less that 80%.

The prespecified times for collection of data at each visit were:

a) within 30 days prior to initiation of treatment at baseline and

b) $\pm$ 14 days for postbaseline visit.

Data collected outside these time limits were excluded from evaluable-patient subset analysis. There were total of 1019 (508 in the Didronel and 511 in risedronate groups) post baseline visits. Of these visits, 49 (6 in the Didronel and 33 in the risedronate groups) were excluded from evaluable-patient subset analysis.

Comments: The sponsor has provided full accounts for patients who were included in the evaluable patient analysis (Sponsor's Table 8.4, vol. 1.116, p. 178). Serum alkaline phosphatase data for baseline as well as at Endpoint 1 (last measurement during the treatment period) were 100% for the two treatment groups. At Endpoint 2, SAP data were collected for 100% of patients for two groups, but between the Endpoint 1 and 2 there were visits (e.g., at Days 240, 300 and 360), percentage of patients with

SAP data varied between These minor changes do not seem to affect the final efficacy outcome. Table 15 (sponsor's Panel 11, vol. 1.116, p.65) presents the number of patients in various groups for statistical analyses.

Table 15. Presents the number of patients randomized in the study and in three different subsets.

Panel 7

Serum Alkaline Phosphatase and Bone Turnover Marker Values at Baseline[a]

Study RPD-001694

Parameter	400 mg Didronel (N = 61)	30 mg Risedronate (N = 62)
Serum Alkaline Phosphatase (U/L)	495.2 ± 42.4	481.5 ± 49.2
Serum Alkaline Phosphatase Excess (U/L)	421.5 ± 42.5	407.4 ± 49.2
Skeletal Alkaline Phosphatase (Ostase) (µg/L)	151.2 ± 14.7	150.8 ± 22.0
Urinary Deoxypyridinoline/Creatinine (pmol/µmol)	60.0 ± 4.4	50.2 ± 6.3
Serum 25-hydroxy-vitamin D_3 (ng/mL)	25.6 ± 1.4	26.0 ± 1.1

[a] Values shown are mean ± S.E.
Corresponding data can be found in Table 4.

Primary efficacy endpoint (ITT analysis):

Table 16 (modified from sponsor's Table 10.2, vol. 1.116, p. 188) summarized the results.

Table 16. Percent of patients with maximum response in total SAP excess.

Trial Periods	Didronel (400mg/day)	Risedronate (30mg/day)
Treatment Period (N=60)	20% (12)	85% (51)*
Both periods** (N=60)	23.3% (14)	85% (51)*

* P < 0.001; ** Combined treatment and follow-up periods.

The results demonstrated significantly higher percentage of patients who achieved ≥ 75% reduction in elevated levels of SAP excess. Furthermore, the median Days to maximum response was 67 for the risedronate group compared to > 360 for the Didronel group (p < 0.001).

Based on the magnitude of percent change from baseline in total SAP excess, the response to treatment was further categorized into high,

moderate, minimum, and no response.

Table 17 (Panel 13, vol. 116, p. 67) summarizes these results.

Table 17. Number and percent of patients showing high, moderate, minimum, and no response to test drugs.

Panel 13

No. (%) of Patients by Response Category

Study RPD-001694

	400 mg Didronel (N = 60)	30 mg Risedronate (N = 60)
Treatment Period		
No response	7 (11.7)	0
Minimum response		
Moderate response	15 (25.0)	3 (5.0)
High response		
Maximum response		
Both Periods*		
No response	7 (11.7)	0
Minimum response		
Moderate response	14 (23.3)	3 (5.0)
High response		
Maximum response		

* Both the treatment and follow-up periods.
No response = < 10% reduction; minimum response = ≥ 10% < 30% reduction; moderate response = ≥ 30% < 50% reduction; high response = ≥ 50% < 75% reduction; maximum response = ≥ 75% reduction in total serum AP excess.
Corresponding data can be found in Table 10.1.

It was shown earlier that majority of patients in the risedronate group achieved maximum response (≥ 75% reduction in SAP) to therapy. Fifty percent of patients in the Didronel group achieved moderate to high (≥ 30%< 75% reduction) response to treatment. There were no marked differences between treatment period and both periods (that included follow-up) with respect to percentage of patients by response categories. There was no patient in the risedronate group with no response (< 10% reduction) as opposed to about 12% non-responders in the Didronel group.

In the risedronate group, about 60% of patients achieved maximum response by Visit Day 60 and more than 80% of patients achieved such response by Visit Day 90. In the Didronel group, only about 5% of patients achieved maximum response by Visit Day 90 (none at Visit day 60) and 21% by Visit day 180. More than 81% of patients in the risedronate group maintained their maximum response during Visit days 90 through 360. On the other hand, in the Didronel group, 21% to 22% of patients exhibited maximum response from Visit days 180 through 360.

Sponsor states that baseline covariates (age, sex, race, and smoking

status) showed no effect on the "percentage of responders in either treatment group."

Normalization of Total SAP excess
The results are summarized in Table 18.

Table 18. Number and percent of patients with normalization of total SAP excess in two treatment groups.

Panel 13

No. (%) of Patients by Response Category

Study RPD-001694

	400 mg Didronel (N = 60)	30 mg Risedronate (N = 60)
Treatment Period		
No response	7 (11.7)	0
Minimum response		
Moderate response	15 (25.0)	3 (5.0)
High response		
Maximum response		
Both Periods*		
No response	7 (11.7)	0
Minimum response		
Moderate response	14 (23.3)	3 (5.0)
High response		
Maximum response		

* Both the treatment and follow-up periods.
No response = < 10% reduction; minimum response = ≥ 10% < 30% reduction; moderate response = ≥ 30% < 50% reduction; high response = ≥ 50% < 75% reduction; maximum response = ≥ 75% reduction in total serum AP excess.
Corresponding data can be found in Table 10.1.

Seventy-three percent of patients in the risedronate group were reported to achieve normalization of total SAP excess either in the treatment period or both periods as opposed to only of patients during corresponding periods in the Didronel group. There was a significant difference between the two treatment groups with respect to median days to achieve normalization (91 days vs > 360 days). In the Didronel group, 85% to 90% of patients never achieved normalization of total SAP excess during the entire study period.

Figure 1 (Sponsor's Figure 2, vol. 1.116, p. 71) presents Time to Normalization curve.

Figure 1. Time to Normalization in total SAP excess.