

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

In all three formulation groups, OHPr/Cr decreased as a result of risedronate treatment:

<u>Formulation</u>	<u>% Decrease (nadir) from Baseline</u>	<u>Day</u>
	51.9	140
	51.2	196
	59.4	140

APPEARS THIS WAY  
ON ORIGINAL

The fall in OHPr/Cr started earlier than in SAP and this is in agreement with previous findings from clinical trials with approved drugs for Paget's disease of bone. On Day 29 of the first treatment period, patients in all three treatment groups showed about 30% decrease from baseline mean values. In all three treatment groups, percent change from baseline after 29 days of treatment was significant. (P=0.0001). During the retreatment period, significant decreases in OHPr/Cr values occurred at all visit Days up to Day 196. On Visit Day 140, decrease in OHPr/Cr in the beads group was significantly greater than that observed in the capsule and E-C tablet groups.

*Changes in evaluable subgroup*

The results showed statistically significant decreases on treatment Day 56 and on retreatment Visit Day 112.

**Secondary efficacy endpoint**

**APPEARS THIS WAY  
ON ORIGINAL**

*Bodily pain*

During the first treatment period, about 30% of patients (n=162) were without pain. During the course of risedronate treatment and the follow-up period, up to 46% of patients became pain free at some Visit Day. During retreatment period, improvement in bodily pain was reported in similar percentage of patients as reported during the first treatment. The overall pain data showed slightly higher percentage of patients with a trend of improvement of pain.

Sponsor has also analyzed the effect of risedronate treatment on the frequency of pain. All 162 patients at baseline were categorized (based on pain frequency) into the following subgroups: missing response, no pain, less than once per week, times per week, several times per day, and continuously. During the first treatment period, on Day 196, risedronate treatment resulted in reduction in only those patients who experienced pain continuously at baseline. In other subgroups, changes in frequency were marginal and clinically insignificant. Sponsor claims that pain over the skull and spine seemed to decrease during the course of the study. Data seem to be inadequate to draw any definitive conclusion.

*Severity of pain*

**APPEARS THIS WAY  
ON ORIGINAL**

Number (%) of patients with slight, moderate, and severe pain showed an overall decreases (from baseline numbers of patients) during the course of the study. Number of patients (%) with no pain progressively increased during the course of the study and reached a maximum number (%) at Visit Day 140. The results with retreatment are marginal and inconsistent. However, the number patients with severe pain at baseline, decreased from 16 to 10 at the end of retreatment.

*Effect on sleep pattern*

**APPEARS THIS WAY  
ON ORIGINAL**

Sponsor claims that "there was general improvement in the sleep pattern of patients who participated in this study." Data on sleep pattern were available for about 46% of patient who participated in this study. The number (%) of patients who showed improvement during the course of initial therapy was variable and differences from baseline were small. The results are inconsistent during retreatment period.

*Activities affected by pain*

The following activities affected by pain were evaluated: walking, arising from lying position, bending arms or legs, and carrying bags. Sixty-eight percent of patients at baseline experienced pain during walking. Risedronate therapy had no effect on the number of patients with pain during walking or carrying bags. During the course of the study there was slight improvement in bending arms and legs, and arising from lying position on Visit Day 196.

Risedronate treatment did not affect patients' ability to dress themselves. Risedronate therapy resulted in little or no effect on the various methods of pain relief during the course of the study. The methods of pain relief that were analyzed included sitting down, warmth, change of position, lying down, exercise, and medication.

### **Reviewer's comments on pain efficacy endpoint**

With respect to the effect of risedronate on bodily pain, only consistent data presented here showed increased number of pain-free patients during the course of the study. Data are equivocal with respect to the effect of therapy on the frequency of pain, severity of pain, sleep disturbance, physical activities affected by pain, and methods used to relieve pain.

### **SAFETY RESULTS**

APPEARS TO BE  
ON ORIGINAL

#### *Exposure to study drug*

There was no major difference between the three treatment groups with respect to the mean number of weeks exposed to risedronate. The number of weeks exposed to risedronate varied from . . . . One patient assigned to receive capsules withdrew voluntarily before risedronate dosing.

#### **Overview of AEs**

APPEARS TO BE  
ON ORIGINAL

The number of patients with AEs was similar in all three groups. Two patients in the . . . . and 3 in the . . . . groups dropped out of the study because of AEs. A total of 31 patients were reported to experience upper GI AEs. Eight of 31 had moderate to severe GI AEs. Upper GI AEs listed in this study were similar to those evaluated in active-controlled and open trials.

Review of summary AEs (based on body system) showed no significant difference between the three treatment groups. Frequently reported AEs in the three treatment groups included pain, diarrhea, and headache.

Twenty-eight patients were reported to experience a total of 38 severe AEs. (17 with beads, 12 with tablets and 9 with capsules). Sponsor has not provided any information regarding relationship of these AEs to

risedronate therapy. Except for pain in the joints, most of other AEs appeared to be unrelated to therapy. Pain could be related to the study drug or to the disease process itself.

*Deaths and serious AEs*

APPEARS THIS WAY  
ON ORIGINAL

Deaths:

Pt. # 58750606 - Patient had a history of CHF and died of that condition.

Pt. 33910605 - Patient died from MI.

Pt. # 33900625 - Patient died from oat-cell lung cancer.

The sponsor/investigator did not relate deaths to the study drug.

Nineteen patients were reported to experience 23 serious AE (CFR 314.80); 3 in the \_\_\_\_\_ group, 8 in the \_\_\_\_\_ group and the rest in the \_\_\_\_\_ group. Except for osteoarthritis and liver enzyme elevation, most of these serious AEs appeared to be unrelated to known pharmacodynamic effects of the drug or bisphosphonates (marketed or unapproved) in general.

*Changes in treatment regimen due to AEs*

APPEARS THIS WAY  
ON ORIGINAL

*There were no changes in the treatment regimen due to AEs.*

*GI adverse events*

Fifty-seven, 83 and 50 percent of treated patients in \_\_\_\_\_ groups, respectively experienced GI AEs. Mild to moderate diarrhea was the most common GI event that occurred in about 10% of patients (lowest in the beads group). GI adverse events that occurred in more than 5% of patients in any treatment group, included diarrhea (10.5%), dyspepsia (9.3%), nausea (8.0%), abdominal pain (6.8%), and constipation (6.2%). Four patients (2.5%) experienced esophagitis. Sponsor states that no patients discontinued the study due to GI adverse events.

Seven patients were reported to experience 9 moderate to severe upper GI adverse event (2 severe and seven moderate). These events included pain abdomen, dyspepsia, esophagitis, and melena. Three of seven patients underwent endoscopic examinations. In two of the three patients results were negative, but one patient showed mild erosive esophagitis in the distal esophagus on two separate occasions.

*Non-vertebral fractures*

Two patients (one male and one female) were reported to experience non-vertebral fractures during the study. The female patient (75-year-old) sustained a traumatic fracture (from a fall) of left humerus. The male patient (80-year-old), sustained an atraumatic rib fracture (without radiographic confirmation) while crawling in the attic.

**Other clinically relevant Events**

Iritis during the course of the study.

APPEARS THIS WAY  
ON ORIGINAL

Pt. # 14700604 ( ) - Experienced a single episode of moderately severe iritis. Topical steroid therapy resulted in recovery.

Pt. # 33820610 - Similar episode as in pt. 14700604.

Pt. # 36420612 ( ) - Experienced severe iritis and relapse. Recovered after topical steroid therapy.

Risedronate therapy was continued during the episode of iritis in all three patients. Each of these patients had previous history of "eye problems."

**(Reviewer's comments:** It is difficult to determine the relationship between iritis and risedronate therapy. In clinical trials with Aredia (pamidronate), rare cases of uveitis, iritis, scleritis, and episcleritis were reported (including one case of scleritis and one case of uveitis upon separate rechallenge). With Skelid (tiludronate for Paget's disease of bone), about 2.7% of patients (n=75) were reported to develop eye problems (cataract, conjunctivitis, glaucoma) during the course of the study. These ocular adverse events should be included in the labeling.

**Vital signs.**

Systolic blood pressure- During the retreatment period, mean systolic blood pressure slightly increased in the \_\_\_\_\_ groups and decreased in the \_\_\_\_\_ group.

Body weight- Slightly increased in all three treatment groups. These changes were marginal and clinically insignificant.

**Reviewer's comments** Clinical significance of these minor changes in vital signs are difficult for interpretation.

*Clinical laboratory safety assessment*

APPEARS THIS WAY  
ON ORIGINAL

**Bone metabolic parameters**

Serum calcium- Mean serum calcium decreased from baseline in all three treatment groups on treatment Visit Day 29 and values remained relatively stable until completion of the treatment phase of the initial treatment

period. The mean decreases were between . After the Visit Day 84, mean values returned towards baseline mean values. During the retreatment period, the magnitude change in serum calcium from baseline was much less and variable.

Serum phosphorus- During the initial treatment period, mean serum phosphorus values decreased from baseline on Visit Day 29 and remained decreased until Day 84. Thereafter, returned towards baseline values around day 112. The magnitude of decrease in serum phosphorus during the retreatment period was slightly less than that of the initial treatment period.

Intact PTH- Mean iPTH increased in all three treatment groups from baseline by at Day 84 and returned to baseline on treatment Visit Day 196. During the retreatment period, mean iPTH values increased by by Day 84 and never quite returned to baseline during the follow-up period (Day 196 of retreatment). At baseline, about 22% of patients had "high" iPTH value ( $> 55$  pg/mL). On day 84, a significantly ( $p < 0.05$ ) higher percentage of patients (76.3%) showed "high" iPTH values. On Day 196, the percent of patients with "high" iPTH values was similar to that at baseline. During the retreatment period, about 60% of treated patients had "high" iPTH values on Day 84. On day 196, about 41% of retreated patients maintained "high" iPTH values.

Serum  $1,25$  (OH) $_2$  D - This vitamin D metabolite followed similar pattern of change (from baseline) as serum iPTH on Day 84 of the treatment and retreatment period. At the end of follow-up (Day 196) of the two treatment periods, the mean values returned to near baseline. Serum  $25$  OHD $_3$  values showed no meaningful change either during treatment or retreatment period.

Urinary calcium/Cr- In all three treatment groups urinary calcium/Cr decreased over Days 29-84, and thereafter gradually returned to near baseline on day 196. Changes in urinary calcium/Cr ratios were irregular, but showed some decrease over Days 84-196, and returned to near baseline at Day 196.

#### Reviewer's comments

Overall changes in these bone metabolic parameters were relevant with respect to the known pharmacodynamic effects of bisphosphonates. No patient was reported to be symptomatic due to lowering of serum calcium. The clinical significance of sustained levels of elevated iPTH in long-term clinical trials needs to be determined.

#### Hematology

Except for minor decreases in hemoglobin and increases in hematocrit

APPEARS THIS WAY  
ON ORIGINAL

during risidronate therapy (over 84 days), there were no major changes in RBC, WBC, polymorphs, bands, lymphocytes, monocytes, eosinophils, and basophils. At the end of follow-up periods, altered mean values of hemoglobin and hematocrit returned to near baseline values.

The overall results of shift analyses of hematological parameters showed more patients with downward shifts (from baseline to minimum values) for the majority of these parameters. Shifts from baseline to maximum values were somewhat inconsistent. Some of these parameters ((e.g., RBC) showed equal distribution of upward and downward shifts in baseline to the last values recorded. For the mean corpuscular volume, more patients showed upward shifts (baseline to maximum values) than downward shifts (baseline to minimum values). For platelets, downward shifts from baseline to minimum values and upward shifts from baseline to maximum values were reported to be similar in number. For lymphocytes and polymorphocytes shifts from baseline to the last recorded values showed no imbalance in shifts.

**Reviewer's comments:** During risidronate therapy, mean corpuscular volume increased with decreased MCHC and the effects seemed to reverse after stopping therapy. The platelet counts showed slight decrease during the treatment with risidronate. The magnitude of the changes in some of these parameters was small and was inadequate for any meaningful evaluation. Infrequent cases of anemia, leukopenia and leukemia have been reported with the use of marketed bisphosphonates. Causal relationship of these AEs to bisphosphonate therapy is not clear. The labeling for the marketed bisphosphonates includes reference to these AEs.

#### **Liver Function Tests (LFTs)**

APPEARS THIS WAY  
ON ORIGINAL

Serum albumin showed no major change. There were slight decreases in GGT, SGOT and SGPT during early visits of both treatment and retreatment periods. There was no major change in serum total bilirubin.

#### **Renal Function Tests:**

Sponsor states that there were no major changes in serum creatinine, urinary RBCs, WBCs, or urinary total protein.

#### **Sponsor's discussions and conclusions**

APPEARS THIS WAY  
ON ORIGINAL

Based on a preset definition of response (reduction in SAP and OHP<sub>r</sub>/Cr) to therapy, patients responded during both initial and retreatment periods. Patients responded to all three formulations of risidronate. Over 93% of treated patients were considered resistant to previous antipagetic drugs and they were found to be responsive to risidronate.

Only about 14.9% of treated patients experienced a relapse after initial therapy with risedronate. There was no difference between the three formulations of risedronate with respect to duration of response. The time to response was shortest with the beads formulation.

About 54% of treated patients experienced normalization of SAP excess at the end of treatment period. With the : approx. 69% of patients achieved normalization of SAP by the end of the treatment period. Based on percent decreases in SAP from baseline at Visit Day 29, the data seem to suggest that patients with higher baseline SAP may require longer treatment with risedronate.

Urinary hydroxyproline/creatinine decreased earlier than AP. (Comments: This always happens because of initial inhibition of bone resorption).

Changes in other metabolic parameters (e.g., serum calcium, PTH, 1,25 (OH)<sub>2</sub> D<sub>3</sub>, and urinary calcium /Cr) reflected the pharmacodynamic effects of risedronate directly or indirectly. Similar results were observed with other marketed bisphosphonates for the treatment of Paget's disease of bone. Risedronate treatment resulted in rise in iPTH level which returned to near baseline values after cessation of treatment. During the second course of treatment, there appeared to be a slightly higher residual level of PTH compared to the initial treatment. Patients on risedronate therapy should probably be followed up for longer period after completion of treatment, in order to monitor residual effect of treatment on PTH levels.

Risedronate therapy resulted in "general reduction" in the number of patients with pain. At the end of initial treatment period, about 18% of patients who had pain at study entry showed no pain. Risedronate therapy also decreased the number of patients with frequent sleep disturbance. Pretreatment activities associated with pain also showed some improvement with treatment. Since the study was not placebo-controlled, a definitive claim about improved activities of daily life with risedronate therapy could not be determined.

Adverse events profile of risedronate did not raise any major safety issue. Causality assessment of AS could not be clearly performed as the study was not placebo-controlled. Ocular AS have also been reported with the use of i.v. pamidronate for either hypercalcemia of malignancy or Paget's

disease of bone. The mechanism of ocular events associated with risedronate is unclear at present.

Adverse events related to GI system were mild and did <sup>not</sup> cause discontinuation of treatment. There was no difference between three treatment groups with respect to incidence of upper GI adverse events.

Asymptomatic hypocalcemia is known to occur with the use of bisphosphonates (p.o. and i.v. formulations). It is related to their antiresorptive action on bone turnover. Risedronate therapy also caused asymptomatic hypocalcemia and the degree of hypocalcemia can be minimized with calcium supplementation, particularly during the first few weeks of risedronate therapy.

Since this study was not placebo-controlled, the causality of minor changes in hematology and other biochemical parameters was not clear. Some of these changes (decreases in LFTs and serum creatinine) were favorable.

In conclusion, risedronate therapy at a dose of 30 mg/day for 84 days resulted in decreases (> 50%) in SAP and urinary OHPr/Cr in patients with moderate to severe Paget's disease of bone. Improvement in biochemical parameters was accompanied by reduction in pain and increased ability to perform daily activities. Patients who relapsed after a non-treatment period of 112 days, also showed effective reduction in biochemical parameters. In general, risedronate was well tolerated by the patients and provided an acceptable safety profile. Upper GI safety profile of risedronate in this study population was similar among three formulations.

#### 8.3.5 Reviewer's Comments/Conclusions of Study results

*Study design-* The design of this multicenter, randomized, open-label study was adequate to achieve the stated objectives: (i) to determine the response of biochemical markers of Paget's disease of bone (SAP and urinary OHPr/Cr) during and following administration of 3 different oral dosage forms of risedronate and (ii) to determine its safety profile in this patient population.

A placebo-controlled trial would have been more desirable with respect to determine the causality of the AEs (e.g., iritis) observed in this study. Currently, there are four bisphosphonates (etidronate, pamidronate, alendronate, and tiludronate) approved for the treatment of Paget's disease of bone. During the past several years considerable postmarketing efficacy and safety data have been accumulated. Efficacy and safety data for risedronate generated from this open-label study should be compared with available data on marketed bisphosphonates.

The trial design, number of patients in each of the three treatment groups and the duration of the trial allowed objective assessment of the study endpoints. Patients accountability and demographics were appropriate. Sponsor provided adequate reasons for dropouts of 11 patients (6.8%) from the study. None of these dropouts were due to AS of the test drug. The dropout rate was comparable to trials carried out with the approved bisphosphonates for this indication.

The results demonstrated significant decreases from baseline in excess SAP and urinary OHPr/Cr after 29 days of treatment with risedronate in all three dosage forms. Overall, approx. 87.5% of treated patients (n=160) achieved 50% or more decrease in excess SAP and the time to response was 74.7 days (mean value). Risedronate-induced biochemical improvement was accompanied by reduction in pain and improved ability to perform activities of daily living.

Overall, about 8.6% of patients among responders during the first treatment period relapsed after 196 days of follow-up. The results of retreatment were similar to those of the first treatment period.

Most frequently reported AEs included pain, headache, and diarrhea. The incidence of upper GI AEs were similar in three dosage forms of risedronate. However, the severity of GI adverse events was mild in nature and did not require discontinuation of treatment.

In conclusion, this randomized, open-label study of three dosage forms of risedronate demonstrated the efficacy (in terms of biochemical improvement and reduced pain symptoms) in patients with moderate to severe Paget's disease of bone. With regard to safety of risedronate therapy, the data seem to indicate the drug was well tolerated by the patients population.

Long-term skeletal safety and benefits of risedronate therapy remain to be established from postmarketing clinical experience. Results of this study provide evidence in support of the efficacy and safety data obtained from the other two controlled trials.

#### 8.4 Trial # 4/ Study # 90009

APPEARS THIS WAY  
ON ORIGINAL

##### 8.4.1 Objective/ Rationale

To determine the time course of biochemical changes (SAP and urinary OHPr/Cr for efficacy), safety, and tolerance of risedronate in patients with resistant (to previous anti-pagetec treatments) Paget's disease of bone. The rationale for using risedronate (a bisphosphonate) is the same as for other marketed bisphosphonates for this indication.

##### 8.4.2 Design

An open-label study.

8.4.3 Protocol

APPEARS THIS WAY  
ON ORIGINAL

**Protocol amendments**

a. Protocol was revised with respect to administration of risedronate; patients were instructed to take the medication with water (> 8 oz) and not to recline or lie down for at least 1 hour after dosing.

b. An endoscopy should be requested in patients who develop a moderate to severe complaint of upper GI symptoms (heartburn, mid-sternal pain, esophageal burning, epigastric pain, odynophagia, and dysphagia). Although endoscopy was not mandatory.

Principal investigator: Frederick R. Singer, M.D.  
Ceders-Sinai Medical Center  
Los Angeles, CA

APPEARS THIS WAY  
ON ORIGINAL

8.4.3.1 Population, procedures

The study enrolled male and female patients with active Paget's disease of bone (scintigraphically or radiologically determined, and with SAP at least 9 X the ULN and above normal urinary OHPr/Cr; who were resistant to or relapsed after previous anti-pagetic treatment. At least 10 such patients were expected to complete the study.

Twelve of 13 patients received more than one previous anti-pagetic treatment [calcitonin (s.c. or nasal), etidronate, pamidronate (oral), and risedronate (10 mg dose)]. Analgesics and antipyretics were the most common concomitant medications they received. Seven of 13 patients had daily calcium intake of < 700 mg.

Exclusion criteria were similar to those of other preceding studies.

Following prestudy evaluation, patients received 30 mg of risedronate (3x 10 mg cap) daily for 56 days and were followed-up until Days 168 of study. A dose of 30 mg/day was selected on the basis of the results of the controlled study 88040. Patients were **instructed to take the medication 2 hours before bedtime and not to eat or drink for 2 hours before and after dosing.**

Patients were monitored periodically at designated intervals during treatment and follow-up periods.

Patients who had partial response or relapsed during the treatment period, received a second course of treatment with risedronate 30 mg/day for 56 days. During either treatment or retreatment period, if a patient achieved normalization of SAP, treatment was stopped and the patient was monitored according to the protocol.

BEST POSSIBLE COPY

#### 8.4.3.2 Endpoints

##### *Efficacy -*

Primary efficacy endpoint- Percent change from baseline in SAP excess.

Response- A 100% decrease from baseline in excess SAP.

Partial response- A decrease in excess SAP, but without a return within normal range.

Relapse- Increase in excess SAP above the ULN after normalization from initial treatment.

Secondary efficacy and safety endpoints were similar to those of the preceding studies.

#### 8.4.3.3 Planned statistical analyses

APPEARS THIS WAY  
ON ORIGINAL

Basically statistical methods for efficacy and safety endpoints were similar to those of the preceding studies.

#### 8.4.4 Results

APPEARS THIS WAY  
ON ORIGINAL

##### 8.4.4.1 Patient disposition and comparability

Thirteen patients were enrolled into the study. Five of them discontinued the study, three due to AEs, one due to protocol violation, and one withdrew voluntarily.

##### Dropouts due to AEs:

Pt. 25170301- A 73-year-old male patient was treated with risedronate 30 mg/day for 45 days. About 15 hours after the last dose of risedronate, patient suffered a transient ischemic attack (TIA) associated with a fall, followed by dizziness/lightheadedness and left-sided weakness. Patient was hospitalized for 3 days and gradually recovered. Patient was dropped from the study at the request of the monitor. The investigator considered the relationship of TIA to the study drug as doubtful.

Pt. 25170303- A 55-year-old female patient received risedronate 30 mg/day for about 5 weeks. Patient had a history of mild anemia of unknown etiology and during the course of treatment both hematocrit and RBC decreased below the baseline values (< LLN). The investigator attributed these abnormal findings to patient's chronic mild anemia unresponsive to iron therapy.

After receiving risedronate for about five weeks, patient experienced moderately severe substernal discomfort. Risedronate was discontinued and an endoscopy was performed. Endoscopy showed "a completely normal esophagus, stomach,

and duodenum." Risedronate was restarted, but patient again experienced GI discomfort. Risedronate was discontinued and patient felt better thereafter.

Pt. 251703306- A 78-year-old female patient received risedronate (30 mg/day) for about 2 weeks. One day after starting risedronate, she experienced moderately severe diarrhea which lasted for 1 day. After about receiving risedronate for 2 weeks, it was discontinued and she was off drug for about 11 days. On restarting risedronate, she began to experience moderately severe diarrhea (six episodes over 36 hours) with abdominal cramp. Patient was dropped from the study because of recurring events of diarrhea.

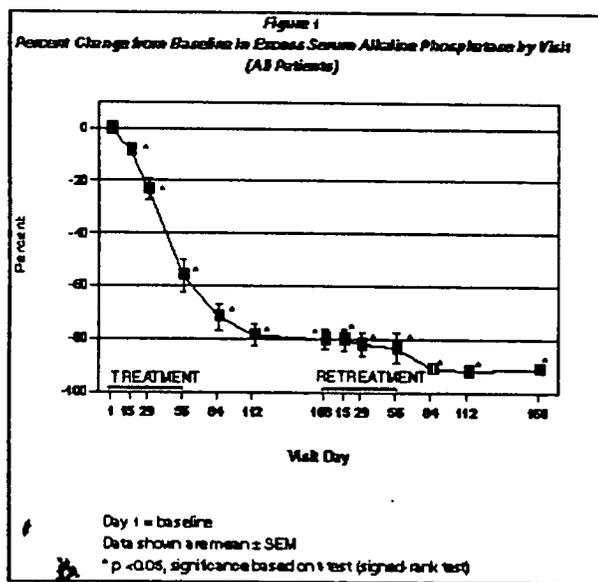
#### 8.4.4.2 Efficacy endpoint outcomes

APPEARS THIS WAY  
ON ORIGINAL

*Serum alkaline phosphatase (ITT analysis)*

The results are shown in Figure 14 (Sponsor's Figure 1, vol. 1.145, p. 37)

Figure 14. Per cent change in excess SAP from baseline.



APPEARS THIS WAY  
ON ORIGINAL

The mean baseline SAP value was 1792.5 IU/L, almost 17 x the ULN (108 IU/L). Ten to thirteen patients were included in the analysis of the results during the first treatment and retreatment periods.

During the treatment period, risedronate therapy resulted in significant decreases in excess SAP at all Visit Day; reaching the nadir of -80% at visit Days 112. (n=10) end of follow-up. All 10 patients (with a mean SAP of 344.1 IU/L) received retreatment with risedronate, starting on Day 168 of the study. SAP continued to drop further and decreased about 90.9% at Visit Day 168 of retreatment period. None of the patients achieved 100% decrease in excess SAP. The mean

maximum decrease from baseline in excess SAP was  $67.5\% \pm 28.8$  (all patients' response taken into account).

In this study, except for one patient none achieved normalization of excess SAP during the first and retreatment periods. However, in 9 out of 13 patients excess SAP decreased by more than 85%. The remaining 4 patients were dropped from the study and their response to therapy could not be assessed.

*SAP changes in the evaluable subgroup*

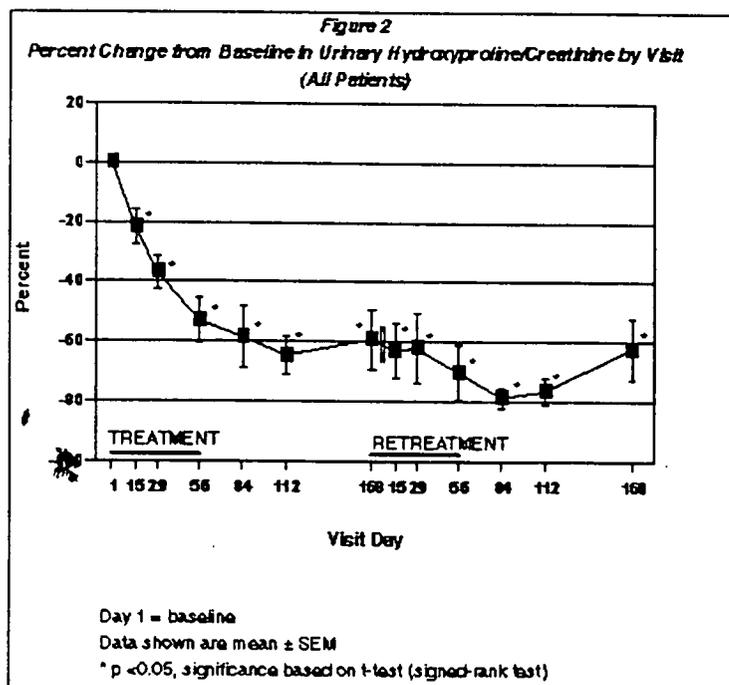
Basically same pattern of response was reported in this subgroup. There were 8 patients in this subgroup and all had partial response to therapy. Five (63%) had maximum decreases in excess SAP, which ranged between 75% and 99%; two had maximum decreases between 50% and 70%, and one had about 16% maximum decrease from baseline.

*Hydroxyproline/Creatinine (ITT analysis)*

APPEARS THIS WAY  
ON ORIGINAL

The results are presented in Figure 15 (Sponsor's Figure 2, vol. 1.145, p. 39).

Figure 15. Percent change from baseline in OHP/Cr.



APPEARS THIS WAY  
ON ORIGINAL

BEST POSSIBLE COPY

There was a progressive decrease in OHP/Cr immediately after starting risedronate treatment and a nadir was reached on Day 112 of first treatment period. Decreases from baseline at all Visit Days were significant during the first treatment period. During the retreatment period, a maximum decrease of 78.6% was observed at Visit Day 84. As expected, the rate of reduction in OHP/Cr was

more rapid than reduction in excess SAP. In the evaluable subgroup, the response to risedronate therapy was similar to that of the ITT population.

#### 8.4.4.2 Safety

For safety evaluation all 13 patients were included. Risedronate (30 mg/day) was given for a mean of 13.5 weeks. A total of 41 AEs occurred in these patients and 4 patients were reported to experience serious AEs. Infection, diarrhea, dizziness, and pharyngitis occurred in more than 10% of patients. Of 41 total AEs, only 5 were considered severe and these included one episode each of asthenia, cerebral ischemia, traumatic bone fracture, and abnormal coordination and dizziness. Relationship between risedronate and serious AEs was not clear and considered doubtful by the sponsor.

There were no deaths reported in this study.

APPEARS THIS WAY  
ON ORIGINAL

#### *Clinical laboratory parameters*

Serum calcium- Both during first treatment and retreatment periods, serum calcium decreased from baseline. The nadirs for the percent change from baseline were -6.3% and -5.3% (both on Days 56 of treatment). After stopping treatment, serum calcium started to return near normal level. Changes in serum calcium did not adversely affect patient safety.

*Serum phosphorus*- The pattern of change in serum phosphorus from baseline during first treatment and retreatment periods was similar to that of serum calcium and patients' safety remained unaffected by these changes.

*Serum iPTH*- Both during the first treatment and retreatment periods, serum iPTH levels significantly increased from baseline and maximum increases (> 100%) were on Day 56. PTH levels started to fall immediately after termination of treatment and returned towards baseline.

**Reviewer's comments:** Risedronate-induced mild hypocalcemia probably is the cause for rise in iPTH levels. Since the recommended duration of therapy with risedronate for this indication is 2 months, it is unlikely that changes in iPTH will have any adverse effects on skeletal system. This reviewer feels that calcium supplementation (not concomitant administration) may help to alleviate the effect of risedronate on serum iPTH level.

*Serum 1,25 (OH)<sub>2</sub> D<sub>3</sub>*- During the first treatment period, a clear increase in serum 1,25(OH)<sub>2</sub> D<sub>3</sub> level was noted with a biphasic response during the retreatment period. Increase in vitamin D metabolite is likely to be due to increase in iPTH level. Biphasic response during the retreatment period cannot be clearly explained.

*Serum 25 OHD*- Slight increase during the first treatment period was observed with opposite response during the retreatment period. These changes seem to have no clinical implications.

*Urinary calcium/creatinine-* During the first treatment and retreatment periods, urinary calcium/Cr decreased sharply and tended to return to baseline level after stoppage of risedronate treatment. Decrease in urinary excretion of calcium/Cr is related to antiresorptive action of the test drug on bone turnover, resulting in decreased release of calcium in the circulation.

*Urinary phosphorus/creatinine-* Changes were inconclusive during both the first treatment and retreatment periods.

*Individual abnormal laboratory values-* Four patients manifested abnormal laboratory values during risedronate therapy and these patients are shown in Table 37 (Sponsor's Table 19, vol.1.145, p.54).

Table 37. Individual abnormal bone metabolism laboratory parameters.

APPEARS THIS WAY  
ON ORIGINAL

Table 19 Selected Bone Metabolism Measurements			
Parameter	Minimum Value	Maximum Value	Normal Range
	Patient Number	Patient Number	
Serum calcium (mg/dL)	25170303 25170312	25170305	
Serum phosphorus (mg/dL)	25170313	25170308	
Parathyroid hormone (pg/mL)	25170311	25170304	
Corresponding data can be found in Appendices 5.1 and 8.1, Tables 7.1.1, 7.2.1, 7.3.1, 7.6.1, 7.8.1, 7.9.1, 7.10.1.			

APPEARS THIS WAY  
ON ORIGINAL

These abnormal values of bone metabolism parameters did not seem to have any effect on the overall safety of the test drug in this patient population.

*Hematology* - Changes in hemoglobin, hematocrit and RBC showed no clear pattern. The causal relationship between out-of-range values and the test drug could not be established. Overall changes in platelet and WBC counts were clinically insignificant. The mean values of neutrophils at baseline, decreased slightly during the course of the study.

One patient (# 25270306) had low hemoglobin and RBC. This patient was diagnosed to have mild anemia of unknown etiology. In patients with resistant Paget's disease of bone, "ineffective erythropoiesis" has been reported in the literature. Chronic use of NSAID (Voltaren) by this patient could have caused mild anemia.

Another patient (# 25170306) manifested minimum and maximum WBC values and minimum values of for lymphocytes and monocytes sporadically. This patient was on Tegretol, which is known to cause bone marrow depression.

Persistent eosinophilia, neutropenia and lymphocytosis were reported in a patient (# 25270307) throughout the study. This patient was on Desipramine (75 mg/day) and it is known to cause neutropenia.

**Reviewer's comments:** Causal relationship between these abnormal hematologic parameters (sustained and sporadic) and risedronate therapy could not be established. Bisphosphonate therapy has been reported to be associated with wide spectrum of hematological abnormalities and currently they are mentioned in the labeling. All marketed bisphosphonates (etidronate, pamidronate, alendronate, and tiludronate) are critically monitored and periodically evaluated for their association with reported hematological AS.

*Liver function tests-* Serum total protein, albumin, GGTP, SGOT, SGPT, total bilirubin were all reported to be within the normal range, except for two patients; one with high GGTP and the other with high SGOT values. These elevations appeared to be isolated events and unrelated to risedronate.

*Renal function tests-* The mean values for serum creatinine and BUN were within normal limits. One patient had persistent elevation in BUN and creatinine throughout the study. This patient was hypertensive and was treated with anti-hypertensive drugs. Rise in BUN and creatinine was probably due to pre-renal azotemia resulting from diuretic therapy. Another patient had presence of WBC in the urine, which increased further during the treatment.

There were couple of patients with high microscopic value of RBC in urine or elevated urinary protein. These patients had existing conditions that contributed to the presence of RBC in the urine and proteinuria.

*Vital signs-* Slight rise in systolic blood pressure during the first treatment period and similar rise in diastolic pressure during retreatment period were reported. These minor changes in systolic and diastolic pressure were clinically insignificant.

### **Sponsor's discussion and conclusion**

The results of this small study (n=13) showed marked decreases in biochemical markers of the disease activity during the first treatment period and when repeated for the second time, decreases were of greater magnitude. Therefore, repeated courses of risedronate in this patient population, are likely to maintain remission for an extended period of time. Most of these patients were resistant to prior treatment with anti-pagetec drug(s). At the end of about 4 months of follow-up period, urinary OHP<sub>r</sub>/Cr value tended to rise, indicating relapse of the disease process.

Changes in other bone metabolic parameters (serum calcium, phosphorus, iPTH,

and vitamin D metabolites) were related to pharmacodynamic effects of the drug and tended to return to baseline after termination of treatment.

In general, small safety data generated from this study corroborated the findings of preceding larger studies. One patient experienced hip fracture, but the investigator felt that relationship between risedronate and hip fracture was doubtful.

In conclusion, the results of this small open-label study demonstrated the efficacy of risedronate in significantly reducing the biochemical markers of the disease activity. The patients were resistant to prior anti-pagetec treatment. Safety profile of risedronate was similar to that of the preceding studies.

#### 8.4.5 Reviewer's comments and conclusion:

APPEARS THIS WAY  
ON ORIGINAL

This is a small open-label study (n=13). Both from efficacy and safety points of view, the results should be taken into consideration with certain reservations. The overall efficacy data seem to indicate that risedronate therapy at a daily dose of 30 mg for extended period markedly decreased elevated levels of biochemical markers in a group of pagetic patients resistant to prior antipagetec treatment.

#### 8.5 Trial # 5/Study # 90003

APPEARS THIS WAY  
ON ORIGINAL

##### 8.5.1 Objective /Rationale

To determine the efficacy and safety of risedronate when administered for variable periods to patients with Paget's disease of bone, including the time course of biochemical (SAP and urinary OHP<sub>r</sub>/Cr) changes. Marketed bisphosphonates for the treatment Paget's disease of bone established the rationale for risedronate use for the same study population.

##### 8.5.2 Design

APPEARS THIS WAY  
ON ORIGINAL

A multicenter (N. America, Australia, and Scotland) randomized, open-label study

##### 8.5.3 Protocol

##### Protocol amendment

APPEARS THIS WAY  
ON ORIGINAL

The highlights of clinically relevant amendments were:

- All treatment groups (28, 56, or 84 consecutive days) started simultaneously (for the North American study only).
- A prestudy 24-hour urine sample instead of 2-hour urine chemistry at the North American sites.
- Patients on concurrent exogenous thyroid hormone therapy were excluded from

the study at the North American sites.

Patients were instructed to take the medication with more than 8 oz of water and not to lie down or recline for at least 1 hour after post dosing. Patients who developed moderate-to-severe upper GI symptoms, were to undergo an endoscopic examination at the earliest possible time.

APPEARS THIS WAY  
ON ORIGINAL

#### 8.5.3.1 Population, procedure

A total of 73 patients of either sex, were enrolled into this study. All patients had biologically active (SAP at least 3 x the ULN and elevated urinary OHP<sub>r</sub>/Cr) Paget's disease of bone. Additionally, all had scintigraphically and/or radiologically defined pagetic lesions.

Exclusion criteria were the same as preceding clinical trials.

Patients were stratified according to baseline level of SAP excess, and randomly assigned to receive risedronate 20mg/day for 28 (Gr.1), 56 (Gr.2), or 84 (Gr.3) days. Patients were followed-up until Day 169 of the study.

#### Stratification-

Stratum A= 3 x ULN SAP to  $\leq$  5 x ULN  
Stratum B= 5 x ULN SAP to  $\leq$  9 x ULN  
Stratum C= 9 x or more ULN SAP

APPEARS THIS WAY  
ON ORIGINAL

Patients experiencing a relapse (in terms of SAP) on or before Day 169 received retreatment.

The dose (20 mg/day) of risedronate was selected on the basis of findings in experimental models of bone resorption and to keep the dose below the potential toxic thresholds.

Patients were instructed to take the medication (in 120 cc of water) 2 hours before bedtime and not to eat or drink for 2 hours before or after dosing.

Chronic concomitant medications were allowed to continue provided there were no major changes in dosing regimen. All concomitant medications were to be recorded in the CRF. All patients were required to take at least 700 mg of calcium daily. Dietary calcium was supplemented with calcium carbonate tablets if required.

On study visit days, patients were instructed to come to the clinic following an overnight fasting. Patients remained in a fasting state until all investigations were completed.

#### 8.5.3.2 Endpoints

*Efficacy-*

Response- A 30% or more decrease from baseline in excess SAP plus a 50% or more decrease from baseline in urinary OHPr/Cr. The response rate, time to response, and duration of response were evaluated as secondary efficacy endpoints.

Safety-

APPEARS THIS WAY  
ON ORIGINAL

- Routine clinical and laboratory safety parameters were similar to those of preceding trials.

The sponsor has provided information on Clinical Quality Assurance of the study.

8.5.3.3 Planned statistical analyses

Similar to those of preceding clinical trials. Sample size for this study was not based on statistical considerations of power. It was estimated that about 18 patients per treatment group would be adequate for estimating an optimal treatment regimen with risedronate for Paget's disease of bone.

8.5.4 RESULTS

APPEARS THIS WAY  
ON ORIGINAL

8.5.4.1 Patient disposition

Of the total 73 enrolled patients, 8 patients discontinued the study. Of these 8 patients, 7 discontinued the study due to AEs (these AEs are discussed in safety review). The remaining patient was dropped from the study in Gr.3, because of protocol violation.

Distribution of patients in three treatment groups based on baseline SAP is presented in Table 38 (Sponsor's Table 5, vol. 1.152, p. 39)

Table 38. Patient distribution by SAP strata.

APPEARS THIS WAY  
ON ORIGINAL

Table 5 Distribution of Patients by Treatment Group and Alkaline Phosphatase Strata				
Alkaline Phosphatase Stratum	Treatment Group - Risedronate 20 mg/day			
	28 days (N = 23)	56 days (N = 23)	84 days (N = 27)	Overall (N = 73)
3ULN $\leq$ AP $\leq$ 5ULN	7	8	9	24
5ULN $\leq$ AP $\leq$ 9ULN	8	6	12	26
9ULN $\leq$ AP	8	9	6	23

ULN = upper limit of the normal range for serum alkaline phosphatase.  
AP = serum alkaline phosphatase.  
Corresponding data can be found in Appendix 7.2, Table 1.11(ST); Appendix 8.1, Table 2.6.1(C).

APPEARS THIS WAY  
ON ORIGINAL

Twenty, 22 and 23 patients were reported to complete the study in three groups, respectively. **One patient from each group required retreatment.**

Except for some differences in number of male and female patients enrolled into each group, three treatment groups were quite similar with respect to mean age, race, body height, weight, smoking habit, and alcohol intake.

In all three treatment groups, majority of patients were previously treated with other anti-pagetec drugs (sCT, etidronate, pamidronate, etc).

With respect to concomitant medications, all three groups were similar. Most commonly used concomitant medications included analgesics and antipyretics.

Sponsor has provided a list of protocol violations, but most of these violations were related to study entrance criteria such as age and weight. In five additional cases protocol violations were related to elevated LFTs, presence of concurrent cardiac disease, or  $< 3 \times$  the ULN SAP at baseline.

#### 8.5.4.2 Primary efficacy parameters (ITT population)

The proportion of patients with treatment response in three groups is presented in Table 39 (Sponsor's Table 10, vol.1.152,, p. 44).

Table 39. Response to treatment by treatment group

Treatment Group	Responders n (%)	Nonresponders n (%)
Risedronate 20 mg/day		
28 days (N = 23)	6 (26.1) <sup>b</sup>	17 (73.9)
56 days (N = 23)	16 (69.6)	7 (30.4)
84 days (N = 27)	16 (59.3)	11 (40.7)
Total (N = 73)	38 (52.1)	35 (47.9)

<sup>a</sup> Response to treatment was defined as a decrease of 30% or more from baseline in excess serum alkaline phosphatase and a decrease of 50% or more in urinary hydroxyproline/creatinine.

<sup>b</sup> Statistically significantly different from the 56-day group ( $p=0.007$ , Fisher's exact test) and from the 84-day group ( $p=0.024$ , Fisher's exact test).

N = number of patients randomized to the treatment group; n = number of patients in category.

Corresponding data can be found in Appendix 14; Appendix 14.1, Tables 1.1, 2.1, 2.2.

APPEARS THIS WAY  
ON ORIGINAL

Fifty-six- or 84-day treatment with risedronate resulted in significantly greater (compared to 28-day group) percentage of patients with predefined response to therapy. There was a difference between 56- and 84-day treatment groups with respect to percentage responders to therapy.

With respect to baseline SAP and response to risedronate therapy, within the 28-day group, patients with 3 to 5 x the ULN of SAP had the highest response rate (57.1% vs 12.5%) However, in the other two treatment groups, the rate of

BEST POSSIBLE COPY

response increased within the two higher strata.

Overall, higher proportion of patients with elevated SAP and those who had not received previous bisphosphonate therapy responded to risedronate therapy. Patients who had previous bisphosphonate therapy were less responsive to risedronate.

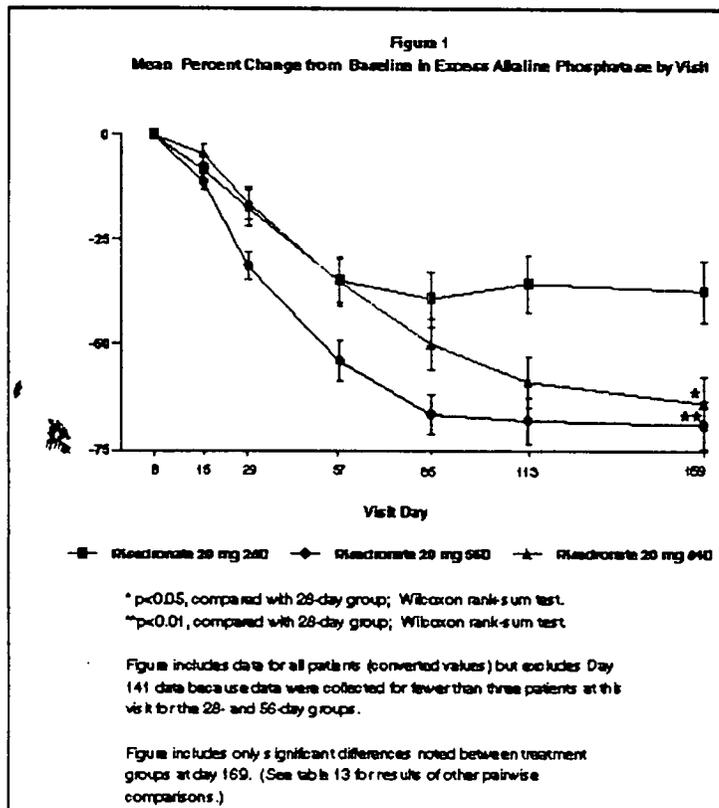
Subset analysis of response rate to risedronate therapy showed no evidence of interaction between treatment, center and stratum.

*Separate analysis of SAP changes (ITT population).*

Visit Day 85 covered the end of treatment for all three groups and the percent change from baseline in excess SAP for 28-, 56- and 84-Day treatment groups were -32.2%, -66.6% and -49.9%, respectively. Overall treatment effect was statistically significant in all three groups ( $p < 0.001$ ). Pairwise comparison of treatment groups (28D vs 56D; 28D vs 84D) also showed significant difference ( $p < 0.001$ ). There was no significant difference between 56D vs 84D groups with respect to mean percent change from baseline in excess SAP. Figures 16 and 17 (Sponsor's Figures 1 and 2, vol. 1.152, pp. 49,52) present the results.

Figure 16. Mean percent change in SAP

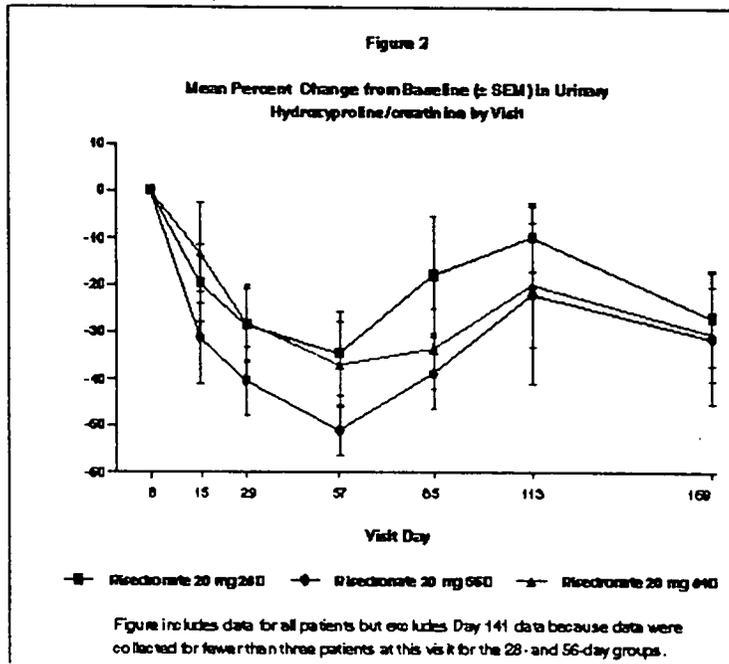
**BEST POSSIBLE COPY**



**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

Figure 17. Mean percent change from baseline in urinary OHPr/Cr.

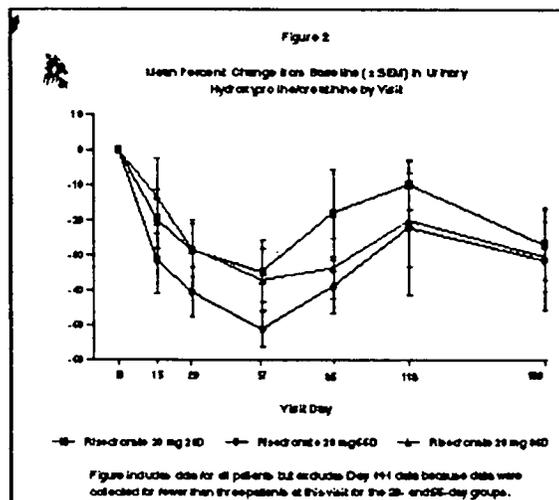


BEST POSSIBLE COPY

*Time to response* (Defined as the time between the onset of treatment and the time of response in days)

The results are summarized in Figure 18 (Sponsor's Figure 3, vol. 1.152, p.53).

Figure 18. Time to response .



BEST POSSIBLE COPY

The mean times to respond for three groups were 31.3, 45.6 and 67.5 days, respectively.

#### *Duration of response*

Since there was no relapse in this study, no analysis on the duration of response was performed..

#### *Retreatment*

APPEARS THIS WAY  
ON ORIGINAL

The protocol called for retreatment of patients who achieved a complete response followed by a relapse. Relapse was defined as increase in SAP by at least 50% of the original total decrease from baseline. None of the risedronate treated patients in this study qualified for retreatment. Two patients, one each in 28D and 56D groups had partial response to risedronate and were retreated. One patient in the 84D group had no response (27% decrease from baseline) to risedronate. These three patients were retreated.

APPEARS THIS WAY  
ON ORIGINAL

#### 8.5.4.3 Safety

Overall 78% of patients in the study experienced one or more AEs. Six patients (one each in 28D and 56D groups) and 4 in the 84D group experienced serious AEs. A total of 7 patients were dropped from the study due to AEs; 3 in 28D, one in 56D, and 3 in 84D groups. Sixteen patients experienced upper GI adverse events, and in 6 of them AEs were considered serious. There was one patient in the 84D group who suffered a humerus fracture after falling.

**Dyspepsia** (mild to moderate) was the most frequent GI adverse event experienced by about \_\_\_\_\_ of patients. One patient in the 28D group discontinued the study due to dyspepsia. Nausea and diarrhea were also experienced by about \_\_\_\_\_ of patients. One additional patient discontinued study due to **dysphagia**.

Seven patients reported skeletal pain during the course of the study. In 5 patients **pain was at known pagetic sites.**

There were no deaths in this study

APPEARS THIS WAY  
ON ORIGINAL

#### **Serious AEs**

Six patients experienced 9 serious AEs (vascular anomaly, carcinoma skin, atrial fibrillation, melanoma skin, infection, UT disease, D.T., humerus fracture). Basal cell carcinoma of skin and atrial fibrillation were considered by the investigators as doubtfully related to the study drug. The investigators did not comment on the causality of serious AEs in 6 patients who completed the study and recovered from these AEs. Only one patient with malignant melanoma of the skin discontinued the study.

#### **Vital signs**

Sponsor reports that vital signs were comparable in three treatment groups.

**Bone safety (metabolism) parameters** (Serum calcium, phosphorus, PTH, urinary calcium, phosphorus, and collagen crosslinks)

There were isolated cases of highest and lowest recorded values of these parameters. Almost equal number of patients (generally one to two patients in each treatment group) recorded these high and low abnormal values. Table 40 (Sponsor's Table 24, vol. 1.152, p.66) presents the number of patients with markedly altered bone metabolism parameters.

Table 40. Patients with out-of-range bone metabolic parameters.

Parameter	Treatment Group - Risedronate 20 mg/day	No. of Patients with ≥1 Markedly High Value	No. of Patients with ≥1 Markedly Low Value
Serum calcium (mmol/L)	28 days	0	0
	56 days	0	1
	84 days	0	0
Serum phosphorus (mmol/L)	28 days	1	1
	56 days	0	4
	84 days	2	0
Serum PTH (pmol/L)	28 days	6	0
	56 days	10	0
	84 days	11	0

<sup>a</sup> Urinary bone safety parameters are not included because no normal ranges were available.  
PTH = parathyroid hormone.  
Corresponding data can be found in Appendix 6.1, Table 2.26.2; Appendix 6.2, Tables 2.1.3, 2.2.3, 2.3.3.

**BEST POSSIBLE COPY**

Mean serum calcium in all three treatment groups decreased from baseline during the treatment period and started to rise generally after stopping of risedronate therapy and reached near baseline at visit Day 169. None of these patients were symptomatic, and received no treatment for abnormal values.

Mean serum phosphorus levels showed similar pattern of changes. Three patients recorded elevated levels of serum phosphorus, but in all three cases their baseline phosphorus levels were high.

A total of 27 patients recorded markedly elevated levels of serum PTH levels, but almost half of these patients had high PTH levels at baseline. PTH level started to increase early (by about Day 15) and reached a plateau during the treatment period. Following completion of treatment serum PTH levels tended to return toward baseline. Two patients (one each in 28D and 56D groups) recorded elevated levels of PTH from Day 15 through Day 169. These two patients did not show any markedly "out-of-range" serum calcium and phosphorus values.

Urinary calcium levels showed slight decrease during the course of treatment with risedronate and tended to return toward baseline after stopping treatment.

Changes in urinary phosphorus/Cr were equivocal. **Urinary collagen crosslinks were measured in insufficient number of patients in this study.**

**Other laboratory parameters**

APPEARS THIS WAY  
ON ORIGINAL

Hematology

-Five patients were reported to experience markedly decreased serum hemoglobin and hematocrit levels; but in 4 of five cases their baseline values were low. Decreased RBC counts were recorded in 6 patients, but all 6 had low baseline counts.

APPEARS THIS WAY  
ON ORIGINAL

LFTs

Three patients recorded elevated (out-of-range) GGTP and AST levels during the study, but their values were elevated at baseline.

Renal function tests

APPEARS THIS WAY  
ON ORIGINAL

One patient in the 84D group recorded markedly elevated serum creatinine and BUN values during the study, but the patient had high values at baseline.

**Sponsor's Discussion and Conclusion**

Treatment with risedronate (20 mg/day for 28, 56 and 84 days) resulted in significantly higher response rates in 56-Day and 84-Day treatment groups (70% and 59% responders, respectively) compared to 28-Day group. Treatment for 84 days did not produce a more rapid or greater magnitude of suppression of biochemical markers than the 56-Day group.

Risedronate was well tolerated by the patient population in this study. The number of patients dropped from the study due to AS were few and equally distributed among three treatment groups. In general, more AS occurred in the 84-Day group than two other treatment groups. More patients in the 84-Day group experienced dyspepsia.

In conclusion, 20 mg of risedronate per day for 84 days appear to be safe and effective for the treatment of patients with Paget's disease of bone.

**8.5.4.5 Reviewer's Comments/ Conclusions of Study results**

Objectives of this open-label study in patients with Paget's disease of bone were to assess the efficacy (biochemical improvement), safety, and time course of action of risedronate. This study is different from preceding trials with respect to dose of the test drug. In other studies, risedronate was primarily tested at a dose of 30 mg/day for 28-84 consecutive days. The inclusion and exclusion criteria of the patients were similar to those of other trials.

The primary (percent change in excess SAP and urinary OHP/Pr/Cr) and secondary

(time to response and duration of response) efficacy endpoints were also similar to those of the preceding trials. Safety evaluations were routine.

The results of this study demonstrated that risedronate, 20 mg/day for variable periods of treatment (28-84 days) was effective in decreasing (to predefined levels) excess of SAP and urinary OHP<sub>r</sub>/Cr. Seventy percent and 59% of treated patients were considered responders based on predefined criteria. Patients who had no previous bisphosphonate treatment appeared to be more responsive to risedronate. The time course of action of risedronate observed in this study was similar to those of other studies.

The data on safety of risedronate at this dose for variable periods showed no differences between the three groups, and overall safety profile of risedronate was similar to that obtained from other trials.

In conclusion, the results of this trial provide evidence in support of safety and efficacy of risedronate in the treatment of patients with moderate to severe Paget's disease of bone.

## 8.6 Trial # 6/ Study # 91020

This study was conducted at City Hospital, Nottingham, U.K. under David Hosking, M.D..

### 8.6.1 Objective/Rationale

To determine the pharmacodynamic activity (changes in biochemical markers and bone pain) and safety of risedronate in patients with increased bone turnover due to Paget's disease of bone. Attempts were also made to assess skeletal bisphosphonate distribution in this patient population.

### 8.6.2 Design

Open-label, single-center study.

**APPEARS THIS WAY  
ON ORIGINAL**

### 8.6.3 Protocol

Protocol amendments included a sample of the informed consent form, and a copy of the CRF.

#### 8.6.3.1 Population, procedure

Male patients  $\geq$  18 years of age and female postmenopausal women were enrolled into this study. There was no upper limit of age for either male or female patients with biologically active (SAP at least 3 x the ULN and scintigraphically or radiologically defined) Paget's disease of bone. The inclusion and exclusion criteria were similar to those of the preceding studies.

All patients received 30 mg of risedronate (3 x 10-mg daily for 84 days, followed by a no treatment of 112 days. This 196-day cycle was repeated in partial responders and in patients with relapse.

Patients were instructed to take risedronate 2 hours before or after a meal with 240 mL of water, and not to recline or lie down for 1 hour postdosing. Patients were also instructed not to drink or eat anything within 2 hours of dosing.

Concomitant medications (other than plicamycin and bisphosphonates) were allowed to continue at stable doses and recorded in CRF.

#### 8.6.3.2 Endpoints

##### Primary efficacy endpoints

APPEARS THIS WAY  
ON ORIGINAL

Percent change from baseline in excess SAP and urinary OHPr/Cr.

##### Secondary efficacy endpoints

Assessment of pain based on patients' subjective perception of pain. The following aspects of pain were evaluated: presence of pain, frequency, location, and severity of pain, ability to perform physical activities, and use of analgesics.

Using a computer model bisphosphonate space (BPS) was calculated at the pretreatment visit and used to predict the dose of risedronate required to decrease elevated levels of SAP.

BPS was calculated as follows:

APPEARS THIS WAY  
ON ORIGINAL

$$\text{BPS} = \frac{\text{Sample count for } ^{51}\text{Cr}}{\text{Sample count for } ^{99m}\text{Tc}} \times \frac{\text{Std. Count for } ^{99m}\text{Tc}}{\text{Std. Count for } ^{53}\text{Cr}} \times \frac{\text{Dilution of std. For } ^{99m}\text{Tc}}{\text{Dilution of std. For } ^{51}\text{Cr}}$$

Tracers injected simultaneously for calculating BPS, were 600 MB of <sup>99</sup>Tc-HMDP and 2.8 MB of <sup>51</sup>Cr-EDTA. BPS space was determined by assaying the count rates of two tracers in plasma samples, collected at 2, 3, 4, and 6 hours after injection.

(Comments: Calculated bisphosphonate space does not appear to be an efficacy endpoint).

##### Safety endpoints

APPEARS THIS WAY  
ON ORIGINAL

Routine clinical and laboratory AEs were monitored following procedures similar to those of preceding trials.

##### Reviewer's comments:

APPEARS THIS WAY  
ON ORIGINAL

Study objectives were clear. Efficacy and safety endpoints were pertinent and conformed with the past and present requirements to demonstrate the effectiveness of the test drug for the treatment of Paget's disease of bone. The criteria for efficacy were the same as used for preceding trials.

#### 8.6.3.3 Statistical considerations

The methodology used for evaluation of efficacy and safety of risedronate was similar to

that used in others trials. All of the efficacy and safety parameters were predefined. Definitions for excess SAP, response (complete and partial and no response), time to response, duration of response, and relapse were the same as used for other trials.

#### 8.6.4 Results

APPEARS THIS WAY  
ON ORIGINAL

##### 8.6.4.1 Patient disposition and comparability

Twenty patients (12 M and 8 F) were enrolled in this study. Except for one patient (voluntarily withdrew from the study), all patients completed the study. With regard to demographic and baseline characteristics, age range for patients was 60-87 years, and the majority of patients (12 of 19) had circulatory secondary diagnosis at baseline. Eight patients had deafness and 8 patients reported histories of upper GI discomfort.

All patients had active Paget's disease of bone (moderate-to-severe) with a mean SAP 1693.3 IU/L and urinary OHP<sub>r</sub>/Cr 0.82 mmol/mmol.

The mean BPS (an index of the extent and activity of Paget's disease) value at baseline was 3.11; approximate 1.8 times higher than the ULN range. Analgesics and antipyretics were the most commonly used concomitant medications.

Protocol violations-

Two patients had baseline (the last values collected before the first dose of risedronate) SAP < 840IU/L. However, these two patients had their pretreatment values at least 3 x the ULN.

Three patients had their pretreatment LFTs (GGPT and total bilirubin) elevated. One patient needed elective surgery of the hip during the retreatment period, but completed the follow-up visits (Days 141 and 196).

**Comments:** Minor protocol violations seem to have occurred in this study, but these violations appear to have no major effects on treatment outcomes.

##### 8.6.4.2 Efficacy endpoint outcomes

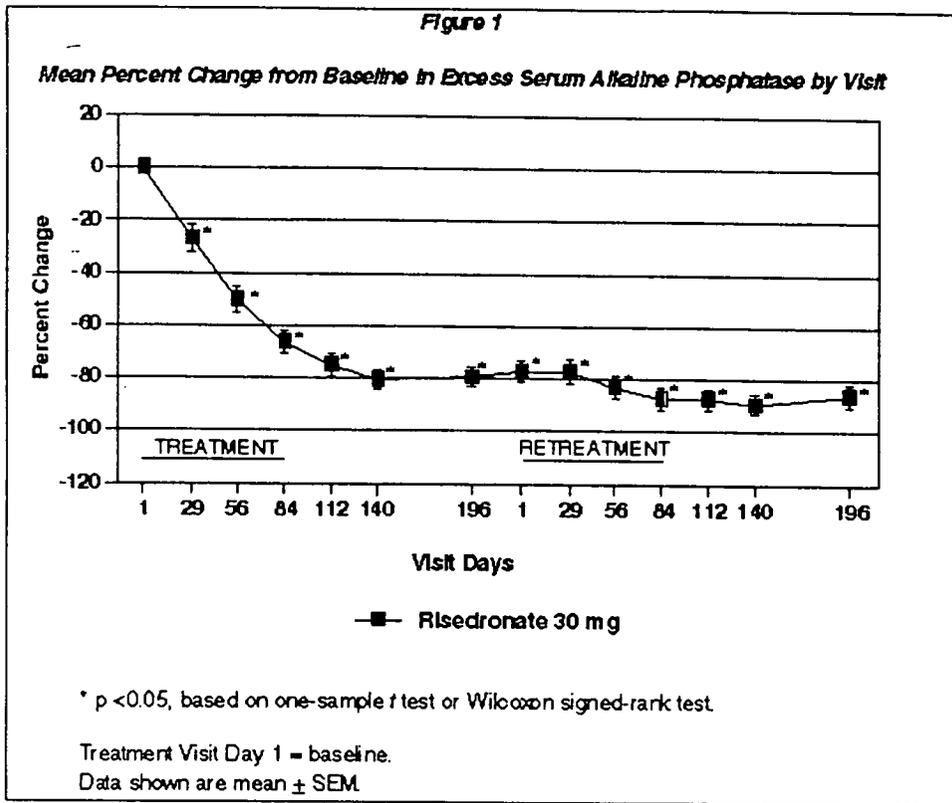
APPEARS THIS WAY  
ON ORIGINAL

SAP

The result is presented in Figure 19 (Sponsor's Figure 1, vol. 1.149, p. 36)

Figure 19. Mean percent change in excess SAP

APPEARS THIS WAY  
ON ORIGINAL



**BEST POSSIBLE COPY**

Immediately after initiation of risedronate treatment, excess SAP started to decrease and on Visit Days 140 reached the nadir (-80%). Decreases were statistically significant from baseline during initial treatment and retreatment periods. The mean of the maximum percent change for each patient during the initial treatment period was -84%, and during combined initial and retreatment periods was -92.6%. The days to maximum mean percent change from baseline during the initial treatment period was about 148 days. During the retreatment period, SAP continued to decrease and on day 140 reached the nadir (-89.5%).

The response rates and time to response are shown in Table 41 (Sponsor's Table 11, vol. 1.149, p. 28).

Table 41. Summary of response to risedronate treatment.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 11  
Summary of Response to Treatment, Relapse, Time to Response, and Duration of Response

	Risedronate 20 mg (N = 20)		
	n	%	Total*
<b>Complete Responses</b>			
Initial Treatment Period	1	5	20
Retreatment Period	5	25	19
Both Treatment Periods Combined	5	25	20
<b>Partial Responses</b>			
Initial Treatment Period	19	95	20
Retreatment Period	13	65	19
Both Treatment Periods Combined	15	75	20
<b>Nonresponses</b>			
Initial Treatment Period	0	0	20
Retreatment Period	1	5	19
Both Treatment Periods Combined	0	0	20
<b>Patients Who Experienced Relapses</b>			
Initial Treatment Period	5	25	20
Retreatment Period	3	16	19
Both Treatment Periods Combined	7	35	20
<b>Time to Response<sup>b</sup></b>			
Initial Treatment Period	70.9 ± 6.9		20
Retreatment Period	250.4 ± 6.4		18
Both Treatment Periods Combined	70.9 ± 6.9		20
<b>Duration of Response<sup>b</sup></b>			
Initial Treatment Period	53.4 ± 8.1		5
Retreatment Period	91.5 ± 28.5		3
Both Treatment Periods Combined	90.9 ± 25.7		7

\* Total number of patients with available numeric/nonrelapsing values.  
<sup>b</sup> Data shown are mean ± SEM (days).  
 N = number of patients enrolled in the study; n = number of patients; % = (n/Total) × 100.  
 Corresponding data can be found in Appendix 8.1, Tables 4.1, 4.2, and 4.3; and Appendix 8.2, Tables 4.1.1, 4.1.2, 4.1.3, 4.5.1, 4.5.2, 4.5.3, 4.6.1, 4.6.2, 4.6.3, 4.7.1, 4.7.2, and 4.7.3.

APPEARS THIS WAY  
ON ORIGINAL

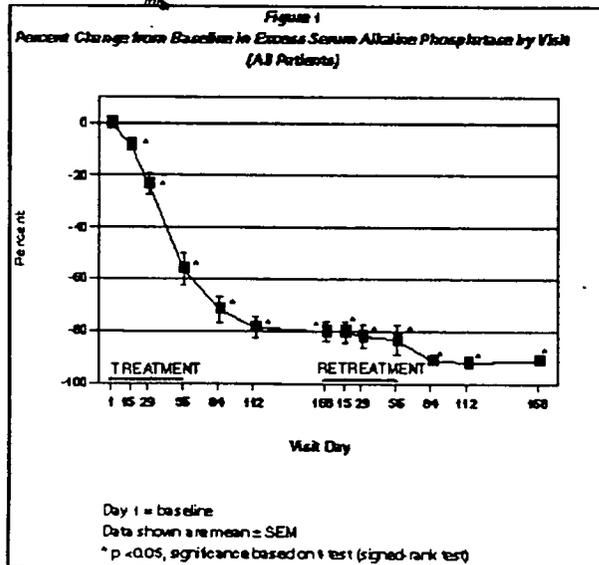
**BEST POSSIBLE COPY**

One patient achieved complete response to therapy during the initial treatment period, and four additional patients responded similarly during the retreatment period. During both treatment periods, the duration of response varied from 53.4 to 91.5 days.

During the entire study period, about 65% of patients treated with risedronate achieved normalization of excess SAP. There were no statistically significant differences between normalized and non-normalized patients with respect to age, sex, body weight, BMI, baseline SAP and urinary OHPr/Cr values, and percent change from baseline in SAP.

Urinary OHPr/Cr

The result is shown in Figure 20 sponsor's Figure 2, vol. 1.149, p. 40).  
 Figure 20 Mean percent change in urinary OHP/Cr.



APPEARS THIS WAY  
ON ORIGINAL

**BEST POSSIBLE COPY**

Risedronate therapy resulted in significant decreases from baseline at all visit days during the initial and retreatment periods. Maximum decrease was reported on Visit Day 112 of retreatment period.

#### **Pain assessment**

APPEARS THIS WAY  
ON ORIGINAL

At baseline, 6 of 20 patients reported no pagetic bone pain. By the end of follow-up period of the first treatment period, 15 of 20 reported bone pain, and by Day 56 of the retreatment period, 18 of 18 patients were reported to be free of pagetic bone pain. Six patients who had no pagetic bone pain at baseline remained pain free through 196 days of the first treatment period.

#### **BPS**

APPEARS THIS WAY  
ON ORIGINAL

BPS was evaluated in 18 patients at baseline and the mean BPS value was 3.11. Risedronate therapy resulted in decrease in mean value to 2.54 at treatment Day 84. In five patients, BPS value decreased to within normal range. The model also showed decrease in percent change from baseline in urinary OHPr/Cr.

#### **8.6.4.3 Safety outcomes**

APPEARS THIS WAY  
ON ORIGINAL

Extent of exposure to risedronate- At dose of 30mg/day of risedronate, 20 patients were reported to a mean total exposure to 4704.0 mg of risedronate over a mean 22.4 weeks.

Overview of AEs- Fifteen of 20 patients experienced 45 AEs. Only 2 patients were reported to experience serious AEs. One patient withdrew from the study voluntarily. There were no deaths in this study and no patient discontinued the study due to AEs.

Adverse events related to digestive and musculoskeletal systems were reported to be most frequent. Four (20%) and six (30%) patients experienced 8 digestive events and 7 musculoskeletal events, respectively.

Two patients were reported to experience serious AEs; one patient required "sigmoid colectomy for diverticulitis" and atrial fibrillation during active treatment, and the other required right total hip replacement. No action was taken regarding risedronate treatment and both patients recovered from AEs (except for At. Fib. which is ongoing). Two patients developed moderate-to-severe digestive AEs; one patient (#14590506) reported exacerbation of baseline indigestion, and the other (#14590510) with a history of duodenal ulcer, experienced moderate dyspepsia, but had normal endoscopic findings.

Risedronate treatment was interrupted/discontinued in four patients due to AEs:

Pt. (#14590506)- Four days of interrupted treatment due to a severe episode of influenza.

Pt. (# 14590510)- Treatment discontinued during a diabetic foot infection.

Pt. (#14590512)- Treatment was interrupted due to moderate dyspepsia.

Pt. (#14590517)- Had hip replacement surgery and treatment discontinued..

**Comments:** Except for the last patient, risedronate treatment was restarted after a short period of interruption.

**Individual relevant cases with adverse events-** There were few cases with episodes of abnormal pulse rates and/or blood pressure readings. These episodes were not associated with any AEs.

#### Laboratory evaluations

APPEARS THIS WAY  
ON ORIGINAL

*Serum calcium-* During the initial treatment period serum calcium decreased slightly ( $< 0.1$  mmol/L) and started to return toward baseline after stopping risedronate treatment. During the retreatment period serum mean serum calcium levels remained close to baseline. Mild hypocalcemia was asymptomatic.

*Serum phosphorus-* During both the initial and retreatment periods with risedronate, mean serum phosphorus level decreased slightly  $< 0.1$  mmol/L and returned towards baseline after stopping of treatment.

*Urinary calcium/Cr-* Urinary calcium/Cr (2-hour/ mmol/mmol) decreased (about  $- 0.5$  mmol/mmol) from mean baseline after initiation of treatment with risedronate and remained below baseline during the remainder of the study.

**Comments:** Similar minor changes in bone metabolism parameters were observed with other approved bisphosphonates for the same indication. These changes related to the effects of bisphosphonates on bone turnover and/or kidney.

*Hematology -* Sponsor reports no clinically relevant mean changes in hemoglobin, RBC, hematocrit, MCV, MCHb, ESR, and platelet counts.

*LFTs-* There were no clinically relevant changes from baseline in serum total protein, serum albumin, total bilirubin, SGPT, or GGPT. A few patients had elevated levels of one or more of the LFTs at baseline and during the course of the study.

*Renal function tests-* The overall results showed no clinically relevant changes from baseline in serum creatinine, urinary RBC and WBC, total protein, or sodium. There were two patients who had their baseline serum creatinine values elevated and it remained stable or increased further during the course of the study. One patient had a history of nephrolithiasis and a positive (2+) urine dipstick for RBCs. Urine dipstick for RBC was positive in another patient at visit Day 56.

*Other serum chemistry values-* No clinically relevant changes from baseline were reported for serum lactic dehydrogenase and electrolytes.

#### Sponsor's Discussion and Conclusion

APPEARS THIS WAY  
ON ORIGINAL

Risedronate therapy at a dose of 30 mg daily for 84 days resulted in significant decreases in biochemical markers (SAP and urinary OHP/Cr) of patients with moderate to severe Paget's disease of bone. The number of patients with Paget's disease related

bone pain also decreased following risedronate treatment. All patients treated with risedronate responded (based on predefined decrease in SAP and urinary OHPr/Cr) to initial treatment and continued to show further improvement during retreatment. Repeated courses of risedronate treatment maintained the reduced level of biochemical markers and induced remission of the disease process. After the initial treatment, about 25% of patients (5 of 20) experienced relapse based on predefined criteria. Relapse generally occurred at the end of treatment period. Risedronate-induced biochemical improvement generally lasted for 3 to 4 months after discontinuation of therapy.

During the initial treatment period about 40% of treated patients achieve normalization of SAP. Additional 5 patients achieved normalization of SAP during the retreatment period. Patients who failed to achieve normalization of SAP during this study, had higher baseline values for SAP and urinary OHPr/Cr. It appears that patients with very high baseline SAP may require longer duration of treatment with 30 mg/day dose of risedronate or higher dose of the drug.

At baseline, 14 of 20 (70%) patients had bone pain related to Paget's disease of bone. At the end of the initial treatment period, 75% of patients were free of bone pain. During the retreatment period (by Visit Day 56), all patients were free of bone pain and remained pain free during the rest of the study.

Bisphosphonate space (BPS) study indicated that this model "cannot be reliably used to determine the dose of risedronate required to normalize either AP activity or OHP/Cr excretion."

Change in the bone metabolism parameters (serum calcium, phosphorus, and urinary calcium/Cr) were reflective of pharmacologic effects of risedronate on bone turnover and kidney. Mild and short lasting hypocalcemia and hypophosphatemia were asymptomatic. Return of serum calcium and phosphorus levels to baseline after completion of risedronate treatment probably resulted via homeostatic regulatory mechanisms.

AE profile of risedronate raised no major safety issues and none of the serious events (3 in 2 patients) were related to risedronate. Asymptomatic hypocalcemia occurred in about 15% of treated patients.

Moderate to-severe dyspepsia occurred in two patients during the study. Both patients completed the study, and in one patient endoscopic examination revealed no abnormalities. Both received H<sub>2</sub> blockers and recovered.

Risedronate treatment did not cause major changes in hematologic parameters, LFTs, renal function tests. Since this study had no parallel control group, minor changes in these variables could not be compared objectively.

In conclusion, risedronate therapy (30 mg/day for 84 days) initially, led to significant decreases in biochemical markers (SAP and urinary OHPr/Cr excretion) in patients with moderate-to-severe Paget's disease of bone. Retreatment resulted in "additional suppression" of the biochemical indices of the disease activity. Risedronate therapy also resulted in improvement of pagetic bone pain, but this was not a controlled study.

BPS study did not appear to reliably predict the dose of risedronate required to normalize the biochemical indices (SAP and urinary OHPr/Cr excretion) of disease activity.

Risedronate was well tolerated and provided a safe AE profile.

#### 8.6.5 Reviewer's Comments/Conclusions

APPEARS THIS WAY  
ON ORIGINAL

A small uncontrolled study was carried out to provide supporting evidence for efficacy (biochemical improvement and relief of pagetic bone pain) and safety of risedronate for the treatment of patients with moderate-to-severe Paget's disease of bone.

The dosage regimen of risedronate for initial and retreatment of patients with moderate-to-severe Paget's disease of bone was similar to that of most other trials (controlled and uncontrolled). The duration of treatment was longer than those of the controlled studies, but similar to that of two other uncontrolled trials.

Decreases in excess SAP and urinary OHPr/Cr from baseline were statistically significant throughout the study over 196 days. The maximum mean percent changes in SAP and OHPr/Cr were -89.5% and -83.5%, respectively. About 65% (13 of 20) of patients achieved normalization of SAP values ( $\leq 280$  IU/L).

The overall efficacy results in terms of biochemical response and improvement in pagetic bone pain following treatment with risedronate were in agreement with the results of two large uncontrolled trials (# 91007 and 90003). Though the risedronate treatment duration was not the same as followed in two controlled trials (#RPD-001694 and 88040), the efficacy results of this small uncontrolled study in terms of the effects of risedronate on primary disease activity, i.e., biochemical response rate, maximum response, proportion of patients with normalization of biochemical markers, duration of response, response to retreatment were both qualitatively and quantitatively similar to those of controlled studies. Improvement in pagetic bone pain observed in this study was also noted in studies RPD-001694, 91020, and 91007). These studies were carried out in patients with moderate-to-severe Paget's disease of bone. (SAP  $\geq 3$  x the ULN).

Changes in bone metabolic parameters were similar to those of other controlled and uncontrolled trials and they confirmed the pharmacodynamic effects of risedronate on bone turnover.

From the safety standpoint, the results of this study are in agreement with those of other trials. The safety profile appears to be comparable to that emerged from other trials. Additionally, the safety profile is quite similar to that of marketed bisphosphonates (oral and i.v. formulations) for the treatment of Paget's disease of bone.

In conclusion, the results of this small uncontrolled study provides supporting evidence of efficacy and safety of risedronate for the treatment of patients with moderate-to-severe Paget's disease of bone.

#### 9 Overview of Efficacy- Comparative results between studies

The sponsor has conducted six studies to demonstrate the efficacy and safety of risedronate for the treatment of patients with Paget's disease of bone. Of these six studies, one was active-controlled trial in which the efficacy and safety of risedronate were compared with etidronate disodium (Didronel), an approved bisphosphonate for the treatment patients with symptomatic Paget's disease of bone. Active control design of this study was quite valid to compare the efficacy and safety of the new drug (risedronate) with that of etidronate at the the recommended dose (400 mg/day for 180 days). -

In the risedronate (30 mg/day for 60 days) treated group, 80% of patients achieved  $\geq$  75% reduction (maximum response) in excess SAP, compared to the Didronel group (20%). The time to achieve maximum response was significantly faster than the Didronel group (31.33 vs 79.4 days). Also, risedronate therapy was found to cause normalization of SAP in significantly greater percentage of patients compared to the etidronate group (73% vs 15%). During the entire study period, a smaller percentage of patients showed a relapse in the risedronate group compared to the Didronel group (3.3% vs 15.1%). In both groups, non-responders to previous treatment for Paget's disease of bone were found to be responders to current treatment; with slightly more patients in the risedronate than Didronel group. Irrespective of baseline mean values of SAP (2 times to  $\geq$  7 x the ULN), risedronate treated patients achieved greater mean reductions in baseline SAP values. With respect to change in serum skeletal AP and urinary OHP<sub>r</sub>/Cr ratio, patients in the risedronate group showed significantly greater reduction than the Didronel group.

Improvement in bodily pain (determined by Short Form Health Survey, SF-36) was noted in the risedronate group immediately after completion of treatment and it was maintained up to the end of follow-up period (Day 360). Didronel treatment did not result in significant change from baseline in bodily pain during the corresponding time period. Risedronate treated patients also showed improvement in their ability to perform physical activities (based on Quality of Life assessment).

Postmarketing clinical experience with Didronel (as well as from clinical trials), has shown reduced radionuclide uptake (in bone scans), and reductions in pagetically elevated cardiac output and skin temperature.

From safety point of view, the proportion of patients who reported AEs (related or unrelated to study medications) in either treatment group was similar. Clinically, the upper GI adverse events are important with respect to oral bisphosphonates and in this respect such AEs were similar in distribution between the two groups. None of the patients in either treatment group experienced severe upper GI adverse events. Risedronate in this trial demonstrated a safety profile comparable to that of Didronel for the treatment of Paget's disease of bone.

The remaining five studies (# 88040, 91007, 90009, 90003, and 91020) are all open studies. Study # 88040 is a short-term (28 days) multicenter dose-response trial (at doses of 10, 20, and 30 mg daily) involving a patient population similar to that of the active-controlled trial. The efficacy endpoints were the same objective parameters as used in the latter study. The overall results of this trial demonstrated a dose response with respect to: a) the proportion of patients who responded to treatment and, b) percent

decrease in baseline excess SAP. The 30-mg group showed about 80% of treated patients as responders and maximum decrease in baseline SAP excess occurred at this dose. The safety profiles of all three doses of risedronate were similar. Bone biopsy was performed in a small number of patients in one center, and the results showed normal lamellar bone formation during treatment with risedronate. One patient in this trial had esophageal "pill erosion" with the use of risedronate (suggestive of adherence to esophageal mucosa). This led to the development of [redacted] with shorter esophageal transit time. Histomorphometric data were inadequate to draw any definitive conclusion on this issue. Data from postmarketing clinical experience are likely to generate more information.

Study 91007 was carried out with three different dosage forms (30-mg [redacted], 10-mg [redacted] and [redacted], containing 30 mg of risedronate as [redacted]), and the overall results showed efficacy of all three dosage forms in reducing SAP and OHPr/Cr. The frequency and severity of pain decreased slightly during the course of the study. The study reports improvement in sleep disturbance as well as in activities affected by pain. The study also provided data on the effect of retreatment in relatively small groups (n=24 to 34 per group) of patients who were either resistant to initial treatment or experienced a relapse. These patients showed mean decreases ( [redacted] ) in SAP values at Day 196 of the follow-up period for the retreatment. The gelatin-capsule with [redacted] showed maximum decrease in mean value.

In one center, sponsor analyzed the effects of risedronate treatment on pagetic bone lesions. These data were not presented in the study report in vol. 1.134 of the NDA. Data were presented in Integrated Summary of Efficacy in vol. 1.157. The results are summarized in Table 42 (sponsor's Panel 30, vol. 1.157/p71)

Table 42 Summary of radiographic changes in pagetic skeletal lesions.

Panel 30			
Summary of Radiographic Changes in Pagetic Lesions			
	Baseline to 6 months (N = 25)*	Baseline to 12 months (N = 16)*	Six to 12 months (N = 17)**
Improvement	22 (42.3%)**	17 (46.0%)	5 (14.3%)
Deterioration	3 (5.8%)	2 (5.4%)	5 (14.3%)
No change	24 (46.1%)	16 (43.2%)	24 (68.6%)
Can't assess	3 (5.8%)	2 (5.4%)	1 (2.8%)
p-value	< 0.001	< 0.001	not significant
* N = number of patients with available data. ** Percent is calculated as a column percentage.			

APPEARS THIS WAY  
ON ORIGINAL

Radiographic changes from Month 6 to 1 year showed no difference in the proportion of pagetic lesions (%) demonstrating improvement (in 5 patients) from the proportion of lesions (%) with deterioration (5 patients). Majority of skeletal lesions (68.6%) remained unchanged during this period. Pagetic lesions associated with skull and weight bearing bones were reported to show improvement. Data are too small to draw any definitive conclusion). There was some improvement in lesions of femur and tibia with osteolytic

BEST POSSIBLE COPY

fronts. There was one patient with preexisting femoral fissure fracture, which progressively worsened during the course of the study. Pagetic skeletal lesions are known to improve spontaneously. A larger data base on radiologic changes in pagetic lesions is needed to demonstrate improvement of lesions due to risedronate treatment.

Study # 90009 included patients with severe Paget's disease of bone with baseline SAP at least 9 times the ULN and non-responsive to other treatment regimens (calcitonin, etidronate, pamidronate, or 10-mg dose of risedronate) for this indication. Although the number of patients in this study was small (n=13), the mean percent decrease from baseline in SAP was about 80% after initial treatment (30 mg/day for 56 day) and about 90% after a second course of treatment.

Study # 90003 provides information on the time course of action of biochemical changes to 20 mg (10 mg caps) of risedronate /day for 28, 56, or 84 days with non-treatment follow-up for up to 140 days. Risedronate 20 mg/day was also effective in decreasing excess SAP and urinary OHP<sub>r</sub>/Cr. At this dose of risedronate, 70% of patients achieved at least 30% or more decrease in excess SAP from baseline. Risedronate, 30 mg/day for 60 days in other trials resulted in a maximum response ( $\geq 75\%$  decrease in excess SAP) in about 85% of treated patients. Normalization of excess SAP occurred in about 73% of patients. A dose of 30mg/day (as in Study # 88040) for 28 days showed 80% of patients as responders compared to 67% in the 20-mg group. These data support selection of 30 mg/day for 60 days as the recommended dose for this indication. There were no significant differences between capsules and tablets with respect to biochemical improvements in this patient population.

The overall efficacy results of these Phase II and III studies seem to provide substantial evidence of efficacy of 30 mg of oral risedronate (for 60 days) for the treatment of patients with Paget's disease of bone. Compared to other oral bisphosphonates (etidronate, alendronate, and tiludronate), the recommended duration of treatment is shorter; 60 days vs 6 months for etidronate and alendronate, and 3 months for tiludronate. At the recommended dose, risedronate also showed normalization of SAP in 73% of patients compared to 10% of patients treated with etidronate, 63% of patients treated with alendronate (as reported in the literature), and 24% of patients treated with tiludronate. In responsive patients, risedronate seemed induce biochemical and symptomatic remission for 6 months or more. Patients with relapse are likely to respond to retreatment. Patients who are non-responsive to other antipagetic treatment regimens also responded to risedronate therapy

In addition to biochemical and symptomatic (bodily pain, physical activity, sleep disturbances) improvements, one would expect to see some evidence in support of radiographic improvement in skeletal lesions and/or improvements in neurological deficits resulting from risedronate therapy. These trials have provided minimal or no such data.

10 Overview of Safety

APPEARS THIS WAY  
ON ORIGINAL

Assessment of safety of risedronate 10 to 30 mg/day for 28 to 84 days was made by evaluating AEs (including upper GI and non-vertebral fractures), laboratory tests, hematology, blood and urine chemistries), PE, body system reviews, vital signs, and eye

examination with slit lamp.

The most frequently reported AEs in these trials included infection, arthralgia, diarrhea, dyspepsia, headache, pharyngitis, and hypocalcemia (asymptomatic). Serious AEs (including acute myelogenous leukemia, TIA, atrial fibrillation, cancer), in most of these trials were considered not related to risedronate, or relationship to the study drug was doubtful or not determinable.

There were 7 deaths (one in Didronel and 6 in risedronate patients) in these trials, and none were considered study drug-related. One patient in the risedronate group was diagnosed to have acute myelogenous leukemia about 2 years after completing the study and died about a year later. The patient was reported to operate a "dry cleaning" business for many years and was exposed to dry cleaning organic solvents (including benzene). The investigator of this trial felt this AE was unrelated to risedronate.

Review of cases of withdrawals due to AEs, revealed no definitive information regarding their relationship to study drugs ( Didronel or risedronate) in these trials. Some of these AEs (colitis, substernal pain, nausea, lapse of consciousness, elevated liver enzymes, dyspepsia, diarrhea, cerebral ischemia and related symptoms), which led to discontinuation of treatment were all appeared to have no clear relationship to risedronate treatment.

Because risedronate is a bisphosphonate, its GI (particularly upper GI) AEs needed critical review with reference to those of marketed bisphosphonates for Paget's disease of bone. In the active-controlled trial (#RPD 001694), there were no significant differences between the two groups (risedronate and Didronel) with respect to upper GI AEs. One patient in the risedronate group was reported to experience moderate abdominal pain due to gastritis (confirmed by endoscopic examination). Another GI adverse events reported in these trials included a case with reflux esophagitis (confirmed by endoscopy), In Study # 91007

7 patients were reported to experience moderate-to-severe upper GI AEs. (dyspepsia, melena, dysphagia, abdominal pain, and esophagitis The patient with melena showed severe diverticulitis by colonoscopy. The same patient exhibited small gastric erosion with gastroscopic examination. Concomitant use of NSAIDs or aspirin may increase the incidence of diarrhea, nausea, and dyspepsia. The overall GI AEs need to be addressed in the product labeling and Patient Package Insert.

A small number of patients experienced non-vertebral fractures. Except for one patients who developed an atraumatic rib fracture while crawling in the attic, all other fractures were reported to be traumatic.

In one study (#91007), three patients experienced acute iritis, but did not require discontinuation of risedronate treatment. Acute iritis was also reported to occur in association with the use of i.v. pamidronate.

No formal drug-drug interaction study was carried out. Sponsor has attempted to obtain some information on drug interaction from the Study RPD-001694, under nine drug categories: NSAIDs; H2-blockers, proton pump inhibitors, and antacids; calcium channel blockers; thiazides; glucocorticoids; anticoagulants; anticonvulsants; and cardiac

glycosides. The number of patients with possible drug-drug interactions were too small to draw any conclusion.

Continuous use of risedronate is likely to cause some changes in biochemical parameters of bone metabolism based on its pharmacodynamic action on bone remodeling process. These changes are asymptomatic (e.g., hypocalcemia) and will be mentioned in the product labeling as done with other marketed bisphosphonates.

In conclusion, the safety profile of risedronate appears to be similar to that of other oral bisphosphonates. Most of the safety issues discussed earlier could be addressed adequately in the draft labeling and Patient Package Insert (PPI).

#### 11 Labeling Review

An Annotated Package Insert has been provided by the sponsor and each Section of the proposed labeling has been commented.

##### DESCRIPTION

APPEARS THIS WAY  
ON ORIGINAL

The first sentence on its mechanism of action should be deleted. DESCRIPTION section is not the appropriate place for this statement.

##### CLINICAL PHARMACOLOGY

APPEARS THIS WAY  
ON ORIGINAL

**Mechanism of Action-** No comments from clinical standpoint. Pharmacology reviewer may have some comments on statements related to preclinical findings.

##### Pharmacokinetics:

**Absorption-** Biopharm reviewer may have comments on this subsection. In a recent amendment (dated October 16, 1997) to the NDA the sponsor has removed the option of taking Actonel 2 hours after the last meal of the day. Under this subsection the statement regarding dosing 2 hours after **dinner needs revision.**

**Distribution-** Pharmacology and Biopharm reviewers may have some comments on statements presented under this subsection.

**Metabolism-** Like other bisphosphonates there is no evidence in support of systemic metabolism of risedronate.

**Renal Insufficiency-** The sentence "Exposure to risedronate was estimated to increase...clearance of 20 mL/min." It is not clear what this statement means clinically. This statement needs revision. Biopharm reviewer may have some suggestion.

A separate subsection with a heading of **Elimination** should be included. The Biopharm reviewer may suggest the contents under this subsection. A statement on the elimination rate from the human bone should be added.

A new subsection with a heading of **Special Populations** needs to be added to this section. The contents of these subsections should be similar to those of SKELID (tiludronate disodium).

**Pharmacodynamics.**

APPEARS THIS WAY  
ON ORIGINAL

**Paget's Disease**

A brief description of the disease with clinical manifestations should be added to this subsection. Phase III clinical trial that has been referred to in this subheading is the active-controlled trial. Clinical Studies subsection is the appropriate place for mentioning the results of Phase III study. This subsection needs revision.

**Clinical Studies**

This subsection needs major revisions. Six clinical studies referred to here need brief description regarding design, objective, and study endpoints. The Active-control trial is the major trial described under this subsection. From the clinical reviewer's standpoint there are several issues regarding presentation of results from the active-controlled trial. These and other issues pertinent to chemistry, pharmacology, biopharm could be resolved by teleconference with the sponsor.

**INDICATIONS AND USAGE**

APPEARS THIS WAY  
ON ORIGINAL

This section should be revised to read:

"ACTONEL is indicated for treatment of Paget's disease of bone (osteitis deformans).

Treatment is indicated in patients with Paget's disease of bone (1) who have a level of serum alkaline phosphatase (SAP) at least twice the upper limit of normal, or (2) who are symptomatic, or (3) who are at risk for future complications from their disease, or (4) who are nonresponsive to previous anti-pagetic therapy."

**CONTRAINDICATIONS.**

Sponsor's statements are appropriate and acceptable.

APPEARS THIS WAY  
ON ORIGINAL

**WARNINGS**

This section should include the following statements:

"Bisphosphonates may cause upper gastrointestinal disorders, such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer (See ADVERSE REACTIONS)."

**PRECAUTIONS**

Under **General** subsection, the last statement regarding use of Actonel in

patients with severe renal impairment, needs revision based on pK data in this target population or based on clinical experience with other approved bisphosphonates.

Under subsection **Paget's Disease**, The last sentence starting with "Of nine patients..." should be deleted. This statement has no relevance to **PRECAUTIONS** (also mentioned under Clinical Pharmacology section).

**Information to Patients:**

A the end of this subsection the following statement should be added "Concomitant use of NSAIDs or aspirin and Actonel may increase the incidence of GI adverse experiences." The biopharm reviewers may have some comments regarding dosing instructions.

**Laboratory Tests:**

Not applicable for this indication.

APPEARS THIS WAY  
ON ORIGINAL

**Drug Interactions:**

Regarding interactions with calcium supplements or antacids, can biopharm reviewers provide some data on % decrease in bioavailability of the drug with concomitant use of these agents.

Other:

APPEARS THIS WAY  
ON ORIGINAL

Delete "wide" from the second line. Add the following sentence at the end "Since NSAID or aspirin use is associated with gastrointestinal irritation, caution should be used during concomitant use with Actonel (See ADVERSE REACTIONS).

**Drug Laboratory Test Interactions:**

Statements are appropriate and acceptable.

APPEARS THIS WAY  
ON ORIGINAL

**Mutagenesis, Impairment of Fertility and Pregnancy:**

Pharmacology reviewer may have some comments on these sections.

**Nursing Women and Pediatric Use:**

These sections are appropriate and acceptable.

APPEARS THIS WAY  
ON ORIGINAL

**ADVERSE REACTIONS**

Add to the end of the second paragraph "Among these adverse experiences, nausea and headache (in the Didronel group) and colitis (in the risedronate group) were considered possibly drug-related. The remaining adverse experiences were considered doubtfully drug related."

It would be desirable to include a table showing the most common adverse events (%) reported in > 5% of pagetic patients from active-controlled study. Followed by the table showing drug-related adverse experiences from the same study. **All tables and figures need to be numbered.**

To add a brief description of minor changes in hematological parameters (hemoglobin, WBC, hematocrit and RBC, platelets, etc) before the subheading Laboratory Test Findings.

#### OVERDOSAGE

APPEARS THIS WAY  
ON ORIGINAL

The following sentence should be added to the end of the second paragraph "Dialysis would not be beneficial." Pharmacology reviewer may have some comments on the last paragraph regarding lethal effect of risedronate in laboratory animals.

APPEARS THIS WAY  
ON ORIGINAL

#### DOSAGE AND ADMINISTRATION

The recommended risedronate dose and duration of initial and retreatment are based on clinical trials submitted in support of the efficacy and safety of the drug. Statements to avoid lying down for 10 minutes after taking risedronate and dosage adjustment in patients with severe renal impairment may need revisions based on biopharm review.

#### HOW SUPPLIED

Chemistry reviewer may have some comments.

APPEARS THIS WAY  
ON ORIGINAL

#### ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY

This section should be located after **CLINICAL PHARMACOLOGY** section before **INDICATIONS AND USAGE**.

#### 12 Conclusion

APPEARS THIS WAY  
ON ORIGINAL

The results from both active-controlled and open-label trials provide substantial evidence of efficacy and safety of risedronate (30 mg daily for 2 months) for the treatment of patients with Paget's disease of bone. From efficacy standpoint, the results have demonstrated decrease in disease activity as manifested by marked and sustained reductions (and normalization in majority of patients) in markers of bone turnover. Biochemical improvement with risedronate treatment was accompanied by improvements in bodily pain and osteolytic pagetic bone lesions in some patients. Data on improvement of cardiac output, elevated skin temperature, or hearing loss were not available from these studies.

Demonstrated safety profile of risedronate at the recommended dose is quite similar to that of other approved oral bisphosphonates for this indication.

**The overall benefits of risedronate treatment in this patient population outweigh**

the risks.

13 Recommendation

The NDA 20-835, has provided substantial evidence of efficacy and safety of risedronate for the treatment of patients with Paget's disease of bone, and it is approvable

APPEARS THIS WAY  
ON ORIGINAL

S/  
S.N.Dutta, M.D.  
S/  
1-23-98

CC: Orig. NDA 20-835  
HFD-340  
HFD-510/SND/12/4/97

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

792-5114

*No additional Safety Update is necessary after 30 1997*

December 29, 1997 */S/ 3-10-98*

NDA 20-835  
 Actonel (risedronate sodium)  
 P and G

Review and Evaluation of 120-Day Safety Update Data  
 (Addendum to MOR)

1. Data reviewed: Additional data obtained since data cutoff date (October 1, 1996) for the NDA on the following:

- a. Safety data for the non-treatment extended follow-up period (Days 361 to 540) for Study RPD-001694.
- b. Final report of Study 1996028, a GI endoscopy study in healthy volunteers with aspirin-induced stomach erosion.
- c. Tables of normal reference ranges, conversion units, marked abnormality criteria for laboratory data in the original report on Study RPD-001694. This information was not provided in the original NDA submission.
- d. In addition to safety data, sponsor has provided some data on percentage of patients with biochemical remission or relapse in Study # RPD-001694.

2. Summary review:

APPEARS THIS WAY  
 ON ORIGINAL

- a. Safety data during extended follow-up period.

Summary of AEs is presented in Table 1

Table 1. Summary of AEs in Didronel and risedronate groups during extended follow-up period.

	400 mg Didronel (N=40)	30 mg Risedronate (N=50)
No. (%) of Patients with AEs	19 (47.5)	27 (54.0)
No. (%) of Patients with Serious AEs	4 (10.0)	6 (12.0)
No. (%) of Patients with Upper GI AEs	0	5 (10.0)
No. (%) of Patients with Mod. to Severe Upper GIAEs	0	1 (2.0)

Table 1 Contd.

No. (%) of Dropouts Due to AEs	0	1(2.0)
No. (%) of Deaths	0	1 (2.0)

There were no differences between two treatment groups with respect to AEs that occurred during the extended follow-up period. None of the serious adverse events in either treatment group appeared to be related to the study medication, except for one patient in the Didronel group who experienced severe hip pain (considered possibly related to study drug). This patient withdrew from the study.

About twice the number of patients in the risedronate group experienced musculoskeletal (11 vs 5) and digestive (8 vs 3) AEs compared to the Didronel group.

Following AEs occurred in  $\geq 5\%$  of patients in either treatment group: back pain, pain (unspecified), infection (unspecified), arthralgia, bone pain, cataract, and UTI.

There were no clinically significant differences between two treatment groups with respect to the proportion of patients with serious AEs, deaths, or dropouts due to AEs. The percentage of patients in the risedronate group with upper GI AEs was higher compared to the Didronel group, but their relationship to the study medication was doubtful since treatment was stopped for at least 10 months.

b. GI endoscopy study

**APPEARS THIS WAY  
ON ORIGINAL**

The effects (esophageal and gastroduodenal) of oral administration of risedronate (5 or 30 mg/day for 28 days) or no treatment were assessed in normal healthy volunteers with aspirin-induced (325 mg tablet Q.E.D.) stomach erosion. The report indicated no interference with risedronate in healing of stomach mucosa due to aspirin.

This short-term (28 days of treatment) study provides no new significant information regarding safety of risedronate for pagetic patients.

c. Tables of normal reference ranges for laboratory data for Study RPD 001694. Normal reference ranges for laboratory data, conversion factors and units, and abnormal criteria are appropriate and have no direct bearing on the safety update report of this study.

d. Effectiveness update data. At Month 18, 17 of 32 (53.1%) risedronate-treated patients with available data were reported to be in biochemical remission (normalized total SAP) compared to 4 of 29 patients (approx.14%) with available data in the Didronel group.

Six of sixty patients (10.0%) in the risedronate group were reported to relapse during the non-treatment follow-up period, compared to 14/53 patients (26.4%) in the Didronel group.

3. Conclusion and recommendation: This NDA amendment (dated 7/31/97) on 120-Day Safety Update data from the extended, off-drug, follow-up period of the pivotal trial (# RPD 001694), provide no new clinically significant information on risedronate and Didronel in the treatment of Paget's disease of bone.

APPEARS THIS WAY  
ON ORIGINAL

/S/   
 S.N.Dutta, M.D.   
 /S/ 12-130-97

CC: Orig. NDA 20-835 (MOR)  
HFD-340/HFD-510/SND/12/30/97

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL