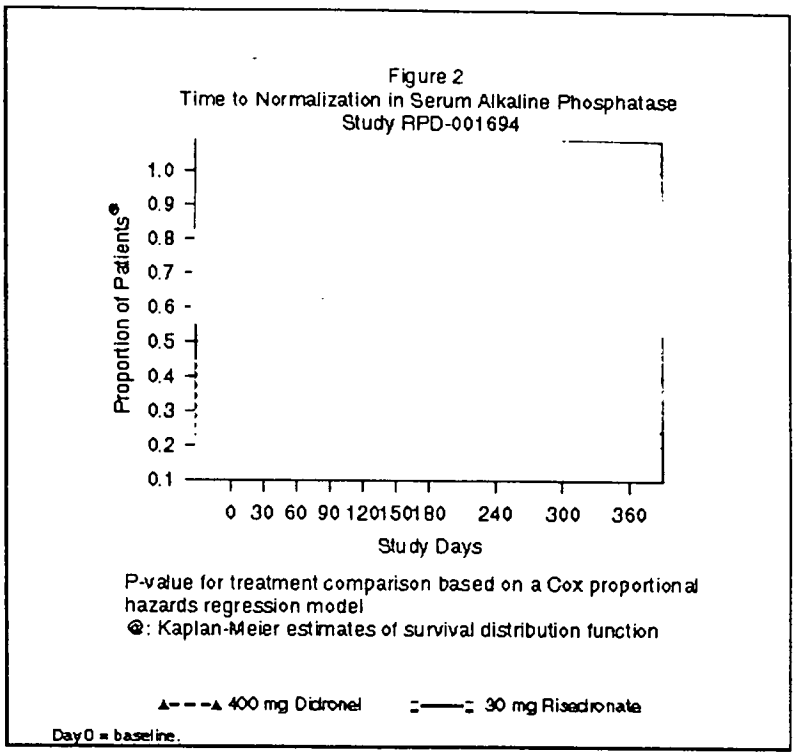

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Percent change in baseline total SAP excess

Baseline excess was defined as:

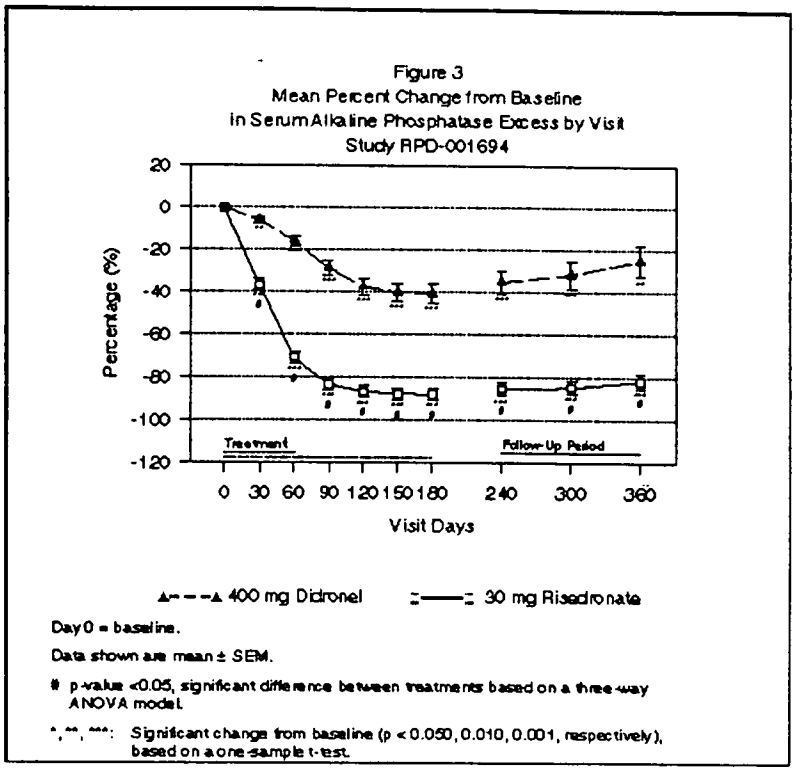
Baseline excess= Measured baseline total SAP-midpoint of normal SAP range for the reference laboratory.

Normal range for SAP:

Age (Years)	*Male* (U/L)	*Female* (U/L)
15 to 19		
20 to 58		
≥ 59		
	15-58	
	≥ 58	

Figure 2 (Sponsor's Figure 3, vol. 1.116, p. 72) presents the results.

Figure 2. Mean percent change from baseline in total SAP excess.



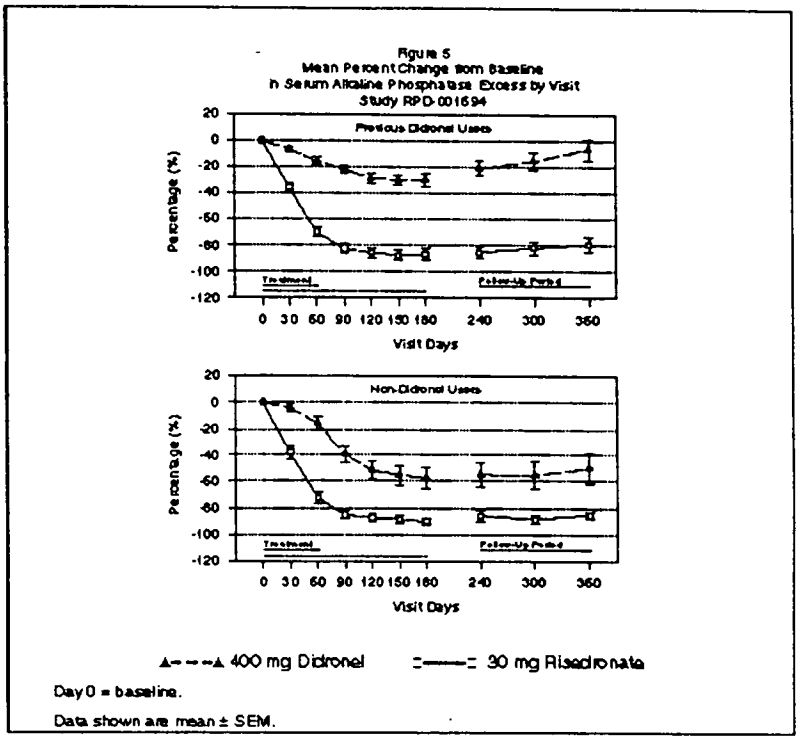
In both the Didronel and risedronate groups significant decreases from baseline excess occurred at Day 30 of treatment and thereafter continued to decrease during the treatment and follow-up periods. At baseline, there was no significant difference between the two treatment groups with respect to mean baseline total SAP values (497.4 U/L Didronel vs 482.4 U/L risedronate). Between-group comparison of reductions in baseline total SAP showed significantly higher decreases ($p < 0.001$) at all visit Days during both treatment and follow-up periods.

Treatment-by-investigator interaction

Sponsor states that there was no treatment-by-investigator interaction with respect to reduction in total SAP excess.

Subgroup analysis was performed based on previous Didronel users and non-users, and a quantitative type of interaction was reported. In the risedronate group, there were greater percent reductions compared to the Didronel group, irrespective of previous Didronel treatment The results are shown in Figure 3 (Sponsor's Figure 5, vol. 1.116,p.79).

Figure 3. Mean percent change from baseline in total SAP excess relative to previous Didronel treatment.



In the Didronel group, patients who had no prior Didronel therapy achieved greater reductions in total SAP excess compared to those who had received Didronel treatment previously.

Other subgroup analysis

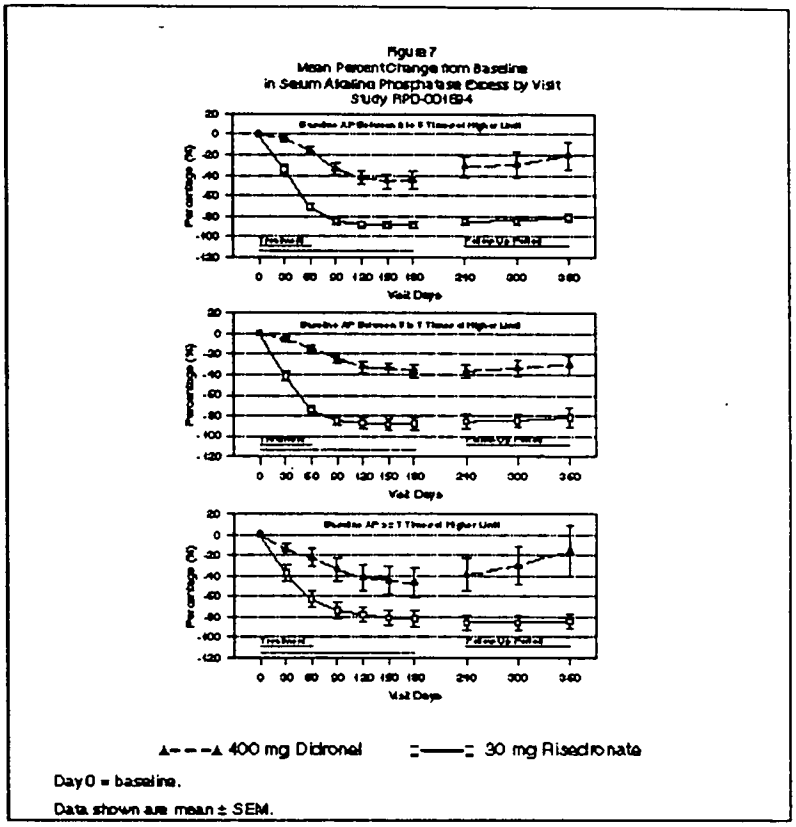
Defined by baseline excess in total SAP:

a) Baseline total SAP $\geq$ 2 to 3 times the ULN.

b) Baseline total SAP $\geq$ 3 to 7 times the ULN.

c) Baseline total SAP $\geq$ 7 times the ULN.

The results are shown in Figure 4 (Sponsor's Figure 7, vol. 1.116, p.80).



The risedronate group took slightly longer period to maximum response (> 75% reduction) in total SAP excess in the subgroup with baseline AP > 7 times the ULN. But all subgroups achieved 80% or more reduction in SAP at endpoint 1 (Visit Day 180). During the follow-up period all three subgroups showed similar response. The subgroup with baseline SAP > 7 times the ULN showed a slightly greater reduction at endpoint 1.But due to small number of patients in the latter group (n=6), no meaningful interpretation could be made about this observation.

Maximum reduction in total SAP

In the risedronate group maximum reduction from baseline in total SAP was significantly greater than that observed in the Didronel group during both treatment and combined treatment and follow-up periods. However there was no significant difference between two treatment groups with respect to Days to maximum reduction from baseline (181 vs 183 days).

Relapse

A patient was considered to suffer a relapse during the study, if he or she manifested at least 50% increase in SAP from the nadir and total SAP

value was > 2 times the ULN. The results are summarized in Table 19 (Sponsor's panel 17, vol. 1.116, p. 75).

Table 19. Patients with relapsed SAP.

Panel 17

No. (%) of Patients Who Had a Relapse in Total Serum Alkaline Phosphatase[a]

Study RPD-001694

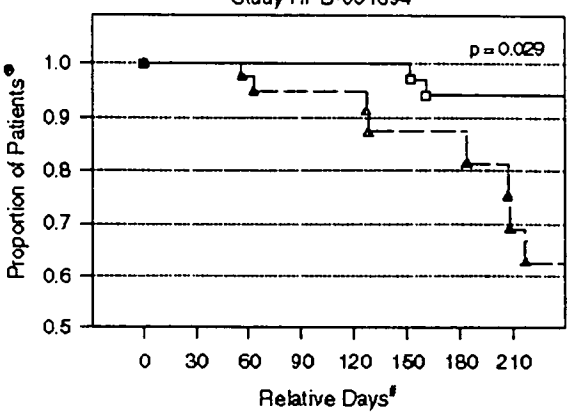
	400 mg Didronel (N = 60)	30 mg Risedronate (N = 60)	P-value
No. (%) of Patients Who Relapsed[a]			
Treatment Period			
Yes	0	0	
No	53 (100.0%)	60 (100%)	
Both Periods[b]			0.045
Yes	8 (15.1%)	2 (3.3%)	
No	45 (84.9%)	58 (96.7%)	

[a] Only those patients who demonstrated at least a 10% reduction in total serum AP were included in the analysis (53 Didronel; 60 risedronate). Patients were considered to have a relapse if they experienced at least a 50% increase from their lowest level of total serum AP and had a total serum AP value greater than two times the upper limit of the normal range.
[b] Both the treatment and follow-up periods.
Corresponding data can be found in Tables 13.1 and 13.2; Appendix 7.1, Listings 7.1 and 7.2.

The results showed no relapse during the treatment period in either group. During the combined treatment and follow-up periods, 3.3% in the risedronate ans 15.1% of patients in the Didronel groups showed relapse (p=0.045). The time-to-event (relapse) distribution curve is presented in the Figure 5 (Sponsor's Figure 4, vol. 1.116, p. 76).

Figure 5. Time to relapse in SAP.

Figure 4
Time to Relapse in Serum Alkaline Phosphatase
Study RPD-001694



P-value for treatment comparison based on a Cox proportional hazards regression model
@: Kaplan-Meier estimates of survival distribution function
#: Number of days relative to the day when total serum AP was at the lowest level

▲---▲ 400 mg Didronel □——□ 30 mg Risedronate

There was a significant difference (favoring risedronate group) in the time-to-relapse distribution of patients in two treatment groups. Response to the study drugs was further evaluated with respect to previous treatment for Paget's disease of bone. The results are shown in Table 20.
(Sponsor's Panel 18, vol. 1.116, p. 77).

Table 20. Response to current treatment in patients with prior therapy.

Panel 18

No.(%)of Patients Who Responded to Current Therapy by Response to Previous Paget's Treatment

Study RPD-001694

Response to Previous Paget's Treatment	400 mg Didronel			30 mg Risedronate		
	N	< 30% Reduction	≥ 30% Reduction	N	< 30% Reduction	≥ 30% Reduction
< 30% Reduction	12	4 (33.3)	8 (66.7)	5	1 (20.0)	4 (80.0)
≥ 30% Reduction	17	8 (47.1)	9 (52.9)	20	0	20 (100)
Unknown Response	15	3 (20.0)	12 (80.0)	18	0	18 (100)

Corresponding data can be found in Tables 14.1, 14.2, and 14.3.

Of 12 non-responders (in the Didronel group) to previous antipagetic treatment, 8 (66.7%) showed ≥ 30% reduction in total SAP (responders) to current Didronel treatment. In the risedronate group, there were total 5 such patients (non-responders to previous treatment), and 4 of 5 patients were reported to be responders risedronate therapy. Almost equal number of patients (n=15-18) with "unknown" response to previous antipagetic treatment were enrolled into two treatment groups. Of these patients, 80% to 100% of them adequately responded to current Didronel or risedronate treatment.

Results analyzed in evaluable-patient subgroup

Both primary and secondary efficacy parameters were analyzed.

Mean decreases (from baseline excess) in total SAP were 39% and 87.4% in the Didronel and risedronate groups, respectively at end point 1 ($p < 0.001$). Similarly, at endpoint 2, in both groups total SAP decreased significantly from baseline. Decreases in the risedronate group at both endpoints were significantly more than that observed in the Didronel group ($p <= 0.001$). (Sponsor's Table 21.1, vol. 1.116, p. 222

Eighty-five percent of patients in the risedronate group (n=58) as opposed to 21.1% of patients in the Didronel group (n=57) achieved maximum response (> = 75% reduction) in total SAP. Similar percentages of paints in respective treatment groups showed maximum response during the 360-day study period (Sponsor's Table 21.2, vol. 1.116, p.223).

About 76% of evaluable patients in the risedronate group achieved normalization of total SAP at endpoints 1 and 2 compared to 10.5% and 15.8% in the Didronel group at corresponding endpoints.

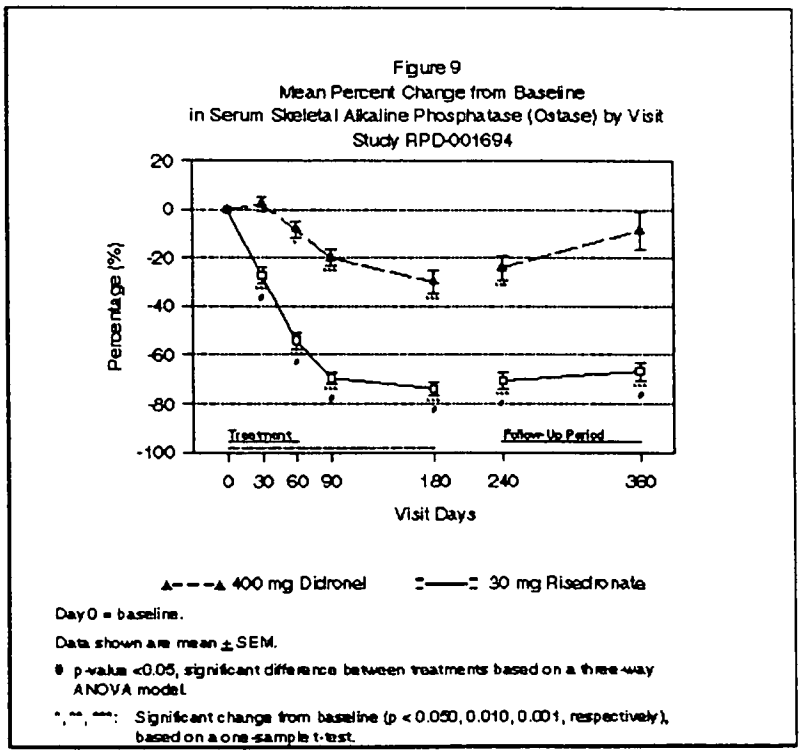
No relapse occurred during the treatment period. in either group. In the risedronate group, 3.3% of patients showed a relapse during the entire study period as opposed to 15.1% in the Didronel group (p=0.045)..

Serum Skeletal AP (Ostase)
ITT analysis

Normalization with treatment- Seventy-three percent of patients in the risedronate group (n=60) were reported to achieve normalization of serum skeletal AP (during the treat and follow-up periods) as opposed to about 17% to 18% of patients in the Didronel group (n=60) during corresponding periods. Median time to normalization was significantly shorter (93 days) in the risedronate group than the Didronel group (> 360 days) The difference between two treatment groups with respect to time to normalization was significant ($p < 0.001$).

Change from baseline- The results are shown in Figure 6 (Figure 9, vol. 1.116, p.83).

Figure 6. Percent change from baseline in serum skeletal AP.



Baseline mean values were almost identical for the two treatment groups. In the risedronate group, decreases in serum skeletal AP were significant at all Visit Days 30, 60, 90, 180, 240, and 360 (Endpoint 2). In the Didronel group, significant decreases were observed on Visit Days 60-240. During the treatment period and the entire duration of the study, maximum reductions in serum skeletal AP were -114 μg/L and -66.5 μg/L for the risedronate and Didronel groups, respectively. During the entire study period, similar differences were observed between two treatment groups with respect to maximum reductions in serum skeletal AP. With regard to time to maximum reduction in serum skeletal AP, there was no difference between the two groups.

Subgroup analysis

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Subgroup analysis was performed with regard to response to test drugs in patients with or without previous antipagetic treatment.

In the risedronate group, response to current treatment at endpoints 1 and 2 was similar, irrespective to previous Didronel treatment. Decreases in serum skeletal AP ranged between [redacted] at two endpoints. Whereas, in the Didronel group, mean decrease in serum skeletal AP in previous non-users was greater than that in previous Didronel users.(about 41% vs 20%).

Changes in Urinary deoxypyridinoline /creatinine ratio (DPyr/Cr)

ITT analysis- The results are summarized in Table 21 (Sponsor's Panel 21, vol. 1.116, p. 86).

Table 21. Percent of patients with normalized DPyr/Cr.

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Panel 21

No. (%) of Patients Who Achieved Normalization of Urine Deoxypyridinoline/Creatinine and Days to Normalization

Study RPD-001694

	400 mg Didronel (N = 60)	30 mg Risedronate (N = 60)	P-value
Treatment Period			< 0.009
Yes	33 (55.0%)	51 (85.0%)	
No	27 (45.0%)	9 (15.0%)	
Both Periods[a]			< 0.008
Yes	34 (56.7%)	52 (86.7%)	
No	26 (43.3%)	8 (13.3%)	
Days to Normalization			< 0.001
Median	182	31.0	

[a] Both the treatment and follow-up periods.
Corresponding data can be found in Tables 20.1 and 20.2; Appendix 7.1, Listings 7.1, 7.2, and 7.3.

In the risedronate group, , of patients achieved normalization of DPyr/Cr during the entire study period compared to of patients in the Didronel group. Differences in response to treatment between the two groups at the two endpoints were significant. Also, in the risedronate group, median days to normalization were significantly shorter in comparison to the Didronel group.

Percent change from baseline in DPyr/Cr is shown in Table 22.

Table 22. Mean percent change from baseline in Dpyr/ Cr ratio.

Day	400mg Didronel			30 mg Risedronate		
Treatment Period	Mean	SEM	N	Mean	SEM	N
Visit Day 30	-10.1	4.4	60	-43.5*	4.0	59
Visit Day 60	-21.7	3.6	58	-57.2*	2.9	57
Visit day 90	-27	3.8	58	-48.1*	2.7	57
Visit day 180	-39.5	3.6	56	-51.0**	2.3	54
Endpoint 1	**-38**	**3.5**	**60**	**-50.3‡**	**2.2**	**59**
Follow-up Period						
Visit Day 240	-25.6	4.4	53	-47.0*	3.1	53
Visit Day 360	-15,6	5.5	47	-47.1*	3.6	52
Endpoint 2	**-15.9**	**4.5**	**60**	**-45.9***	**3.4**	**59**

* $p < 0.001$; ** $p=0.007$; ‡ $p= 0.002$ (Between group comparison).

There were greater reductions from baseline in mean urinary DPyr/Cr ratios in the risedronate group at all Visit Days compared to the Didronel group. Evaluation of maximum reduction from baseline in urinary Dpyr/Cr ration showed no significant differences between treatments during the treatment and follow-up periods (See sponsor's Table 19.2, vol. 1.116, p. 218). Also, there was no significant between-treatment difference with respect to time to maximum reduction (defined as the number of days from the first dose to the first occurrence of the lowest level).

With respect previous Didronel use or not, percent change from baseline in DPyr/Cr was reported to be comparable between the previous Didronel users and non-users. Previous non-Didronel users showed greater reduction in urinary DPyr/Cr ratio to current Didronel treatment than previous users. Similar results were reported with respect to any previous treatment for the Paget's disease of bone.

Attempts were made to evaluate the correlation between the percent change from baseline in serum AP excess and the percent change from

baseline in serum skeletal AP at Visit Days 30, 60, 180, and 360. The two efficacy parameters were reported to be positively correlated at all time points of the study (See sponsor's Figure 12, vol. 1.116, p. 91).

Quality of Life (QOL) assessment

The SF-36 questionnaire form measured the eight health scales (Physical functioning, social functioning, role-physical and role-emotional, mental health, vitality, bodily pain, and general health).Two additional components (physical and mental) were derived from these 8 scales. A high score in any scale and/or components indicated "better health state."

The results related to QOL (bodily pain scale) are summarized in Table 23 (Sponsor's Panel 23, vol. 1.116, p.93).

Table 23. QOL assessment based on SF-36 questionnaire.

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Panel 23

Mean Change From Baseline in Quality of Life: Bodily Pain by Visit

Study RPD-001694

Day	400 mg Didronel			30 mg Risedronate			P-value
	Mean	SEM	n	Mean	SEM	n	
Baseline	54.95	3.1	57	50.92	3.2	59	0.340
Treatment Period							
Day 60	5.3	2.9	56	10.6**	2.8	59	0.233
Day 180	3.2	3.3	53	9.0**	3.2	53	0.270
Endpoint 1	1.8	3.2	57	8.4**	2.9	59	0.210
Follow-up Period							
Day 360	6.5	3.6	46	9.1**	3.4	49	0.805
Endpoint 2	1.6	3.4	57	9.9**	3.0	59	0.130

Endpoint 1: Last measurement during the treatment period.
Endpoint 2: Last measurement during the study.
, *: Significant change from baseline ($p \leq 0.010$ and 0.001, respectively).
Corresponding data can be found in Table 30.2 and Appendix 7.1, Listing 15.4.

The results showed significant improvement from baseline in bodily pain scale in the risedronate group at all Visit days studied. The Didronel group also manifested improvement in bodily pain, but the difference from baseline scores was not statistically significant.

Improvement in bodily pain as a result of treatment regimens was further analyzed to assess the number and percentage of patients with no pain at each study visit. The results are summarized in next table.

Table 24 (Sponsor's panel 25, vol. 1.116, p. 95).

Table 24. Shift table for patients without bodily pain.

Panel 25

Shift Table for Patients Who Were Without Bodily Pain

Study RPD-001694

Day		400 mg Didronel Baseline		30 mg Risedronate Baseline	
		Pain	No Pain	Pain	No Pain
Day 60	Pain	47	3	49	1
	No Pain	2	2	5	3
P-value		0.655		0.102	
Day 180	Pain	44	3	43	1
	No Pain	3	3	5	3
P-value		1.000		0.102	
Endpoint 1	Pain	46	3	46	1
	No Pain	3	3	6	3
P-value		1.000		0.059	
Day 360	Pain	36	3	35	1
	No Pain	4	2	8	3
P-value		0.705		0.020	
Endpoint 2	Pain	47	4	45	1
	No Pain	4	2	9	3
P-value		1.000		0.011	

Note: P-value based on McNemar's test.
Endpoint 1: Last measurement during the treatment period.
Endpoint 2: Last measurement during the study.
Corresponding data can be found in Table 30.4; Appendix 7.1, Listing 15.4.

In the risedronate group, 8 patients who had pain at baseline were reported to have no pain at Visit day 360 (p=0.020). Similar results were reported at Endpoint 2 (last measurement of the study). Percent of patients without bodily pain by Visit is shown in Table 25 (Sponsor's Panel 26, vol. 1.116, p. 96).

Table 25. Percent of patients without bodily pain.

Panel 24

Mean Change From Baseline in Quality of Life: Physical Component Scale by Visit

Study RPD-001694

Day	400 mg Didronel			30 mg Risedronate			P-value
	Mean	SEM	n	Mean	SEM	n	
Baseline	40.46	1.4	54	39.72	1.3	58	0.725
Treatment Period							
Day 60	0.8	1.1	50	3.2**	1.2	53	0.131
Day 180	0.7	1.2	47	1.5	1.3	51	0.741
Endpoint 1	0.3	1.1	54	1.9	1.1	58	0.455
Follow-up Period							
Day 360	2.0	1.2	42	1.6	1.2	47	0.862
Endpoint 2	0.2	1.1	54	2.6*	1.0	58	0.190

Endpoint 1: Last measurement during the treatment period.
Endpoint 2: Last measurement during the study.
*, **: Significant change from baseline ($p \leq 0.050$ and 0.010, respectively).
Corresponding data can be found in Table 32.2; Appendix 7.1, Listing 15.4.

QOL (Physical component scale)

Greater improvement in physical component was also reported in the risedronate group at Visit Days 60, 180, Endpoint 1, and Endpoint 2 than the Didronel group. However, the differences in improvement between two groups were statistically significant only at Visit day 60 and Endpoint 2.

8.1.4.3 Safety

Exposure to study drugs
In both treatment groups, more than 98% of patients were reported to be compliant of , regarding the dosing schedule.

Summary of adverse events (AES):

There were no significant differences between two treatment groups with respect to AE profile. Some relevant AS are presented in Table 26.

Table 26. Adverse events

	Didronel 400 mg/day	Risedronate 30 mg/day
No. Of Serious AEs	10	26
No. (%) of Pt. With Serious AEs	9 (14.8)	15 (24.6)
No. of Expeditable AEs	16	33
No.(%) of Pt. With Expeditable AEs	14 (23.0)	20 (32.8)
No.(%) of Pt. With non-vertebral Fx	1 (1.6)	4 (6.6)
No. Of Upper GI AEs*	16	19
No.(%) of Pt. With Upper GI AEs	12 (19.7)	12 (19.7)
No. (%) of Pt. With Mod. To Severe Upper GI AEs	2 (3.3)	3 (4.9)
No.(%) of Dropouts	14 (23.0)	8 (13.1)
No. (%) of Deaths	1 (1.6)	2 (3.3)

* "Upper GI AEs included duodenitis, dyspepsia, dysphagia, esophagitis, gastritis, gastritis hemorrhagic, GI disorder, hemorrhage esoph.

hemorrhage GI, hematemesis, melena, pain abd., pain chest substernal, ulcer duoden, ulcer duoden hem, ulcer duoden perforation, ulcer duoden perhem, ulcer duoden react, ulcer esoph, ulcer peptic, ulcer peptic hem, ulcer peptic per, ulcer peptic perhem, ulcer peptic react,ulcer stomach, ulcer stomach hem, ulcer stomach per, ulcer stomach perhem, and ulcer stomach react."

Between of patients in either treatment group experienced AS. Though a larger percent of patients in the risedronate group was reported to experience serious AEs (sAEs), none of these sAEs were considered related to study medication. In the risedronate group, except for colitis and enterocolitis, other serious AEs appeared non-drug related. In the Didronel group, only one patient experienced enteritis that could have some relation to medication. The remaining sAEs appeared non-drug related.

In each treatment group, 4-5 patients discontinued the study due to AEs One patient with colitis in the risedronate group, and one patient with nausea and headache were considered "possibly drug related." One patient in the Didronel group and two patients in the risedronate group died during the course of the study, but none appeared to be drug related.

Musculoskeletal and digestive AEs occurred most commonly. There were no significant differences between two treatment groups with respect to percent of patients with musculoskeletal and/or digestive AEs. However, in the risedronate group, slightly higher percentages of patients experienced arthrosis, bone disorder, and joint disorder. Myalgia was more common in the Didronel group than risedronate group.

Similar percentage of patients in either treatment group experienced possibly or probably drug related AEs that included digestive, musculoskeletal and body as a whole (abdominal pain, headache, infection, and pain).

Upper GI AES

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Oral bisphosphonates are known to cause upper GI AEs. The number and percent of patients with upper GI AES are presented in Table 27 (sponsor's Panel 34, vol.1.116/p108).

Table 27. Patients with upper GI AEs.

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Panel 34

No. (%) of Patients With Upper Gastrointestinal Adverse Events[a] by Intensity[b]

Study RPD-001694

	400 mg Didronel (N=61)				30 mg Risedronate (N=61)			
COSTART	Mild	Moderate	Severe	Overall	Mild	Moderate	Severe	Overall
Dyspepsia	6 (9.8)	1 (1.6)	0 (0.0)	7 (11.5)	3 (4.9)	0 (0.0)	0 (0.0)	3 (4.9)
Dysphagia	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)
GI Disorder	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.3)	2 (3.3)	0 (0.0)	4 (6.6)
Abdominal Pain	4 (6.6)	1 (1.6)	0 (0.0)	5 (8.2)	5 (8.2)	2 (3.3)	0 (0.0)	7 (11.5)
Pain Chest Substernal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)
Total	12 (19.6)	2 (3.2)	0 (0.0)	14 (23.0)	11 (18.0)	5 (8.2)	0 (0.0)	16 (26.2)

[a] Upper GI adverse events includes the following COSTART descriptions: duodenitis, dyspepsia, dysphagia, esophagitis, gastritis, gastritis hemorrhagic, GI disorder, hemorrhage esoph, hemorrhage GI, hematemesis, melena, pain abdo, pain chest substern, ulcer duoden, ulcer duoden hem, ulcer duoden perforation, ulcer duoden pe hem, ulcer duoden react, ulcer esoph, ulcerpeptic, ulcerpeptic hem, ulcerpeptic per, ulcer peptic pe hem, ulcer peptic react, ulcer stomach, ulcer stomach hem, ulcer stomach per, ulcer stomach pe hem, and ulcer stomach react.

[b] This table contains counts of patients. If a patient experienced more than one episode of an adverse event, only the most severe was included in the patient counts.

Corresponding data can be found in Tables 42.5 and 42.7; Appendix 8.1, Listings 11, 13.1, and 13.4.

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There were no serious upper GI AEs in either treatment group. The two treatment groups were similar with respect to overall upper GI AEs. **One patient in the risedronate group was reported to experience possibly drug related abdominal pain. An endoscopic examination confirmed gastritis.**

Non-vertebral fractures

Higher percentage of patients in the risedronate group was reported to experienced non-vertebral fractures compared to the Didronel group (6.6 vs 1.6). All fractures were reported to be related to trauma, except for one in the risedronate group. **This patient developed a non-traumatic hairline fracture of the right femur**. With respect to healing of non-vertebral fractures, sponsor claims that all fractures "had a normal healing time."

Vital signs and anthropometric measurements

There were no clinically meaningful mean changes in blood pressure, pulse rate, body weight, and height during the course of the study in either treatment groups (Sponsor's Tables 34.1-34.4, vol.1.116, pp. 299-307).

Slit-lamp eye examination

Three patients from each treatment group showed "worsening" of

cataract. One patient in the risedronate group had worsening of diabetic retinopathy. (**Comments**: With regard to worsening of cataract, there was no difference between two treatment groups and the causality could not be assessed because of small number patients in each group. Similarly, an objective evaluation of the possible cause for worsening of diabetic retinopathy in a risedronate-treated patient is difficult. None of the approved bisphosphonates for either Paget's disease of bone and/or postmenopausal osteoporosis have shown treatment-related worsening of cataract in clinical trials. With Aredia (pamidronate for injection) rare cases of uveitis, iritis, scleritis, and episcleritis have been reported).

Clinical laboratory evaluations

a. Hematology

Hemoglobin- . At baseline there was no significant difference between two treatment groups with respect to mean hemoglobin values. During the treatment period mean baseline values decreased slightly in both treatment groups (more so in the Didronel group) and tended to return toward baseline during the follow-up period. Decreases in hemoglobin values were not accompanied by any decreases in hematocrit and RBC count. **A downward shift from normal to low hemoglobin values was noted in the risedronate group (n= 4) at Day 150, compared to none in the Didronel group.** (**Comments:** Clinical significance of this observation is not clear. Attempts will be made to address this issue in the final discussion of the safety results of all clinical trials submitted to NDA).

There were no significant changes from baseline values in either treatment group with respect to neutrophils, lymphocytes, monocytes, and eosinophils. One patient in the Didronel group(# 36421801) and two (# 33901831 and 58751825) in the risedronate group were reported to have abnormal WBC and/ or differential counts at baseline and/or during the study.

Patient # 36421801- This patient had high WBC , and lymphocytes (77%) at baseline and during the course of the study. Neutrophils were below the lower limit of normal , during the study. Clinical significance of these finding was not clear to the investigator. The patient was found to have breast cancer following Day 360.

Patient # 33901831- This patient had low lymphocyte count at Days 30-90. However, baseline and at other time points lymphocyte values were within normal range. **The investigator felt that mild lymphopenia was related to the study drug.**

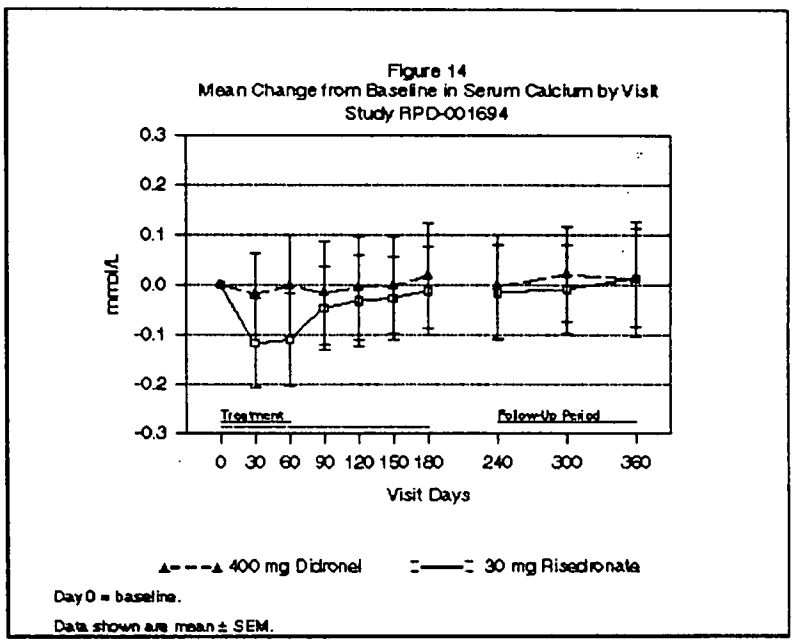
Patient # 58751825- This patient manifested a high atypical lymphocyte value , at Day 250 only. The investigator felt that the level of elevation was not clinically significant.

Chemical laboratory parameters

a. Serum Glucose - No clinically meaningful changes were reported to occur during the study.

b. Serum calcium- Changes in serum calcium during the study are shown in Figure 7 (Sponsor's Figure 14, vol.1.116, p. 114).

Figure 7. Changes in serum total calcium.



In the risedronate group, serum calcium decreased by about 0.1 mmol/L at Days 30 and 60, Thereafter, the values returned toward baseline values. The Didronel group showed no significant changes over time in serum calcium.

Phosphorus - In the risedronate group, serum phosphorus decreased by 0.2 mmol/L at days 30 and 60. Thereafter, returned near baseline level and remained stable during the rest of the study. In the Didronel group, serum phosphorus initially increased at Day 30 by about remained elevated until Day 180. Thereafter, returned toward baseline during the follow-up period. Patients in the Didronel group were reported to show upward shifts (from normal to high and low to normal values). There was no upward shift in serum phosphorus in the risedronate group.

Three patients in the Didronel group and 5 in the risedronate group were reported to manifest clinically significant changes or marked abnormality in glucose, phosphorus or calcium values. There were 4 patients with elevated serum glucose levels at several visits. In all the patients elevated

serum glucose levels were due to existing diabetic condition.
One patient in the Didronel group experienced hyperphosphatemia during the entire treatment period and it was attributed to Didronel therapy. Three patients in the risedronate group had low serum calcium (asymptomatic) at various time points of the treatment period. Hypocalcemia was attributed to study drug.

Liver function tests

There were no clinically significant changes from baseline in mean ALT/SGPT, AST/SGOT, GGT, total bilirubin, and serum albumin values,

Seven patients (4 risedronate and 3 Didronel) had markedly elevated values of liver function tests at several time points of the study. None of these abnormal values were attributed to either risedronate or Didronel.

Renal function tests

No clinically relevant changes from baseline in urinary protein, urinary RBCs and WBCs, or serum creatinine were reported in either of the treatment groups.

Sponsor's Discussion and Conclusions

An active controlled study was designed to evaluate the efficacy and safety of risedronate in the treatment of Paget's disease of bone. Didronel (etidronate disodium) was selected as active-control medication because it is an approved drug for this indication and it has several years of accumulated clinical experience. An active-control design of the study provided the opportunity of comparing the therapeutic benefits (e.g., percent of patients with normalization of SAP, onset of significant reduction in SAP, duration of biochemical remission, and percent of patients with durable remission) of risedronate with those of Didronel.

Decrease in SAP was the primary efficacy endpoint as used in clinical trials with other approved regimens for this indication. Treatment with risedronate (30mg/day for 60 days) resulted in normalization of SAP in 73.3% of patients as opposed to 15% of patients in the active-control (Didronel, 400 mg/day for 180 days) group. The duration of biochemical remission in majority of risedronate treated patients was significantly longer than that resulting from Didronel therapy. The median time to normalization for the risedronate group was significantly shorter than that for the Didronel group (90 days vs > 360 days). Eighty-five percent of patients in the risedronate group achieved greater than 75% reduction in elevated levels of SAP, compared to 20% of patients in the Didronel group.

Biochemical improvement induced by risedronate was accompanied by marked improvement in pain. Improvement in pain was evident at the end

of risedronate treatment (Day 60) and improved pain status was maintained over a period of about 300 days. Didronel-treated patients also showed some improvement in pain but difference from baseline was never statistically significant.

Risedronate therapy also showed significant difference in the rate of relapse at the end of the study; Fifteen percent of patients in the Didronel group relapsed as opposed to 3.3 % in the risedronate group.

In terms of safety, there was no major clinically significant difference between the risedronate and Didronel treatment groups. The overall safety profile of these two products are quite similar and similar to those of bisphosphonates as a class of compounds.

Didronel is an approved drug that has accumulated considerable safety data from post-marketing clinical experience. The results of this active-control study demonstrate the safety of risedronate for the treatment of Paget's disease of bone and it is comparable to Didronel,

Risedronate, 30 mg/day for 60 days is a safe and effective treatment regimen for Paget's disease of bone based on its demonstrated induction of rapid and sustained biochemical remission, improvement in pain, and decrease in the rate of relapse. All of the efficacy endpoints showed significantly greater benefits compared to Didronel, 400mg/day for 180 days. There was no significant differences between two treatment regimens with respect to their safety profiles in this patient population.

Reviewer's Comments:

This multi-center active-controlled study was well designed to demonstrate the safety and efficacy of risedronate compared to Didronel in the treatment of patients with Paget's disease of bone. Study objectives were clear and appropriate for the stated objectives.

Both the efficacy (primary and secondary) and safety endpoints of the study were commensurate with those of the approved drugs for this indication. In this study, the maximum response with respect to the primary efficacy endpoint (i.e., reduction in total SAP excess) was based on $\geq$ 75% reduction in baseline total SAP excess, This standard was more stringent than that generally used in clinical trials with other approved drugs for this indication.

Study population with appropriate inclusion and exclusion criteria was enrolled. The number of subjects randomly assigned to two treatment groups were adequately explained and supported by sample size estimation. Therapeutic intervention was prospectively planned and selection of the risedronate dose (30 mg/day) was based on the results of several Phase II safety and tolerance studies.

Planned outcome measures were appropriate and planned methods of statistical analysis of results were routine for demonstrating the efficacy and safety of the test drugs.

The overall efficacy results of risedronate with respect to both primary and secondary endpoints can be compared with those of Didronel and other approved treatment regimens. Significantly greater percent (85%) of risedronate treated patients achieved maximum reduction (≥ 75% in SAP excess),.compared to 20% in the Didronel group. In the risedronate group, 73% of patients showed normalization of SAP compared to 15% in the Didronel group. At day 30 of the treatment, risedronate treated patients showed significantly greater mean percent decreases from baseline than the Didronel group. Percent decreases from baseline in serum bone specific AP and urinary DPYr/Cr ratio were greater in the risedronate group than the Didronel group at all study visits. With respect to symptomatic improvement (QOL assessment), risedronate-treated patients showed significant improvement from baseline at Days 60-360. Didronel-treated patients showed no significant change from baseline.

In clinical trials with **Calcimar Injection (another approved drug for this indication)**, about 30% decrease in SAP was noted in approx. 75% of patients, and bone pain was reported to improve in some patients. However, following Calcimar therapy, relatively small subset of patients were reported to manifest reversal of neurologic deficits, improvement of hearing loss, and/or decrease in high-output cardiac failure.

Controlled clinical trial with **Aredia** (approved for this indication) has demonstrated ≥ 50% decrease in SAP in about 33% and 60% of patients treated with Aredia at doses of 45 mg and 90 mg/day doses, respectively. At 90 mg dose, time to response (50% decrease in SAP from baseline) was similar to that of risedronate (Day 30). Significant decrease in SAP from baseline was maintained up to 372 days. With risedronate in this trial, decreased level of total SAP was also maintained throughout the entire study period (360 days). With Aredia biochemical improvement was also manifested by significant decrease in urinary hydroxyproline/creatinine ratio in about , of treated patients. Aredia, however, showed no statistically significant difference between the treatment groups (placebo and Aredia) or from baseline for the bone pain response. On the other hand, biochemical improvement with risedronate was accompanied by a significant improvement in bodily pain (based on QOL assessment).

Risedronate therapy compared favorably with **Fosamax** in terms of response (SAP normalization or ≥ 60% reduction) to therapy. Both drugs showed normalization of SAP in about 85% of treated patients. Fosamax, however, did not show any significant improvement in pain.

Compared to tiludronate (400 mg/day for 3 months), treatment with risedronate resulted in normalization of SAP in 85% of patients as

opposed tc . of tiludronate treated patients with at least a 50% reduction in SAP at 3 months.

The overall safety data were comparable for the two treatment groups. GI adverse events (listed in the text), were common to both approved and investigational bisphosphonates, There was no significant difference between the two treatment groups. However, flu-like syndrome, GI disorders, arthrosis, neuralgia, and epistaxis were reported to occur with slightly higher frequency in the risedronate group. Attempts will be made to reflect all relevant side effects of risedronate observed in this and other trials, in the labeling of the product, if it is approved.

In conclusion, the results of this active-controlled trial have provided clear evidence in support of efficacy and safety of risedronate for the treatment of patients with Paget's disease of bone. Compared to Didronel, another bisphosphonate previously approved for the same indication, risedronate seems to be superior with respect to duration of initial therapy, proportion of patients with normalization of SAP, improvement in bodily pain, and quality of life with no significant differences in the nature and incidence of adverse events.

8.2 Trial # 2/ Study # 88040

8.2.1 Title: Open, multi-center, multiple oral dose, Phase II study to determine the efficacy, safety and tolerance of NE-58095 in patients with Paget's disease of bone.

Objective and rationale

To evaluate the efficacy, safety and tolerance of three doses risedronate in patients with Paget's disease of bone. Risedronate, an antiresorptive bisphosphonate, has the same rationale as Didronel (an approved bisphosphonate) for the treatment of Paget's disease of bone.

8.2.2 *Design*

Multi-center, open-label study carried out in the USA, Canada and Europe under a common protocol. Principal investigator was Jacques P. Brown, M.D. of Le Centere Hospitalier de l' Universie laval, Quebec, Canada. .

8.2.3 *Protocol*

Amendments:

- Women of child-bearing potential were excluded from the study.
- Dosage adjustment to next higher dose and retreatment at a dose of 30 mg/day if relapse occurs after responding to 20 or 30

mg/day.

- To perform iliac crest bone biopsy after triple tetracycline labeling at Center 1459 (David J. Hosking, M.D.,PI) after the completion of 28-day treatment.

- Urinary collagen crosslinks excretion to assess therapeutic response.

8.2.3.1 Population and procedures

A total of 62 patients (35 M and 27 F) were enrolled into the study. Patients were ≥ 18 and ≤ 75 years of age. All patients must have biologically active disease process (i.e., SAP ≥ 3 X times the ULN) and radiologically demonstrated evidence of pagetic lesions of tibias and fibulas. The exclusion criteria were routine and approved by the Agency.

Three patients at each center were to receive 10 mg/day of risedronate initially for up to 28 days. After determination of safety tolerance of 10 mg/day dose, three additional patients given 20 mg/day for 28 days. Then after determining the safety and tolerance of 20 mg/day, three additional patients were to receive 30 mg/day for 28 days.

The results of prior dose escalation studies indicated that a 30-mg daily dose could be a safe and effective dose.

Risedronate was administered in the morning following an overnight fasting with about 4 ounces of water (no dairy milk or any dairy product). Patients were instructed not to eat or drink for 2 hours before or after dosing.

Patients were allowed to receive steady concomitant medications but had to record them.

8.2.2.2 Endpoints

Efficacy endpoints were I) ≥ 30% decrease from baseline in SAP excess at any visit, and ii) ≥ 50% decrease in urinary OHP/Cr ratio (could meet this criteria at different time). A dose of risedronate was considered effective if > 50% of patients achieved ≥ 30% decrease in SAP excess.

Safety endpoints were routine as monitored in the active-control study. Additionally, iliac crest bone biopsy after triple tetracycline labeling was performed in order to evaluate the possibility of drug-induced defective mineralization.

A patient was removed from the study if one or more of the following happened:

I) Normalization of SAP excess before 28 days of treatment.

Ii) If a patient developed intercurrent illness.

Iii) If a patient developed serious AEs.

Timing of all the procedures is presented in Table 28 (Sponsor's Table 2, vol. 1.129, p. 24).

Table 28. Timing of study procedures.

Table 2

Schedule of Study Procedures - Study 88046

Procedure	Visit Day										
	Prestudy	1	4	8	15	22	29	43	57	71	85
Informed consent	X										
Demographic data	X										
Medical/drug history	X										
Vital signs and anthropometric measurements[a,b]	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X	X			X		X				X
Electrocardiogram[b]	X	X					X[c]				
2-hour urine collection[b,d]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Adverse events[b]		X	X	X	X	X	X	X	X	X	X
Hematology[b,e]	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[b,f]	X	X	X	X	X	X	X	X	X	X	X
Serum Intact PTH		X		X	X		X				
Urinalysis[b,g]	X	X			X		X		X		X
Iliac crest bone biopsy[b,h]							X				

[a] Included sitting blood pressure, pulse rate, oral temperature, respiration rate, weight and height (height was measured only prestudy and Day 85)

[b] Safety measure

[c] If changes were noted on this ECG, the ECG was to be repeated at the remaining follow-up visits

[d] 2-hour urine collection to measure creatinine, calcium, phosphorus, pyridinoline, deoxypyridinoline and hydroxyproline levels (hydroxyproline/creatinine was used as an efficacy measure)

[e] Hematology included RBC, WBC, hemoglobin, hematocrit, MCH, MCHC, MCV, segmented neutrophils/polymorphs, bands, lymphocytes, monocytes, eosinophils, basophils, and platelet count

[f] Serum chemistry included BUN, creatinine, total protein, albumin, calcium, phosphorus, serum alkaline phosphatase (used as an efficacy measure), total bilirubin, SGOT, SGPT, GGTP, and LDH.

[g] Urinalysis included protein, RBC and WBC

[h] Performed at Center 1459 only

Reviewer's Comments

Timing schedules for study procedures (including primary and

secondary efficacy and safety endpoints) were appropriate.

8.2.3.3 *Statistical considerations*

The following definitions were used for statistical analyses (V1.129/p27):

Serum alkaline phosphatase excess = alkaline phosphatase value minus the midpoint of the normal range at baseline.

Response to treatment = decrease of ³ 30% in serum alkaline phosphatase excess and decrease of ³ 50% in urinary hydroxyproline/creatinine. These two criteria did not have to be met at the same visit. That is, a patient was considered to be a responder if, at any visit during the study, the alkaline phosphatase excess criterion was met and, at any visit during the study, the hydroxyproline/creatinine criterion was met.

Responder = a patient who experienced a response to treatment as defined above.

Relapse = increase of ³50% in serum alkaline phosphatase above the lowest level reached during evaluation days and follow-up period, provided the patient had responded.

Response time = the later of the following two visits: 1) the earliest visit at which the serum alkaline phosphatase excess response criteria was met; 2) the earliest visit at which the hydroxyproline/creatinine response criteria was met.

Time to response = time between onset of treatment and response time.

Duration of response = the relapse time minus the response time. Note: it is possible for a responder to have a duration of response of 0 (e.g., a patient first met the serum alkaline phosphatase excess criteria at Day 3, and first met the hydroxyproline/creatinine criteria at Day 5, and also relapsed at Day 5).

Demographic and baseline measurements- Similar to those of the active-control study with Didronel. Also, baseline demographic characteristics similar to those of the later study were compared among three treatment groups.

Efficacy data analysis-

Statistical methods used for analysis of response to treatment included logistic regression analysis for the proportion of patient who responded and the proportion of patients who relapsed.

Routine statistical methods were applied to analyze the data on time to response and duration of response.

Sponsor states that sample size was not based on statistical power calculation.

With respect to analysis of data on SAP excess, the percent change from baseline was analyzed (using two-way ANOVA) for treatment -group differences with group, center and treatment-by-center interaction as factors. Pairwise comparisons of the treatment groups were performed by using Fisher's Protected LSD test (**Comments**: Statistical reviewer will be requested to comment on the usefulness of this test).

Safety data were analyzed by using routine statistical methods.

Reviewer's comments on Planned Statistical Analysis of efficacy and safety data

Statistical methods for analysis of primary and secondary study endpoints are appropriate and seem adequate. Statistical reviewer may have some additional comments on the usefulness and adequacy of tests used.

The duration of response was not analyzed since only one patients had "relapse" based on specified definition.

There were 18 bone biopsy parameters were specified to be measured. Only 8 parameters (trab. bone vol., relative osteoid vol., osteoid surfaces, thickness index of osteoid seams, eroded surfaces, mean cortex thickness, trab. Mineralization rate, and cortical mineralization rate) were analyzed. Due to bad quality of biopsy samples other 10 parameters could not be analyzed.

8.2.4 RESULTS

8.2.4.1 *Patient disposition, comparability*

Of 62 enrolled patients, three (2 on 20 mg and one on 10 mg risedronate) discontinued study at different time points of the study.

Patient # 33800201 (20 mg) discontinued study due to hepatic dysfunction during the treatment period.

Patient # 33810203 (20 mg) discontinued study because she was diagnosed to have biclonal gammopathy during the interval between treatment and retreatment periods.

Patient # 33800101 (10 mg) was found ineligible after entry into the treatment period and removed from the study.

There were small differences in demographic and baseline characteristics of patients in three treatment groups. Patients in 30 mg group were older (Approx. Mean age 5 years higher) older than those of other two groups. Older pagetic patients were reported to be less responsive to risedronate in another study. Sponsor states that the overall outcome of the 30 mg group was probably not influenced significantly by the marginal higher mean age.

With respect to baseline diagnoses all three groups were quite similar except for higher number of patients with baseline "endo,Nutr,Metab.or Immune" diagnoses entered 30 mg group. Sponsor felt none of these diseases interfered with the results of this dose group.

The baseline mean SAP was reported to be higher in the 20-mg group compared to 10-mg group and higher in the 30-mg than 20-mg group (table 29, sponsor's Table 7, vol. 1.129, p. 35).

Table 29. Mean baseline SAP values and UOHPr/Cr ratios in three treatment groups.

Table 7

Mean Serum Alkaline Phosphatase and 2-hour Urinary Hydroxyproline/Creatinine at Baseline - Study 88040

Parameter	Risedronate 10 mg (N = 20)		Risedronate 20 mg (N = 21)		Risedronate 30 mg (N = 21)	
	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	n
Serum alkaline phosphatase (IU/L)*	714.8 ± 103.3	20	881.0 ± 123.3	21	949.7 ± 170.3	21
Urinary hydroxyproline/ creatinine (mg/mg)	0.14 ± 0.03	17	0.11 ± 0.02	18	0.16 ± 0.04	15

* p-value from Kruskal-Wallis test = 0.118; Appendix 14.2, Table 1.1.1

N = number of patients randomized to the treatment group
n = number of patients with baseline data

Corresponding data can be found in Appendix 8.1, Tables 2.5.1 and 2.8.1; Appendix 8.2, Table 2.5.1 and 2.8.1

The mean urinary OHP/Cr was slightly lower in the 20-mg group compared to two other treatment groups. (**Comments** After reviewing the data, attempts will be made to comment on the clinical significance of differences in baseline mean SAP values and UOHPr/Cr ratios among three treatment groups. Sponsor states that "it would be more difficult to demonstrate a dose response among groups because of the differences in disease severity at baseline.

There were no clinically relevant differences between three treatment groups with respect to concomitant medications. Overall, 10 to 20 patients in all three groups received antibiotics, cardiac drugs, analgesics and antipyretics, anxiolytics/sedatives/ hypnotics, replacement preparations (calcium carbonate, potassium chloride), and/or diuretics.

There was at least 80% compliance with respect to study medication.

The following protocol deviations were mentioned:

a) Instead of 24- hour collection of urine for OHP/Cr ratio determination, all investigators collected 2-hour samples for the same purpose. Twenty-four-hour collection of urine was initially planned to confirm the diagnosis of Paget's disease of bone. The latter became less clinically important since the diagnosis was made on the basis of marked elevation of SAP and radiologic/scintigraphic demonstration of pagetic lesions.

A total of 30 patients were reported to violate inclusion criteria. All of these violations were considered minor and were not expected to influence the study outcome. Fourteen of 30 patients were over 75 years of age (upper age limit for recruitment).

In one center, two groups of patients (each consists of 3 patients) received risedronate 10 mg and 20 mg/day, respectively at the same time. The protocol called for dose escalation after determination safety of the preceding smaller dose.

At one center (in Belgium), patients gave verbal informed consent. Sponsor gave consent to this without protocol amendment. (DSI to comment on this violation).

Three patients who were treated initially at a dose of 10 mg day were reported to receive risedronate at 30 mg/day dose instead of 20 mg/day the next higher dose (i.e., 20 mg/day) Patients who were retreaded with risedronate were reported not to meet the criteria for relapse.

Comments: .Protocol deviations were minor in nature and do not appear to influence the final outcome of the study in a clinically significant way,

8.2.4.2 **Efficacy endpoint outcome**

Data analyzed- Intent-to-treat (ITT) analysis involved all 62 enrolled patients. The response-to-treatment analysis was performed on 50 patients. Twelve patients did not have OHP/Cr

data and they were excluded from the analyses of duration of response, time to response, and the proportion of patients responding.

One patient from the 10-mg group, 3 from the 20-mg and 6 from the 30-mg group were reported to be retreated. The patient from the 10-mg group entered into retreatment period, but did not receive retreatment because of ineligibility.

Response to treatment- Table 30 (Sponsor's Table 10, vol. 1.129, p.40) summarizes the response to treatment.

Table 30. Summary of response to risedronate treatment.

Table 10

Summary of Response to Treatment, Relapse, Time to Response, and Duration of Response - Study 68040

Parameter	Risedronate 10 mg (N = 17) n (%)	Risedronate 20 mg (N = 18) n (%)	Risedronate 30 mg (N = 15) n (%)	Overall (N = 50) n (%)
Responders[a]	9 (52.9)	12 (66.7)	12 (80.0)	33 (66.0)
Non-responders	8 (47.1)	6 (33.3)	3 (20.0)	17 (34.0)
Relapse[b]	1 (5.9)	0	0	1 (2.0%)
Time to response[c]	71 (43, -)	43 (29, -)	29 (22, 71)	

[a] Response to treatment was defined as a decrease of ≥30% from baseline in serum alkaline phosphatase excess and a decrease of ≥50% in urinary hydroxyproline/creatinine.

[b] Increase of ≥50% in serum alkaline phosphatase excess above the lowest level reached during evaluation days and follow-up period, provided the patient has responded.

[c] Data shown are Kaplan-Meier estimates of the median (25th percentile, 75th percentile) time to response. A dash for the 75th percentile indicates that <75% of patients responded.

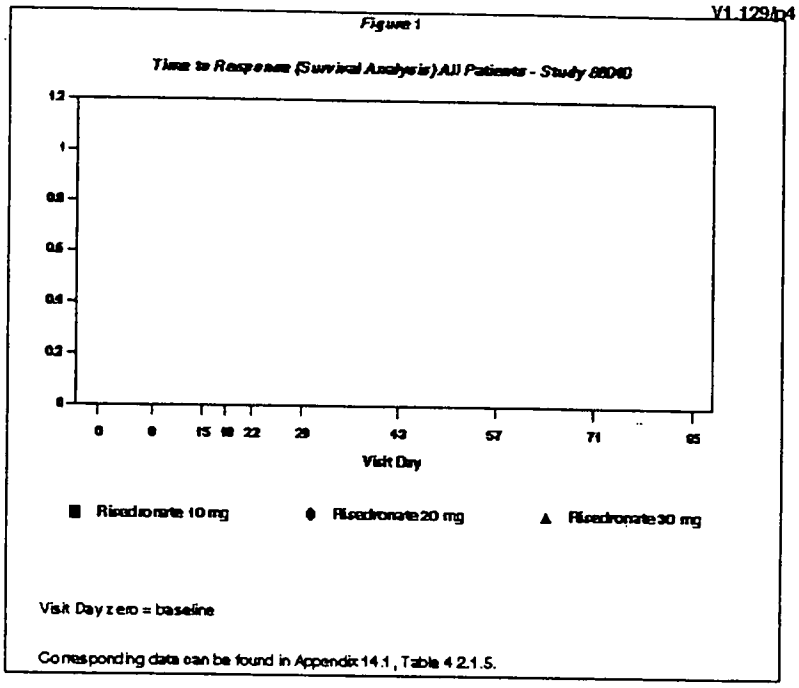
N = number of patients who had both hydroxyproline/creatinine and alkaline phosphatase data
n = number of patients in category
% = (n/N) x 100

Corresponding data can be found in Appendix 8.1, Table 4.1; Appendix 8.2, Table 4.6.1; and Appendix 14.1, Tables 4.1.1.1, 4.2.1.3, and 4.2.1.5.

The percent of responders to risedronate therapy for 28 days showed dose-dependent increases with increasing doses (10-30 mg/day), with a maximum of about 80% responders at a dose of 30 mg/day. When the three doses of risedronate were combined (n=50), 66% of treated patients were found to be responders. The percent of non-responders showed progressive decrease with increasing daily dose of risedronate.

The median time to response (respecified decreases in SAP excess and UOHPr/Cr) decreased from 71 days at a dose of 10 mg/day to 29 days at 30 mg/day. The equality of time to response over three doses of risedronate is shown in Figure 8 (Sponsor's Figure 1, vol. 1.129, p.41).

Figure 8. Equality of time to response curves (survival analysis).



Significantly improved response times were noted with higher doses of risedronate. However, there was significant treatment-by-center interaction, probably due to small number of samples within each center.

Percent change from baseline in SAP excess in presented in Figure 9 (Sponsor's Figure 2, vol. 1.129, p. 42) and Table 31 (Sponsor's Table 11, vol. 1.129, p. 43).

Figure 9. Percent change from baseline in SAP excess.

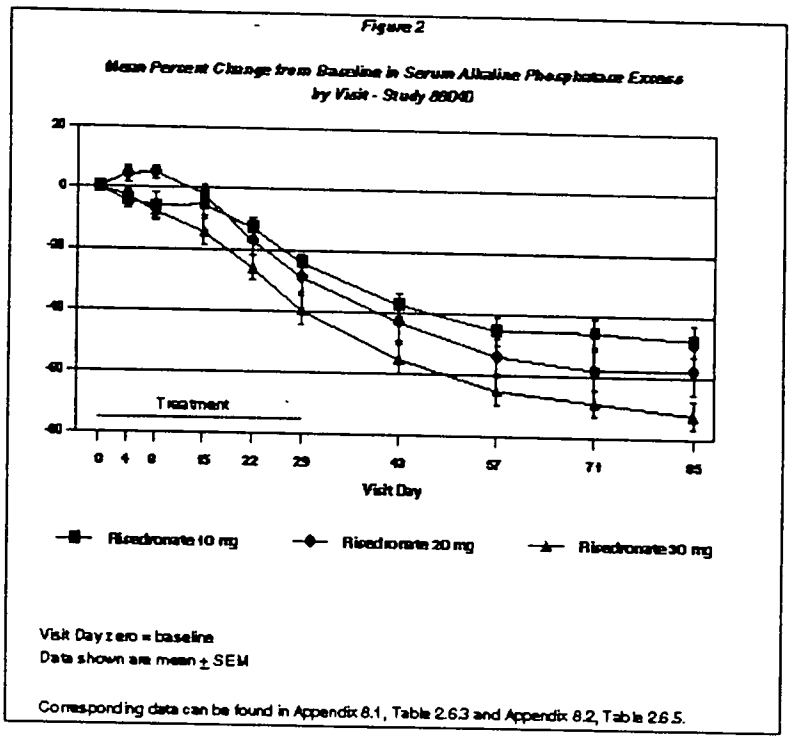


Table 31. Mean percent change from baseline in SAP excess.

Table 11

Mean Percent Change from Baseline in Serum Alkaline Phosphatase Excess (IU/L) by Visit - Study 88040

	Risedronate 10 mg (N = 20)			Risedronate 20 mg (N = 21)			Risedronate 30 mg (N = 21)			Overall Treatment Effect
Visit Day	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	p-value[a]
Baseline	714.8	103.3	20	861.0	123.3	21	949.7	170.3	21	
Day 4	-4.2[A]	2.8	20	4.4	2.4	20	-2.6[A]	1.7	21	0.030
Day 8	-6.0[A]	4.3	20	5.1	2.1	21	-7.6[A]	2.3	21	< 0.001
Day 15	-5.4	3.7	20	-1.9	3.1	21	-14.4	4.3	20	0.086
Day 22	-12.8	3.4	20	-17.1	4.8	20	-25.1	4.0	21	0.079
Day 29	-24.2[A]	3.1	20	-28.8[A,B]	4.9	21	-39.8[B]	4.8	21	0.043
Day 43	-37.4	3.9	20	-43.1	6.1	20	-55.2	4.6	21	0.066
Day 57	-45.8[A]	4.5	20	-54.0[A,B]	5.6	21	-65.1[B]	4.4	20	0.043
Day 71	-45.8[A]	4.6	19	-58.0[A,B]	6.5	20	-68.6[B]	4.6	21	0.042
Day 85	-48.0[A]	5.1	20	-57.9[A,B]	7.3	21	-72.2[B]	4.6	21	0.040

[a] Overall treatment p-value from ANOVA with the interaction term included in Appendix 14.1, Table 3.1.1.1. Means marked with the same capital letter on a given Visit Day are not significantly different per the Fisher's Protected LSD test (e.g., at Day 4, the 10- and 30-mg groups were both significantly different from the 20-mg group but were not significantly different from each other)

N = number of patients randomized to the treatment group; n = number of patients with available data at each visit day.

Corresponding data can be found in Appendix 8.1, Table 2.6.3; Appendix 8.2, Table 2.6.5; Appendix 14.1, Table 3.1.1.1.

At day 85, risedronate at all three doses caused significant decreases from baseline in SAP excess.

The mean number of days to reach maximum response at the three doses of risedronate are shown in Table 32 (Sponsor's Table 12, vol. 1.129, p.44).

Table 32. Number of days to cause maximum percent change from baseline.

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Table 12

Maximum Percent Change from Baseline and Days to Maximum Percent Change in Serum Alkaline Phosphatase Excess[a] - Study 68048

Parameter	Risedronate 10 mg (N = 20)	Risedronate 20 mg (N = 21)	Risedronate 30 mg (N = 21)
Maximum % change	-63.8 ± 4.4	-62.8 ± 6.1	-73.8 ± 3.8
Days to maximum % change	64.4 ± 5.3	74.8 ± 2.5	78.0 ± 3.1

[a] Data shown are mean ± SEM

N = number of patients randomized to the treatment group

Corresponding data can be found in Appendix 8.1, Table 4.1; Appendix 8.2, Tables 4.2.1, 4.3.1

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The mean number of days to achieve maximum decreases from baseline in SAP ranged between

Normalization of SAP excess occurred in 1 (5%), 2 (9.5%), and 3 (14.3%) patients at 10, 20, and 30 mg/day doses, respectively.

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Retreatment was performed in 3 patients at 20 mg dose and in 6 patients at 30 mg dose. Because of small number of patients in the 20 mg dose, the results of retreatment were equivocal. At 30 mg dose, 5 of the 6 patients showed a mean decrease of 35.8% at Day 85.

Urinary OHPr/Cr data

The percent change from baseline in UOHPr/Cr ratio is presented in Figure 10 (Sponsor's Figure 3, vol. 1.139, p. 45) and Table 34 (Sponsor's Table 13, vol.1.129, p. 46).

Figure 10. Mean percent changes in UOHPr/Cr ratios.

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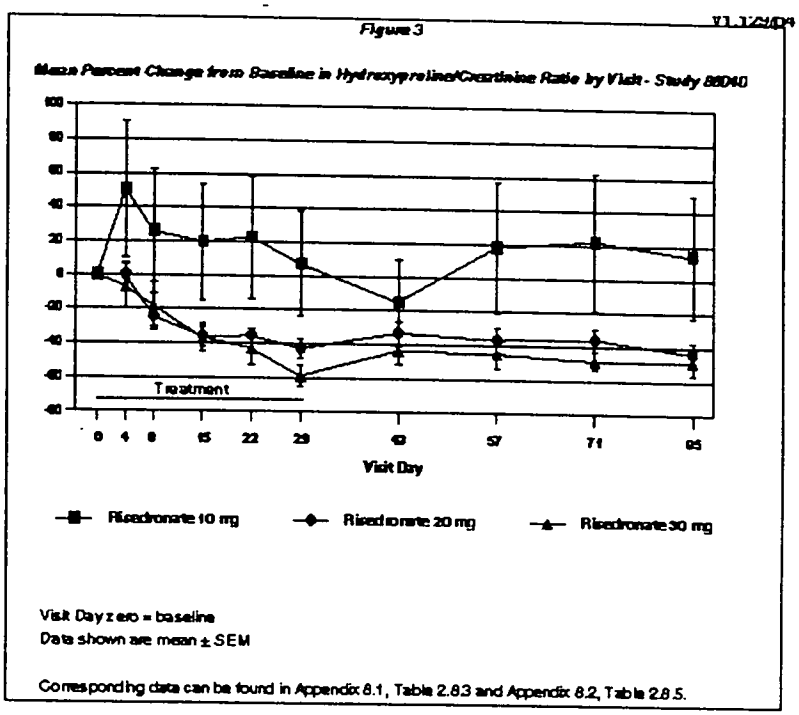


Table 33. Mean percent changes in UOHPr/Cr ratios.

Table 13

Mean Percent Change from Baseline in Hydroxyproline/Creatinine, by Visit - Study 86040

	Risedronate 10 mg (N = 20)			Risedronate 20 mg (N = 21)			Risedronate 30 mg (N = 21)			Overall Treatment Effect
Visit Day	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	p-value[a]
Baseline (U/L)	0.14	0.03	17	0.11	0.02	18	0.16	0.04	15	
Day 4	60.4	39.9	16	0.04	7.6	17	-6.7	13.0	15	0.287
Day 8	25.7	37.0	17	-24.5	5.4	17	-18.2	13.8	14	0.307
Day 15	19.6	34.0	17	-35.9	5.9	16	-35.7	8.0	15	0.131
Day 22	22.5	36.3	16	-35.6	4.9	16	-42.9	9.8	15	0.169
Day 29	7.2	30.8	17	-42.8	6.1	18	-58.9	6.5	15	0.056
Day 43	-15.2	25.8	17	-33.1	6.5	17	-43.4	8.1	15	0.554
Day 57	18.2	38.7	16	-36.5	6.8	17	-44.8	8.7	11	0.284
Day 71	22.2	40.5	16	-35.7	6.8	16	-48.4	5.5	13	0.160
Day 85	14.0	35.3	17	-43.5	5.0	17	-48.3	7.8	14	0.130

[a] Overall treatment p-value from ANOVA with the interaction term in Appendix 14.1, Table 3.2.1.1

N = number of patients randomized to the treatment group; n = number of patients with available data at each visit day.

Corresponding data can be found in Appendix 8.1, Table 2.8.3; Appendix 8.2, Table 2.8.5; Appendix 14.1, Table 2.8.3.

At 20 and 30 mg/day doses, UOHPr/Cr decreased progressively immediately after initiation of treatment and by Day 29, mean decrease were about 43% and 59%, respectively. By Day 85, mean decreases were 43.5% and 48.3%, respectively at these doses. There was a statistically significant difference between the 10-mg dose, and the 20 or 30 mg dose. However, differences between two higher doses were not significant. The mean decreases from baseline in UOHPr/Cr increased in a dose-dependent way. **Days to maximum percent changes from baseline were 41.8, 34.6 and 46.1 days for 10, 20, and 30 mg doses, respectively.** All 4 patients who received retreatment with risedronate, showed decreases with risedronate retreatment (**Reviewer's comments**: Data on retreatment are too small to draw any valid conclusion. Postmarketing clinical experience will allow generation of adequate data on this issue).

8.2.4.3 **Safety Outcomes.**

All 62 patients were evaluated for safety. The extent of exposure to the study drug during the first treatment period is presented in table 34 (Sponsor's Table 15, vol. 1.129, p.48).

Table 34. Extent of exposure to risedronate.

Table 15

Extent of Exposure to Study Therapy During the First Treatment Period - Study 88040

Treatment Group	Number of Patients Entered	Mean Number of Weeks Exposed to Risedronate[b]	Mean Total Exposure to Risedronate (mg)[c]
Risedronate 10 mg	20	4.0	280
Risedronate 20 mg	21	3.8	532
Risedronate 30 mg	21	4.0	840

[a] Calculated as $\frac{\text{Number of patient-weeks on study}}{\text{Number of patients entered}}$

[b] Calculated as $\frac{\text{Number of patient-weeks on risedronate}}{\text{Number of patients entered}}$

[c] Calculated as (Mean number of weeks exposed to risedronate) × (dose amount × 7 days)

Corresponding data can be found in Appendix 9.1, Table 11.1.1; and Appendix 9.2, Table 11.2.1.

The 20-mg dose group was exposed to the study drug for a slightly shorter period than 10 and 30 mg doses. This minor difference in exposure time is unlikely to affect the overall safety profile of risedronate noted in this trial.

With regard to the extent of exposure to risedronate during retreatment, 9 patients (3 in 20 mg and 6 in 30 mg groups) received the study drug for similar mean number of weeks and mean total amount of the drug.

Adverse Events (AEs)

AE excluded in this report.

A 73-year-old female patient (#33820203) with Paget's disease of bone was treated with risedronate (dose not stated). About 2 years after completion of treatment, patient was diagnosed to have *acute myelogenous leukemia* (presented with substernal pain). Patient had a history of exposure to "dry cleaning solvents" including benzene and other dry cleaning solvents for undetermined period of time. The patient died after about a year following an episode of cerebrovascular accident. The investigator considered both the leukemia and cerebrovascular accident as unrelated to risedronate, since the AE occurred 2 years after risedronate treatment.

A total of 40 AEs in 21 patients were reported in this trial. Of these 40 AEs, 16 each occurred at the 10 and 20 mg doses and 8 with the 30 mg dose. The percentage of patients with AEs was 19 with the 30 mg dose. as opposed to 40% to 42.9% of patients with the 10 and 20 mg doses, respectively.

Table 35 (Sponsor's Table 19, vol. 1.129, p. 52) presents AEs with an incidence of ≥ 3%.

Table 35. AEs with an incidence of ≥ 3% during the first treatment period.

Table 19

Adverse Events Occurring at ≥ 3% Overall Incidence During the First Treatment Period[a] - Study 33048

Body System COSTART Term	10 mg/day (N = 20) n (%)	20 mg/day (N = 21) n (%)	30 mg/day (N = 21) n (%)	Overall (N = 62) n (%)
Body As A Whole				
INFECT	1 (5.0)	2 (9.5)	0	3 (4.8)
ASTHENIA	1 (5.0)	1 (4.8)	0	2 (3.2)
FEVER	0	1 (4.8)	1 (4.8)	2 (3.2)
FLU SYND	1 (5.0)	0	1 (4.8)	2 (3.2)
HEADACHE	1 (5.0)	1 (4.8)	0	2 (3.2)
PAIN	1 (5.0)	0	1 (4.8)	2 (3.2)
Digestive				
DYSPEPSIA	0	1 (4.8)	2 (9.5)	3 (4.8)
ESOPHAGITIS	0	2 (9.5)	0	2 (3.2)

[a] Data shown are number and percent of patients with at least one occurrence of an adverse event as classified by COSTART term.

N = number of patients randomized to the formulation group
n = number of patients with available data; % = (n/N) x 100

Corresponding data can be found in Appendix 9.1, Table 11.5.1 and Appendix 9.2, Table 11.7.1.

There were no major differences between the three treatment groups with respect to occurrences of AEs listed under Body As A Whole heading.

Dyspepsia and esophagitis occurred in 2 patients (9.5%) at each 30 and 20 mg doses, respectively.

Only one case of headache (which lasted for about 5 hours) occurred at the 20 mg dose and was considered severe by the investigator. The patient experienced the headache after approx. 5 weeks of treatment with risedronate.

AEs during the retreatment period

Three patients in the 30-mg group were reported to experience AEs , which included biclonal gammopathy (mild), moderate to severe upper GI symptoms (substernal pain, nausea), or metallic taste. The patient with biclonal gammopathy never received the test drug during retreatment.

Deaths and serious AEs

One patient each in the 10 and 20 mg groups experienced serious AE (left hemispheral transient ischemic attack or onset of atrial fibrillation). Both patients recovered and the events were not considered to be drug-related.

Discontinuation

One patient in the 20-mg group discontinued the study due to "disturbed hepatic function." Hepatic dysfunction was later on attributed to related to gall bladder stone. The other patient with biclonal gammopathy (in the 30-mg group) was also reported to discontinue the study.

Moderate upper GI AEs

Patient # 14590201- This patient was reported to develop reflux esophagitis (without endoscopic confirmation) after 2 weeks of risedronate treatment at a dose of 20 mg/day. The sponsor states that the investigator did not do a causality evaluation. The patient recovered and completed the study.

Patient # 33820103- Two weeks after initiation of retreatment with risedronate at a dose of 30 mg daily, this patient was reported to experience nausea, burning in the esophagus and pain during swallowing. The patient was diagnosed with "pill esophagitis" accompanied by mild antral gastritis and two ulcerated lesions in the mid and distal esophagus. The patient had no prior history of GI problems. It was determined that the patient was taking the medication improperly. The study drug was discontinued and the patient was treated for esophageal ulcers. Patient recovered and completed risedronate therapy at a dose of 30 mg daily.

Patient #14590202- This patient was reported to experience "mild reflux esophagitis (without endoscopic confirmation) for one day only. Patient recovered and completed the study.

Non-vertebral fractures

There were no reports of non-vertebral fractures in this trial.

Vital signs and anthropometric measurements

There were no clinically meaningful changes in body temperature, pulse rate, blood pressure, respiration rate, body weight and height during the study. One patient (# 14590302) was reported to experience bradycardia : on day 22 of the study. Sponsor considered the event to be an isolated episode (possibly a recording error).

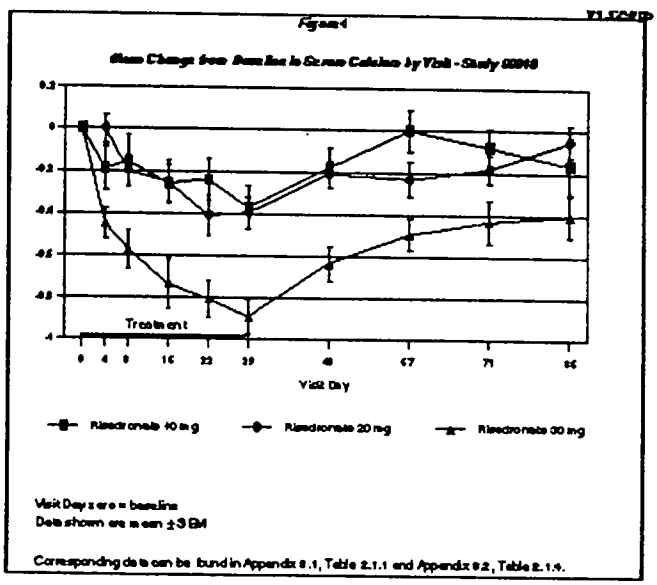
Clinical Laboratory Evaluations

Collagen crosslinks- Deoxypyridinoline (DPyr) and pyridinoline (Pyr) were analyzed in 2 of 6 study centers. Eight to nine subjects (in each dose group) had urine samples collected, but again samples were not collected at all time points. At all three doses of risedronate, 3-4 patients (of total 6 pt.) showed a 30% or more decrease in collagen crosslinks.

Urinary phosphorus/creatinine- The study reported no meaningful changes in phosphorus/creatinine ratio as a result of risedronate treatment.

Serum calcium- The results are show in Figure 11 (Sponsor's Figure 4, vol. 1.129, p. 57).

Figure 11. Changes in serum calcium (total).



During the treatment period, serum calcium decreased from baseline at all

doses of risedronate; maximum was in the 30-mg dose. During the follow-up period serum calcium returned towards baseline mean value.

Serum phosphorus- Risedronate treatment showed similar pattern of change as serum calcium.

Serum iPTH- Serum iPTH increased from baseline mean values at all doses of risedronate during the treatment period. **Sponsor states that there were insufficient data during the follow-up period**.

Urinary calcium/creatinine ratio- Urinary calcium/creatinine ratio decreased slightly at all doses of risedronate. These changes were not clinically relevant

Sponsor has provided the results of shift analyses of bone metabolism parameters (serum calcium, serum phosphorus, and iPTH). Both serum calcium and phosphorus showed downward shifts initially in the 20- and 30-mg groups. The shift appeared to be transient as the baseline-to-last value results indicated similar number of patients manifested upward or downward shift. With respect to changes in iPTH, the numbers of observations were relatively small for a valid conclusion. Nevertheless, serum iPTH showed an upward shifts in baseline-to-maximum value at all three doses (generally during the initial phase of treatment).

Two patients in 30 mg group experienced asymptomatic hypocalcemia (serum calcium 7.4 mg/dL),.on Day 22 of treatment. One additional patient in 30 mg dose group had serum calcium values of 7.9 and 7.8 mg/dL on Days 8 and 15, respectively. These changes were transient and probably had no clinical implications in this trial. Two patients in the 30-mg group were reported to experience asymptomatic hypophosphatemia during the treatment period, but returned within the normal range by Day 85.

Reviewer's Comments:

Changes in parameters of bone metabolism could be attributed to normal pharmacodynamic effects of bisphosphonates as a class. Decrease in serum calcium is generally attributed to the inhibition of skeletal resorption. Decrease in serum phosphate could be due to secondary increase in PTH or due to decreased release of phosphate from the skeleton. Of the oral bisphosphonates (etidronate, alendronate, tiludronate) approved for various metabolic bone diseases (Paget's disease of bone, postmenopausal osteoporosis, heterotopic ossification of bone), all are known to cause a decrease in serum calcium after long-term use. Most of hypocalcemic episodes are asymptomatic with rare occurrences of mild symptomatic hypocalcemia. Transient mild decreases in serum calcium and phosphorus were reported in controlled clinical trials with alendronate. Asymptomatic hypocalcemia and hypophosphatemia were more frequent with pamidronate i.v. infusion in osteolytic bone metastases and Paget's disease controlled trials.

Hematology

There were more patients who showed downward shifts in hemoglobin (baseline-to-minimum value) than upward shifts (baseline-to-maximum value). Similar shifts occurred in hematocrit and RBC as a result of risedronate treatment. However, baseline-to-last value evaluation showed no significant differences between downward and upward shifts. Thus, indicating temporary changes in hematological parameters. The overall changes in hemoglobin, hematocrit, RBCs, MCH, MCHC, MCV, platelets were reported to be clinically irrelevant.

With regard to individual low values, one patient each in the 10, 20 and 30 groups was reported to show low value of RBCs, hemoglobin, and hematocrit, respectively. Couple of patients in 20 or 30 mg group had low RBCs. Almost all of these patients had low values at baseline or screening, and experienced low values throughout the study.

Sponsor reports that there were no clinically significant changes in WBCs, and differential cell counts.

Liver function tests

Sponsor states that no clinically relevant changes were observed in serum albumin, serum total protein, SGOT, SGPT, GGTP, and total bilirubin, The results of shift analyses showed shifts in serum albumin and serum total protein (baseline-to-minimum and baseline-to-last values) with the 10, 20 and 30 mg doses.

The sponsor has provided information on some individual patients with abnormal LFTs and these are follows:

Patient # 33900101-2: These two patients were in the risedronate 10-mg group and both had elevated baseline levels of serum albumin and total protein. One of these two patients maintained high serum total protein value during the course of treatment, but from Days 43 to 71, the high values returned within the normal range. **The same patient had high baseline GGTP value and it continued to rise during risedronate treatment (20 mg/day), reaching a maximum value at Day 22 which resulted in discontinuation of treatment. The GGTP value returned to within normal range at Day 85.**Two additional patients (one each at 20 and 30 mg group) had low baseline serum albumin values.

Patient # 339202203: This patient showed increased SGPT value on Day 15 of treatment with risedronate (20 mg/day) and it increased to a maximum on Days 18. SGPT value returned to the normal range by Day 26 and remained normal during the rest of the study.

Reviewer's Comments: Changes in LFTs were sporadic and showed no consistent pattern. The events were too few to draw any definitive

conclusion.

Renal function parameters

No clinically relevant changes were reported in renal function tests.

Bone histology/Histomorphometry

Qualitative histomorphometry of bone biopsy material was performed in a small number of patients at the site of Dr. David D. Hosking in Nottingham, UK. Histomorphometric analysis was performed by Louis-Georges Ste-Marie, M.D. of Montreal, Canada. Sponsor states that based on "qualitative assessment of the small number of biopsies made in normal bone, that there was no evidence of an impairment of bone mineralization induced by risedronate." Dr. Ste-Marie also reported that microscopic examination of pagetic bone samples, the osteoid tissue was "mainly lamellar bone instead of woven bone."

Reviewer's Comments:

It appears that iliac crest bone biopsy (after tetracycline labeling) was performed in only 15 patients. Of the 15 biopsies, 10 were pagetic and 5 had normal bone. Almost all of pagetic bone samples had some problems related to poor quality of biopsy impregnation, imperfect sampling of cortical bone, small biopsy diameter, or defective tetracycline labeling. There were only 5 biopsies of normal bone. Sponsor's (Dr. Ste-Marie's) conclusion about the quality of mineralization (in normal bone) and observation of lamellar bone in pagetic sites needs further confirmation, based on analysis of a larger data base.

Sponsor's Discussion and Conclusions

The safety, efficacy and tolerance of risedronate (at doses of 10, 20, and 30 mg/day for 28 days) were studied in a Phase II multicenter, open-label study with a follow-up through day 85. The patient population of this study was similar to that of the active-controlled study.

The results of the study showed 53%, 67% and 80% responders (based on $\geq$ 30% decrease in baseline SAP excess) at 10, 20, and 30 mg/day doses, respectively. Patients benefitted most at 30 mg/day dose for 28 days.

The data on changes in baseline hydroxyproline/creatinine ratio were variable due to variations in the results of different participating laboratories. Nevertheless, changes from baseline in hydroxyproline and other bone metabolism parameters (serum calcium, serum phosphorus, iPTH, and urinary calcium) demonstrated antiresorptive effects of risedronate on bone turnover in this patient population.

Side effects (including GI events) of risedronate were similar amongst the three doses. Major AEs included one patient with acute myelogenous leukemia (AM) and one patient with esophageal "pill erosions." The patient with AM was diagnosed to have this condition approximately 2 years after termination of risedronate treatment and had a history of prior exposure to dry cleaning organic solvents including benzene. Esophageal "pill erosions" developed while the patient was taking risedronate gelatin capsules and it was suggested that adherence of capsules to the esophageal mucosa led to erosions. Subsequently, risedronate cellulose-film-coated tablets were developed to minimize esophageal AS.

Asymptomatic transient hypocalcemia developed in some patients, but this event was not clinically significant.

Preliminary results of bone biopsies in 15 patients showed no evidence of osteomalacia and bone formed on pagetic bone was lamellar in nature during risedronate therapy.

In conclusion, the effects of risedronate therapy showed a dose response and all three doses were well tolerated.

8.2.4.4 **Reviewer's Comments/Conclusions of Study Results**

This Phase II study was designed to demonstrate safety, efficacy and tolerability of risedronate (10, 20, and 30 mg/day for 28 days) in patients with Paget's disease of bone with SAP values at least 3 x the ULN, and scintigraphically and/or radiologically confirmed pagetic skeletal lesions.

The study design was adequate and the patients served as their own controls. The study population was similar to that of the active-controlled study with respect to the severity of the disease process, inclusion and exclusion criteria. Risedronate capsules were taken **early in the morning** and patients were instructed not to eat or drink 2 hours before or after dosing. The drug was taken with 4 ounces of water only.

Since it was an open-label study, risedronate was administered in an ascending dosage schedule. Outcome measures were appropriate and similar to those of the active-controlled study. The planned number of patients in each arm of the study was adequate and it was based mainly on clinical consideration. Nevertheless, the numbers were adequate for routine statistical analyses of data for efficacy and safety of the product.

Planned intervention with the test drug was prospectively defined and timing was appropriate and consistent with the protocol for the active-controlled study.

The primary efficacy endpoint was prospectively defined and it was appropriate for demonstrating the efficacy of the test drug for the

treatment of Paget's disease of bone. The study included secondary endpoints, which were appropriate for the trial of antipagetic drugs and similar to those studied in clinical trials of approved drugs (i.e., salmon calcitonin, etidronate, pamidronate, alendronate, and tiludronate).

The safety endpoints were adequate and appropriate for bisphosphonates and were consistent with the safety parameters used in trials of other approved drugs (including calcitonin) for the treatment of Paget's disease of bone.

The results of the study clearly demonstrated that risedronate at all three doses (10, 20, and 30 mg/day for 28 days) was effective (based on decrease of ≥ 30% or more from baseline in SAP excess) in of treated patients. The follow-up data showed decreases in baseline SAP at Day 85. None of the patients showed relapse in 20 and 30 mg doses during the evaluation days and follow-up period. With the 30 mg dose, the median time to response was 29 days and in about 78 days the maximum % change occurred. In terms of normalization of SAP excess, about 14.3% of patients in the 30 mg dose group achieved it. At a 30 mg dose, there were 5 patients who had data on retreatment. A mean decrease of about 36% occurred in reelevated levels of SAP excess by "retreatment Day 85."

At both the 20 and 30 mg doses, the secondary efficacy endpoint (i.e., hydroxyproline/creatinine ratio), showed decreases from baseline. The mean decrease from baseline was about 59% at Day 29 (p=0.066). Risedronate retreatment (30 mg/day) also resulted in decrease in hydroxyproline/creatinine ratio. However, data on hydroxyproline/creatinine ratio were small and additional data will be generated from postmarketing clinical experience.

The overall safety data from this study presented no major concerns. Most frequently reported AEs were considered by the investigators to be unrelated to risedronate. All three treatment groups had similar distribution of AEs. One patient developed "pill erosions" and this case should be mentioned in the labeling. Relevant safety information will be incorporated in the labeling.

The quantitative histomorphometric data though inadequate, seem to indicate no deleterious effects of short-term risedronate therapy on bone mineralization. Postmarketing (If approved) clinical experience will likely generate additional data on the long-term safety of the drug relative to the quality of bone form during risedronate therapy.

In conclusion, the results of this Phase II open-label study have demonstrated the efficacy and safety of oral risedronate (30 mg/day for 28 days) for the treatment of Paget's disease of bone. The overall results of this study seem to confirm the major clinical endpoints relative to the efficacy and safety of the drug.

UNCONTROLLED TRIALS

8.3 Trial # 3/ Study # 91007

8.3.1 Objective/Rationale

To determine the biochemical and symptomatic efficacy (qualitative assessment of bone pain) and safety of **three oral dosage forms** of risedronate in patients with moderate-to-severe Paget's disease of bone.

8.3.2 Design

Multicenter, randomized, open-label study.

8.3.3 Protocol

Protocol amendments:

There were several revisions that included increase in the number of enrollment (from 25 to 35 subjects at each center), pretreatment pain score assessment, definition of biologically active Paget's disease of bone based on baseline SAP value (≥ 345 IU/L), criteria for inclusion of postmenopausal women, investigator's determination of clinical relevance of baseline elevated values of LFTs, repeat serum chemistries at visit Day 196 of the study, criteria for retreatment at the end of non-treatment follow-up period, establishment of normal AP range, response time points at visit Days 29 and 56, rationale for sample size and power calculations, and pretreatment clinic visit for drug disbursement.

8.3.3.1 Population, procedures

Patients of either sex between [redacted] were enrolled into this study. Inclusion and exclusion criteria for patients were similar to controlled trials. Female patients had to be at least 2 years postmenopausal (based on the date of the last menstruation).

Three different dosage forms of risedronate were used:

I) 10-mg gelatin capsules.

ii) 30-mg enteric-coated tablets.

iii) Gelatin capsule containing 30 mg of risedronate as enteric-coated beads.

All patients received 30 mg of residronate (one of three formulations) daily for 84 days, followed by a no treatment period of 112 days(196-day cycle). The study medication was taken **2 hours before or after a meal.** Risedronate was taken with 120 ml of water and patients were instructed

not to lie down for at least 1 hour after dosing. Patients were told not to take dairy products, vitamins, iron, or antacids containing calcium, magnesium, or aluminum, within 2 hours of dosing.

Regarding concomitant medications, drugs like gallium nitrate, plicamycin, were not permitted, because they were likely to interfere with the evaluation of risedronate effects. Other chronic concomitant medications which were needed by the patients were kept "stable." The CRF's were reported to contain records of concomitant medications.

Reviewer's comments:

The timing of risedronate dosing, it was similar to that followed in controlled trials and likely to generate additional information on treatment efficacy of three different formulations of the drug, as well as on their relatively long-term safety (particularly GI adverse events).

8.3.3.2 Endpoints

Two primary efficacy endpoints:

- Percent change from baseline in SAPexcess.
- Percent change in OHPr/Cr ratio.

Secondary efficacy endpoints:

- Pain (frequency, location and severity) assessment questionnaire.

Safety endpoints

Routine clinical laboratory parameters were monitored.

Reviewer's comments:

Primary efficacy endpoints are pertinent and conformed with the past and present requirements to demonstrate the biochemical and symptomatic (bodily pain) improvements due to effective antipagetic therapy. A decrease of 100% or more in baseline SAP excess was considered as a complete response to therapy. A decrease of , in baseline excess SAP was defined as partial response to treatment. Predetermined criteria for demonstration of the efficacy of the test drug are adequate and acceptable.

Safety endpoints were routine and included monitoring of GI adverse events during a relatively long-term therapy with risedronate. Oral bisphosphonates are known to cause GI adverse events.

8.3.3.3 Statistical considerations

Statistical analyses of efficacy data were similar to those of the controlled study. Analyses were based on intent-to-treat population and an "evaluable" subgroup of patients.

To determine statistically significant difference from baseline SAP excess within the treatment group, relevant data were subjected to one-sample *t* test at the 0.05 significance level. Routine statistical methods similar to those of the controlled studies were applied to analyze the primary and secondary efficacy measurements and safety data. **(See Statistical review for additional comments on statistical methods).**

8.3.4 **Results**

8.3.4.1 Patient disposition, comparability

A total of 162 patients were randomized to enter three groups of the study: 54 , 53 and 55 . A total of 11 patients were discontinued from the study due to various reasons. Two in the and 3 in the were discontinued due to AS. The remaining 6 patients were dropped from the study because of protocol violation, intercurrent illness, or voluntary withdrawal. The AS that led to discontinuation of patients from two of three groups will be discussed later on.

There were no significant differences between three treatment groups with respect to age and height. The mean weight of patients in the beads group was slightly higher than those of the other two groups.

All three groups had baseline mean SAP values greater than 3 x the ULN (range :). Baseline urinary OHPr/Cr ratios varied between

With respect to secondary diagnoses at baseline, three treatment groups did not differ from each other.

Overall, up to 60% of patients received previous treatments (etidronate, calcitonin, pamidronate oral or i.v., risedronate, plicamycin, or gallium nitrate) for Paget's disease of bone. Etidronate and calcitonin were the common drugs that most patients received prior to test drug formulations.

Overall, : of 162 enrolled patients in the treatment groups had lumbar spine, skull, and femur affected by the pagetic process. Distribution of affected pagetic bones was even among three treatment groups.

There were no significant differences between three treatment groups with

respect to concomitant medications taken during the study. Analgesics and antipyretics were the most common concomitant drugs listed.

All patients were reported to be at least 80% compliant with self dosing of risedronate.

Protocol deviations

A total of 4 patients
, had baseline SAP value < 345 IU/L These patients were allowed to stay in the study because they fulfilled all other entrance criteria and baseline SAP mean values were within the narrow range of variability of the reference laboratory.

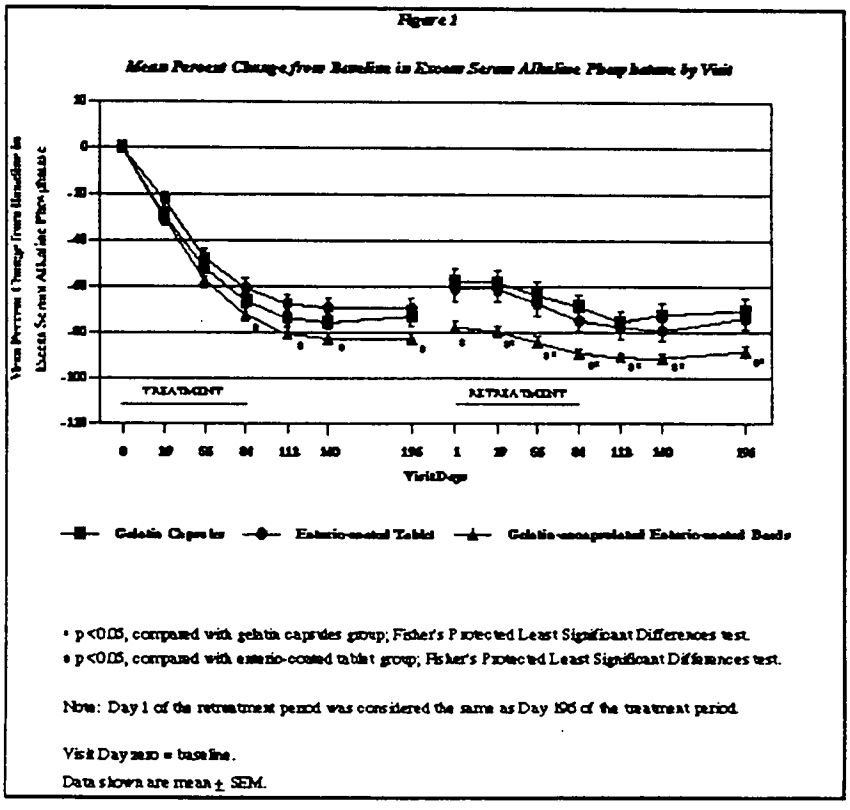
8.3.4.2 **Efficacy endpoints outcome**

Of total 162 patients, two patients in the , group were excluded from ITT and evaluable subgroup analyses. One patient withdrew voluntarily and the other withdrew before the first treatment visit on Day 29. One additional patient was excluded because of non compliance. In the evaluable subgroup analysis, data from visits outside the specified window (± 5 days) were excluded.

SAP (primary efficacy endpoint)/ *ITT population*

The results are presented in Figure 12 (sponsor's Figure 1, vol. 134, p.51)

Figure 12. Mean percent change in excess SAP.



In all three groups significant decreases from baseline in SAP occurred. By Visit Day 84 (end of treatment period) percent decreases from baseline means were 65.9, 60.6 and 72.1 in the
groups, respectively. Maximum reduction was reported in the beads group and the difference between the tablets and beads groups was significant. Whereas, there was no significant difference between the and the groups with respect to decrease in SAP. These patients were followed-up and at Visit Days 196, mean decreases were 73%, 69.4% and 82.7% in the capsule, E-C tablet and beads groups, respectively.

Retreatment

Twenty-four to 33 patients in each group received retreatment with risedronate (capsule, tablet or beads). In these resistant patients SAP did not decrease to a value below 115 IU/L on or before treatment Visit Day 196, regardless of the percent decrease in SAP or experienced a relapse. **The results are shown in Figure 12.** These patients at least partially responded

Retreatment resulted in decreases in SAP, which ranged between in all three groups. The maximum decrease was observed in the group retreated with risedronate beads.

Maximum mean percent change and Days to happen

The data are shown in Table 37 (sponsor's table 13, vol. 1.134, p. 53).

Table 37. Maximum % change and Days to change.

Table 13

Maximum Mean Percent Change and Days to Maximum Mean Percent Change From Baseline in Excess Serum Alkaline Phosphatase[a]

	Formulation Group		
	Gelatin Capsules (N = 52)	Enteric-coated Tablet (N = 53)	Gelatin-encapsulated Enteric-coated Beads (N = 55)
Maximum Mean Percent Change			
First Treatment Period	-78.0 ± 3.2	-73.0 ± 3.6	-83.2 ± 2.5
Both Treatment Periods	-83.7 ± 2.8	-82.3 ± 3.3	-90.2 ± 2.3
Days to Maximum Mean Percent Change			
First Treatment Period	165.3 ± 5.4	165.6 ± 5.6	171.4 ± 5.8
Both Treatment Periods	245.8 ± 15.5	271.9 ± 13.4	259.3 ± 14.1

[a] Data shown are mean ± SEM.

N = number of patients randomized to the formulation group (two patients who received gelatin capsules withdrew from the study before treatment visit Day 29 and were excluded from all analyses of effectiveness).

Corresponding data can be found in Appendix 8.1, Tables 4.1 and 4.2; and Appendix 8.2, Tables 4.2.1, 4.2.2, 4.3.1, and 4.3.2.

Either during the first treatment period or both treatment periods, maximum mean percent change from baseline in excess SAP occurred in the beads formulation group. Compared with gelatin capsules or E-C

tablet group, differences were statistically significant at Days 29 through 196. With respect to Days to achieve maximum response, there was no major difference between three formulation groups (range

Response to risedronate treatment in patients who received previous treatment for Paget's disease of bone

A total of 111 patients received previous treatment for Paget's disease of bone. Sponsor has termed these patients as "resistant to previous treatment.." as SAP decreased < 30 % from the pretreatment values. Of 111 patients with previous treatment for Paget's disease of bone, 95 were treated with Didronel, calcitonin or Aredia iv (42, 42, 11). The remaining patients received drugs which (except plicamycin) are not approved (in the US) for use in the treatment of Paget's disease of bone. Except for 3 patients (one of Didronel and 2 of calcitonin), all other patients with previous treatment for Paget's disease of bone responded to risedronate therapy (any formulation) with > 30% reduction in SAP from baseline values.

Reviewer's comments:

Sponsor has classified above-mentioned 111 patients as resistant to previous treatment for Paget's disease of bone. From sponsor's footnote in Table 14 (vol. 1.134, p. 54) it appears that lack of treatment response was based on investigators' note in cases where SAP values were not available. This reviewer feels that sponsor has provided adequate and pertinent data to claim that " most patients who were resistant to previous treatment for Paget's disease of bone experienced clinically relevant reductions in SAP (i.e., a 30% or more reduction).

Risedronate response in patients considered not resistant to previous treatment for Paget's disease of bone

Eighty-three to one hundred percent of patients who received previous treatment with Didronel, calcitonin or pamidronate (iv) for Paget's disease of bone and considered non-resistant to therapy achieved > 30% reduction in SAP.

Percentage of responders

During the first treatment period, 84.6%,81.1% and 96.6% of patients in the capsule, E-C tablet and beads groups, respectively had 50% or more reduction from baseline in SAP. The percent of patients with response as defined above was significantly higher than those in the other two formulation groups. Overall, 87.5% of patients (n=160) were responders (with 50% or more decrease in SAP).

A total of 12 patients) in three groups experienced relapse

(increase of 25% or more in SAP above the lowest value during the study period) after first treatment period. Based on this subset of population, sponsor has attempted to define the duration of response to risedronate. Eighty-five, 56 and 59 days were reported as the duration of response in There was no difference between three treatment groups with respect to time to response (range

The sponsor has compared responders with non-responders with respect to number of variables such as age, sex, BMI, baseline SAP, baseline OHPr/Cr, number of active pagetic disease site, etc. There were no major differences between responders and non-responders with respect to these factors. However, with respect to baseline SAP and OHP/Cr values, non-responders had overall higher values (statistically significant for OHP/Cr) than responders. Overall baseline iPTH was reported to be higher in the responders than non-responders, but clinical significance of this difference with respect to response to risedronate is not clear.

Normalization of SAP

The overall data showed that during the first period of treatment with risedronate, 33.1% of patients (53 of 160 pt) achieved normalization of SAP. During both treatment periods, about 69% of patients in the beads group were reported to achieve normalization of SAP. (**Comments**: From clinical standpoint, normalization rate for each of three formulation groups during each of treatment period (first and retreatment) is more meaningful than a combination of both.

Overall comparison of normalized and non-normalized groups with respect to number of variables, reveled no difference between two groups with respect to age, sex, body weight, and BMI. However, with respect to baseline SAP, OHPr/Cr and number of active pagetic sites, overall normalized patients had significantly ($p < 0.05$) less baseline values than non-normalized patients.

Evaluable subgroups

Sponsor claims that the results are similar to those of the ITT population **[see Appendix 14.1, Tables 2.1.1.1.(P)-2.1.1.4(P)]**.

Urinary OHPr/Cr

ITT population