CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020835

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

DEC 24 1997

NDA#: 20-835/Class 3S

Applicant: Proctor & Gamble Pharmaceuticals

Name of Drug: Actonel (risedronate sodium) tablet

Indication: Paget's disease of bone

Document Reviewed: Vols. 1.1, 1,2, 1.162-1.185
Submission dated April 3, 1997

Medical Reviewer: Samarendra N. Dutta, M.D., Ph.D.

Background:

Risedronate is a pyridinyl bisphosphonate. It inhibits osteoclast-mediated bone resorption. Paget's disease, also called osteitis deformans, is an idiopathic, progressive disease marked by increased bone resorption and excessive attempts at repair, resulting in weakened, deformed bones of increased mass. Both urine hydroxyproline (a measure of bone resorption) and serum alkaline phosphatase (SAP, a measure of bone formation) are increased in Paget's disease; these biochemicals are thus useful markers of metabolic activity and therapeutic response. SAP, therefore, has been chosen as the primary efficacy parameter for the clinical studies.

Controlled Clinical Studies:

The submission included two studies (RPD-001694 & 88040). Study RPD-001694 was a multicenter (12), randomized, double-blind, active-controlled (Didronel 400 mg) parallel study conducted in the U.S. and Canada. Study 88040 was a Phase II multicenter, open-label, dose-comparison trial conducted in the U.S., Canada, and Europe.

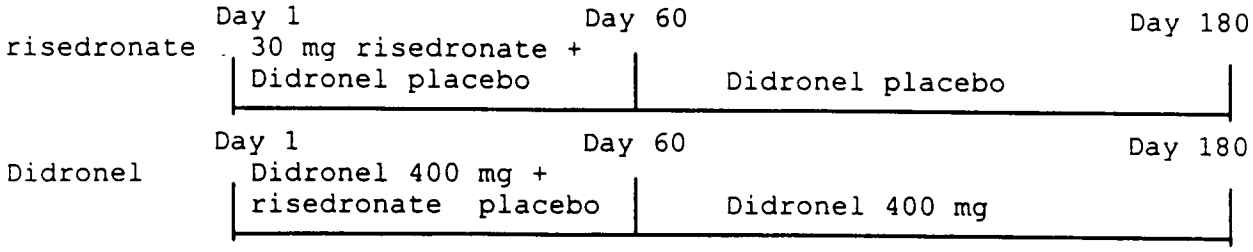
Study RPD-001694

The primary objective of this study is to compare the efficacy of risedronate to Didronel® in treating patients with Paget's disease of bone as determined by reduction in total serum alkaline phosphatase excess (the level of serum alkaline phosphatase above the mid-point of the reference range).

Study Design

This was a multicenter, double-blind, randomized, active-controlled, parallel group Phase III study conducted in 12 centers in Canada and the U.S. The total study duration was 540 days. It consisted of a 180 day treatment phase, followed by a 180 day follow-up period and a 180 day extended follow up to monitor duration of response and time to relapse for total serum alkaline phosphatase and bone markers. During the 180 day treatment phase

alkaline phosphatase and bone markers. During the 180 day treatment phase patients were randomized to one of the two groups: 1) risedronate + Didronel placebo days 1-60, Didronel placebo days 61-180, and 2) risedronate placebo + Didronel days 1-60, Didronel days 61-180. The treatment phase of the study was displayed in the following diagram:



The 60 day treatment duration for risedronate is based upon a Phase II study which showed approximately 56 days of treatment with 30 mg of risedronate to be the optimum regimen.

Randomization was stratified by center and by past Didronel® use with stratum I (no prior use of Didronel) comprising at least 30% of total patients enrolled and Stratum II (patients with prior Didronel treatment) comprising no greater than 70% of total patients enrolled.

Efficacy Result

A total of 123 patients were randomized, 61 to the 400 mg Didronel group and 62 to the 30 mg risedronate group. Three patients (1, Didronel & 2, risedronate) were excluded from the intent-to-treat population. The Didronel patient received one tablet of study medication and withdrew on Day 30 because of an adverse event (blurred vision). One of the risedronate patients withdrew voluntarily on Day 20 and the other withdrew before receiving any study medication this patient also violated one of the study entry criteria by taking Florical (calcium carbonate and sodium fluoride) at a dose greater than allowed by the protocol. Five additional patients were excluded from the evaluable-patient population. Two Didronel patients one with a history of bladder cancer and the other with colon cancer before entering the study, one risedronate patient who took a prohibited bisphosphonate (tiludronate) during the study period, and one patient each from the 2 treatment groups who had a less than 80% cumulative compliance at Day 30 were excluded. Table 1 displays the number of patients in each patient population.

Table 1 Number of patients by Patient Population

Patient Population	400 mg Didronel	30 mg risedronate	Total
Randomized	61	62	123
Safety	61	61	122
Intent-to-Treat	60	60	120
Efficacy	57	58	115

The number of patients enrolled by the 12 investigators as follows:

Table 2 Number of Patients by Investigator

Investigator	400 mg Didronel	30 mg risedronate	Overall
Adachi	1	1	2 (1.6%)
Brown	17	17	34 (27.6%)
Khairi	2	2	4 (3.3%)
Lang	4	6	10 (8.1%)
Licata	4	5	9 (7.3%)
McClung	3	3	6 (4.9%)
Miller, P.	5	5	10 (8.1%)
Ryan	16	14	30 (24.4%)
Singer	2	1	3 (2.4%)
Siris	5	4	9 (7.3%)
Tenenhouse	0	1	1 (0.88%)
Wallach	2	3	5 (4.1%)
Total	61	62	123

The demographic characteristics and baseline measurements of the study population were as follows:

Table 3 Patient Demographic Characteristics and Baseline Measurements

Baseline	400 mg Didronel n=61	30 mg Risedronate n=62	Overall	p-value
Age (years)				
Mean (S.E.)	67.1 (1.1)	66.5 (1.3)	66.8 (0.87)	0.71
Median(Range)	68.0	66.5	68.0	
Sex				
Male	40 (65.6%)	45 (72.6%)	85 (69.1%)	0.40
Female	21 (34.4%)	17 (27.4%)	38 (30.9%)	
Race				
Caucasian	57 (93.4%)	56 (90.3%)	113 (91.9%)	0.72
Black	3 (4.9%)	5 (8.1%)	8 (6.5%)	
Oriental	1 (1.6%)	0	1 (0.8%)	
Hispanic	0	1 (1.6%)	1 (0.8%)	
SAP (U/L)				
Mean (S.E.)	496.2 (42.4)	481.6 (49.2)		
Median(Range)	385.0	307.5		
SAP excess (U/L)				
Mean (S.E.)	421.5 (42.5)	407.4 (49.24)		
Median(Range)	310.0	234.5		
Serum Ostase (ug/L)				
Mean (S.E.)	151.2 (14.68)	150.8 (21.95)		
Median (Range)	111.6	88.2		
Urine Deoxypyridinoline/ Creatinine(pmol/umol)				
Mean	60.0 (4.41)	50.2 (6.27)		
Median (Range)	50.4	38.4		

Efficacy Variables

The primary efficacy variable was the percentage of patients who exhibited maximum response which is defined as ≥75% reduction in total serum SAP from baseline alkaline phosphatase excess at any time up to and including Day 360.

The secondary efficacy variables were as follows:

a) Time to exhibiting maximum response
b) Maximum change from baseline per patient defined as the difference between the baseline total SAP level and the lowest total SAP level achieved through Day 360.
c) Time to exhibiting maximum change
d) Percent change from baseline total SAP excess[1]
e) Percentage of patients who achieved normalization[2] of alkaline phosphatase
f) Percentage of patients who relapse[3] by Day 540
g) Time to relapse

[1] Baseline total SAP excess is defined as the difference between the measured baseline total SAP level and the midpoint of the normal total SAP range for the reference laboratory.

[2] Total SAP falls within the normal range for the reference laboratory at any time prior to and including Day 360.

[3] Patients have relapse if after response they have a 50% increase from their lowest level of total serum alkaline phosphatase and have total SAP values > 2X the upper limit of normal anytime prior to or on Day 540.

h) Percentage of patients resistant to treatment[4]

Efficacy Results

1. Percentage of patients who exhibited maximum response
The percentage of patients in the maximum response category (i.e., ≥75% reduction from baseline in total SAP excess) up to and including Day 360 was the primary efficacy variable. The following table displays the results in the treatment period.

Table 4 Number (%) of Patients with Maximum Response (≥75% Reduction) in SAP Excess and Days to Maximum Response

	400 Didronel n=60	30 mg risedronate n=60	p-value
Treatment Period maximum response	12 (20%)	51 (85%)	<0.01
Both Treatment & follow-up Period maximum response	14 (23.3%)	51 (85%)	<0.01
Days to maximum response			<0.01
Median	>360	67.0	
Mean (S.E.)	313.3 (13.12)	79.4 (3.12)	

During the treatment period, 51 risedronate patients (85%) achieved a maximum response compared to 12 Didronel patients (20.0%). During the entire study period, 51 risedronate patients (85%) compared to 14 Didronel (23.3%) patients achieved a maximum response.

2. Time to maximum response
Time to maximum response was defined as the number of days from the day of the first dose to the first time when patients were included in the maximum response category. Patients who did not have a maximum response were censored at the last day of the study period in the analysis. The Kaplan-Meier estimated mean time to achieve maximum response were 313.3 days for Didronel patients and 79.4 days for risedronate patients.

3. Normalization with treatment
The number and percentage of patients whose total SAP was normalized (i.e., within normal range) during the treatment period and the entire study period is displayed in table 5.

Table 5 Number (%) of Patients with Normalization of Total SAP and Days to Normalization

	400 Didronel n=60	30 mg risedronate n=60	p-value
Treatment Period # Normalized	6 (10.0%)	44 (73.3%)	<0.01
Both Treatment & follow-up Period # Normalized	9 (15.0%)	44 (73.3%)	<0.01
Days to maximum response			

4 Patients baseline SAP decrease by >10% of their baseline total SAP excess at no time prior to or at Day 360

	400 Didronel n=60	30 mg risedronate n=60	p-value
Median	>360	91.0	<0.01
Mean (S.E.)	289.2 (7.32)	107.1 (5.49)	

3. Change from baseline

Change or percentage change from baseline in total SAP excess was defined as the change or percentage change from baseline relative to baseline excess SAP. Baseline excess was defined as the difference between the measured baseline total SAP level and the midpoint of the normal total SAP range for the reference[5] laboratory.

Table 6 Mean Change and Mean Percent Change from Baseline in Total SAP Excess by Visit

	Change from Baseline (U/L)							Percent Change from Baseline (%)						
	400 mg Didronel			**30 mg risedronate**				**400 mg Didronel**			**30 mg risedronate**			
	Mean	SE	n	Mean	SE	n	p[a]	Mean	SE	n	Mean	SE	n	p
Baseline	497.4	43.1	60	482.4	50.7	60		497.4	43.1	60	482.4	50.7	60	.875
Treatment Period														
Day 30	-36.5	11.8	60	-152.9	25.5	60	<.01	-5.7	1.8	60	-36.4	2.8	60	<.01
Day 60	-75.6	17.8	59	-272.6	35.8	58	<.01	-15.6	2.4	59	-70.8	2.7	58	<.01
Day 90	-125.6	24.7	59	-316.4	39.9	59	<.01	-28.5	3.4	59	-83.3	2.5	59	<.01
Day 120	-165.9	29.8	59	-333.6	42.7	57	<.01	-37.3	3.7	59	-86.5	2.7	57	<.01
Day 150	-173.8	31.0	59	-337.9	44.1	57	<.01	-39.8	4.2	59	-87.7	2.6	57	<.01
Day 180	-182.1	34.1	57	-342.1	45.4	56	<.01	-40.6	4.7	57	-87.9	2.6	59	<.01
Endpoint 1[b]	-178.3	32.5	60	-336.8	42.7	60	<.01	-39.7	4.5	60	-86.2	2.7	60	<.01
Follow-up Period														
Day 240	-168.8	37.8	53	-325.7	45.7	56	<.01	-35.0	5.5	53	-85.4	3.2	56	<.01
Day 300	-154.7	39.9	52	-325.2	45.7	55	<.01	-31.5	6.5	52	-84.6	3.1	55	<.01
Day 360	-122.5	41.0	50	-316.9	47.5	53	<.01	-24.8	7.5	50	-81.6	3.5	53	<.01
Endpoint 2[c]	-126.3	36.9	60	-318.0	43.1	60	<.01	-23.7	6.4	60	-79.3	3.4	60	<.01

[a] p-value based on analysis of variance model with treatment, investigator and stratum (previous Didronel use) as factors

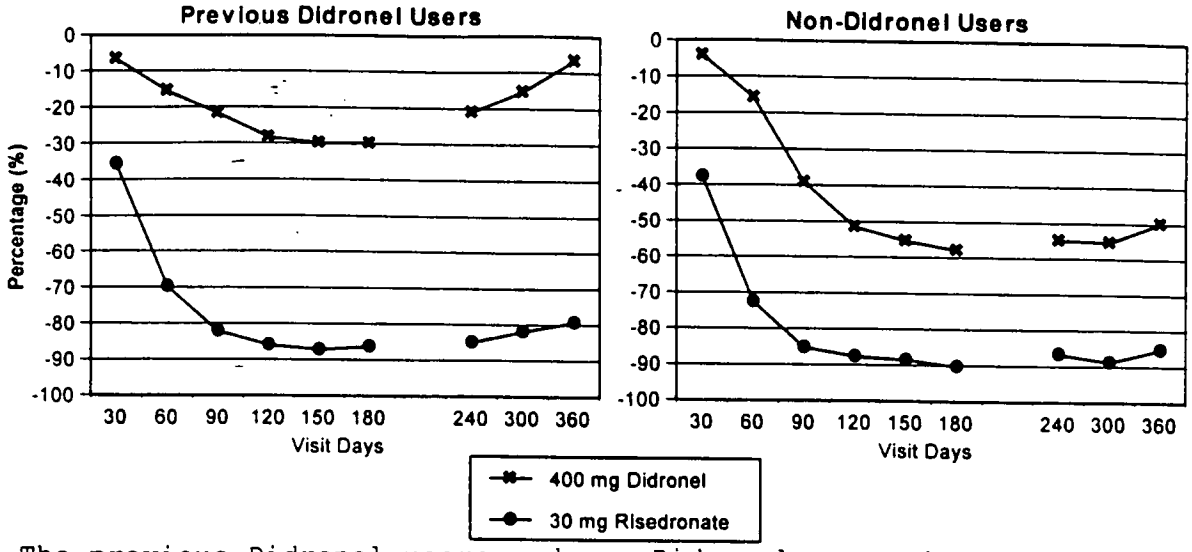
[b] Endpoint 1: Last measurement during the treatment period

[c] Endpoint 2: Last measurement during the study

Preliminary tests for treatment-by-investigator and treatment-by-stratum interactions were performed. No treatment-by-investigator interaction was found; however, there was a quantitative treatment-by-stratum interaction. The between-treatment difference in percent reduction was greater among patients who used Didronel within 10 years prior to study entry. The following figure displays the percent change from baseline in SAP excess by visit and treatment for the two strata.

5 Normal range for SAP: male (15 to 19 years)=50-250 U/L, (20 to 58 years)=31-110 U/L, (≥59years)=35-115 U/L; female(15 to 58 years)=31-110 U/L, (≥59 years)=35-115 U/L.

Mean % Change from Baseline in SAP Excess by Visit
Study RPD-001694



The previous Didronel users and non-Didronel users demonstrated comparable mean reduction of SAP in the risedronate treated patients; however, in the Didronel treated patients, the mean reduction is greater in the non-Didronel users.

4. Maximum Reduction

The maximum reductions from baseline in total SAP during the treatment period and the entire study period and time to maximum reduction are summarized in table 7.

Table 7 Maximum Reduction from Baseline in total SAP and Days to Maximum Response

	Didronel n=60	risedronate n=60	p-value
Maximum reduction from baseline			
Treatment Period	-212.9±32.8	-344.8±42.3	0.012
Both Treatment & follow-up Period	-230.8±34.8	-349.6±43.1	0.027
Days to maximum reduction from baseline			0.02
Median	183.0	181.0	
Mean (S.E.)	214.1(14.35)	189.9(10.36)	

5. Relapse

Relapse were defined only for those patients who demonstrated a ≥10% reduction of total SAP excess as a 50% increase from the lowest level of total SAP and had a total SAP value greater than two times the upper limit of the normal range. Out of the 120 patients in the intent-to-treat population, 113 patients were included (53 Didronel and 60 risedronate) in the relapse analysis. The number and percentage of patients who had a relapse during the study is in table 8.

Table 8 Number (%) of Patients with Relapse in Total SAP

	400 Didronel n=53	30 mg risedronate n=60	p-value
Treatment Period			
# Relapsed	0	0	-
Both Treatment & follow-up Period			
# Relapsed	8 (15.1%)	2 (3.3%)	0.045[1]
Days to relapse[2] (both period)			
Mean[3] (S.E.)	199 (7.7)	161 (0.37)	0.029[4]

[1] p-value for treatment comparison using logistic regression
[2] number of days from patient's lowest level of SAP to patient's first relapse, censored at last day of the study period if no relapse
[3] calculated using Kaplan-Meier method
[4] p-value for treatment comparison using Cox proportional hazards model

This reviewer used the Fisher's Exact test and yielded similar result (p=0.044) for the treatment comparison of number of patients with relapse.

Evaluable Patient Population

The efficacy results for the evaluable patient population are similar to those of the intent-to-treat population.

APPEARS THIS WAY ON ORIGINAL

Adverse Events

Summary of adverse events is displayed in the following table:

Table 9 Summary of Adverse Events (AEs) – Study RPD-001694

Number (%) of Patients	400 mg Didronel n=61	30 mg Risedronate n=61
AEs	58 (95.1%)	56 (91.8%)
Serious AEs	9 (14.8%)	15 (24.6%)
Expeditable AEs	14 (23.0%)	20 (32.8%)
Non-Vertabral Fractures	1 (1.6%)	4 (6.6%)
Upper GI AEs	12 (19.7%)	12 (19.7%)
Moderate-to-Severe upper GI AEs	2 (3.3%)	3 (4.9%)
Dropouts	14 (23.0%)	8 (13.1%)
Dropouts Due to AEs	5 (8.2%)	4 (6.6%)
Death	1 (1.6%)	2 (3.3%)

The most frequently reported adverse events in both treatment groups were of the body as a whole, musculoskeletal, and digestive systems. Table 10 displays the adverse events by body system.

APPEARS THIS WAY ON ORIGINAL

Table 10 No. (%) of Patients With Adverse Events by Body System

Body System	400 mg Didronel n=61	30 mg Risedronate n=61
Number (%) of Patient With Adverse Events	58 (95.1%)	56 (91.8%)
Body as a Whole	47 (77.0%)	40 (65.6%)
Musculoskeletal	26 (42.6%)	**35 (57.4%)**
Digestive	29 (47.5%)	26 (42.6%)
Special Senses	23 (37.7%)	20 (32.8%)
Nervous	18 (29.5%)	19 (31.1%)
Respiratory	14 (23.0%)	**17 (27.9%)**
Cardiovascular	10 (16.4%)	**13 (21.3%)**
Skin & Appendages	17 (27.9%)	11 (18.0%)
Urogenital	18 (29.5%)	11 (18.0%)

More risedronate patients had musculoskeletal adverse events compared to Didronel patients. In addition, adverse events in cardiovascular and respiratory are ~5% higher in the risedronate treatment group then the

Didronel group.

Study 88040

This study was not a randomized, placebo-controlled trial. The sample size was based on clinical considerations rather than on statistical considerations of power to detect differences among the three risedronate treatment groups. Therefore, it can not be considered an adequate well-controlled trial. In addition, the insignificant statistical comparisons among treatment groups can not be interpreted as similar efficacy among the treatment groups.

The objectives of this study were: A. to assess the efficacy, safety and tolerance of three different doses of NE-58095 when administered to patients with Paget's disease of bone, B. to determine the dose-relationship and time-course of biochemical changes (urine hydroxyproline and serum alkaline phosphatase) for NE-58095.

Study Design

This was an open-label, multi-center, multiple oral dose, phase II study. Thirty-six patients were expected to complete this study with each study site enrolling 9 to 15 patients each. The first three patients at each site received 10 mg of NE-58095 daily for a maximum of 28 days and were evaluated. If this dose was determined to be safe and well tolerated then the next group of patients received 20 mg of NE-58095 and be followed. If this dose also was determined to be safe and well tolerated, the next group of patients received 30 mg of NE-58095 and was followed in the same manner. All patients were evaluated within 14 days prior to dosing, on the first day of dosing and on days 4, 8, 15, 22 and 29. Additional follow-up every two weeks for a total of two months on days 43, 57, 71, and 85. All 3 tablets were taken at the same time with water in the morning at least 2 hours before, and at least 2 hours after, taking food.

Study Results

A total of 62 patients were enrolled in 6 centers. Patients were between 49 and 89 years old. All were Caucasian patients except one black patient. The baseline mean (SD) SAP values were 714.8 (103.3), 881.0 (123.3), and 949.7 (170.3) IU/L for 10 mg, 20, mg and 30 mg risedronate, respectively.

Primary Efficacy Variable

Treatment response was defined as decrease of 30% or more from baseline in SAP excess and a decrease of 50% or more from baseline in urinary OHP/Cr. The protocol criterion for success of treatment was more than 50% of patients responded.

Data Analysis

All analyses were performed on the intent-to-treat population using data from the initial treatment period. The responder analysis was conducted on 50 out

of 62 patients because the other 12 patients did not have OHP/Cr data reported.

The sponsor's reported that although the percentage of patients responding increased with the dose level, the differences did not reach statistical significance (p=0.287)

Table 11 displays a summary of response to treatment, relapse, time to response and duration of response.

Table 11 Response, Relapse, and Time to Response by Dose Levels

	Risedronate 10 mg n=17	Risedronate 20 mg n=18	Risedronate 30 mg n=15
Responders[a]	9(52.9%)	12 (66.7%)	12 (80.0%)
Relapse[b]	1	0	0
Time to response[c]	71 (43, -)	43 (29, -)	29 (22, 71)

[a] ≥30% decrease from baseline in SAP excess and a decrease of ≥50% in urinary hydroxyproline/creatinine

[b] ≥50% in SAP excess above the lowest level reached during evaluation days and follow-up period, provided the patient has responded

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

The descriptive statistics of the mean percent change from baseline in SAP excess by visit is displayed in Table 12.

Table 72 Mean Percent Change from Baseline in Serum Alkaline Phosphatase Excess (IU/L) by Visit – Study 88040

Visit Day	Risedronate 10 mg n=20[a]	Risedronate 20 mg n=21[b]	Risedronate 30 mg n=21[c]
Baseline	714.8 (103.3)	881.0 (123.3)	949.7 (170.3)
Day 4	-4.2 (2.8)	4.4 (2.4)	-2.6 (1.7)
Day 8	-6.0 (4.3)	5.1 (2.1)	-7.6 (2.3)
Day 15	-5.4 (3.7)	-1.9 (3.1)	-14.4 (4.3)
Day 22	-12.8 (3.4)	-17.1 (4.8)	-26.1 (4.0)
Day 29	-24.2 (3.1)	-28.8 (4.9)	-39.8 (4.8)
Day 43	-37.4 (3.9)	-43.1 (6.1)	-55.2 (4.6)
Day 57	-45.6 (4.5)	-54.0 (5.6)	-65.1 (4.4)
Day 71	-45.8 (4.6)	-58.0 (6.5)	-68.6 (4.6)
Day 85	-48.0 (5.1)	-57.9 (7.3)	-72.2 (4.6)

[a] n=19 at Day 71

[c] n=20 at Days 4, 22, 43, 71

[b] n=20 at Days 15 and 57

Conclusion of Study 88040

The study was not powered to detect differences between doses of risedronate. The p-value of the primary efficacy analysis, the responder analysis, is not statistically significant (Chi-Square test, p=0.27 and trend test p=0.14). It is concluded that the study did not demonstrate a clear dose response in

term of response to treatment. On the other hand, without adequate power, we cannot conclude that the three doses are similar. The descriptive statistics of the responders were 9/17 (53%), 12/18 (67%) and 12/15 (80%) for risedronate 10 mg, 20 mg, and 30mg, respectively. The mean percent changes from baseline of SAP excess at Day 29 were -24.2%, -28.8%, and -39.8% for the three risedronate groups, respectively.

Subgroup Analysis

A total of 63 patients from Studies RPD-001694 and 90009 were pooled in the subgroup analysis. Study 90009 is an uncontrolled, open-label study with a total of 13 patients who received 30 mg risedronate daily for 56 days and a no treatment follow-up of 112 days. Table 13 displays the maximum percent reduction from baseline in total serum AP excess along with the 95% confidence intervals for each demographic subgroup of gender, age, and race for the 30 mg risedronate group.

Table 13 Maximum Percent Reduction from Baseline in Total Serum Alkaline Phosphatase Excess of 30 mg Risedronate by Subgroup Studies RPD-001694 and 90009

Subgroup	n	Baseline SAP (U/L) Mean±SEM	Mean Maximum % Reduction
Age (years)			
<65	27	563.7± 86.0	-84.3
≥65	36	764.4±153.3	-90.3
Gender			
Male	46	621.4± 76.2	-85.9
Female	17	856.8±288.7	-92.5
Race			
Caucasian	54	585.7± 70.0	-89.8
Other	9	1234.3±502.0	-75.1

APPEARS THIS WAY
ON ORIGINAL

Conclusion:

In study RPD-001694, treatment with risedronate is statistically significantly better ($p<0.01$) than Didronel in percentage of patients in the maximum response (i.e., ≥75% reduction from baseline in total serum alkaline phosphatase excess). During the treatment period, 51 of the 60 risedronate patients (85%) versus 12 of the 60 Didronel patients (20%) achieved a maximum response. Study 88040 was not powered to detect difference between the three treatment doses (risedronate 10 mg, 20 mg, and 30 mg), therefore, the nonsignificant result of the responder analysis does not imply that they are similar.

/S/

Lee-Ping Pian, Ph.D.
Mathematical Statistician

APPEARS THIS WAY

Concur: Dr. Nevius /S/ 12/24/97

cc: Arch NDA 20-835/AP
HFD-510
HFD-510/SSobel
HFD-510/SDutta
HFD-510/EGalliers
HFD-510/RHedin
HFD-715/Division file, LPian
HFD-344/ALisook
Chron.

APPEARS THIS WAY

Pian/word/actonel/n20835.doc
This review contains 12 pages

APPEARS THIS WAY
ON ORIGINAL