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APPLICATION NUMBER: 20-835/S001-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 18 1999

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-835**
	Supplements
	SE 01
	SE 02
	SE 03
Generic Name:	**Risedronate Sodium Tablets**
Brand Name:	**Actonel®**
Sponsor:	**Proctor & Gamble**
	Cincinnati, OH
Submission Date:	**18 December 98**
	19 December 98
	09 February 99
	01 March 99
Type of Submission:	**Efficacy Supplements**
Reviewer:	**Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.**

Synopsis

Risedronate is a bisphosphonate that is currently approved for Paget's disease of the bone at a dose of 30 mg daily for a duration of 2 months. Risedronate binds to hydroxyapatite crystals in the bone and decreases the rate of bone resorption.

An efficacy suppliment was submitted for the following three indications:

1. Prevention of postmenopausal osteoporosis (PMOP)
2. Treatment of postmenopausal osteoporosis (PMOP)
3. Prevention of corticosteroid induced osteoporosis (CIOP)

Subsequently, this supplement was unbundled to create 3 separate efficacy supplements. Each efficacy supplement has a phase III clinical trial. The proposed dose for each of these indications is 5 mg po daily.

The three efficacy supplements share the following pharmacokinetic studies:

A single 6.5 month pharmacokinetic/pharmacodynamic study in post-menopausal women treated with either 2.5 or 5 mg daily.

Several small Japanese pharmacokinetic studies evaluating ____ formulations that will not be marketed in the US

- pharmacokinetics of single doses from 1 to 20 mg
- pharmacokinetics of 5 mg dosed daily for 7 days
- Comparative bioavailability of a 2.5 mg tablet and a 2.5 mg ____ formulation
- A food effect study comparing various dosing regimens with respect to breakfast.

Dissolution studies of the new formulation
Assay validation data
Proposed revised labeling

The proposed 5 mg formulation is similar to the currently marketed 30 mg formulation, differing only in the amount of active ingredient with a commensurate change in the amount of diluent, and a change in the color of the film coating.

Conclusions

Residronate shows a pharmacodynamic effect on markers of bone resorption. This pharmacodynamic effect was fit to an Emax model using the minimum plasma concentration and resorption markers. However, the fit was poor with high variability. The pharmacokinetics are linear and the effect is dose dependent, consequently the mean effect is greater with the 5 mg dose compared with the 2.5 mg dose.

The proposed labeling includes changes to allow dosing with [redacted] These changes are unacceptable.

Drug administration in all trials was with 8 oz. of water. Due to safety concerns with alterations in esophageal transit with this class of drugs. The lack of bioavailability and safety data with administration of a smaller volume of water, and the use of larger volumes in all clinical studies, the proposed labeling change to decrease the volume of water with dosing to [redacted] is unacceptable.

Dosing in the phase III clinical trial was 0.5 – 1.0 prior to breakfast. When dosed 2 hours after dinner the relative bioavailability is 1.08 with a 90% confidence interval of 0.82 - 1.40 relative to dosing 0.5 hours before breakfast. However there is a delayed absorption resulting in a 64% decrease in Cmax. When dosed 3 hours after breakfast there is a decrease in relative bioavailability of 60%. Since the pharmacodynamic effect is concentration dependent, the proposed change in labeling to allow [redacted] is unacceptable.

Dissolution is extremely rapid and using the same dissolution method and criteria for the 5 mg tablet as the currently approved 30 mg tablet is acceptable.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II has reviewed NDA 20-835 initially submitted December 18, 1998 and finds it acceptable.

Please convey recommendation and comments to the sponsor as appropriate.

Please convey labeling comments to the sponsor as appropriate.
Please note that not all comments are currently incorporated into edited labeling. Labeling will need additional editing in consultation with the medical reviewer prior to communication to sponsor.

Comments for Sponsor

1. Dosing in the phase III clinical trial was 0.5 – 1.0 prior to breakfast. When dosed 2 hours after dinner the relative bioavailability is 1.08 with a 90% confidence interval of 0.82 - 1.40 relative to dosing 0.5 hours before breakfast. However there is a delayed absorption resulting in a 64% decrease in Cmax. When dosed 3 hours after breakfast there is a decrease in relative bioavailability of 60%. Since the pharmacodynamic effect is concentration dependent, the proposed change in labeling to allow [redacted] is unacceptable.
2. Drug administration in all trials was with 8 oz. of water. Due to safety concerns with alterations in esophageal transit with this class of drugs. The lack of bioavailability and safety data with administration of a smaller volume of water, and the use of larger volumes in all clinical studies, the proposed labeling change to decrease the volume of water with dosing to [redacted] is unacceptable.
3. The [redacted] assay for residronate is biased and in-process quality control samples frequently indicated that the assay was performing outside the specifications specified by the sponsor. Any future submissions that are to include data generated with this [redacted] assay must have in-process controls that are acceptable to the agency. The high degree of bias with this assay indicates possible problems with the assay. If this assay is used in the future, this bias will also need to be addressed.

4. In the future, assays for pharmacodynamic measures in addition to assays for drug concentrations must be adequately validated and reports on their validation and in-process controls shall be submitted for review.

Labeling Comments for Sponsor

n.b. not all comments are currently incorporated into edited labeling. Labeling will need additional editing in consultation with reviewers from other disciplines prior to communication to sponsor.

~~Double-struck-out~~ text should be removed from the proposed labeling; <u>double underlined text</u> should be added

➢ Indicates additional comments to be sent to the sponsor.

3 PAGE(S) REDACTED

Draft Labeling

Signatures

/S/ 6/18/99

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. Date

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 6/18/99
FT

CC: **NDA 20-865 (orig., 1 copy)**
HFD-510 (Colman, Hedin)
HFD-850 (Lesko)
HFD-870 (M. Chen, Kavanagh, Ahn)
Central Document Room (Barbara Murphy)

6/15/1999

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Table of Contents

List of Tables

List of Figures

List of Appendices

Appendix	Protocol No.	Protocol Title/Description	Comments
Appendix 1	92110	Safety and Pharmacokinetics of Risedronate (NE-58095) in Healthy Volunteers Administered Orally in a Single Dose	Different formulation than for US - 2.5 mg for Japan – Study demonstrates linearity
Appendix 2	92111	Study on Safety and Pharmacokinetics of NE-58095 (Risedronate) After Repeated Administration to Healthy Volunteers	Different formulation than for US - 2.5 mg for Japan – Study demonstrates linearity
Appendix 3	92136	Study on the Bioavailability of NE-58095 (Risedronate) Preparations Tablets) in Healthy Volunteers	Different formulation than for US - 2.5 mg for Japan – Study demonstrates linearity
Appendix 4	92115	Effect of Meal on Absorption of NE-58095 (Risedronate) After Single Administration to Healthy Volunteers	Different formulation than for US - 2.5 mg for Japan – Study demonstrates greater food effect 3 hours after breakfast than 0.5 hours before breakfast.
Appendix 5	Not Applicable	Summary of other Food Effect Studies	Compares food effect studies and puts in perspective
Appendix 6	RMD008894	A Study to Determine the Linearity of Risedronate Pharmacokinetics Over Time, Upon Multiple Dose Oral Administration of 2.5 or 5 mg to Postmenopausal Women	PK/PD study with to be marketed US formulation
Appendix 7	Not Applicable	Sponsor's Draft Labeling	

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Assay Validation

An —— assay for residronate was used for the pharmacokinetic/pharmacodynamic study. The assay appears to be the same as was previously reviewed for the original NDA. The assay was demonstrated to be biased during the validation procedure with *mean* control values often 20% below the true values. The assay was accepted as adequate during the original review.

A large number of the quality control (QC) samples run during the analysis of clinical samples in the current submission were outside the sponsor's self-defined 'acceptable range'. Due to the manner is which the sponsor presented the data it was impossible to determine which clinical samples may have had spurious concentrations reported for them. Never-the-less the conclusions from the pharmacokinetic/pharmacodynamic study are consistent with what would be expected with this compound. However the fit of the data to a PK/PD model (i.e. Emax model) was poor, and it's unknown to what extent this poor fit is due to the variability in the assay.

Formulation and Dissolution Data

Formulation

The proposed to be marketed residronate 5 mg tablet formulation is qualitatively and quantitatively similar to the currently approved 30 mg formulation. The formulations differ only in the amount of the active ingredient with a corresponding change in the amount of diluent and the addition of yellow ferric oxide in the tablet coating of the 5 mg tablet. (See Table 1 Risedronate Sodium Film-Coated Tablets Formulations for the qualitative-quantitative compositions and proportions.)

Table 1 Risedronate Sodium Film-Coated Tablets Formulations

Ingredient	Phase III 5 mg Tablet	Commercial 5 mg Tablet		Commercial 30 mg Tablet		Function
Core Tablet:		Amount (mg)	%	Amount (mg)	%	
Risedronate sodium	5.0	5.0	——	30.0	——	Active
Lactose, monohydrate						
Microcrystalline cellulose						
Crospovidone						
Magnesium stearate						
Subtotal Core Tablet (mg)						
Film Coating:						
——						
——						
Ferric oxide, yellow						
Total Coated Tablet (mg)						

Dissolution Data for 5 mg tablets

Dissolution profiles were examined in four different media.

Conditions used in dissolution studies for the 5 mg tablet were similar to those currently approved for the 30 mg tablet. (See **Table 2** - Approved and Proposed Dissolution Specifications.)

Table 2 Approved and Proposed Dissolution Specification

	Approved	Proposed
Tablet Strength	30 mg	5 mg
Status	Approved Original NDA #20-835	Proposed NDA Supplement 1 # 20-835
Apparatus	USP 2 (paddles)	Same
Paddle Speed	50 RPM	Same
Media	Water	Same
Volume	500 ml	Same
Specification	Not less than	Same

Four dissolution media were investigated:

SGF	Simulated Gastric Fluid without Enzymes
SIF	Simulated Gastric Fluid without Enzymes
pH 5 Buffer	Citrate Buffer, pH 5
Water	Purified Water

Sampling times were 10, 20, 30 and 45 minutes.

The dissolution studies were conducted on 3 'clinical' biobatches and 1 'commercial product lot'. (See Table 3 - Batch Information.)

Table 3 Batch Information

Batch Use	Pivotal Phase III Clinical Trials	Commercial Production
Lot Numbers	065320 065972 065973	MAN216133
Batch size		
P&GP plant	Manati, Puerto Rico	North Norwich, NY

Twelve tablets were used from each of the four batches for each of the 4 media used in the dissolution profile studies.

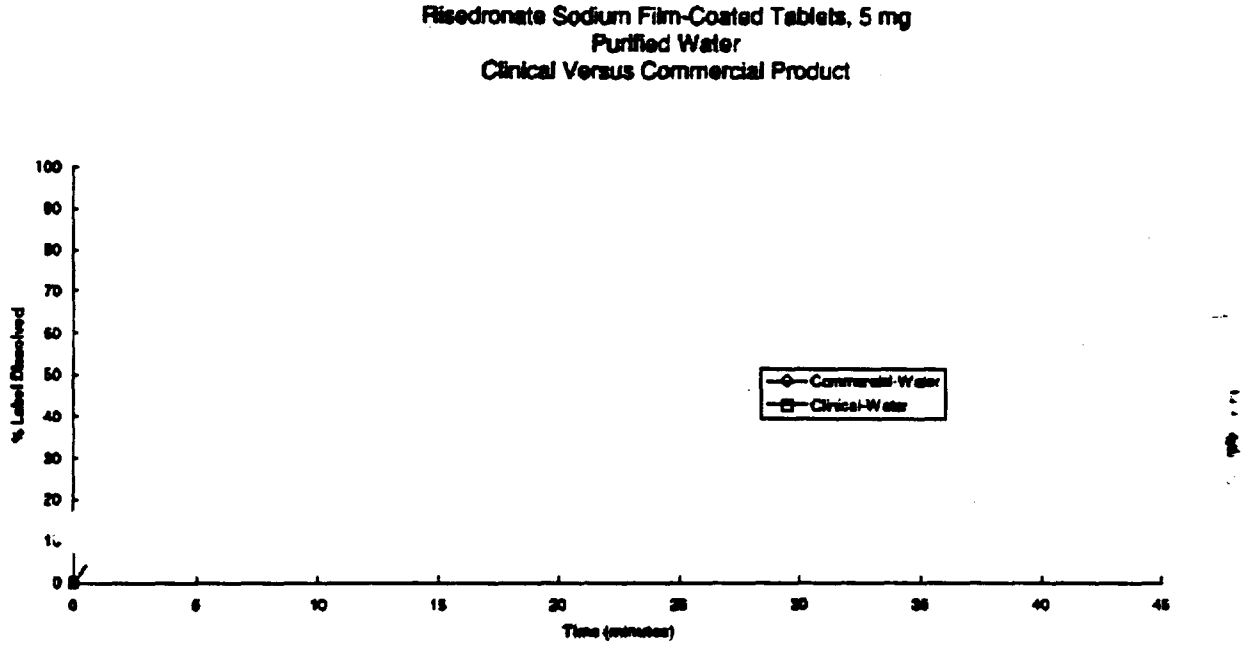
Data reviewed can be found on page Vs1.004/p155 of the application.

Results:

Dissolution profiles were very similar across all four media. The clinical and commercial batches had virtually identical dissolution profiles to each other in water and citrate buffer. The commercial product had a slightly more rapid dissolution profile than the clinical batches in SIF (mean % dissolved 94% vs. 92% at 20 minutes) and a slightly slower dissolution profile in SGF (mean % dissolved 83 vs. 88% at 30 minutes).

Only SGF demonstrated a statistical difference in the 30 minute mean dissolution ratios (commercial/clinical) when analyzed by ANOVA, and it also had the lowest f2 similarity factor which is still within the acceptable range of 50-100. The worst dissolution was obtained with the commercial product lot in SGF at the 10 minute time point. Even so the mean dissolution ± SD was 74 ± 9.8 % at 10 minute time point with a CV of 13.2% and a range of

Figure 1 Dissolution Profile of Residronate 5 mg Tablets in Purified Water



Reviewer Assessment/Recommendation:

Due to the rapid dissolution under various conditions a single point dissolution specification is acceptable. The proposed dissolution specification for the 5 mg tablet is the same as those currently approved for the 30 mg tablet. This specification is acceptable for the 5 mg tablet (See **Table 2** - Approved and Proposed Dissolution Specifications).

Bioavailability and Bioequivalence

Food Effects

Food effects are present.

An earlier study with the 30 mg tablet (Study RRF008593 - see appendix for synopsis) demonstrated similar mean bioavailability (amount eliminated in urine or AUC) for the 30 mg tablet when dosed 0.5 hours before a high fat breakfast after a 10 hour fast compared with dosing 2 hours after a 'standard' dinner. However, the extent of absorption was highly variable (90% CI of the ratios 0.82-1.40). In addition the Cmax after the dinner dose was 36% of the Cmax after the breakfast dose with an increase in time required for absorption, (mean Tmax's 1.99 vs. 0.35 hours).

Both regimens result in approximately 36-45% relative bioavailability —— compared with dosing 4-4.5 hours before lunch, when lunch is the first meal of the day after a 14 hour fast, (i.e. drug administration occurs at 9.5-10 hours into a 14 hour fast).

In a Japanese study (Study 92115) using a 5 mg dose (2 x 2.5 mg) the extent of absorption —— when dosed 3 hours after breakfast resulted in approximately 40% of the bioavailability of the compared to dosing 0.5 hours before breakfast, when assessed by AUC. When assessed by the amount eliminated in the urine the mean extent of absorption when dosed 3 hours after breakfast was 29% compared with dosing 0.5 hours before breakfast. In this study the mean Cmax when dosed 3 hours after breakfast was 18% of the mean Cmax when dosed 0.5 hours before breakfast. Again there was an increase in mean Tmax from 0.86 hours to 2.27 hours.

This study utilized 2 x 2.5 mg ——— consequently the formulation used was dissimilar to the US to be marketed formulation.

These two studies demonstrate bioinequivalence when dosing is 2-3 hours after dinner or breakfast compared with dosing 0.5 hours before breakfast. In addition both studies dosing even as early as 1 hour before the first meal of the day can increase bioavailability by 2 fold or greater compared with dosing 0.5 hours before breakfast.

The phase III clinical studies utilized dosing 0.5 to 1.0 hour before breakfast, consequently the extent of absorption may be even higher in the clinical trials when compared with any dosing during the day after eating.

There is a dose response relationship in the phase III clinical trial with the minimum concentration. The sponsor has not demonstrated that these concentrations are achieved when dosing after meals. Since there is a high likelihood that dosing after a meal will significantly decrease the extent of absorption, there is no justification for the sponsor's request to alter the labeled dosing to include ———

Pharmacokinetic/Pharmacodynamic Relationships

Pharmacodynamics

Mean values for markers of bone resorption (Pyr/crt, dPyr/crt) decreased in a dose-dependent manner, with near maximal suppression by Day 29.

In general, formation markers (TAP, BAP, BGP) had a transient increase initially with both the 2.5 and 5 mg doses. By day 113 the mean percent decreases below baseline were -3.8%, -15.3%, and -17.3% (TAP, BAP, BGP) for the 5 mg dose. For the 2.5 mg dose, the mean ± SE usually included the baseline value and thus were not significantly different than baseline. In addition, formation markers were occasionally increased above baseline, instead of decreasing as would be expected.

According to the sponsor neither fractures nor concomitant use of thyroid replacement medication appeared to impact on the mean pharmacodynamic response to risedronate.

Pharmacokinetic/Pharmacodynamic Relationships

No direct relationship between Cmax, Cavg, Cmin, or cumulative AUC and formation bone markers was identified.

An Emax model was fit to the data in order to explain the relationship between Cmin and the *absolute change from baseline* in the resorption markers, Pyr/crt and dPyr/crt.

Although it does appear that the Emax model fits the data, the prediction is often poor as indicated by a high variability in the estimate of the intersubject variance in Emax (See Table 4 NONMEM Parameter Estimates).

Table 4 NONMEM Parameter Estimates

Final Parameter Estimates from NONMEM Analysis of Pyridinoline/Creatinine vs. C_{min} and Deoxypyridinoline/Creatinine vs. C_{min}
Protocol No. RMD000894

Parameter	Meaning	Estimated Value	Variability of Estimation (CV)[a]
Pyridinoline/Creatinine vs. C_{min}:			
θ_1	E_{max} (pmol/µmol)	-23.8	28.4%
θ_2	K_m (ng/mL)	0.143	46.7%
$\omega^2_{E_{max}}$	Intersubject variance in E_{max}	13.0%	259%
$\omega^2_{K_m}$	Intersubject variance in K_m	147%	42.2%
σ^2	Intrasubject variability	11.7%	17.5%
Deoxypyridinoline/Creatinine vs. C_{min}:			
θ_1	E_{max} (pmol/µmol)	-8.62	19.1%
θ_2	K_m (ng/mL)	0.103	35.9%
$\omega^2_{E_{max}}$	Intersubject variance in E_{max}	27.6%	100%
$\omega^2_{K_m}$	Intersubject variance in K_m	129%	43.0%
σ^2	Intrasubject variability	18.2%	14.8%

[a] CV is the Coefficient of Variation.

This poor predictability is also shown by the plots of the % change from baseline in resorption markers vs. Cmin, and the plots of their weighted residuals showing some of the extremely large weighted residuals.

Figure 2 Change from Baseline for Pyr/Cr vs. Cmin

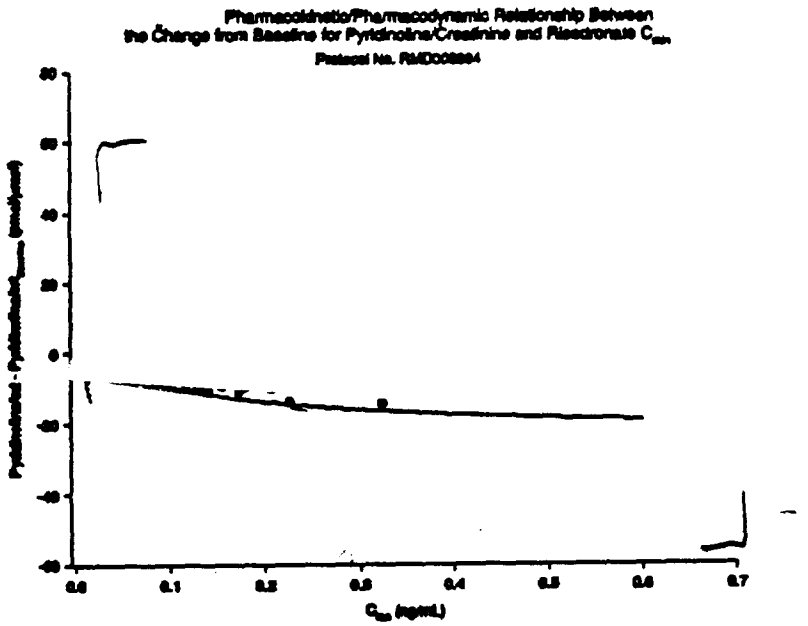


Figure 3 **Weighted Residuals vs. Predicted Pyr/Cr Concentrations**

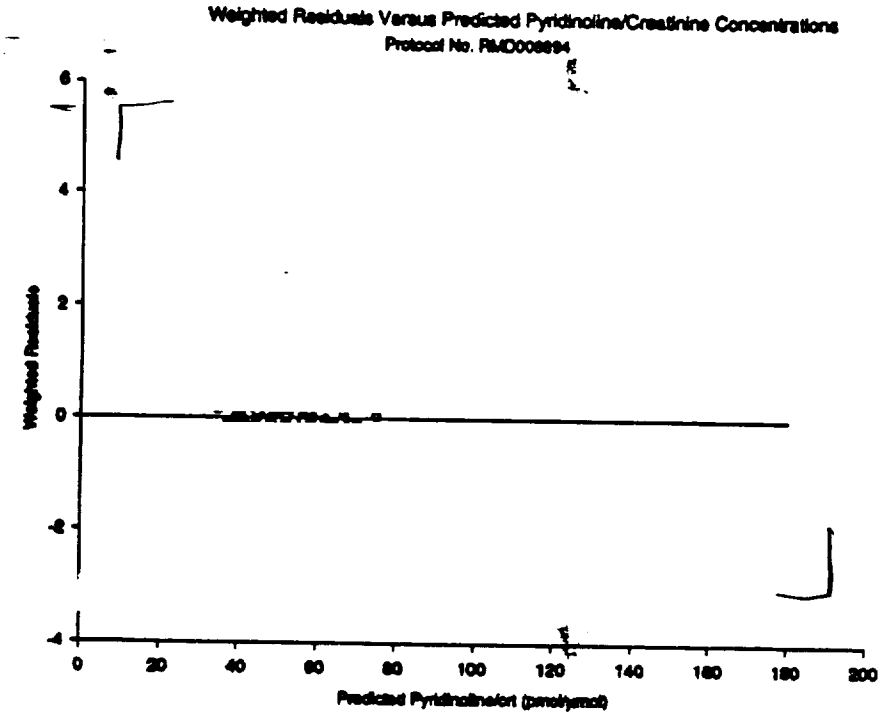


Figure 4 **Change from Baseline for dPyr/Cr vs. Cmin**

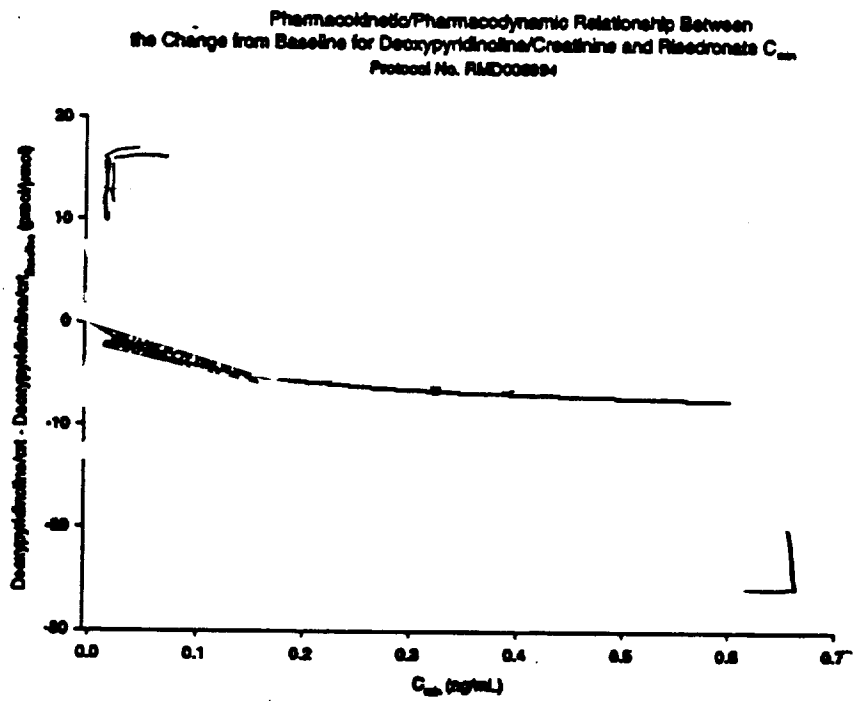
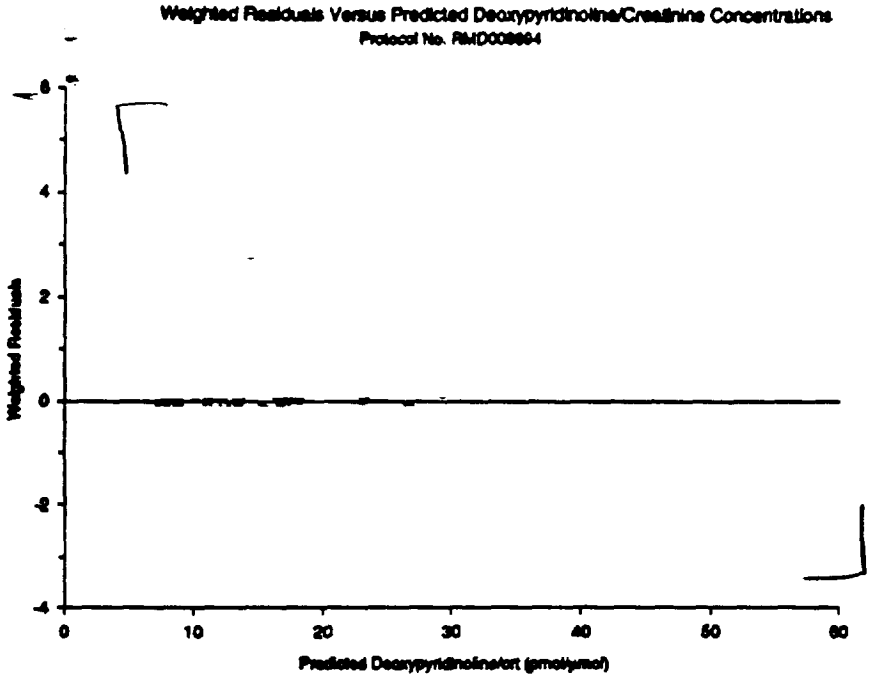


Figure 5 Weighted Residuals vs. Predicted dPyr/Cr Concentrations



None of the covariates investigated (e.g. age, years postmenopausal, body weight, concomitant medication) explained the variability in Pyr/crt and dPyr/crt adequately to significantly decrease the objective function; therefore, no covariates were included in the model.

In conclusion, there does appear to be a relationship between Cmin and markers of bone resorption, which is what would be expected for a deep tissue compartment such as bone. However, the relationship between concentration and effect is poorly defined due to a high degree of intersubject variability, part of which may be due to the high degree of variability in the assay used.

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Appendix 1 Protocol 92110 Study Synopsis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-835

Name of Company: Proctor & Gamble Pharmaceuticals
Cincinnati, OH

Tradename: Actonel®

USAN: Risedronate Sodium

Active Ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt

Title: Safety and Pharmacokinetics of Risedronate (NE-58095) in Healthy Volunteers Administered Orally in a Single Dose

Protocol Number: 92110

Objectives: **Primary:** To assess the safety of risedronate after a single dose of 1, 2.5, 5, 10, 20-mg or placebo in a controlled environment.

Secondary: To determine the linearity of risedronate pharmacokinetics after a single dose of 1, 2.5, 5, 10, or 20-mg.

Study Design: Placebo-controlled, sequential group, ascending single-dose

Study Population: 26 Healthy male volunteers, 20-50 years of age (inclusive), weight within 20% of (height-100) x 0.9, who had never received bisphosphonates.

Study Formulations:

1-mg	Lot # CS900107	Batch Size
2.5-mg	Lot # CS900069	Batch Size
10-mg	Lot # CS900070	Batch Size
Placebo	Lot # 900052	Batch Size

Drug Administration: Single-dose oral administration of 1, 2.5, 5 (2x2.5), 10, or 20 (2x10)-mg risedronate or placebo with 150 mL water to subjects in fasted state (duration of fast not defined).

Pharmacokinetic Evaluation: Pharmacokinetic parameters were determined from serum and urine samples obtained at predose and over 48 hours after dosing for the 1.0-mg dose, and from serum and urine samples obtained at predose and over 72 hours after dosing for the 2.5, 5, 10, 20-mg doses.

Safety Evaluation: Safety was evaluated by monitoring adverse events, clinical laboratory measurements (including ionized calcium, PTH, alkaline phosphatase, GGTP, SGOT, SGPT, creatinine. and isoenzymes), vital signs, ECGs, and performing physical examinations.

Subject Accountability/ Demographics: Thirty-four male subjects, aged 20-50 years, entered and completed the study. The subjects mean (SD) age and weight were 28.4 (10.0) years and 62.6 (6.2) kg.

Results:

Pharmacokinetic:
The rate (Cmax) and extent (AUC) of risedronate absorption increased in a statistically significant, linear manner from 1 to 20-mg. There were no significant correlations between t max, t½, or A'e and dose (p = 0.39, 0.89 and 0.085, respectively).

Safety Results:
There were no deaths or serious adverse events during the study. Overall, ten of the 26 subjects (38%) receiving risedronate reported 19 adverse events, and three of the eight subjects (38%) receiving placebo experienced an adverse event. None of these adverse events were concluded to be drug related. The most common adverse event was headache. There were no clinically significant changes in vital signs or clinical laboratory measurements.

Sponsor's Conclusions: Risedronate pharmacokinetics were linear following single dose, oral administration of 1, 2.5, 5, 10, and 20mg. Risedronate was well tolerated by the subjects.

Publications: None

NDA Page Location: Vs1.002/p201

Final Study Report Page Numbers: Vs1.087/p2-p59

Reviewer Comments:

Supportive data. Japanese ——— formulation is different from US formulation. Full study reports not provided.

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Appendix 2 Protocol 92111 Study Synopsis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-835

Name of Company: Proctor & Gamble Pharmaceuticals
Cincinnati, OH

Tradename: Actonel®

USAN: Risedronate Sodium

Active Ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt

Title: Study on Safety and Pharmacokinetics of NE-58095 (Risedronate) After Repeated Administration to Healthy Volunteers

Protocol Number: 92111

Reference: Ref (F040.14B) 2-Oct-98 s1

Study Objective: To investigate the safety and pharmacokinetics of 5 mg of risedronate when administered for 7 consecutive days to adult male volunteers.

Study Design: Placebo-controlled, multiple dose, study of 8 healthy male subjects. Dosing consisted of oral administration of 5-mg risedronate/day for 7 days under fasting conditions with 150 mL of water.

Number of Subjects: Enrolled: 8 Completed: 8

Study Population: Eight healthy male volunteers between the ages 20 and 35 inclusive, weight within 20% of (height-100) x 0.9, who had never received bisphosphonates.

Study Formulations: 2.5 mg —— Lot # CS900069-3. Batch Size ——
Placebo —— Lot # CS900052. Batch Size

Drug Administration: Six of eight subjects received 5 mg/day (2 X 2.5 mg) for seven days. The other two subjects received placebo for seven days.

Pharmacokinetic Evaluation:

Pharmacokinetic parameters were determined from serum and urine samples collected on each day of dosing and for one week after the last dose.

Safety Evaluation: Safety was evaluated by monitoring adverse events, vital signs, physical examinations, ECGs, and clinical laboratory measurements (including ionized calcium, PTH, alkaline phosphatase, SGPT, SGOT, creatinine and CK isoenzymes)

Subject Accountability /Demographics: Eight male subjects entered and completed the study. The subjects mean (SD) age and body weight were 23.8 (3.7) years and 60.9 (5.0) kg.

Results:

Pharmacokinetic Results:

- Multiple dose, daily administration of risedronate resulted in an increase in Cmax and AUC0-24h by days 4 and 7 as compared to day 1. Cmax was greater on day 4 than day 7, primarily due to two subjects; however, the Cmax for these subjects was similar to the other subjects on day 7 indicating a high intrasubject variability in absorption. There were no marked differences in AUC0-24h between day 4 and day 7. Urinary excretion (Ae(0-24h) increased from day 1 to day 4, and remained constant from day 4 today 7.Systemic exposure (AUC0-24h) of risedronate increased ~1.6-fold following the seven days of daily dosing.

Safety Results:

There were no deaths or serious adverse events during the study. Overall, three of the eight subjects(38%) reported seven adverse events. None of these adverse events were concluded to be drug related. The most common adverse event was headache. There were no clinically significant changes in vital signs or clinical laboratory measurements.

Sponsor's Conclusions: The administration of 5 mg risedronate/day for 7 days was safe and well tolerated. The increase in AUC0-24h from day 1 to day 7 (~1.6-fold) indicated that accumulation of risedronate will occur upon multiple dose, daily administration, with steady state apparently achieved by day 4.

Publications: None.

Vs1.002/p210 Vs1.002/p210

Reviewer Comments:

Supportive data. Japanese ——— formulation is different from US formulation. Full study report not provided.

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Appendix 3 Protocol 92136 Study Synopsis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-835

Name of Company: Proctor & Gamble Pharmaceuticals
Cincinnati, OH

Tradename: Actonel®

USAN: Risedronate Sodium

Active Ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt

Title: **Study on the Bioavailability of NE-58095 (Risedronate) Preparations ——— Tablets) In Healthy Volunteers**

Protocol Number: 92136

Reference: Ref (F040.16B) 2-Oct-98 s1

Study Objective: To compare the bioavailability of 2.5 mg risedronate ——— and tablets following single dose, oral administration.

Study Design: This study was an open-label, two-period, cross-over study of twenty subjects. Subjects were randomly assigned to 2 groups by Latin Square method. Subjects were administered either 2x2.5 mg tablets or 2x2.5 mg ——— orally with 150mL of water under fasting conditions. Subjects were crossed-over to the alternate formulation after a two week washout period.

Number of Subjects Enrolled: 20 Completed 18

Study Population: Healthy male adult volunteers between 20-35, inclusive, and are within 20% of (height-100)*0.9.

Study Formulations: 2.5 mg ——— Lot #CS900069-4 Batch Size: ———

2.5 mg tablet, Lot # Z5651011

Drug Administration: 2x2.5 mg capsule or 2x2.5 mg tablet as single dose with 150 mL of water under fasting conditions.

Pharmacokinetic Evaluation: Serum samples were collected before dosing and at 30 minutes, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after dosing. Cumulative urine samples were collected from 12 hours prior to dosing, and at intervals of 0-4, 4-8, 8-12, 12-24, and 24-48 hours after dosing. AUC0-24, Cmax , tmax, and mean residence time for the two formulations were compared using an analysis of variance, and mean, standard deviation and 90% confidence intervals were calculated.

Safety Evaluation: Safety was evaluated by monitoring adverse events, clinical laboratory measurements (including ionized calcium, PTH, alkaline phosphatase, GGTP,

SGOT, SGPT, creatinine, and CK isoenzymes), vital signs, ECGs, and performing physical examinations.

Subject Accountability/ Demographics: Twenty male subjects enrolled in the trial with 18 completing the study. Two subjects (nos. 11 and 13) withdrew from the study after period one for personal reasons. The mean (S.D.) age was 21.5 years (1.4). The mean (S.D.) weight was 64.3 kg (7.3).

Results: Mean pharmacokinetic parameters are summarized in the following table.

	Tablet Mean (SD)	——— Mean (SD)	Ratio (Tablet ———	Bounds of 90% Confidence Interval
AUC0-24h (ng•h/mL)	7.36 (3.49)	7.06 (4.10)	104.2	87.5, 131.1
Cmax (ng/mL)	2.20 (1.21)	1.83 (0.89)	120.2	90.5, 149.8
tmax (h)	1.17 (0.49)	1.39 (0.88)	84.0	56.0, 111.1
MRT0-24h (h)	3.20 (0.79)	3.26 (0.91)	98.0	88.0, 107.9

Pharmacokinetic Results:

AUC0-24h, Cmax, tmax, and MRT0-24h were not statistically significantly different between the ——— and the tablet formulations; however, Cmax for the tablet was 20% greater than that of the ——— suggesting a slightly greater rate of absorption. The mean (SD) cumulative urinary excretion (expressed as a percentage of dose) was 0.58 (0.40)% and 0.45 (0.23)% for the tablet and ——— respectively.

Safety Results:

There were no deaths or serious adverse events during the study. Ten subjects experienced 19 adverse events (AEs). None led to subject withdrawal. Headache was the most frequently reported AE; eight subjects with 11 headaches. Diarrhea was the second most frequently reported AE; four subjects with four episodes of diarrhea. None of these adverse events were concluded to be drug related. There were no clinically significant changes in vital signs or clinical laboratory measurements.

Conclusions: There was no statistically significant difference in rate (Cmax) or extent (AUC) of risedronate absorption after single dose, oral administration of the ——— and the tablet. Risedronate was well tolerated by all the subjects. These results indicate that safety and efficacy should be maintained when switching from ——— o tablets.

Sponsor's Conclusions: There was no statistically significant difference in rate (Cmax) or extent (AUC) of risedronate absorption after single dose, oral administration of the ——— and the tablet. Risedronate was well tolerated by all the subjects. These results indicate that safety and efficacy should be maintained when switching from ——— o tablets.

Publications: None

Vs1.002/p205

Reviewer Comments:

Unclear if tablets are same as US formulation. Full study report not provided.

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ON ORIGINAL

Appendix 4 Protocol 92115 Study Synopsis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA	20-835
Name of Company:	Proctor & Gamble Pharmaceuticals Cincinnati, OH
Tradename:	Actonel®
USAN:	Risedronate Sodium
Active Ingredient:	1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt
Title:	**Effect of Meal on Absorption of NE-58095 (Risedronate) After Single Administration to Healthy Volunteers**
Protocol Number:	92115
Reference:	Ref (F040.15B) 2-Oct-98 s1
Study Objective:	To determine the effects of a meal on the rate and extent of absorption after single oral dose administration of 5 mg risedronate (NE-58095).
Study Design:	The study was an open-label, randomized, crossover study. Twelve healthy male subjects were randomly divided in to 4 groups and assigned to one of four treatments. Subjects were fasted overnight and then administered risedronate as follows: 1) administration of drug followed by a 4.5 h fast; 2) administration of drug 30 minutes prior to breakfast; 3) administration of drug 30 minutes after breakfast; 4) administration of drug 3 hours after breakfast and no lunch the day of administration. The washout period between each period was two weeks.
Number of Subjects	Enrolled: 12 Completed: 11
Study Population:	Healthy male adult volunteers between 20-35, inclusive, and are within 20% of (height-100)*0.9.
Study Formulations:	2.5 mg [redacted] Lot # CS900069-2 Batch size: [redacted]
Drug Administration:	12 subjects received single dose, oral administration of 2x 2.5 mg [redacted] with 150 mL of water on four separate occasions separated by a 2 week washout period
Pharmacokinetic Evaluation:	Blood and urine were collected for 48 and 72 h after dosing, respectively.
Safety Evaluation:	Safety was evaluated by monitoring adverse events, vital signs, physical examinations, ECGs, and clinical laboratory measurements (including ionized calcium, PTH, alkaline phosphatase, SGPT, SGOT, creatinine and CK isoenzymes).

Subject Accountability/ Demographics: Twelve male subjects entered the study, and 11 subjects completed the study. One dropped out after the completion of the second period for a personal reason. The mean (S.D.) body weight was 61.3 (7.4). The mean (S.D.) height was 172.0 (7.7) The mean (S.D.) age was 23.0 (3.4).

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Results: Mean pharmacokinetic parameters are summarized in the following table.

Mean (SD) Pharmacokinetic Parameters	Dosed 4.5 h Before Lunch	Dosed 0.5 h Before Breakfast	Dosed 0.5 h After Breakfast	Dosed 3 h After Breakfast
AUC0-24h (ng/mL x h^{-1})	10.42 (6.20)	3.83 (2.27)	0.67 (0.51)	1.52 (1.50)
Cmax (ng/mL)	2.85 (1.46)	2.11 (1.25)	0.19 (0.13)	0.38 (0.23)
tmax (h)	1.36 (0.78)	0.86 (0.23)	3.22 (1.86)	2.27 (0.65)
t½ (h)	2.16 (1.11)	1.16 (0.41)	2.66 (0.67)	2.64 (1.18)
Ae (g)	36.29 (19.43)	16.08 (10.63)	2.13 (2.55)	4.65 (4.78)

AUC0-24h is the area under the plasma concentration-time profile from time 0-24 h after dosing,
Cmax is the maximum plasma concentration;
tmax is the time that Cmax occurs;
t½ is the half-life
Ae is the cumulative urinary excretion.

Pharmacokinetic Results:

The AUC of subjects dosed 4.5 h before lunch (fasting conditions) was markedly greater than the other dosing regimens; however, as this dosing regimen is not suitable for clinical practice, statistical analysis was only conducted on AUC data from subjects dosed 0.5 h before, 0.5 h after, and 3 h after breakfast. AUC for subjects dosed 0.5 h before breakfast was significantly larger (2.5- to 5.7-fold) than for subjects dosed 0.5 h or 3 h after breakfast ($p = 0.0003$ and 0.0012, respectively), with a similar trend observed for Ae. Cmax were 5- to 15-fold greater for subjects dosed before a meal, than after breakfast. Additionally, tmax was delayed by 2- to 3-fold when risedronate was administered after breakfast as compared to risedronate administered before a meal.

Safety Results:

Seven subjects (58.3%) experienced 16 adverse events (AEs). None of those events were considered serious and no subjects withdrew due to adverse events. Headache was the most frequently reported AE (37.5%). There was no trend for the occurrence of headaches in relation to dosing regimen or treatment sequence (Step I: 2 AE's, Step II 1 AE, Step IV: 3 AEs). All AEs were of unknown or not related causality.

Sponsor's Conclusions: Similar to other bisphosphonates, food decreases the absorption of risedronate. The rate (Cmax) and extent (AUC, Ae) of risedronate absorption is greatest when dosing is before a meal (0.5 or 4.5 h) as compared to after breakfast (0.5 or 3 h). These results suggest that to optimize risedronate absorption, oral administration of risedronate should occur at least 30 minutes before breakfast. The single oral dose of risedronate was well tolerated by the subjects with each of the dosing regimens.

Publications: None

Vs1.002/p216 Vs1.002/p216

Reviewer Comments:

Supportive data. Japanese data and japanese ——— formulation is different from US formulation. Full study report not provided. According to sponsor study design is sufficiently different so no direct

assessment to US formulation can be made. Dose normalized data shows bioavailability is several fold higher than with the 30 mg US tablet formulation.

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Appendix 5 Summary of other Food Effect Studies

The following is taken directly from the application

10. Food Interaction

Three studies evaluated the effect of food on risedronate pharmacokinetics following oral administration to normal, healthy volunteers. These studies were:

- Comparison of risedronate bioavailability when administered as a film-coated tablet before breakfast and after dinner (Study RRF006593);
- Comparison of risedronate bioavailability when administered before and after breakfast (Study 92115);
- Comparison of risedronate bioavailability when immediate-release and delay-release dosage forms are administered 0.5 h prior to breakfast (Study 91023).

These studies are summarized below.

10.1 Comparison of the Time of Risedronate Administration in Relation to Food and Time of Day Using Four Different Dosing Regimens After a Single 30 mg Oral Dose to Normal Healthy Volunteers (Study No. RRF006593 / United States / September 1993 - October 1993)

Study Purpose and Design

The recommended regimen for risedronate in phase II clinical studies was dose administration at least 2 h apart from any meal (generally dinner). The regimen in the phase III clinical study was dosing between 0.5 and 1 h prior to breakfast. Therefore, the purpose of this study was to compare the extent and rate of risedronate absorption for four different dosing regimens based on the time of day and the relationship to meals following oral administration of a single 30 mg dose to normal healthy volunteers.

Risedronate was orally administered using a single dose, randomized, parallel study design to healthy male and female volunteers. All subjects were administered a single oral 30 mg dose of risedronate with 240 mL of water. Subjects were randomized to receive one of the four following treatments:

1) Treatment 1:
   30 mg of risedronate administered after a 10 h fast and 4 h before lunch;
2) Treatment 2:
   30 mg of risedronate administered after a 10 h fast and 1 h before standard high fat breakfast;
3) Treatment 3:
   30 mg of risedronate administered after a 10 h fast and 0.5 h before standard high fat breakfast;
4) Treatment 4:
   30 mg of risedronate administered 2 h after a standard dinner.

The high fat breakfast consisted of 2 slices of white toast, 2 pats of butter, 2 eggs fried in butter, 2 slices of bacon, 2 oz of hash browns (potatoes), and 8 oz of whole milk [redacted]. This breakfast contained approximately 55 gm of fat. The dinner consisted of 4 oz baked boneless chicken breast, 1 oz lite gravy, 1 baked potato, 1 pat of margarine, ½ cup carrot rounds, ½ cup applesauce, 1 large peanut butter cookie, and 10 oz of lemonade.

Methods

Venous blood and urine for risedronate assay were collected from each subject immediately prior to dosing and for 168 h postdose. Risedronate serum and urine concentrations were determined by ——. Risedronate serum concentration-time and urinary excretion rate-time data were simultaneously analyzed using nonlinear regression.

Results

Median serum risedronate concentration-time profiles are illustrated in Figure 10.1.1. The median risedronate urinary excretion rate-time profiles are graphically depicted in Figure 10.1.2. Serum and urine concentrations of risedronate were quantifiable in all subjects.

Risedronate pharmacokinetic parameters are summarized in Table 10.1.1. Significant differences in AUC and A_e were observed among treatment groups. AUC and A_e for subjects dosed 4 h before lunch and 1 h before breakfast (Groups 1 and 2) were significantly larger than for subjects dosed 0.5 h before breakfast and 2 h after dinner (Groups 3 and 4). Additionally, AUC and A_e for subjects dosed 4 h before lunch (Group 1) were significantly greater than for subjects dosed 1 h before breakfast (Group 2). Comparison of AUC and A_e between subjects dosed 0.5 h before breakfast and 2 h after dinner (Groups 3 and 4) indicated that risedronate dosed before breakfast or after dinner results in similar drug exposure (Table 10.1.2), and were considered equivalent for highly variable drugs (Shah VP, 1996).

Differences in C_{max} among the four treatment groups were statistically significant. C_{max} for subjects dosed before a meal (Groups 1-3) was significantly larger than for subjects dosed 2 h after dinner (Group 4). In addition, C_{max} for subjects dosed 4 h before lunch (Group 1) was significantly larger than for subjects dosed 0.5 h before breakfast (Group 3).

The t_{max} for subjects dosed 2 h after dinner (Group 4) was significantly larger than the other treatment groups (Groups 1-3). Additionally, the t_{max} for subjects dosed 4 h before lunch (Group 1) was significantly larger than for subjects dosed 0.5 and 1 h before breakfast (Groups 2 and 3).

The $t_{1/2}$ was significantly different among the treatment groups. The $t_{1/2}$ for subjects dosed 0.5 h before breakfast (Group 3) was significantly shorter than those subjects dosed 1 or 4 h prior to a meal (Groups 2 and 1).

The median CL_R was not significantly different among Groups 1-4. The median CL_O was 26.4, 40.5, 67.5 and 59.9 L/h/kg for Groups 1-4, respectively. The V_z/F was significantly different among the treatment groups, with the subjects dosed 4 h before a meal (Group 1) having a significantly lower V_z/F than the other subjects (Groups 2-4).

ood Interaction, Special Populations, Protein Binding Summaries

able 10.1.1. Risedronate Pharmacokinetic Parameters After Single Dose Oral Administration of 30 mg Risedronate.

Pharmacokinetic Parameters	Estimate of Central Tendency[a,b,c] (95% Confidence Interval) Group 1 Dosed 4 h Before Lunch	Group 2 Dosed 1 h Before Breakfast	Group 3 Dosed 1/2 h Before Breakfast	Group 4 Dosed 2 h After Dinner	Overall P-value	Multiple Comparisons[d]
AUC[a] (ng-h/mL)	15.28	10.44	6.71	7.35	0.0001	3 4 2 1
C_{max}[a] (ng/mL)	3.65	3.38	2.66	0.97	0.0001	4 3 2 1
t_{max}[b] (h)	0.58	0.38	0.81	1.64	0.0001	3 2 1 4
$t_{max,obs}$[b] (h)	0.70	0.58	0.85	1.99	0.0001	3 2 1 4
$t_{1/2,Z}$[c,e] (h)	69.6	92.8	65.8	74.3	0.0231	3 4 2 1
CL_R[c] (L/h/kg)	0.0743	0.0732	0.0616	0.0677	0.1232	4 2 1 3
V_Z/F[a] (L/kg)	3699	5368	6254	7264	0.0002	1 2 3 4
A_e[c] (mg)	68.7	49.6	39.2	33.8	0.0001	4 3 2 1

AUC is the area under the serum concentration-time profile from time 0 → ∞; C_{max} is the maximum serum concentration; t_{max} is the time that the maximum serum concentration occurs, corrected for lag time (t_{lag}); $t_{max,obs}$ is the sum of t_{max} and t_{lag}; $t_{1/2,Z}$ is the half-life of the terminal exponential phase; CL_R is the renal clearance; V_Z is the terminal volume of distribution uncorrected for bioavailability; and A_e is the cumulative amount of drug excreted in urine from 0 → ∞.

[a] The parameters AUC, C_{max}, and V_Z/F were analyzed using log-transformed data; therefore, geometric least-squares means are reported as the estimate of central tendency.

[b] The parameters t_{max} and $t_{max,obs}$ were analyzed using raw data; therefore, arithmetic least-squares means are reported as the estimate of central tendency.

[c] The parameters $t_{1/2,Z}$, CL_R and A_e were analyzed nonparametrically using raw data; therefore, medians are reported as the estimate of central tendency.

[d] Groups are ordered from smallest to largest using either mean, geometric mean, or mean rank score, in accordance with the statistical analysis used. Underlined subsets indicate no significant difference between treatments.

[e] Mean rank scores are the basis for treatment comparisons in the nonparametric analysis. In the case of $t_{1/2,Z}$, the ordering for mean rank scores differs from the ordering for medians.

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Food Interaction, Special Populations, Protein Binding Summaries

Vs1.066/p91

Table 10.1.2. Comparison of Pharmacokinetic Parameters Following Single Dose, Oral Administration 0.5 h Before Breakfast and 2 h After Dinner
Protocol No. RRF006593

	Ratio of Pharmacokinetic Parameters with Respect to After Dinner Dosing Regimen (%, [90% CI])		
Pharmacokinetic Parameter	Dosing 2 h After Dinner	Dosing 0.5 h Before Breakfast	Dosing 1 h Before Breakfast
AUC	100	91	142
C_{max}	100	276	348
A_e	100	108	147

Figure 10.1.1. Median Serum Risedronate Concentration - Time Profiles Following Single Dose Oral Administration of 30 mg Risedronate to Normal Healthy Volunteers
Protocol No. RRF006593

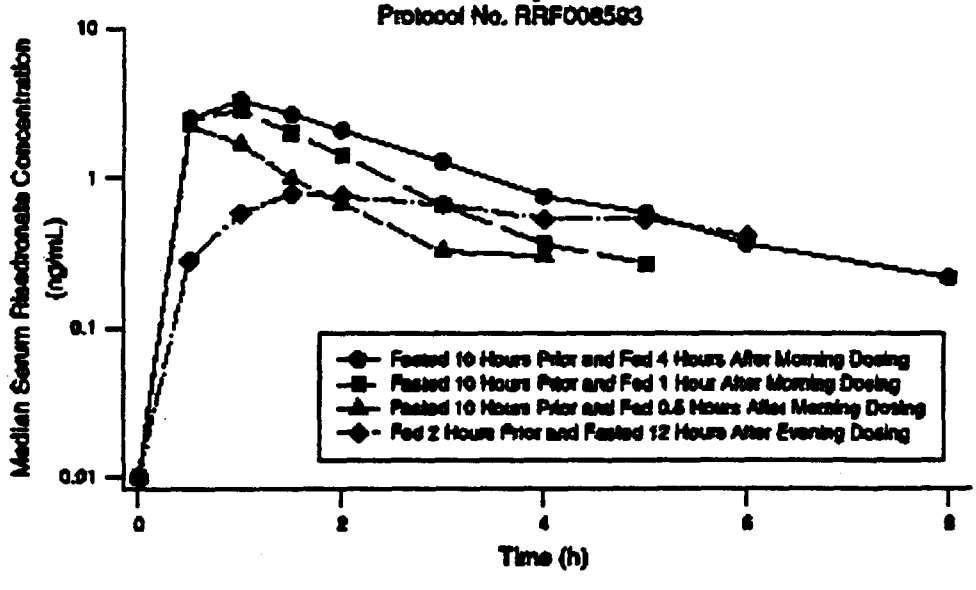
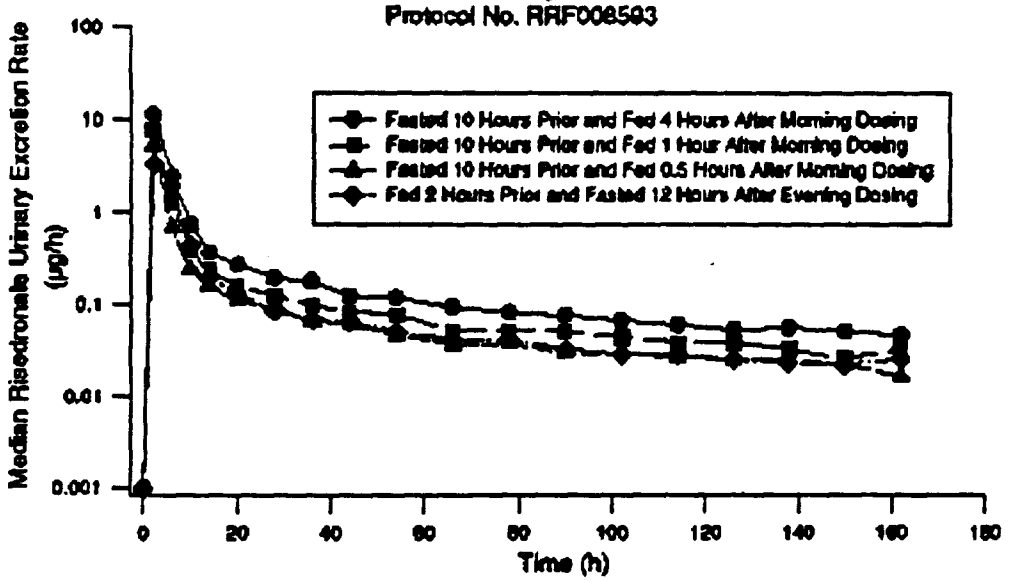


Figure 10.1-2. Median Risedronate Urinary Excretion Rate - Time Profiles Following Single Dose Oral Administration of 30 mg Risedronate to Normal Healthy Volunteers Protocol No. RRF006593



Conclusions

Phase II studies were conducted with risedronate administered 2 h after a meal (generally dinner) and the phase III study was conducted with risedronate administration 0.5-1 h prior to breakfast. Serum concentrations were quantifiable in all subjects, indicating that risedronate was absorbed after all dosing conditions. The extent of absorption (AUC, A_e) was not statistically significantly different between dosing 2 h after dinner and 0.5 h before breakfast, and were equivalent based on the criteria for highly variable drugs (Shah VP, 1996); however, the rate of absorption (C_{max}) was 2.5-fold greater when risedronate was administered before breakfast. The rate and extent of absorption were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. These results indicate that the phase III dosing regimen should provide extent of absorption equal to, or greater than, the phase II dosing regimen, and with a significantly greater rate of absorption.

10.2 Effect of Meal on Absorption of NE-58095 (Risedronate) After Single Administration to Healthy Volunteers (Study No. 92115 / Japan / February 1993 - March 1993)

This study was conducted by [redacted] English translations of copies of [redacted] reports made available to P&GP under this licensing agreement have been included in the submission for completeness.

Vs1.066/p93

Food Interaction, Special Populations, Protein Binding Summaries

Study Purpose and Design

The purpose of this study was to determine the effects of a meal on the rate and extent of absorption after single oral dose administration of 5 mg risedronate (NE-58095).

The study was an open-label, randomized, crossover study. Twelve healthy male subjects were randomly divided in to 4 groups and assigned to one of four treatment sequences. Subjects were fasted overnight and then administered risedronate (with 150 mL of water) as follows: 1) administration of drug followed by a 4.5 h fast; 2) administration of drug 30 minutes prior to breakfast; 3) administration of drug 30 minutes after breakfast; and 4) administration of drug 3 hours after breakfast and no lunch the day of administration. The washout period between each period was two weeks.

Methods

Blood for risedronate analysis was collected from each subject immediately prior to dosing and for 48 h after the first dose of each period. Urine was collected prior to dosing and for 72 h after the first dose of each period. Serum risedronate concentrations were determined by ——— and urine risedronate concentrations were determined by ———

Pharmacokinetic parameters were obtained using "noncompartmental" analysis. Subjects who completed all treatment periods were included in the analyses of the pharmacokinetic parameters.

Results

Mean pharmacokinetic parameters are summarized in Table 10.2.1.

Plasma concentrations were quantifiable after all dosing conditions studied, including the dosing 30 minutes after breakfast. The AUC of subjects dosed 4.5 h before lunch (fasting conditions) was markedly greater than the other dosing regimens; however, as this dosing regimen is not suitable for clinical practice, statistical analysis was only conducted on AUC data from subjects dosed 0.5 h before, 0.5 h after, and 3 h after breakfast. AUC for subjects dosed 0.5 h before breakfast was significantly larger (2.5- to 5.7-fold) than for subjects dosed 0.5 h or 3 h after breakfast ($p = 0.0003$ and 0.0012, respectively), with a similar tendency observed for A_e. C_{max} were 5- to 15-fold greater for subjects dosed before a meal, than after breakfast. Additionally, t_{max} was delayed by 2- to 3-fold when risedronate was administered after breakfast as compared to risedronate administered before a meal.

Table 10.2.1 – Risedronate Pharmacokinetic Parameters After Single Dose Oral Administration of 5 mg Risedronate
Protocol 92115

Pharmacokinetic Parameters	Mean (SD)			
	Dosed 4.5 h Before Lunch	Dosed 0.5 h Before Breakfast	Dosed 0.5 h After Breakfast	Dosed 3 h After Breakfast
$AUC_{0\text{-}24\ h}$ (ng•h/mL)	10.42 (6.20)	3.83 (2.27)	0.67 (0.51)	1.52 (1.50)
C_{max} (ng/mL)	2.85 (1.46)	2.11 (1.25)	0.19 (0.13)	0.38 (0.23)
t_{max} (h)	1.36 (0.78)	0.86 (0.23)	3.22 (1.86)	2.27 (0.65)
$t_{½}$ (h)	2.16 (1.11)	1.16 (0.41)	2.66 (0.67)	2.64 (1.18)
A_e (µg)	36.29 (19.43)	16.06 (10.63)	2.13 (2.55)	4.85 (4.78)

$AUC_{0\text{-}24h}$ is the area under the plasma concentration-time profile from time 0-24 h after dosing, C_{max} is the maximum plasma concentration; t_{max} is the time that C_{max} occurs; $t_{½}$ is the half-life; and A_e is the cumulative urinary excretion.

Conclusions

Similar to Study RRF006593, food decreased the absorption of risedronate. Plasma concentrations indicate that risedronate was absorbed after all dosing conditions studied, including dosing 30 minutes after breakfast, although absorption was clearly affected by food. The extent ($AUC_{(0\text{-}24h)}$, urinary excretion) and rate (C_{max}) of absorption showed the following tendency: fasting conditions > dosing 30 minutes before breakfast > dosing 3 hours after breakfast > dosing 30 minutes after breakfast. Direct extrapolation of data from the Japanese study to the US population is difficult due to marked differences in study design and demographic characteristics of the subjects. In addition, when Japanese subjects were dosed under fasting conditions in this study and others (92110, 92136), the overall dose-normalized extent of absorption was approximately 2-3 fold greater than that observed in the US pharmacokinetic studies under fasting conditions (see Studies RSD005794, RRF006593, RAB011594, and 1994022).

10.3 Bioavailability of Risedronate (NE-58095) When Administered Randomly in Different Solid Dosage Forms to Normal, Healthy Male Volunteers (Study No. 91023 / United States / November 1991 - January 1992)

Study Purpose and Design

The purpose of this study was to determine the relative bioavailability of 30 mg risedronate after oral administration of enteric-coated and immediate release formulations to healthy, male volunteers.

The study was designed as a randomized, multiple dose (3 consecutive daily doses), three period complete crossover in twelve male subjects. Risedronate (30 mg) was orally administered as either three 10 mg immediate-release [redacted] one [redacted] containing 30 mg [redacted] or one 30 mg enteric-coated tablet with 250 mL of water for three consecutive days in each of the 3 periods. The enteric-coated dosage forms were formulated

to release risedronate at pH 5.5. Subjects were fasted for 10 h prior to and 4 h after the first dose of each period, and for 10 h prior to and 0.5 h after the second and third dose of each period. The first dose of each period was separated by 21 days.

Methods

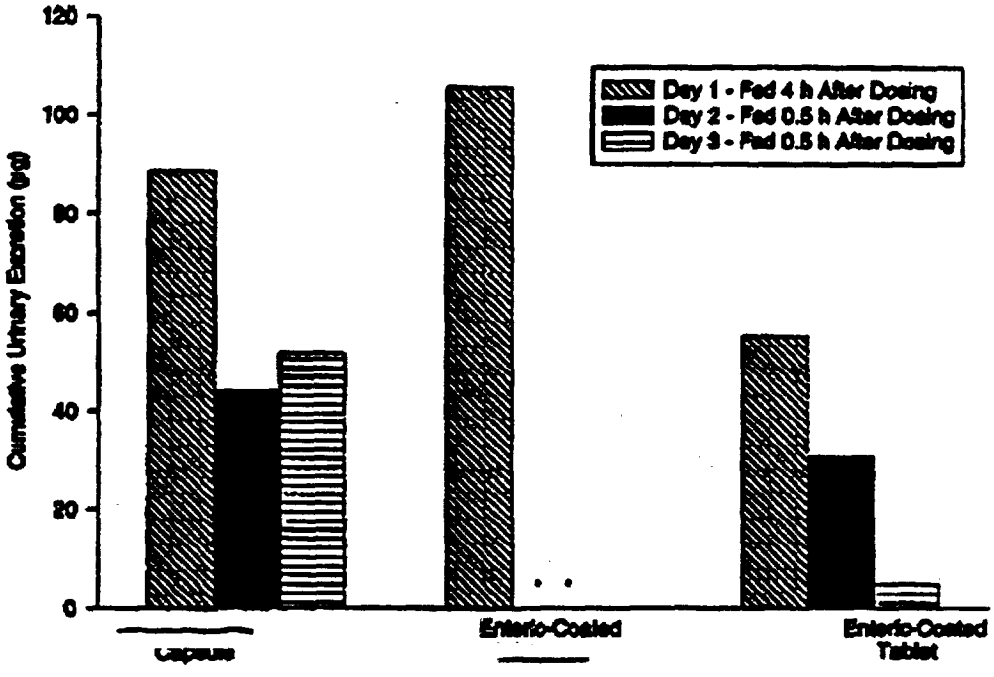
Blood for risedronate analysis was collected from each subject immediately prior to dosing and for 48 h after the first dose of each period. Urine was collected prior to dosing and for 72 h after the first dose of each period. Serum risedronate concentrations were determined by —— and urine risedronate concentrations were determined by ——

Pharmacokinetic parameters were obtained using "noncompartmental" analysis. Subjects who completed all treatment periods were included in the analyses of the pharmacokinetic parameters.

Results

Median A_e per day for each dosage form is summarized in Figure 10.3.1. The administration of food 0.5 h after dosing on days 2 and 3 of each period resulted in a marked reduction in the A_e as compared to the fasting for 4 h after dosing as in day 1. As expected with a later t_{max}, the absorption of risedronate from the enteric-coated dosage forms was most severely affected (50-100% reduction in A_e), with the absorption of risedronate from the immediate-release —— reduced by approximately 40%.

Figure 10.3.1 Median Cumulative Urinary Excretion Per Day Following Multiple Dose Daily Oral Administration of Three Risedronate Solid Dosage Forms
Protocol No. 91023-995.86.51-0912



* Median cumulative urinary excretion values were zero.

Conclusions

The administration of food 0.5 h after dosing on days 2 and 3 of each period resulted in a marked reduction in the absorption of risedronate (as measured by the decreased A_e). The 40% reduction in the median A_e on days 2 and 3 after administration of the immediate-release ——— is similar to that observed in a risedronate food interaction study (Study RRF006593). The 50-100% decrease in median A_e of the enteric-coated dosage forms probably reflects a greater interaction of risedronate with the food due to the delay in dissolution of the dosage form.

Vs1.066/p97

Food Interaction, Special Populations, Protein Binding Summaries

Summary of Conclusions

Phase II studies were conducted with risedronate administered 2 h after a meal (generally dinner) and the phase III study was conducted with risedronate administration 0.5-1 h prior to breakfast. The extent of absorption (AUC, A_e) was not statistically significantly different between dosing 2 h after dinner and 0.5 h before breakfast, and were equivalent based on the criteria for highly variable drugs; however, the rate of absorption (C_{max}) was 2.5-fold greater when risedronate was administered before breakfast. The rate and extent of absorption were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. These results indicate that the phase III dosing regimen should provide extent of absorption equal to, or greater than, the phase II dosing regimen, and a significantly greater rate of absorption.

Similarly, a small study conducted in Japan indicated that risedronate absorption was decreased if administered 0.5 h prior to breakfast, 0.5 h after breakfast, or 3 h after breakfast.

The administration of food 0.5 h after oral administration of an immediate-release ——— or an enteric-coated dosage form resulted in a marked reduction in the absorption of risedronate (as measured by the decreased A_e). The 40% reduction in the A_e after administration of the immediate-release ——— is similar to that observed in a risedronate food interaction study (Study RRF008593). The 50-100% decrease in median A_e of the enteric-coated dosage forms probably reflects a greater interaction of risedronate with the food due to the delay in dissolution of the dosage form.

Appendix 6 Protocol RMD008894 Study Synopsis

NDA 20-835

Name of Company: Proctor & Gamble Pharmaceuticals
Cincinnati, OH

Tradename: Actonel®

USAN: Risedronate Sodium

Active Ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt

Title: A Study To Detemine The Linearity of Risedronate Pharmacokinetics Over Time, Upon Multiple Dose Oral Administration of 2.5 or 5 mg to Postmenopausal Women

Protocol Number: RMD008894

Objectives:

Primary: To determine the linearity of risedronate pharmacokinetics over time upon long term, multiple dose, oral administration of 2.5 or 5 mg to postmenopausal women in the dose range to be used in osteoporosis.

Secondary: To explore the relationship between risedronate pharmacokinetic parameters and the pharmacological effect of the study drug on bone metabolism upon multiple dose, oral administration of 2.5 or 5 mg to postmenopausal women.

Study Design:

This two-site study utilized a randomized, two-treatment, multiple oral-dose, parallel-group design, in which 96 postmenopausal female subjects received risedronate. Subjects were randomized to receive either 2.5 or 5 mg risedronate for 169 days (24 weeks 1 day; 5.5 months), with pharmacokinetic and pharmacodynamic samples collected periodically during dosing and for 28 days following the last dose.

Number of Subjects:

96 subjects were enrolled in the study;
55 subjects completed the study.

Significant Criteria for Inclusion:

Female at least one year postmenopausal
Within 10% of ideal body weight.
Nonsmoker

Significant Exclusion Criteria:

Has a condition that requires medical attention or may be associated with acute symptoms during the trial
Use of any medications that might alter bone metabolism, including bisphosphonates
Ulcer disease or hx of heartburn necessitating Rx during the study
Hx of drug or alcohol abuse within 5 yrs.
Us or enzyme inducer or inhibitor within 30 days of study

Dosage Description:

2.5-mg cellulose-film-coated tablets -Lot # 72865 (14241-23B), Batch Size - [redacted] tablets
2.5-mg cellulose-film-coated tablets -Lot # 72867 (14241-23B), Batch Size - [redacted] tablets
5-mg cellulose-film-coated tablets -Lot # 73063 (14241-040B), Batch Size - [redacted] ablets
5-mg cellulose-film-coated tablets -Lot # 73077 (14241-040B), Batch Size - [redacted] tablets

Drug Administration:

Daily oral administration of a 2.5 or 5 mg tablet for 169 consecutive days.
Taken fasting 1 hour before breakfast. Subjects may not lie down for at least 1 hour post administration.

Pharmacokinetic Sampling:

Serum: Samples for risedronate were collected on study Days 1, 8, 29, 57 and 113

Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20 and 24 hours post-administration.

and on days 169-171 at times.

Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24 28, 32, 40, 48, 60 and 72 hours post-administration.

Urine: Samples for risedronate were collected on study Days 1, 8, 29, 57, 113

Blank, 0-1, 1-2, 2-4, 4-8, 8-12, 12-16, and 16-24 hours.

and on days 169-171 at times.

Blank, 0-1, 1-2, 2-4, 4-8, 8-12, 12-16, 16-24, 24-32, 32-40, 40-48, 48-60, 60-72 hours post-dose

with additional urine samples collected on Days 172-175

72-84, 84-96, 96-108, 108-120, 120-132, 132-144, 144-156, and 156-168 hours post-dose.

and three times per week from Days 176-197

– 8 hour urine samples

'A 10% aliquot of each urine collection from 0-24 hours (i.e., 0-1, 1-2, 2-4, etc.) will be pooled for a 0-24 hour creatinine clearance.'

Serum creatinine collected at 12 hours.

Pharmacodynamic Sampling:

Pharmacodynamic measurements were collected prior to the study (baseline) and on study Days 0, 8, 29, 57, 113, 169, 183 and 197. Plasma samples were obtained at the same time as trough drug concentrations.

Measurements included total serum alkaline phosphatase (TAP), Ostase® (BAP, bone-specific alkaline phosphatase), osteocalcin (BGP), and urinary excretion of collagen crosslinks (dPyr/crt, deoxypyridinoline/creatinine; Pyr/crt, pyridinoline/creatinine).

A 2 hour urine sample was pooled (50% of each sample) from 0-1 and 1-2 hours for collagen crosslinks.

Evaluation of Safety:

Safety was evaluated by monitoring adverse events throughout the study, routine clinical laboratory measurements, physical examination, and vital signs.

Pharmacokinetic Analysis:

Cl_{oral}, Cmax, Cmin, CL_R, AUC_{0-24}, AUC_{0-24} Cmax and Cmin Accumulation Ratios (R) for days 8, 29, 57, 113, and 169 compared to day 1. $Ae_{(0-24)}$ and tmax. Vz/F and $t_{½}z$.

Serum concentration and urine excretion rate data were simultaneously fit to multicompartment models with an absorption lag.

Population pharmacodynamic responses were analyzed using NONMEM IV with both a linear and Emax model. Both additive and exponential error models were evaluated.

Statistical Analysis:

Subject Accountability/Demographics:

Ninety-six subjects were enrolled in the study, with 34 subjects withdrawn upon the closure of the [redacted] site due to poor sample handling procedures and documentation. The remaining 62 subjects were enrolled at the [redacted] site, where 55 completed the study; two withdrew for personal reasons and five withdrew due to an adverse event.

Subject Demographics:

Demographics from the [redacted] site included mean (SD) ages for the 2.5 and 5 mg dose groups of 63.6 (7.7) and 61.5 (8.8) years, respectively, and mean (SD) number of years postmenopausal for the 2.5 and 5 mg dose groups was 15.3 (9.9) and 15.8 (7.6) years, respectively. The mean (SD) weight for the 2.5 and 5 mg dose groups was 66.6 (6.8) and 65.7 (9.7) kg, respectively. All of the subjects were Caucasian.

Results:

Pharmacokinetics:

Pharmacokinetic results are summarized in the table below. Analysis of Cmax, Cavg and Cmin indicated that risedronate pharmacokinetics achieved steady state by Day 57. The steady-state pharmacokinetics were dose proportional, based on Cmax, Cavg, Cmin, AUCτ and A'e. Similarly, tmax, CLR, t½,z, and Vz/F were not significantly different between the 2.5 and 5 mg doses. Risedronate accumulation (R) measured as the ratio of AUCτ (Day 169) to AUCτ(Day 1), was 1.82- and 2.09-fold for the 2.5 and 5 mg doses, respectively. The approximately 15% difference in accumulation was statistically significant between doses, but is unlikely to be clinically significant. Cmax increased by only 15% at steady-state, whereas Cmin increased 8- to 10-fold.

Parameter [Means (SD)]	2.5 mg	5 mg	P-value
Dose-normalized Cmin a (ng/mL/mg dose)	0.024 (0.014)	0.028 (0.015)	0.4317
Dose-normalized Cmax a (ng/mL/mg dose)	0.248 (0.088)	0.234 (0.109)	0.5999
Dose-normalized Cavg a (ng/mL/mg dose)	0.051 (0.022)	0.050 (0.023)	0.9023
Dose-normalized AUC b (ng h/mL/mg dose)	1.23 (0.53)	1.21 (0.55)	0.9030
tmax b (h)	0.74 (0.16)	0.73 (0.12)	0.6508
CLO b (L/h/kg)	14.8 (7.5)	14.9 (5.2)	0.9866
CLR b (L/h/kg)	0.0631 (0.016)	0.0677 (0.015)	0.7045
R b	1.82 (0.37)	2.09 (0.43)	0.0158
A'e b (%)	0.528 (0.24)	0.501 (0.16)	0.6245
t1/2,Z b (h)	442.2 (145.0)	480.9 (170.3)	0.3697
VZ/F b (L/kg)	9248 (4745.3)	10337 (5576.8)	0.4394

a Evaluated at steady-state on Day 169.
b Evaluated over the entire study period.

Pharmacodynamics:

As expected, bone markers of resorption (Pyr/crt, dPyr/crt) decreased in a dose-dependent manner, with clinically relevant suppression by Day 29. In general, formation markers (TAP, BAP, BGP) had a transient increase in activity during the first month of dosing, but decreased in a dose-related manner (5 mg>2.5 mg) during the last five months of dosing. Neither fractures nor concomitant use of thyroid replacement medication appeared to impact on the mean pharmacodynamic response to risedronate.

Pharmacokinetic/Pharmacodynamic Relationships:

An Emax model characterized the relationship between Cmin and resorption markers, Pyr/crt and dPyr/crt. None of the covariates investigated (e.g. age, years postmenopausal, body weight, concomitant medication) explained the variability in Pyr/crt and dPyr/crt adequately to significantly decrease the objective function; therefore, no covariates were included in the model. No direct relationship between Cmax, Cavg, Cmin, or cumulative AUC and formation bone markers was identified.

Safety:

Seventy-seven subjects (80.2%) experienced 373 adverse events during the six month study; 35 subjects that received 2.5 mg risedronate experienced 155 adverse events and 42 subjects that received 5 mg risedronate experienced 218 adverse events. Two subjects in each group experienced serious adverse events that were considered by the investigator as doubtfully related to study drug. Five subjects dropped out of the study due to adverse events; two subjects receiving 2.5 mg risedronate dropped, one due to colon cancer and one due to rheumatoid arthritis. Three subjects receiving 5 mg risedronate dropped, one each for atrial fibrillation, intermittent chest fullness, or intermittent palpitations. Headache was the

most commonly reported adverse event (12 subjects receiving 2.5 mg risedronate, and 12 subjects receiving 5 mg risedronate).

Sponsor's Conclusions:

Steady-state was achieved within 57 days of daily dosing. Risedronate pharmacokinetics were dose proportional following multiple dose, oral administration of 2.5 and 5 mg to postmenopausal women. Approximately 2-fold increase in extent of exposure occurred at steady-state, with a 15% increase in the Cmax and an 8- to 10-fold increase in Cmin. Markers of bone resorption and formation were decreased in a dose-dependent manner, but no oversuppression of bone turnover was evident with either the 2.5 or 5 mg dose. Bone resorption markers decreased quickly (at one month) upon risedronate treatment, and PK/PD relationships could be defined between the decrease in activities of pyridinoline/creatinine and deoxypyridinoline/creatinine with the increase in Cmin. These results suggested a direct effect of risedronate on osteoclast activity, with the Cmin reflecting the concentration of risedronate on bone that inhibits the osteoclast activity. In general, bone formation markers exhibited a transient increase during the early course of risedronate treatment (Day 8 and 29) before being suppressed, and no direct PK/PD relationship could be determined. In general, risedronate was well tolerated by the postmenopausal subjects.

Publications: Sacco-Gibson N, Mitchell DY, Crusan CE, Benesh J, Clay ME, Anderson G. Effects of risedronate on markers of bone turnover in healthy (nonosteoporotic) postmenopausal women. J Bone Miner Res 1996, 11:S346 (abstract).

Location: Vs1.002/p207 Vs1.002/p207 Clinical Study Report RMD008894

Reviewer Comments:

Conclusions regarding PK/PD relationship between Cmin and markers of bone resorption using an Emax model and population analysis and lack of covariates is acceptable, however it's a very poor fit as the variability is so high. This could be partly due to the variability in the assay.

Study was powered (80%) to detect a 50% difference 0.405 on log scale on s = 0.521 for log transformed Cmax Vs.1.088/p23. It should be for 20% difference. Conclusions regarding markers of bone formation not supported by data, except possibly for a dose dependent trend in the last 5 months of treatment. Statistical analysis was not performed and graphical data only shows means and standard errors. The decrease by one month was only seen in one of 3 markers of bone formation, and based on the presented figures it would be difficult if not impossible to show a difference from baseline even during the last 5 months.

APPEARS THIS WAY
ON ORIGINAL

Appendix 7

Sponsor's Proposed Updated Labeling
(Package Insert)
With Sponsor's Revision Marks

ACTONEL®™
(risedronate sodium tablets)

APPEARS THIS WAY
ON ORIGINAL

20 PAGE(S) REDACTED

Draft

Labeling