CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022560Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW AMENDMENT

NDA: 022560	Submission Date(s): 9/24/2009, 2/12/2010, 10/4/2010, 10/5/2010, 10/6/2010, 10/7/2010
Brand Name	Atelvia
Generic Name	Risedronate sodium
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Warner Chilcott Pharmaceuticals, Inc.
Submission Type	Original
Formulation; Strength	Delayed release tablet; 35 mg
Indications	• Treatment of postmenopausal osteoporosis (b) (4) [redacted]

The original Clinical Pharmacology review (DARRTS date 6/15/2010) indicated that the "Acceptable" recommendation was contingent on a satisfactory inspection of the clinical and bioanalytical sites for bioequivalence (BE) study 2008119 by the Division of Scientific Investigation (DSI). The DSI has completed their inspection and entered their recommendations in a memorandum dated 7/21/2010.

Serum risedronate assay and sample collection:
The DSI's inspection of the clinical sites found that blood draw time points of 60 serum samples in 35 subjects were deviated by ≥5 minutes from the nominal (scheduled) time. Therefore, DSI recommends that BE analysis be conducted using the actual sampling time points. Otherwise, DSI found the serum data acceptable for review. This reviewer considers these deviations as minor; therefore, the serum data in study 2008119, which provided the primary basis of BE assessment, is acceptable for review.

Urine risedronate assay and sample collection:
The DSI inspection of the clinical sites found that a total of 10 urine samples were improperly collected (see DSI memorandum dated 7/21/2010 for details). However, this represents about 0.25% (10 out of ~ 3900) of the entire urine samples collected in study 2008119 and is not expected to alter the results.

DSI also indentified two issues relating to incurred samples reproducibility (ISR): 1) In study 2008119, the sponsor only conducted ISR analysis on 20 incurred samples (out of ~20,000 samples analyzed), 2) failure of ISR analysis of a different study (Study 92058 [also known as Study 2009003],) using the same analytical method (b) (4) [redacted]) that was used in study 2008119. Study 92058 was a Phase 2 study of 75 mg and 100 mg strengths of a once-a-month testing formulation of risedronate delayed release (DR) tablets. DSI found that only 42.5 % of ISR samples from study 92058 met the predefined acceptance criteria of within ± 20% of the mean of the original and reassay values. DSI noted that the reason for this high ISR failure (57.5% of ISR samples) is not known. However, the sponsor's investigative report suggested that an unidentified substance in certain urine samples may bind to risedronate and lower its

apparent concentration. Subsequently, a new method (initially noted as [redacted], which later became [redacted] with minor revisions) was devised. Method in [redacted] overcame this issue by adding the internal standard, followed by a freeze/thaw cycle before processing the sample for analysis. DSI commented that because the actual cause of the ISR failure of method in [redacted] is not known, the measured concentration values for any given samples using this method may not be accurate. Therefore, DSI recommends that any samples that were previously analyzed by using [redacted] be reanalyzed using a new method, [redacted] DSI also recommends that ISR analysis be conducted with 5% of the study urine samples.

This reviewer reviewed DSI's findings and recommendations and the sponsor's investigative report of ISR failure in study 92058 (submitted to IND 074086 on 7/21/2010 and 9/28/2010). The following highlights this reviewer's key rationale and observations:

- [redacted] was used in 4 other studies (in addition to study 92058) where ISR analyses were also conducted. These studies evaluated a limited number of ISR samples. However, ISR analyses of these studies (total of 79 ISR samples) all passed the acceptance criteria of at least 2/3 within ±20% of original values. The passing rates from these studies were 70, 89.5, 95, and 100%.
- ISR failure in study 92058 was isolated to only one site, #1000 (one of 7 clinical sites in study 92058), where all samples (n=40) were chosen for ISR analysis. In sponsor's own investigation of the ISR failure, it was found that 18 samples taken from 4 clinical sites (sites 1000, 2000, 3000, and 4000) passed the ISR criteria (confirmation rate 83.3% for all sites combined). Reassaying these 18 samples in a separate run showed a confirmation rate of 94.4% (17 of 18) between the 2 runs, indicating that the method [redacted] was reproducible.
- All samples from study 92058 were reassayed using [redacted] (the same method as [redacted]. When the results were compared to those assayed using [redacted], 85% of the results were consistent (defined as a difference of ≤ 20%) between the 2 methods. When the samples from each clinical site were assessed separately, the percentage of samples that were consistent between the 2 methods were 79, 86, 88, 90, 84, 77, and 86% from sites 1000, 2000, 3000, 4000, 5000, 6000, and 7000, respectively. For samples from site 1000, where the original ISR failure was initially identified, 79% of the results were consistent between the 2 methods.
- Taking into account all 119 ISR samples from 5 studies including Study 92058, 73% of (87/ 119) ISR samples met the reproducibility acceptance criteria, indicating that [redacted] was robust and gave reproducible results.
- Both urinary excretion (Ae) and serum AUC for risedronate were evaluated in the BE study 2008119 (n=485 males and females). BE statistical evaluation showed similar test to reference ratios for risedronate serum AUC and Ae (ratios of 1.001 and 1.031, respectively). A similar observation was made when comparing relative bioavailability in males and females using either serum AUC or Ae data (the male/female ratios were 0.814 and 0.913, respectively). Furthermore, a regression analysis of individual risedronate serum AUC and Ae showed a good correlation (r^2 = 0.845). These data showed that Ae (as measured using the urine assay in [redacted]) results were consistent with serum AUC results.

The observations above suggest that method [redacted] was sufficiently robust with a consistency rate of 85% to the new method in [redacted]. The percent of samples that may have measurement errors is small (likely <10% based on the 85% consistency rate). Therefore, any potential effect on overall ratios of mean PK parameters is expected to be small (particularly if the samples with potential errors are evenly distributed among the treatment arms being compared). However, since the actual cause for ISR failure in certain urine samples is not known, the absolute concentration values of any given urine

samples measured by using [redacted] may not be reliable. Thus, this reviewer considered the potential impact of an error on the primary PK studies in NDA 022560 (see below).

Potential effects of co-administration of food, calcium supplement, or esomeprazole on risedronate bioavailability in NDA 022560:

The analyses of Ae data are important to assess changes in bioavailability of risedronate due to co-administration of food, calcium supplement, or esomeprazole. Potential implications of the DSI findings in each case are discussed below. The BE study (study 2008119) is not discussed here since serum data were used to assess the BE.

Food effect: The primary food effect study was conducted in 74 postmenopausal women in a cross-over design (Study 2007120, urine risedronate concentration was assayed using an older method [redacted]). The results indicated that food decreased the Ae of risedronate DR tablet by about 30%. This effect was consistent with the known properties of risedronate (i.e., food coadministration may cause binding of risedronate and reduce bioavailability). This consistency supported and did not raise doubt into the validity of the urine assay.

With regard to safety and efficacy of risedronate DR 35 mg administered with or without food, the Phase 3 study directly evaluated these dosing conditions in 2 separate treatment arms. In the Phase 3 study, one group was administered risedronate DR 35 mg with food and the second group was administered risedronate DR 35 mg at least 30 minutes before breakfast. Therefore, the food effect study is not critical for evaluating the safety and efficacy of risedronate DR 35 mg tablets with respect to concomitant food intake.

Calcium: The effect of calcium coadministration on the bioavailability of risedronate DR 35 mg tablets was evaluated in a cross-over study in 101 postmenopausal women (Study 2008138, urine risedronate concentration was assayed using method [redacted] The results showed that coadministration with 600 mg calcium reduced risedronate bioavailability by a mean of 38%. The decrease is consistent with the expectation that calcium can bind to risedronate and reduce risedronate bioavailability. The product label will recommend that calcium supplements (as well as other related divalent and trivalent cations) be taken at a different time than risedronate DR to reduce a risk of interaction. Therefore, DSI findings of potential concerns with the urine assay method [redacted] would not affect the overall conclusions and recommendations.

Esomeprazole: The effect of concomitant administration of esomeprazole, a proton pump inhibitor (PPI), on the bioavailability of risedronate DR was evaluated in a cross-over study in 87 postmenopausal women (Study 2007027, urine risedronate concentration assayed using an older method [redacted]). Esomeprazole was used as a model for drugs that could raise gastric pH and therefore may compromise the enteric coating of risedronate DR, leading to reduced bioavailability. The results showed that the bioavailability of risedronate DR (given after breakfast) was reduced by 32% when esomeprazole was administered 1 hour prior to dinner and by 48% when esomeprazole was administered 1 hour prior to breakfast. These decreases in bioavailability are consistent with the expectation that a raise in gastric pH may compromise the enteric coating of risedronate delayed release formulation resulting in release of risedronate in the stomach. The original Clinical Pharmacology review of this NDA (DARRTS, date 6/15/2010) did not recommend any specific instructions (e.g., avoidance) regarding use of esomeprazole. This prior recommendation was based on 1) the small magnitude of change observed, 2) the fact that the bioavailability of risedronate DR 35 mg is 2 – 4 fold higher than approved risedronate immediate release (IR) 35 mg, and 3) limited data in the phase 3 study suggested that changed in lumbar spine bone mineral density was consistent between acid suppressor users and non-users.

In a worst case scenario, complete and immediate failure of the enteric coating may render the risedronate DR tablet to behave similar to an IR tablet. The risedronate DR tablet can be taken with food while the risedronate IR must be taken at least 30 minutes before meals (to prevent reduced bioavailability due to food intake). In a worst case scenario (i.e., complete and immediate failure of enteric coating of a DR tablet taken with food) there may be reduced bioavailability from risedronate DR to a level below that of the IR formulation (when taken per labeled instruction of at least 30 minutes before meals). If this occurs, efficacy of the DR formulation in these instances may not be achieved. Since there is a potential implication on efficacy, this reviewer recommends that the sponsor reanalyze the samples from study 2007027 using the method in (b) (4) to confirm the results. (b) (4) product label should specify that risedronate DR not be used in patients taking acid suppressants. (b) (4)

In conclusion, the findings of these 3 clinical studies showed that the results were consistent with the expected mechanism of action of the potential interactions (i.e., food may decrease risedronate bioavailability, calcium may bind risedronate and lower its bioavailability, and esomeprazole may raise stomach pH and lead to failure of the enteric coating and lower risedronate bioavailability). In the case of food effect and calcium studies, the current available data and/or proposed labeling support the safe use of risedronate DR. Therefore, no further action is recommended at this time. This recommendation may be revisited if additional data becomes available regarding the validity of the urine assay. With respect to esomeprazole, there is a potential effect on efficacy. Therefore, this reviewer recommends that the samples from this study be reassayed. Furthermore, specific dosing restriction should be added to the product label.

Reviewer's notes: The above recommendations regarding the esomeprazole study 2007027 were conveyed to sponsor during a teleconference on 9/29/2010. The sponsor informed the Agency that all samples from study 2007027 have been destroyed. The Agency requested and the sponsor agreed to conduct a new clinical study to evaluate the effect of a PPI on the bioavailability of risedronate DR as a Post Marketing Commitment.

Labeling negotiation has been completed. The sponsor submitted the final agreed upon label on 10/06/2010. There are no pending issues from a Clinical Pharmacology perspective.

1.1 Recommendation

The Division of Clinical Pharmacology III/Office of Clinical Pharmacology has reviewed the Clinical Pharmacology information submitted in NDA 022560 and finds the NDA acceptable.

1.2 Post Marketing Commitment

The sponsor agreed on 10/7/2010 to conduct the following clinical trial:

A drug-drug interaction trial to evaluate the potential effect of a proton pump inhibitor (PPI) on decreasing risedronate bioavailability following administration of Atelvia in postmenopausal women.

Final Protocol Submission:	January 2011
Trial Completion:	December 2011
Final Report Submission:	January 2012

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/s/

DOANH C TRAN
10/07/2010

MYONG JIN KIM
10/07/2010

EDWARD D BASHAW
10/07/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 22, 2010

TO: Warner Chilcott Pharmaceuticals, Inc.

THROUGH : Alvin Howard, Senior Vice President Regulatory Affairs

FROM: CDER DRUP

SUBJECT: Info request re: Study 2009003 and Clinical Protocol No. 2008119-BA

APPLICATION/DRUG: NDA 022560/Atelvia (risedronate sodium) delayed release tablets

At the request of the ClinPharm team, a request was sent on August 2, 2010, to Warner Chilcott Pharmaceuticals, Inc. (WC) requesting additional information regarding Study 2009003 (see email below). WC was also contacted by phone and requested to have the bioanalysis site, (b) (4) send a letter authorizing the Division to allow discussion with WC regarding the DSI inspection related to Clinical Protocol No. 2008119-BA submitted to NDA 022560.

On August 4, 2010, WC provided a response to our question regarding percentage of confirmed results for each clinical site, and a revision of Table 7. <ATTACHMENTS 1 and 2 (contents not included in this memo)>

The letter of authorization was received from (b) (4) on September 17, 2010.

On September 22, 2010, WC was contacted by phone and asked to formally submit to NDA 022560 (1) the amended Appendix 3 (Investigation report for NE-58095 in human urine) of the bioanalytical report for Study 2009003 (including the revised and amended Table 7), and (2) the table of confirmation rate for each study site in that study. Mr. Howard said that the requested information would be submitted to the application either today or tomorrow.

From: Alvin Howard [mailto:AHoward@wcrx.com]
Sent: Wednesday, August 04, 2010 3:28 PM
To: Stiller, Karl
Subject: Re: IND 074086 question

Dear Karl,

Please find attached responses to your questions regarding Study 2009003. We have amended Table 7 to provide the complete subject ID number and clinical site. We will provide this information in a formal submission to the IND, if you deem the responses satisfactory.

Regards,

Alvin D. Howard
Senior Vice President
Regulatory Affairs
(973) 442-3233 Office
(973) 442-3280 Fax
ahoward@wcrx.com

<ATTACHMENTS>

Attachment 1 Attachment 2

From: "Stiller, Karl" <Karl.Stiller@fda.hhs.gov>
To: ahoward@wcrx.com
Date: 08/02/2010 10:05 AM
Subject: IND 074086 question

Refer to final study report for Study 2009003 submitted to IND 074086 on 7-22-2010. Please provide the following information regarding Appendix 3 (Investigation report for NE-58095 in human urine) of the bioanalytical report for Study 2009003.

1. For Table 7 (Comparison of the Results obtained with the Original method Vs. the Improved method), confirm that subjects noted as incomplete subject ID number 10498010 (i.e., the first 95 samples) came from site 1000. Specify the clinical site (e.g., 1000, 2000, etc.) for each subject in that table.

2. Provide the percentage of confirmed results (between the Original method and the Improved method) for each clinical site.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

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/s/

KARL J STILLER
09/22/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 022560	Submission Date(s): 9/24/2009, 2/8/2010
Brand Name	Pending
Generic Name	Risedronate sodium
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
PM Reviewer	Jiang Liu, Ph.D.
PM Team Leader	Pravin Jadhav, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Warner Chilcott Pharmaceuticals, Inc.
Submission Type	Original
Formulation; Strength	Delayed release tablet; 35 mg
Indications	• Treatment of postmenopausal osteoporosis (b) (4)

Table of Contents

1 Executive Summary

Risedronate sodium is a pyridinyl bisphosphonate. It has affinity for hydroxylapatite crystals in bone and is an inhibitor of osteoclast, the cells responsible for bone resorption. Risedronate sodium as an immediate-release (IR) formulation is currently approved under the trade name Actonel for treatment of postmenopausal osteoporosis (PMO) (5 mg/day, 35 mg/week, 75 mg/two consecutive days per month, 150 mg/month), prevention of PMO (5 mg/day, 35 mg/week), treatment to increase bone mass in men with osteoporosis (35 mg/week), treatment and prevention of glucocorticoid-induced osteoporosis (5 mg/day), and treatment of Paget's disease of bone (30 mg daily for 2 months).

The sponsor has now developed a novel 35 mg delayed release (DR) tablet formulation of risedronate sodium for once weekly administration. The Sponsor proposed that risedronate DR can be taken in the morning with food, an advantage over risedronate IR, which must be taken at least 30 minutes before the first food or drink of the day. The Sponsor is seeking approval of risedronate DR 35 mg tablets for (b) (4) treatment of PMO. (b) (4)

1.1 Recommendation

The Division of Clinical Pharmacology III/Office of Clinical Pharmacology has reviewed the Clinical Pharmacology information submitted in NDA 022560 and finds the NDA acceptable pending agreement on labeling recommendations.

The above recommendation is contingent on a satisfactory inspection of the clinical and bioanalytical sites for bioequivalence study 2008119 by the Division of Scientific Investigation (DSI). DSI has indicated that most of the inspections have been performed but the findings are still being reviewed.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The NDA is primarily supported by 9 clinical studies (7 Phase 1 pharmacokinetic (PK)/safety/tolerability studies, 1 Phase 2 efficacy/safety/PK study, and 1 Phase 3 efficacy and safety study). Except for the single dose bioequivalence (BE) study where serum risedronate concentrations were measured, PK assessments of risedronate DR tablets were done by measuring risedronate urinary excretion (Ae).

Single and multiple dose PK: Following single dose administration of risedronate DR 35 mg in healthy men and women under fasting conditions, the arithmetic mean (CV%) serum risedronate maximum concentration (C_{max}) and AUC from time 0 to time of last measurable concentration (AUCtlast) were 25.3 ng/mL (109.8%) and 63.5 ng*h/mL (106.5%), respectively. The median (range) T_{max} was 3 hours (0.75 – 12). The mean (CV%) Ae for 72 hours post dose was 289.5 µg (109.6%).

Limited Ae data were available following multiple dose administration of risedronate DR. No conclusion could be made on drug accumulation.

Relative bioavailability of risedronate DR 35 mg versus risedronate IR 35 mg: Available data indicated that bioavailability (based on Ae) of the DR formulation is higher than IR formulation by approximately

2- to 4-fold under the most likely dosing conditions (i.e., risedronate DR immediately after breakfast and IR under per-label condition of at least 30 minutes before breakfast).

Distribution, Metabolism, and Excretion: No new information was provided. The Sponsor relied on prior knowledge stated in risedronate IR label. The risedronate IR label indicated that there is no evidence of systemic metabolism of risedronate and about half the absorbed dose is excreted in the urine within 24 hours.

Pharmacodynamic (PD), efficacy, and safety for treatment of PMO indication: The pivotal phase 3 study (Study 2007008) evaluated a single dose level of risedronate DR 35 mg once weekly, taken before (DRBB) or after (DRFB) breakfast, compared to active control of risedronate IR 5 mg once a day before breakfast (IRBB) in osteoporotic postmenopausal women for 52 weeks. The risedronate IR 5 mg once a day regimen has been previously demonstrated to reduce risk of fracture in NDA 20835.

The mean percent change from baseline in lumbar spine bone mineral density (BMD) at week 52 (with last observation carried forward) was the primary efficacy outcome in Phase 3. All three dosing regimens increased lumbar spine BMD significantly at week 52 from baseline. The mean percent changes from baseline in lumbar spine BMD were 3.1% for the 5 mg IRBB group and 3.4% for both the 35 mg DRFB and 35 mg DRBB groups. When evaluated in terms of non-inferiority, the DR 35 mg regimens were shown to be non-inferior to the IR 5 mg daily regimen.

All measured bone turnover markers (BTM), namely urinary type-1 collagen cross-linked N-telopeptide corrected for creatinine clearance [NTX/Cr], serum type-1 collagen cross-linked C-telopeptide [CTX]) and bone-specific alkaline phosphatase (BAP), were significantly reduced from baseline for all treatment groups. The mean decreases were slightly greater for risedronate DR 35 mg once a week compared to risedronate IR 5 mg once a day. Similar levels of decrease in these 3 BTMs were observed in a smaller Phase 2 study (Study 2005107) when risedronate DR 35 mg once weekly was compared to risedronate IR 35 mg once weekly in healthy postmenopausal women.

Overall, 69%, 72%, and 77 % of patients suffered at least one adverse event (AE) in IRBB, DRFB, and DRBB groups, respectively. Rates of serious adverse events (about 7% of patients) and withdrawals due to AEs (about 8% of subjects) appeared balanced between groups.

Dose/exposure response for BTM: Results from a Phase 2 study (Study 2005107) indicated a positive dose-response relationship between risedronate DR 35 mg and DR 50 mg doses and the BTMs NTX/Cr, CTX, and BAP. The mean decreases in BTM concentrations for 35 mg DRFB regimen were similar to or greater than those observed for the approved regimen of 35 mg IRBB. This was consistent with the observed higher BA (based on Ae) for the DR 35 mg tablet compared to IR 35 mg tablet. Results of population PK/PD analyses indicated Emax-type exposure-response characteristics for BTM.

Dose proportionality: Analysis of combined data from 6 studies indicated that risedronate DR bioavailability was dose proportional or slightly more than dose proportional in the DR tablet strength range of 20 mg – 100 mg. Population PK analyses also supported dose-proportionality across the 20 mg - 100 mg dose range. However, these 6 studies administered unique tablet strengths (20, 35, 75, and 100 mg) with slightly different formulation compositions that prevented generalization of these results to risedronate itself.

Effect of sex on bioavailability: Following a single dose administration of risedronate DR 35 mg under fasting conditions (Study 2008119), the ratios of serum Cmax and AUCtlast for males to females were 0.825 and 0.814, respectively. The ratio of Tmax for males to females was 1.023. The ratio of Ae for

males to females for was 0.913. Similar sex-related PK differences were seen in an analysis of limited data following risedronate IR 5 mg and 15 mg administration (study 2000009).

Effect of hepatic or renal impairment: The sponsor did not evaluate the effect of hepatic or renal impairment on the PK of risedronate DR. However, prior review of risedronate IR data indicated that there was no evidence of systemic metabolism of risedronate (Actonel label). No dosage adjustment was recommended for risedronate IR in patients with hepatic impairment. A similar recommendation will be applied to risedronate DR.

The approved label for risedronate IR states that the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance (CLcr) of approximately 30 mL/min compared to patients with normal renal function. Phase 3 study with risedronate DR 35 mg enrolled 152 patients with moderate renal impairment (CLcr ≥30 and <60 ml/min). Review of the safety data by the Medical reviewer Dr. Stephen Bienz indicated that the percent of patients that experienced any AEs was similar between patients with or without moderate renal impairment. No dose adjustment is recommended for patients with moderate renal impairment. No clinical experience is available for patients with severe renal impairment (CLcr < 30 ml/min).

Effect of food on bioavailability: Bioavailability (based on Ae) of risedronate DR 35 mg tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to standard fasting conditions (i.e. fasting for 10 hour before and 4 hours after drug administration). Risedronate DR administered after dinner provided greater exposure (approximately 87% increase) compared to administration following breakfast.

Effect of esomeprazole coadministration: The extent of risedronate absorption administered after breakfast was reduced by 32% if esomeprazole was administered prior to dinner and by 48% if esomeprazole was administered prior to breakfast.

Dosing instruction regarding amount of water: Esophageal AEs such as esophagitis, erosions, and ulcers have been reported with oral bisphosphonate use. Administration with a full glass of water (6 – 8 oz) helps minimize esophageal transit time and therefore risk of esophageal AEs. The current Actonel label states that risedronate should be taken with 6 – 8 oz of water. The Sponsor proposed to instruct patients to administer risedronate DR with 'at least 4 oz of water'. This dosing instruction is consistent with the dosing instruction used in most trials with risedronate DR 35 mg, including the Phase 3 trial. The Sponsor's proposal to administer risedronate DR with at least 4 oz of water is acceptable.

Effect of edentate disodium dihydrate (EDTA) from risedronate DR tablet: Risedronate DR tablet contains (b) (4) EDTA. There were concerns that this may affect drug absorption by altering the solubility of a concomitantly administered drug or increase paracellular transport due to its cation chelating effect. Results of in vitro solubility studies indicated that EDTA in risedronate DR 35 mg tablet is not likely to have significant influence on solubility of several drugs (Please see section 2.4.4 for more details). An effect on paracellular transport could not be ruled out. However, when administered under fasting conditions, the bioavailability of the DR 35 mg formulation was approximately 44% higher than the IR 35 mg tablet. This suggested that the maximum potential for both risedronate (itself a chelator of cations and absorbed via the paracellular route) and EDTA from risedronate DR 35 mg formulation on the paracellular transport is approximately 44%.

Effect of calcium coadministration or cations from other coadministered drugs: Coadministration of 600 mg calcium supplement reduced risedronate bioavailability (based on Ae) by a mean of 38% (90% CI 11%, 57%) when risedronate DR was taken after breakfast.

An assessment of commonly used drugs in Phase 3 trial 2007008 with risedronate DR and a prior trial with risedronate IR (Study 2005032) indicated that the amount of divalent or trivalent cations (magnesium, aluminum, iron, and calcium) in those drugs was low except for calcium supplements or antacids. The highest cation content was about 100 mg calcium which was present in atorvastatin (Lipitor) 80 mg tablet. This amount of cation is expected to have less effect on reducing bioavailability of risedronate than a mean of 38% decrease observed following coadministration of 600 mg calcium. Since risedronate DR formulation has higher bioavailability than the approved risedronate IR formulation, a small decrease in bioavailability should not affect the effectiveness of risedronate DR.

Bioequivalence of the to-be-marketed (TBM) formulation and the clinical trial formulation:
The TBM formulation will be manufactured at a different site than the clinical trial formulation. The sponsor conducted a single dose BE study to compare the bioavailability of the TBM formulation (test) to the primary Phase 3 formulation (reference) under a fasting state. The results showed that the 90% CIs for test/reference ratio for risedronate C_{max} and AUCtlast were within the 80 – 125% BE limits indicating that the 2 formulations were bioequivalent.

The Phase 3 study also administered a different risedronate DR 35 mg formulation in a small number of patients. The differences between the two formulations used in Phase 3 were considered minor and bridging studies were not needed.

Potential for dose dumping due to alcohol: The potential for dose-dumping due to alcohol coadministration was evaluated in vitro. The results suggest that alcohol coadministration is not likely to alter the performance of risedronate DR 35 mg tablets.

Bioanalytical methods: For all Phase 1 and 2 studies (studies 2004132, 2007120, 2008052, 2005107, 2007027, 2008076, 2008138, and 2008119), (b) (4)) analyzed human urine specimens for concentrations of risedronate using a validated high performance liquid chromatography / tandem mass spectrometry (HPLC/MS/MS) method. For the BE study, serum specimens were analyzed by (b) (4) for risedronate using a validated HPLC/MS/MS.

Briefing: An Optional Inter-Division Level Office of Clinical Pharmacology Briefing was held on June 8, 2010 with the following in attendance: Doanh Tran, Jiang Liu, Theresa Kehoe, Justin Koteff, Bryant Tran, Sayed Al Habet, Hyunjin Kim, Stephen Bienz, Chinmay Shukla, Zhihong Li, Julia Cho, Darrell Abernethy, LaiMing Lee, Myong Jin Kim, Hae-Young Ahn, and Dennis Bashaw.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is risedronate sodium delayed-release (risedronate DR) tablet?

Risedronate sodium is a pyridinyl bisphosphonate. It has affinity for hydroxylapatite crystals in bone and is an inhibitor of osteoclast, the cells responsible for bone resorption. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (Actonel product label).

Risedronate sodium as an IR formulation is currently approved under the trade name Actonel for treatment of PMO (5 mg/day, 35 mg/week, 75 mg/two consecutive days per month, 150 mg/month), prevention of PMO (5 mg/day, 35 mg/week), treatment to increase bone mass in men with osteoporosis (35 mg/week), treatment and prevention of glucocorticoid-induced osteoporosis (5 mg/day), and treatment of Paget's disease of bone (30 mg daily for 2 months).

The sponsor has developed a novel 35 mg DR formulation of risedronate sodium for once weekly administration. The new risedronate DR tablet has an enteric coating with a pH trigger of 5.5. The intent of the DR formulation was to minimize the effect of food on decreasing risedronate absorption that was seen with the IR formulation. The risedronate DR tablet also contains a competitive chelating agent (b) (4) EDTA) (b) (4) . The proposed dose of risedronate DR 35 mg tablets is one tablet orally once a week.

2.1.2 What are the proposed indications for risedronate DR?

The sponsor is seeking the following (b) (4)

- Treatment of PMO

(b) (4)

(b) (4)

2.1.3 What information is provided in the NDA?

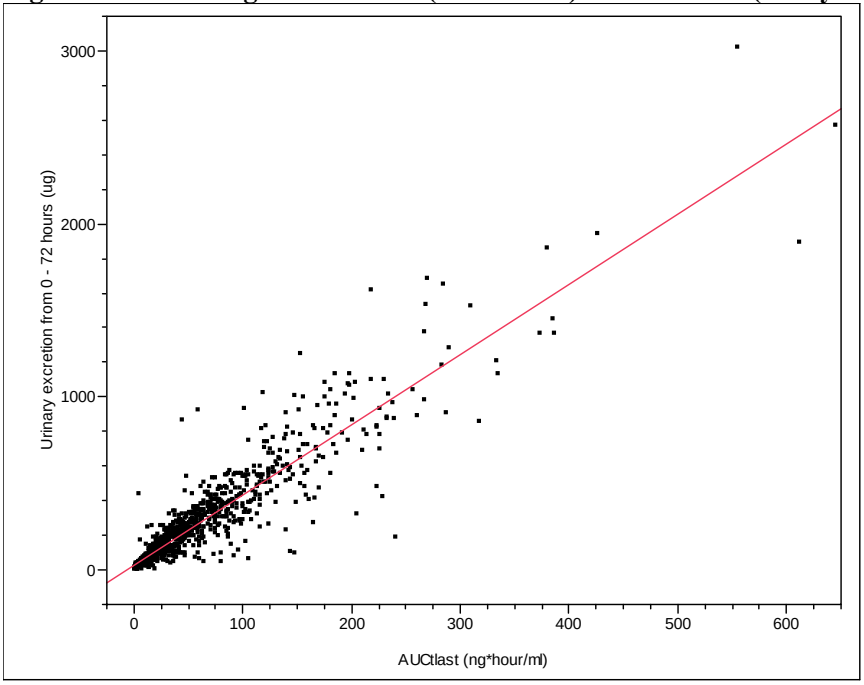
The NDA is primarily supported by 9 clinical studies (7 Phase 1 PK/safety/tolerability studies, 1 Phase 2 efficacy/safety/PK study, and 1 Phase 3 efficacy and safety study). The NDA also contains 2 population PK/ PD reports for the IR and DR formulations. Reports of in vitro studies on 1) potential effect of divalent or trivalent cations in other medications to interfere with risedronate DR absorption, 2) potential effect for EDTA (a component of the DR formulation) to cause change in absorption of other drugs, and 3) potential for alcohol to compromise the modified-release nature of the formulation were also provided.

(b) (4)

Additional supporting data includes a PK study of risedronate 15 mg IR formulation (Study 2000009) and 15 other safety and efficacy studies.

PK assessments of all studies, except the BE study, were done by measuring risedronate Ae instead of serum risedronate. The Division of Metabolism and Endocrinology Products has previously agreed to using Ae for PK assessment of risedronate (End of Phase 2 meeting minutes, DARRTS 8/31/2007). Risedronate Ae is well correlated with serum risedronate AUC (Figure 1). Figure 1 shows the linear regression of the observed risedronate Ae (0-72 hours) and AUCtlast from BE study 2008119 in which single dose of risedronate DR 35 mg was administered under fasting conditions. The fitted equation was Ae = 29.70 + 4.058 * AUCtlast. The results indicated that Ae and AUCtlast were highly correlated (r^2 = 0.845).

Figure 1: Linear regression of Ae (0-72 hours) vs. AUCtlast (Study 2008119)



2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic properties of risedronate DR formulation?

Single dose PK:

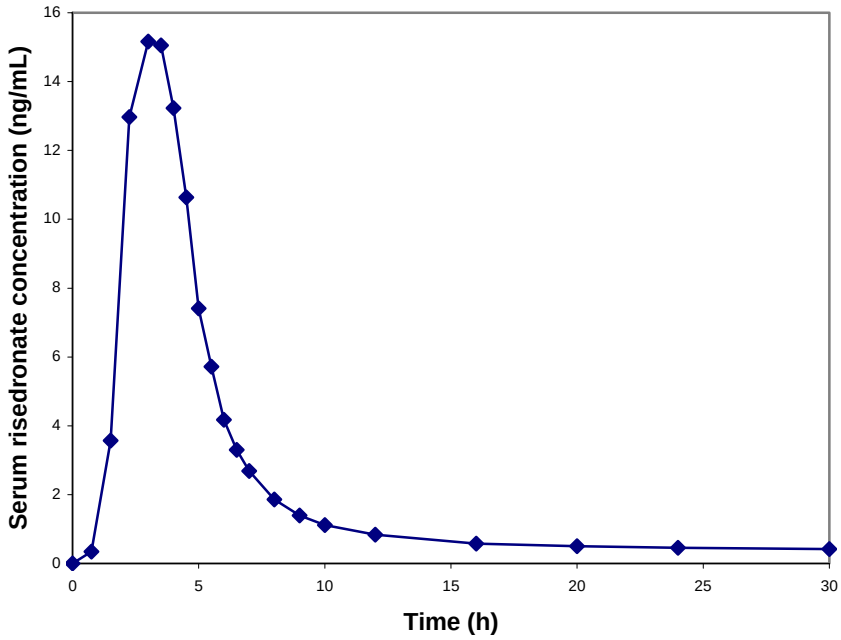
The primary single dose PK data for risedronate DR 35 mg came from BE study 2008119. This study was a single dose, 2-period crossover BE study conducted under standard fasting conditions in healthy males and females. Both serum concentration and Ae for risedronate were measured. Serum concentrations and Ae were measured for 30 and 72 hours post-dose, respectively. Measurable serum and urinary risedronate concentration were detected in all, except for 6 subjects. There was high variability in the exposure to risedronate between subjects within a formulation as well as between formulations within a subject.

Following single dose administration of the TBM formulation, the mean (CV%) serum risedronate C_{max} and AUCtlast were 25.3 ng/mL (109.8%) and 63.5 ng*h/mL (106.5%), respectively. The median (range) T_{max} was 3 hours (0.75 – 12). The mean (CV%) Ae and dose normalized Ae (Ae/Dose or Ae%) for 72 hours post dose were 289.5 µg (109.6%) and 0.83% (109.6%), respectively. Since this study measured

serum risedronate for up to 30 hours post dose, the terminal $t_{1/2}$ (expected to be approximately 500 hours) was not captured. The mean serum risedronate concentration-time profile following a single dose administration is shown in figure 2.

It should be noted that this study was conducted under fasting conditions. Under fed conditions, the concentration time profile is expected to be shifted to the right due to the enteric coating and slower gastric emptying. Consistent with this expectation, a study using scintigraphy showed that the mean (SD) time to initial disintegration of risedronate DR 35 mg tablet under fed and fasted conditions was estimated to be 10.1 (7.3) and 2.0 (0.4) hours, respectively (Study 2004132).

Figure 2: Mean serum risedronate concentration-time profiles following single dose administration of risedronate 35 mg DR (TBM formulation) under fasting conditions.



Multiple dose PK:

Serum risedronate concentrations following multiple dose of risedronate DR are not available. The Actonel label states that for the IR formulation, steady state serum risedronate is observed within 57 days of daily dosing. Risedronate has a long terminal $t_{1/2}$ (~500 hours) that has been hypothesized to represent the dissociation of risedronate from the surface of bone. It is unlikely that risedronate DR formulation would behave differently from the IR formulation in term of time to reach steady state or drug accumulation given that long terminal $t_{1/2}$ are not dependent on drug absorption.

Limited multiple dose bioavailability information is available from Ae data obtained for 48 hours post dose after 1st and 12th dose (days 1 and 85) in a study evaluating weekly administration of risedronate DR 35 mg and 50 mg tablets (Table 1). The sample size for each group was relatively small (n = 18 – 38) for this highly variable drug. When administered after breakfast (DRFB) the Day 85/Day 1 Ae ratios were 1.98 and 1.19 for the 35 mg and 50 mg strengths, respectively, suggesting that there was higher bioavailability on day 85. However, when the 50 mg strength was given 30 minutes before breakfast (DRBB), the Day 85/Day 1 Ae ratio was 0.76.

When Ae from all 72 subjects with data for both Day 1 and Day 85 were evaluated, mean Ae on Day 85 was slightly lower than Day 1 but not statistically significantly different.

Table 1: Mean Ae following single and multiple dose of risedronate DR (Phase 2 study 2005107)

Day/Treatment	N	Geometric LS means Ae (µg)	95% CI	Day 85/Day 1 ratio
Day 1				
35 mg DRFB	19	92.42	46.26, 184.64	NA
50 mg DRBB	18	154.69	75.78, 315.79	NA
50 mg DRFB	38	140.21	85.63, 229.57	NA
Day 85				
35 mg DRFB	18	182.58	104.83, 318.02	1.98
50 mg DRBB	18	118.06	67.61, 206.14	0.76
50 mg DRFB	36	166.48	112.20, 247.00	1.19
DRFB = DR tablet administered following breakfast DRBB = DR tablet administered before breakfast, NA = not applicable				

2.2.2 What are the properties of distribution, metabolism, and excretion for risedronate sodium?

The sponsor did not conduct any studies to evaluate the distribution, metabolism, and excretion of risedronate sodium using the risedronate DR formulation. The sponsor relies exclusively on the available data on risedronate IR formulation (i.e., current approved product label for Actonel). The current Actonel label contains the following information:

> "Distribution
> The mean steady-state volume of distribution for risedronate is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [14C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.
>
> Metabolism
> There is no evidence of systemic metabolism of risedronate.
>
> Excretion
> In young healthy subjects, approximately half of the absorbed dose of risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance was 52 mL/min (CV=25%), and mean total clearance was 73 mL/min (CV=15%)."

2.2.3 What is the relative bioavailability of risedronate DR and IR formulations?

Risedronate IR 35 mg, taken at least 30 minutes before breakfast once a week, is approved for the treatment of PMO. The sponsor proposed to administer a new DR formulation at the same dose and dosing interval for the same indication. The relative bioavailability between the risedronate 35 mg DR formulation and risedronate 35 mg IR formulation was of interest to identify potential safety and/or efficacy concerns.

Risedronate bioavailability data (Ae) were available from several studies that administered both the DR and IR formulations. Table 2 shows the Ae ratios for various dosing conditions. The most comprehensive data came from a food effect study in 76 postmenopausal females (Study 2007120). This was a 4-period, crossover, food effect study that administered the DR formulations under fed and fasted condition and the IR formulation under either fasted or per-label conditions (i.e., at least 30 minutes before breakfast). The ratios ranged from 1.01 to 3.11 depending on administration conditions. Since most patients taking the IR formulation are expected to take it at 30 minutes before breakfast (i.e., per-label), the data indicate that the DR formulation has approximately 2.19- and 3.11-fold higher bioavailability when taken under fed and fasted conditions, respectively.

Additional data from PK subset in Phase 2 study 2005107 collected on days 1 and 85 in 2 groups of subjects (n=18 per group) showed a similar DR fed/IR per-label ratio of 2.11. However, results from crossover study 2008052 (n=90) showed a higher DR fed/IR per-label ratio of 4.18. The reason for this higher observed ratio is not clear. In this study the bioavailability for the 35 mg IR per-label treatment was relatively low (geometric mean Ae of 47.2 µg or 0.13% of administered dose) compared across studies that administered risedronate IR 35 mg. At the same time, the bioavailability for the 35 mg DR fed treatment in this study was relatively high (geometric mean of 197.1 µg or 0.56% of the administered dose) compared across different studies with risedronate DR 35 mg.

Overall the data indicates that bioavailability of the DR formulations is higher than IR formulations by 2- to 4-fold under the most likely dosing conditions (i.e., DR under fed conditions and IR under per-label condition).

Table 2: Relative bioavailability between risedronate 35 mg DR and 35 mg IR formulations based on risedronate Ae.

Study	DR fed/IR per-label	DR fasted/IR per-label	DR fed/IR fasted	DR fasted/IR fasted
2005107	2.11	na	na	na
2008052	4.18	na	na	na
2007120	2.19	3.11	1.01	1.44
na = not available				

2.2.4 What is the effect of risedronate DR 35 mg once weekly on bone turnover marker?

Biochemical markers of bone turnover were assessed in 2 studies (Phase 2 study 2005107 and Phase 3 study 2007008). Bone resorption markers (i.e., urinary type-1 collagen cross-linked N-telopeptide corrected for creatinine clearance [NTX/Cr] and serum type-1 collagen cross-linked C-telopeptide [CTX]) and the bone formation marker bone-specific alkaline phosphatase (BAP) were assessed. These markers provide insights into the presence or absence of risedronate activity. However, it should be noted that changes in these bone turn over markers have not been validated as a surrogate for the clinical endpoint of fracture or the intermediate BMD endpoint. Therefore, these results should be interpreted with this limitation in mind.

The pivotal phase 3 study evaluated a single dose level of risedronate DR 35 mg once weekly compared to active control of risedronate IR 5 mg once a day in osteoporotic postmenopausal women. All measured BTMs in the pivotal phase 3 study were significantly reduced from baseline for all treatment groups at all post-baseline time points tested (Table 3). The mean decreases were slightly greater for risedronate DR 35 mg once a week compared to risedronate IR 5 mg once a day.

Similar decreases in BTMs were observed in the smaller Phase 2 study, which compared risedronate DR 35 mg once weekly to risedronate IR 35 mg once weekly in healthy postmenopausal women (Table 3).

Table 3: Changes in bone turnover markers in Phase 2 study 2005107 and Phase 3 study 2007008

Study/Time point	Risedronate DR 35 mg once a week		Risedronate IR doses*
	LS means (sample size)		LS means (sample size)
	DRBB	DRFB	
NTX/Cr			
Study 2005107			
Week 13 (Day 91)	ND	-46.60 (n=35)	-38.57 (n=34)
Study 2007008			
Week 13	-45.42 (n=275)	-46.37 (n=273)	-42.60 (n=278)
Week 52	-46.86 (n=257)	-47.26 (n=253)	-42.22 (n=256)
CTX			
Study 2005107			
Week 13 (Day 91)	ND	-62.08 (n=35)	-43.20 (n=34)
Study 2007008			
Week 13	-46.05 (n=277)	-46.78 (n=275)	-42.33 (n=280)
Week 52	-50.05 (n=258)	-49.19 (n=256)	-44.41 (n=258)
BAP			
Study 2005107			
Week 13 (Day 91)	ND	-10.41 (n=35)	-10.99 (n=34)
Study 2007008			
Week 13	-25.19 (n=277)	-25.14 (n=275)	-23.39 (n=280)
Week 52	-33.51 (n=258)	-33.45 (n=256)	-31.90 (n=258)

*Study 2005107 included risedronate IR 35 mg once a week and Study 2007008 included risedronate IR 5 mg once a day
LS means – least squares means
ND = Study 2005107 did not include a risedronate 35 mg DRBB regimen
Source: CP Table 17 in section 2.7.2 Summary of Clinical Pharmacology Studies

2.2.5 What is the summary of safety and efficacy for risedronate DR 35 mg once weekly in postmenopausal women?

Efficacy and safety of risedronate DR 35 mg once a week was evaluated in Phase 3 study 2007008. It was a non-inferiority study comparing risedronate DR 35 mg once a week taken after breakfast (DRFB) or at least 30 minutes before breakfast (DRBB) vs. risedronate IR 5 mg once a day taken at least 30 minutes before breakfast (IRBB). Postmenopausal osteoporotic women ≥ age 50 (n=922) were randomized 1:1:1 to risedronate 5 mg IRBB daily (n=307), 35 mg DRFB weekly (n=307), or 35 mg DRBB weekly (n=308) for 24 months. Results based on 52 weeks were submitted to the NDA. The following summary of efficacy and safety results is based on the review of study 2007008 by Medical Officer, Dr. Stephen R. Bienz. Please see Medical Officer's review for more details.

Efficacy:

The mean percent change from baseline in lumbar spine BMD at week 52 (with last observation carried forward) was the primary efficacy outcome. All three dosing regimens increased lumbar spine BMD significantly from baseline to week 52. The mean percent change from baseline in lumbar spine BMD was 3.1% for the 5 mg IRBB group and 3.4% for both the 35 mg DRFB group and 35 mg DRBB group (Table 4).

When evaluated in terms of non-inferiority, the 35 mg DRFB regimen was shown to be non-inferior to the 5 mg IR daily regimen. The upper limit of the 95% two-sided CI for the difference in mean percent change from baseline in lumbar spine BMD between the 5 mg IRBB group and the 35 mg DRFB group was less than the pre-defined non-inferiority margin of 1.5% (mean difference -0.233 [CI: -0.816, 0.349]). In addition, the 35 mg DRBB regimen was also non-inferior to the 5 mg IR daily regimen for percent change from baseline in lumbar spine BMD (mean difference -0.296 [CI: -0.873, 0.281]).

Table 4: Lumbar Spine BMD, % change from baseline (study 2007008)

	5 mg IRBB Daily (N=307)	**35 mg DRFB Weekly (N=307)**	**35 mg DRBB Weekly (N=308)**
Baseline			
n	270	261	271
Least Squares Mean (g/cm2)	0.757	0.758	0.758
Endpoint (52 weeks, LOCF)			
n	270	261	271
Arithmetic Mean (%) (SD)	3.112 (3.487)	3.369 (3.161)	3.404 (3.621)
LS Mean (%Δ from baseline)	3.118*	3.352*	3.414*
95% CI	2.710, 3.526	2.936, 3.767	3.007, 3.822
LS Mean Difference Compared to 5 mg IRBB		-0.233	-0.296
95% CI		-0.816, 0.349	-0.873, 0.281

* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. P-values are not given by the Sponsor
Source: Study 2007008 Year 1 Final Report, Table 11

Safety:
AE rates are shown in Table 5. Overall, 69%, 72%, and 77 % of subjects suffered at least one AE in IRBB, DRFB, and DRBB groups, respectively. SAEs (about 7% of subjects) and withdrawals due to AEs (about 8% of subjects) appear balanced between groups. Of note, one subject in the study had erosive esophagitis (35 mg DRFB group).

Table 5: Common adverse events (≥2% in any treatment group), ITT population

System Organ Class Preferred Term	**5 mg IRBB Daily (N=307) n (%) nAE**	**35 mg DRFB Weekly (N=307) n (%) nAE**	**35 mg DRBB Weekly (N=308) n (%) nAE**
Overall	211 (68.7%) 660	222 (72.3%) 734	238 (77.3%) 804
Gastrointestinal disorders	85 (27.7%) 142	101 (32.9%) 185	105 (34.1%) 214
Diarrhea	15 (4.9%) 21	27 (8.8%) 29	18 (5.8%) 21
Abdominal pain	9 (2.9%) 10	16 (5.2%) 18	15 (4.9%) 18
Constipation	9 (2.9%) 10	15 (4.9%) 15	16 (5.2%) 16
Vomiting	5 (1.6%) 5	15 (4.9%) 18	8 (2.6%) 11
Dyspepsia	12 (3.9%) 14	12 (3.9%) 15	12 (3.9%) 14
Nausea	12 (3.9%) 12	11 (3.6%) 14	10 (3.2%) 11
Abdominal pain upper	7 (2.3%) 8	9 (2.9%) 13	23 (7.5%) 31
Gastroesophageal reflux disease	5 (1.6%) 5	3 (1.0%) 3	8 (2.6%) 9
Hiatus hernia	1 (0.3%) 1	2 (0.7%) 2	8 (2.6%) 8

Infections and infestations	89 (29.0%) 125	100 (32.6%) 149	94 (30.5%) 145
Influenza	19 (6.2%) 21	22 (7.2%) 24	18 (5.8%) 20
Nasopharyngitis	16 (5.2%) 18	21 (6.8%) 23	26 (8.4%) 33
Urinary tract infection	8 (2.6%) 9	15 (4.9%) 18	11 (3.6%) 12
Bronchitis	13 (4.2%) 15	12 (3.9%) 15	13 (4.2%) 13
Upper respiratory tract infection	8 (2.6%) 8	11 (3.6%) 11	9 (2.9%) 11
Cystitis	7 (2.3%) 8	7 (2.3%) 8	5 (1.6%) 5
Pharyngitis	3 (1.0%) 3	4 (1.3%) 4	9 (2.9%) 9
Musculoskeletal and connective tissue disorders	73 (23.8%) 105	78 (25.4%) 115	78 (25.3%) 107
Arthralgia	24 (7.8%) 29	21 (6.8%) 30	19 (6.2%) 23
Back pain	18 (5.9%) 19	21 (6.8%) 24	19 (6.2%) 20
Pain in extremity	7 (2.3%) 7	12 (3.9%) 12	8 (2.6%) 10
Musculoskeletal pain	5 (1.6%) 5	6 (2.0%) 6	8 (2.6%) 8
Osteoarthritis	8 (2.6%) 8	5 (1.6%) 5	1 (0.3%) 1
Muscle spasms	7 (2.3%) 7	3 (1.0%) 3	9 (2.9%) 13
Injury, poisoning and procedural complications	32 (10.4%) 46	29 (9.4%) 41	27 (8.8%) 40
Fall	9 (2.9%) 10	12 (3.9%) 12	4 (1.3%) 4
Contusion	10 (3.3%) 10	7 (2.3%) 8	6 (1.9%) 8
Nervous system disorders	38 (12.4%) 49 10	26 (8.5%) 35	31 (10.1%) 34
Dizziness	(3.3%) 10	8 (2.6%) 8	8 (2.6%) 9
Headache	15 (4.9%) 15	8 (2.6%) 8	14 (4.5%) 14
General disorders and administration site conditions	16 (5.2%) 18	25 (8.1%) 35	29 (9.4%) 39
Skin and subcutaneous tissue disorders	16 (5.2%) 18	21 (6.8%) 23	21 (6.8%) 24
Respiratory, thoracic and mediastinal disorders	17 (5.5%) 21	17 (5.5%) 21	20 (6.5%) 23
Cough	7 (2.3%) 8	7 (2.3%) 7	5 (1.6%) 5
Vascular disorders	14 (4.6%) 18	17 (5.5%) 17	19 (6.2%) 21
Hypertension	11 (3.6%) 12	8 (2.6%) 8	10 (3.2%) 10
Investigations	12 (3.9%) 17	16 (5.2%) 19	24 (7.8%) 27
Blood parathyroid hormone increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7
Metabolism and nutrition disorders	9 (2.9%) 9	12 (3.9%) 16	14 (4.5%) 14
Hypercholesterolemia	2 (0.7%) 2	7 (2.3%) 7	6 (1.9%) 6
Cardiac disorders	10 (3.3%) 10	11 (3.6%) 11	21 (6.8%) 28
Blood and lymphatic system disorders	2 (0.7%) 2	9 (2.9%) 9	4 (1.3%) 4
Psychiatric disorders	8 (2.6%) 9	9 (2.9%) 9	12 (3.9%) 17
Eye disorders	12 (3.9%) 17	8 (2.6%) 11	9 (2.9%) 9
Ear and labyrinth disorders	12 (3.9%) 14	7 (2.3%) 7	7 (2.3%) 7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.6%) 8	7 (2.3%) 7	6 (1.9%) 7
Renal and urinary disorders	7 (2.3%) 7	7 (2.3%) 8	13 (4.2%) 16
Endocrine disorders	7 (2.3%) 8	6 (2.0%) 6	10 (3.2%) 12

Reproductive system and breast disorders	9 (2.9%) 10	5 (1.6%) 5	5 (1.6%) 6
n (%) = number (percent) of subjects within specified category and treatment nAE = number of adverse events within the specified category and treatment Source: Study 2007008 Year 1 Final Report, Table 24			

2.2.6 What are the characteristics of dose-response and exposure-response relationship?

Dose finding was based on effects of suppression of urine NTX/Cr and serum CTX and BAP. These BTMs were evaluated in phase 2 study 2005107, in which the following regimens were administered:

- 35 mg IRBB: risedronate IR 35 mg, dosed at least 30 minutes prior to breakfast (ie, per-label)
- 35 mg DRFB: risedronate DR 35 mg, dosed immediately following breakfast
- 50 mg DRFB: risedronate DR 50 mg, dosed immediately following breakfast
- 50 mg DRBB: risedronate DR 50 mg, dosed at least 30 minutes prior to breakfast

The mean change from baseline at the end of study (day 91) is shown in Table 6. There appears to be a positive dose-response relationship between the 35 mg and 50 mg doses (i.e., 35 mg DRFB vs. 50 mg DRFB) for all 3 markers. The mean decreases in BTM concentrations for 35 mg DRFB regimen were similar to or greater than those observed for the approved regimen of 35 mg IRBB. This was consistent with the observed higher bioavailability (mean Ae) for the DR 35 mg tablet compared to IR 35 mg tablet. The sponsor did not evaluate the response to a lower risedronate DR dose of less than 35 mg. The data of Study 2005107 was included in population exposure-response analysis. An Emax-type exposure-response characteristic for BTM was suggested (see Appendix 4.1, Pharmacometrics review).

Table 6: BTM change from baseline for urine NTX/Cr, serum CTX, and serum BAP at Day 91

Treatment group	N	NTX/Cr	CTX	BAP
35 mg IRBB	34	-38.57 (-56.60, -20.54)	-43.20 (-55.83, -30.58)	-10.99 (-19.62, -2.37)
35 mg DRFB	35	-46.60 (-63.04, -30.17)	-62.08 (-73.59, -50.56)	-10.41 (-18.28, -2.55)
50 mg DRBB	35	-43.65* (-61.62, -25.67)	-65.11 (-77.70, -52.52)	-20.00 (-28.60, -11.40)
50 mg DRFB	65	-54.27 (-70.14, -38.40)	-66.30 (-77.42, -55.18)	-17.36 (-24.96, -9.77)
BTM results shown as mean change (95% CI)				

The phase 3 study evaluated a single dose level (i.e., DR 35 mg once a week) and no serum risedronate or risedronate Ae were measured. Therefore, dose-response and exposure-response assessments regarding BMD were not possible.

2.2.7 What is the linearity or nonlinearity of dose-concentration relationship for risedronate DR?

During the clinical development program, risedronate DR tablets ranging in dose from 20 to 100 mg, namely 20 mg, 35 mg, 75 mg, and 100 mg, were prepared and evaluated in various PK and food effect studies. All of these DR tablets included (b) (4) EDTA in the formulation. All studies included the risedronate Ae as one of the PK endpoints. The cumulative amount excreted over a collection period ranging from 48 to 72 hours for each of the individual studies was utilized in the dose-proportionality analysis. Combining Ae data for collection duration of 48 and 72 hour post dose is acceptable for this assessment since Ae 0-48 hours accounts for about 95% of Ae 0-72 hours. Available risedronate DR Ae(%) data were available from six studies (see Table 7) under either fasting or fed dosing conditions. It should be noted that these studies used slightly different formulations and different meals were used for fed dosing condition.

Table 7: risedronate Ae (µg) in various PK studies

Study number\dose	20 mg	35 mg	75 mg	100 mg
2007027		155.7**		
2007120		126.4**, 180.0*		
2008052	93.1**, 75.4*	197.1**		
2008076			348.1**, 408.6*	507.9**, 583.2*
2008119		157.8*, 162.7*,#		
2008138		120.2**		
* = administered under fasting conditions **= administered with food # = to-be-marketed formulation				

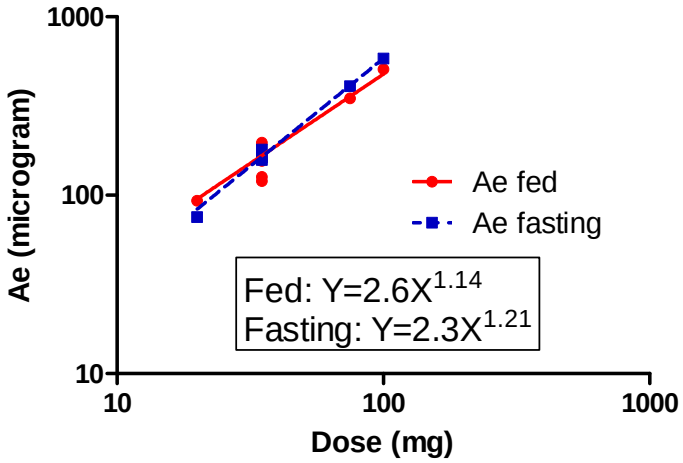
Using the power model ($y=\alpha X^{\beta}$, where y=Ae and X=dose) to assess dose proportionality, under fed conditions the estimated nonproportionality parameter (β) estimate was 1.14 with a 95% CI of 0.89 to 1.40, indicating dose proportionality. However, when assessing under fasting conditions, the estimated nonproportionality parameter estimate was 1.21 with a 95% CI of 1.12 to 1.30, indicating a slightly greater than dose proportional increase in Ae with increasing dose. The power model fitting plot is shown in figure 3.

The sponsor combined Ae data from all six studies (both fasted and fed dosing conditions) and the relationship between log-transformed Ae(%) and log dose was estimated. The slope of this relationship was 1.14 with a 95% CI of 0.93 to 1.35, suggesting dose proportionality. The sponsor also performed population PK analysis of individual data from these studies combined. A review by Pharmacometric reviewer, Dr. Jiang Liu, indicated that there was dose proportionality in the range of 20 to 100 mg risedronate DR dose.

Overall the combined data from 6 studies indicate that risedronate bioavailability increase is dose proportional or slightly more than dose proportional in the tablet strength range of 20 mg – 100 mg. In comparison to the DR 35 mg strength, other tablet strengths used in the above analysis, namely 20 mg, 75 mg, and 100 mg, had the same inactive ingredients as the DR 35 mg strength but differed slightly in actual content of the tablet core and enteric coating. Therefore the dose proportionality assessment is applicable to these specific formulations and may not be applicable to risedronate itself. Additionally, the analysis used data from across studies which may not be as robust as a dedicated dose proportionality study assessing the range of doses.

(b) (4)

Figure 3: Dose proportionality assessment using power model



2.2.8 Does population PK/PD analysis support the risedronate DR 35 mg once weekly dosing regimen administered before or after breakfast?

Review note: This question was addressed by Pharmacometrics reviewer Dr. Jiang Liu. His response is provided below. Please see Appendix 4.1 for further details of the Pharmacometrics review.

Yes. The final PK/PD analysis is generally acceptable based on the goodness of fits, known clearance pathway of risedronate, and good precision of parameter estimates. The population PK/PD model suggests:

1. dose-proportionality of the DR formulation across the 20-100 mg dose range.
2. higher relative bioavailability (135% higher) of the DR formulation compared to the IR formulation if administered per label instructions (overnight fasted, 30-60 minutes before breakfast).
3. 38% reduction in bioavailability of the DR formulation upon concomitant administration of 40 mg esomeprazole.

The population PK analysis did not detect significant food effect on the bioavailability of the DR formulation across studies. Based on population PK/PD modeling and simulation, the 35 mg DR weekly dosing regimen administered before or after breakfast is reasonable from clinical pharmacology perspective.

Efficacy: The efficacy of 35 mg DR weekly dosing regimen is supported by the pivotal Phase 3 study (Study 2007008). The population PK/PD analysis supports the efficacy by matching exposures (AUC) and PD biomarker responses (measured as reduction in BTMs from baseline) between DR and IR formulations. The 35 mg DR weekly dose results in similar or greater exposure and PD responses than the 5 mg/day or 35 mg/week IR dose and is more robust than 20 mg DR weekly dose especially under strict fasting conditions or in combination with esomeprazole. (b) (4)

(b) (4)

Therefore, we think the 35 mg DR weekly dosing regimen is reasonable based on the following safety discussion.

Safety: The drug exposure (based on AUC) after administration of 35 mg DR dose are higher than the 5 mg IR dose. However, the IR doses of 75 and 150 mg (given less frequently) result in higher C_{max} levels than that of the 35 mg DR dose. Moreover, 15 mg IR daily dose results in similar or greater average AUC_{24} than the 35 mg DR dose (figure 4). Two-year, Phase III safety IR data of 150 mg OAM (Study 2005032 in women with PMO), 75 mg 2CDM (Study 2004012 in women with PMO), and 15 mg daily (Study 1998033 and Study 1998034 in women and men with knee osteoarthritis) were submitted. Therefore, exposures (Cmax and AUC) after 35 mg DR dosing regimen administered weekly before or after breakfast are reasonably similar or lower than other regimens or doses used clinically.

Figure 4: Normalized average 24 hour AUC of risedronate at steady state simulated for 5 mg/day and 35 mg/week IR, 15 mg/day IR, and 35 mg/week DR when administered per label instructions (overnight fasted, 30-60 minutes before breakfast)

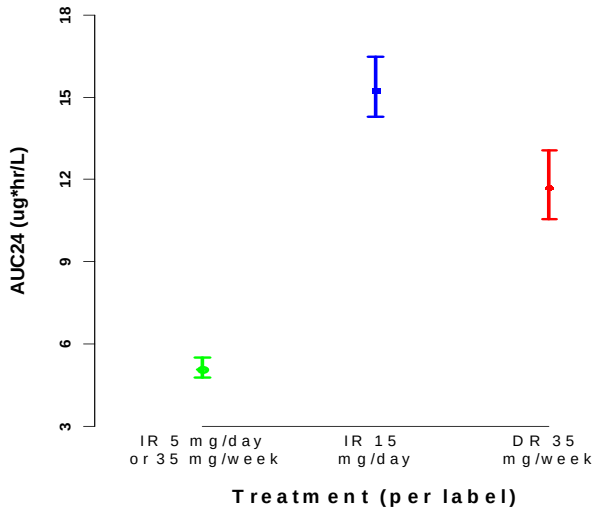


Figure footnote: Points indicate the population means and the vertical bars are the 95% confidence intervals. Patient demographics in Study 2005032 were used for simulation. 300 trial replicates with 1000 subjects for each trial were simulated. The average AUC at steady state was calculated as $AUC_{24avg,ss} = \frac{Dose \bullet F}{\tau / 24 \bullet CL}$. The exposure of 15 mg IR daily dose was derived from the 5 mg IR daily dose assuming linear PK.

2.3 Intrinsic Factors

2.3.1 What is the relative bioavailability of risedronate DR in men and women?

The effect of sex on PK of risedronate DR was assessed based on data from BE study 2008119, where single doses of risedronate DR 35 mg were administered to healthy male (n=298) and female (n=184) volunteers. For Cmax and AUCtlast, the ratios for male to female were 0.825 and 0.814, respectively. The ratio of Tmax for males to females was 1.023. The ratio of Ae for males to females was 0.913 (Table 8). Similar results were obtained when data from each formulation (Phase 3 product and to-be-marketed product) were analyzed separately.

Table 8: Effect of sex on PK of risedronate DR 35 mg tablets

PK parameter	Male to female ratio	90% CI
C_{max}	0.825	0.704, 0.968
AUCtlast	0.814	0.689, 0.962

T_{max}	1.023	0.981, 1.067
Ae	0.913	0.778, 1.071

The above results indicated that risedronate exposure from risedronate DR 35 mg is slightly lower in males compared to females. The sponsor stated that these sex-related differences in the risedronate 35 mg DR tablets were similar to previous data for risedronate IR 5 mg and 15 mg observed in study 2000009 (Table 9). Study 2000009 was a small study that administered risedronate IR 5 mg/day or 15 mg/day for 112 days. 29 subjects were enrolled in the 5 mg/day treatment group (12 men and 17 women) and 30 subjects enrolled in the 15 mg/day treatment group (13 men and 17 women). Twenty four hour serum and urinary risedronate concentration were measured on days 1, 85, and 112. Serum and urinary risedronate were captured up to 72 and 168 hours post dose following the last dose on day 112, respectively. Serum concentration-time and urinary excretion rate-time profiles for individual subjects were simultaneously fitted to a 4-exponential function.

Table 9: Effect of sex on PK of risedronate IR 5 mg and 15 mg tablet (pooled data from both doses, study 2000009)

PK parameter	Male to female ratio	90% CI
C_{max} [a]	0.778	0.621, 0.973
AUC0-tau	0.862	0.689, 1.078
Ae (over 24 hours dosing interval)	1.063	0.828, 1.365
[a] Evaluated using Day 112 data		

As described above, the effect of sex on bioavailability of the IR formulation was based on a relatively small parallel study of 25 men and 34 women. Nonetheless, the results were consistent with that observed for risedronate DR 35 mg from the larger study 2008119. The differences based on sex were small in both studies. Overall, the data indicate that the relative exposure between males and females would likely be similar for both risedronate IR and DR tablets. Since the risedronate DR 35 mg has an approximately 2 to 4 fold higher bioavailability than risedronate IR 35 mg (under DRFB vs. IRBB dosing conditions), risedronate exposure following administration of risedronate DR 35 mg in men would exceed that of risedronate IR 35 mg in either men or women.

The safety of risedronate DR 35 mg once weekly regimen has not been evaluated in large clinical trials in men. Single doses of risedronate DR 35 mg have been administered to healthy men in BE study 2008119. (b) (4)
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2.3.2 What is the effect of hepatic impairment on the PK of risedronate DR?

The sponsor did not conduct a study to evaluate the effect of hepatic impairment on the PK of risedronate DR. However, prior review of risedronate IR data indicated that there is no evidence of systemic metabolism of risedronate (Actonel label). No dosage adjustment was recommended for risedronate IR. A similar recommendation could be applied to risedronate DR.

2.3.3 What is the effect of renal impairment on the PK of risedronate DR?

The sponsor did not conduct a study to evaluate the effect of renal impairment on the PK of risedronate DR. Risedronate is excreted unchanged primarily via the kidney. The current label for risedronate IR states that the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min compared to patients with normal renal function.

The label for risedronate IR states that risedronate IR is not recommended for use in patients with severe renal impairment (CLcr <30 mL/min) because of lack of clinical experience, while no dosage adjustment is necessary in patients with a CLcr ≥30 mL/min. It was considered whether the same recommendation could be applied to risedronate DR. A review by Pharmacometric reviewer, Dr. Jiang Liu, indicated that due to higher exposure of the risedronate DR formulation compared to IR formulation (administered per label instruction at least 30 minutes before breakfast), a 4 – 12 fold higher exposure may be expected in moderate renal impairment patients taking risedronate DR 35 mg when compared to normal renal function patients taking risedronate IR 35 mg. The higher exposure raised a safety concern of applying the same recommendation of no dosage adjustment in patients with moderate renal impairment. However, Dr. Jiang Liu also noted the following: "In the current Phase III DR study (Study 2007008) and previous 15 mg IR daily studies (Study 1998033 and Study 1998034 in women and men with knee osteoarthritis), 55 out of 615 patients and 12 out of 609 patients who had been exposed to the 35 mg DR weekly or 15 mg IR daily high exposure respectively had CLcr ≤50 ml/min. At this time, no major safety problems were raised in these renal impairment patients. In Study 2007008, the clinical fracture incidence in patients with moderate renal impairment (3.64%) was not substantially different from patients without moderate impairment (3.04%)."

When comparing exposure for the DR formulation only, a 2 – 3-fold higher exposure may be present in patients with moderate renal impairment relative to patient with normal renal function. Sponsor's summary data in patients with moderate renal impairment do not appear to indicate a safety concern. However, a request was made to the Medical Officer, Dr. Stephen Bienz, to assess whether there was any increase in adverse events in patients with moderate renal impairment (CLcr = 30 – 60 mL/min) enrolled in Phase 3 study 2007008 and received risedronate DR 35 mg. Phase 3 study 2007008 enrolled 80, 77, and 75 patients with moderate renal impairment in the IRBB, DRFB, and DRBB arms, respectively. Dr. Bienz noted that "[f]or the DR formulation no increase in subjects with adverse events were noted with moderate renal insufficiency (for the DRFB group, 67.9% of subjects with moderate renal insufficiency with AEs, 73.8% without moderate renal insufficiency, for the DRBB group 74.8% and 78.0% respectively)." He also compared rates of select adverse events which might be related to increased systemic risedronate exposure by renal status. Of the AEs analyzed, only PTH increased occurred consistently at a higher rate in subjects with moderate renal impairment (2.5% vs 0.4% for IRBB, 1.3% vs. 0.4% for DRFB, and 5.3% vs. 1.3% for DRBB). Following up on this finding, measured PTH elevation at 26 or 52 weeks with normal baseline was compared between subjects with moderate to severe renal impairment (RI) and subjects with mild or no RI. Dr. Bienze noted that "[l]ittle difference was noted in the proportion of subjects with elevated (>65 pg/ml) or markedly elevated (>97 pg/ml) PTH compared by renal status." Please see Medical review for more details.

The above data suggests that even though greater exposure to risedronate is anticipated in patients with moderate renal impairment, no greater rate of adverse events were observed. Therefore, no dose adjustment is recommended for patients with moderate renal impairment. No clinical experience is available for patient with severe renal impairment (CLcr < 30 ml/min).

2.3.4 What is the bioavailability of risedronate DR in pediatric and geriatric subjects?

No data are available for pediatrics. Risedronate DR is not indicated for use in pediatric patients. A waiver of pediatric study was been granted by the pediatric review committee (PeRC) on 2/17/2010.

Prior review of risedronate IR data have concluded that bioavailability and disposition of risedronate are similar in elderly (>60 years of age) and younger subjects (current Actonel label). No study was conducted to evaluate the effect of age on bioavailability of risedronate DR. However, Phase 3 study (study 2007008) enrolled target population of postmenopausal women with mean age of approximately 66 years of age (range 50 – 87 years).

2.4 Extrinsic Factors

2.4.1 What is the effect of food on bioavailability of risedronate DR 35 mg tablet?

The effect of food on bioavailability of risedronate DR 35 mg was evaluated in a single dose, crossover study in 74 postmenopausal women (study 2007120). There were 4 different treatments in this study. The 2 relevant treatments were 1) risedronate DR 35 mg administered orally after an overnight (10 hour) fast, followed by a 4-hour fast and 2) risedronate DR 35 mg administered orally after an overnight (10 hour) fast, within 5 minutes after ingesting a high-fat meal. The high-fat meal was a standard high-fat breakfast containing approximately 150 protein calories, 250 carbohydrate calories, 500 – 600 fat calories, and 408 mg of calcium. It was to be ingested within 20 – 25 minutes.

The geometric mean (%CV) 0-72 hour Ae following administration of a single dose of risedronate DR 35 mg under fed and fasting conditions were 126.2 µg (189%) and 165.8 µg (148%). The fed/fasting ratio (90% CI) of risedronate Ae was 0.702 (0.539, 0.915). The results indicate that bioavailability of risedronate DR 35 mg tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration of 4 hours before a meal. This effect of food is less than that observed for the IR formulation (~54% reduction) in the same study, suggesting that the DR formulation is less sensitive to food.

The sponsor also conducted studies where risedronate DR strengths of 20 mg (Study 2008052), 75 mg (Study 2008076), and 100 mg (Study 2008076) were administered under standard fasting (i.e., 10 hours before and 4 hours after) and fed conditions. These data showed food slightly increased absorption of risedronate DR 20 mg tablet (Ae ratio for fed/fasted was 1.2) and slightly decreased absorption of risedronate DR 75 and 100 mg tablets (Ae ratio for fed/fasted were 0.85 and 0.87, respectively). Data were also available for the risedronate DR 50 mg strength where it was given under fed or at least 30 minute before breakfast. The fed/30 minute fasted Ae ratio was 0.91. These data support that the risedronate DR formulation is less sensitive to food compared to the IR formulation.

The Sponsor also assessed the effect of food on bioavailability of the DR formulation using all available Ae data in a population PK model. A review by Pharmacometrics reviewer, Dr. Jiang Liu, indicated that the population PK analysis did not detect significant food effect on the bioavailability of the DR formulations across studies (See Pharmacometrics review in Appendix 4.1).

Overall, food decreased the bioavailability of the risedronate DR 35 mg tablet by approximately 30%. Evaluation across tablets strengths of 20 – 100 mg support that the risedronate DR formulation is less sensitive to food effect than that observed for the IR formulation.

2.4.2 What is the effect of concomitant administration of esomeprazole on the bioavailability of risedronate DR?

The effect of concomitant administration of esomeprazole magnesium (Nexium®) on the bioavailability of risedronate DR was evaluated in study 2007027. This was Phase 1, randomized, open-label, 3-treatment, 3-period crossover study in 87 healthy, surgically sterile or postmenopausal (mostly Caucasian) women (mean age 55.4 years, range 40 – 69 years). Each subject received the following 3 treatments in random order. Each period was separated by at least 7 days.

1. Placebo/Placebo: Placebo 1 hour prior to breakfast and 1 hour prior to dinner (the evening meal) on Days 1 through 8 and risedronate 35 mg DR within 15 minutes following completion of breakfast on Day 6;

2. Placebo/Esomeprazole: Placebo 1 hour prior to breakfast and esomeprazole 40 mg 1 hour prior to dinner (the evening meal) on Days 1 through 8 and risedronate 35 mg DR within 15 minutes following completion of breakfast on Day 6;

3. Esomeprazole/Placebo: Esomeprazole 40 mg 1 hour prior to breakfast and placebo 1 hour prior to dinner (the evening meal) on Days 1 through 8 and risedronate 35 mg DR within 15 minutes following completion of breakfast on Day 6.

During each treatment period, urine was collected as single pre-dose samples on Day 1 and Day 6 and as three consecutive 24-hour samples starting immediately prior to administration of risedronate.

Table 10 shows the relative bioavailability between the different dosing regimens. The extent of risedronate absorption (given after breakfast) was reduced by 32% if esomeprazole was administered prior to dinner and by 48% if esomeprazole was administered prior to breakfast. Additional descriptive PK parameters for each dosing regimen are shown in Table 11.

Assessment of the distribution of risedronate Ae did not reveal any apparent bimodal distribution that may be indicative of a complete failure of the enteric coating in the presence of esomeprazole. Therefore, labeling recommendations may be based on the mean changes observed.

Table 10: Mean and ratios of risedronate urinary excretion

PK parameter	Placebo/Esomeprazole vs. Placebo/Placebo Ratio and 90% CI	Esomeprazole/Placebo vs. Placebo/Placebo Ratio and 90% CI
Ae	0.679 (0.504, 0.914)	0.518 (0.385, 0.696)

Table 11: Summary of PK parameters for the 3 treatments in study 2007027

Treatment / Descriptive Statistic	0 – 24 hours		24 – 48 hours		48 – 72 hours		0 – 72 hours	
	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)
Treatment A: Placebo/Placebo								
N	85	85	85	85	85	85	85	85
Mean	257.9955	0.73713	31.3543	0.08959	14.6217	0.04178	303.9715	0.86849
%CVam[a]	125.7	125.7	162.3	162.3	113.3	113.3	122.6	122.6
Geo Mean[b]	118.0105	0.33721	15.5695	0.04451	9.3461	0.02670	147.8285	0.42233
%CVgm[c]	278.6	278.5	177.5	177.2	134.0	134.0	229.0	229.1
Median	153.4340	0.43840	16.3840	0.04680	9.6980	0.02770	172.8650	0.49390
Min	0.000	0.0000	0.862	0.0025	0.000	0.0000	2.815	0.0080
Max	1798.320	5.1381	387.040	1.1058	109.002	0.3114	2082.042	5.9487
Treatment B: Placebo/Esomeprazole								
N	83	83	83	83	83	83	83	83
Mean	175.0633	0.50019	18.8298	0.05380	10.5043	0.03001	204.3975	0.58400
%CVam[a]	122.4	122.4	102.4	102.4	104.9	104.9	117.7	117.7
Geo Mean[b]	83.2953	0.23802	11.4315	0.03265	6.4575	0.01845	103.0807	0.29453
%CVgm[c]	229.3	229.2	157.4	157.7	158.2	158.0	210.6	210.6
Median	101.4900	0.29000	12.9840	0.03710	7.1050	0.02030	119.9370	0.34270
Min	1.643	0.0047	0.000	0.0000	0.000	0.0000	1.643	0.0047
Max	959.124	2.7404	96.557	0.2759	54.877	0.1568	1095.272	3.1293
Treatment C: Esomeprazole/Placebo								
N	84	84	84	84	84	84	84	84
Mean	146.7550	0.41930	15.7106	0.04489	8.8057	0.02515	171.2713	0.48935
%CVam[a]	136.2	136.2	118.6	118.6	116.6	116.6	131.1	131.1
Geo Mean[b]	61.6060	0.17602	8.2769	0.02365	5.3938	0.01540	77.1126	0.22032
%CVgm[c]	243.2	243.2	182.0	182.0	154.5	154.5	218.9	218.9
Median	60.5520	0.17305	7.0945	0.02030	4.8100	0.01375	71.8550	0.20530
Min	4.580	0.0131	0.000	0.0000	0.000	0.0000	5.716	0.0163
Max	940.216	2.6863	75.096	0.2146	40.682	0.1162	1052.487	3.0071

A_e is the amount of drug excreted in urine over the stated time interval; and A'_e is the amount of drug excreted in urine over the stated time interval, normalized for dose, and expressed as a percentage.
[a] %CVam = coefficient of variation for the arithmetic mean.
[b] Geo Mean = Geometric Mean.
[c] %CVgm = coefficient of variation for the geometric mean.
Data calculated using raw data contained in Appendix 13.2.5.2, Tables 1-256.

Source: Table 10, Study 2007027 study report

In the Phase 3 study, the sponsor compared the change in BMD in patients taking a proton pump inhibitor (PPI) or an H-2 antagonist (H2) vs. those who did not. A review of the results by Medical Officer Dr. Stephen R. Bienz indicated that the percent change from baseline in lumbar spine BMD at week 52 was consistent between acid suppressor (i.e., PPI/H2) users and non-users. However, he cautioned that interpretation of that information is limited by small number of patients (a total of 85 patients using PPIs, 129 patients if PPIs and H2 antagonists are considered).

2.4.3 Is the sponsor's proposed dosing instruction to take risedronate DR with 4 ounces (instead of 6 - 8 ounces) of water appropriate?

Esophageal AEs such as esophagitis, erosions, and ulcers have been reported with oral bisphosphonate use. Some of these events have occurred due to prolonged or delayed esophageal transit. Administration with a full glass of water helps minimize esophageal transit time and therefore risk of esophageal adverse events.

The current Actonel label states that it should be taken with 6 – 8 oz of water. This was recommended to minimize the risk of esophageal irritation and based on early phase 3 studies with risedronate IR 5 mg

once daily where risedronate was administered with a full glass of water. In 5 subsequent Phase 3 studies of weekly or monthly dosing of IR tablets, the sponsor stated that the dosing instruction was changed to taking the tablet with at least 4 ounces of water. During development of risedronate DR 35 mg tablets, most studies, including Phase 3 study 2007008, have instructed subjects to take the tablet with at least 4 ounces of water instead of a full glass (6 – 8 ounces). The sponsor indicated that there is no apparent upper gastrointestinal safety issues associated with the new dosing instruction.

In addition, the risedronate DR formulation is enteric coated and may delay the release of risedronate (as compared to the IR formulation). The sponsor conducted in vitro disintegration testing (USP 28 <701> Disintegration procedure, n=6 replicates) using pH 6.8 phosphate buffer and simulated saliva (pH 6.6 McIlvaine's buffer). The results showed that disintegration of the risedronate DR tablet started at 5.6 – 6.7 minutes in phosphate buffer and at 4.0 – 4.9 minutes in simulated saliva. For comparison, disintegration start time for risedronate IR in simulated saliva ranged from 0.4 – 0.8 minute. In pH 6.8 buffer, there was a minimal (mean <5%) dissolution within the first 10 minutes (paddle apparatus, 0.1 N HCl followed by 0.5M phosphate buffer at pH 6.8, 75 rpm).

Based on the above information, the sponsor's proposal to administer risedronate DR with at least 4 ounces of water is acceptable.

2.4.4 Does the EDTA content in risedronate DR tablets have the potential to alter the absorption of other concomitantly administered drugs?

There are 2 potential issues with EDTA that may lead to altered drug absorption, namely 1) EDTA is a (b) (4) chelator that may alter the solubility of a drug, and 2) EDTA has been shown to increase paracellular transport. The results summarized in this section indicate that EDTA in risedronate DR 35 mg tablet is not likely to have significant influence on solubility of the drugs tested. An effect on paracellular transport could not be ruled out. However, the magnitude of any effect on paracellular transport appears to be modest.

Solubility:

To evaluate the potential for EDTA to directly solubilize or precipitate co-administered drugs the sponsor evaluated the effect of EDTA on the solubility of several soluble and poorly soluble drugs with a narrow therapeutic index. The sponsor also evaluated the specific drugs requested by the FDA at the End-of-Phase II meeting held on June 28, 2007. The apparent solubility experiments were conducted in water alone and in the presence of predissolved EDTA at concentrations of 10 mM, 25 mM, and 100 mM. These EDTA concentrations are higher than the intestinal concentration expected in vivo (estimated to be ≤1.5 mM) following administration of risedronate DR. The tested drugs and solubility results are shown in Table 12.

The results showed that there were reductions (> 10%) in solubility for isoproterenol HCl (-14%), phenytoin Na (-20%), digoxin (-33%), and potassium chloride (-24%). These reductions occurred at the highest concentration of EDTA except for digoxin where the solubility decreased from 0.03 mg/mL to 0.02 mg/mL at all 3 EDTA concentrations. The only drug that increased in solubility was lithium carbonate (+28% at 100 mM EDTA). Solubility data for nelfinavir were variable. The sponsor suggested that this was likely due to the insoluble nature of the drug and the fact that after extraction it existed as a combination of the base and mesylate salt form. Nelfinavir is insoluble in water and in the EDTA solutions indicating that there was minimal impact of EDTA on nelfinavir solubility.

Overall, it appears that EDTA has minimal effect on solubility of the drugs tested at EDTA concentrations expected in-vivo.

Table 12: Effect of EDTA on solubility of selected drugs

Drug	Medium	pH	Average Solubility (mg/mL)*	Solubility as defined in the USP (USP 28)
Isoproterenol HCl	Water	5.7	346	Freely soluble
	10 mM EDTA	5.1	341	Freely soluble
		6.0	317	Freely soluble
	25 mM EDTA	4.9	332	Freely soluble
		6.0	310	Freely soluble
	100 mM EDTA	4.8	314	Freely soluble
		6.0	297	Freely soluble
Phenytoin Sodium Salt	Water	10.3	42.8	Soluble
	10 mM EDTA	10.3	55.9	Soluble
	25 mM EDTA	10.2	50.9	Soluble
	100 mM EDTA	10.2	34.4	Soluble
Carbamazepine	Water	6.6	0.13	Very slightly soluble
	10 mM EDTA	4.7	0.13	Very slightly soluble
		6.0	0.12	Very slightly soluble
	25 mM EDTA	4.5	0.12	Very slightly soluble
		6.0	0.13	Very slightly soluble
	100 mM EDTA	4.0	0.12	Very slightly soluble
		6.0	0.12	Very slightly soluble
Theophylline	Water	5.9	6.1	Slightly soluble
	10 mM EDTA	5.4	6.1	Slightly soluble
		6.0	6.6	Slightly soluble
	25 mM EDTA	5.3	5.9	Slightly soluble
		6.0	6.8	Slightly soluble
	100 mM EDTA	4.0	5.5	Slightly soluble
		6.0	5.8	Slightly soluble
Warfarin Sodium Salt†	Water	8.0	534	Freely soluble
	10 mM EDTA	8.2	586	Freely soluble
	25 mM EDTA	8.1	538	Freely soluble
	100 mM EDTA	8.0	517	Freely soluble

* Solubility average of two replicate samples.
† Solubility limit was not determined due to viscosity of solutions.

Drug	Medium	pH	Average Solubility (mg/mL)*	Solubility as defined in the USP (USP 28)
Digoxin	Water	6.6	0.03	Insoluble
	10 mM EDTA	4.3	0.02	Insoluble
		6.0	0.02	Insoluble
	25 mM EDTA	4.2	0.02	Insoluble
		6.0	0.02	Insoluble
	100 mM EDTA	4.0	0.02	Insoluble
		6.0	0.02	Insoluble
Lithium Carbonate	Water	11.6	0.78	Very slightly soluble
	10 mM EDTA	10.8	0.81	Very slightly soluble
	25 mM EDTA	10.3	0.83	Very slightly soluble
	100 mM EDTA	9.5	1.0	Very slightly soluble
Potassium Chloride	Water	5.7	109	Freely soluble
		9.3	106	Freely soluble
	10 mM EDTA	4.7	108	Freely soluble
		6.0	103	Freely soluble
	25 mM EDTA	4.6	108	Freely soluble
		6.0	100	Freely soluble
	100 mM EDTA	4.6	109	Freely soluble
		6.0	83	Soluble
Nelfinavir†	Water	6.0	0.09	Insoluble
		8.0	0.02	Insoluble
	10 mM EDTA	6.0	0.04	Insoluble
		8.0	0.01	Insoluble
	25 mM EDTA	6.0	0.13	Very slightly soluble
		8.0	0.01	Insoluble
	100 mM EDTA	6.0	0.08	Insoluble
		8.0	0.01	Insoluble
Lamivudine	Water	6.8	94	Soluble
	10 mM EDTA	6.2	96	Soluble
	25 mM	6.0	94	Soluble
	100 mM	5.7	97	Soluble
		6.0	95	Soluble
Emtricitabine	Water	5.4	106	Freely soluble
		6.3	108	Freely soluble
	10 mM EDTA	5.2	104	Freely Soluble
		6.1	106	Freely Soluble
	25 mM EDTA	5.1	96	Soluble
		6.0	102‡	Freely soluble
	100 mM EDTA	4.9	87	Soluble
		6.0	95	Soluble

* Solubility average of two replicate samples.
† Because of the low aqueous solubility of nelfinavir a pH of 8 was included, the LOD of the method is believed to be approximately 0.0005 mg/mL and the results of duplicate samples were highly variable suggesting no significant effect of EDTA on solubility.
‡ Dilution error, individual value.

Paracellular transport:

In the paracellular transport process, drug reaches the blood by passively diffusing through the tight junctions between epithelial cells. The tight junctions of epithelial cells are formed by specific proteins and divalent cations, such as calcium and magnesium. EDTA can complex these cations and widen the paracellular tight junctions and potentially increase absorption of risedronate, which is expected to be

absorbed via the paracellular pathway. This concern has been raised by the FDA throughout the development of risedronate DR 35 mg tablet, which contains (b) (4) of EDTA.

The sponsor noted that EDTA in vitro could affect paracellular transport at concentrations ≥2 mM (a lower concentration of 1 mM did not show an effect on paracellular transport [Zakelj et al., Biol Pharmaceut Bul 2005;28(7):1249-53]) while the estimated in vivo intestinal concentration of EDTA following administration of risedronate DR 5 mg is expected to be ≤1.5 mM. This suggests that EDTA from risedronate DR 35 mg tablets may not have a significant effect on paracellular transport. Furthermore, the sponsor noted that when administered under fasting conditions, the bioavailability of the DR 35 mg formulation was approximately 44% higher than the IR 35 mg tablet. This suggests that the maximum potential for both risedronate (itself a chelator of cations) and EDTA from risedronate DR 35 mg formulation releasing in the same region of the intestine on the paracellular transport is approximately 44%. Additionally, other factors that may have contributed to the 44% higher bioavailability for the DR formulation may include 1) EDTA binding of calcium in intestinal fluid and making more risedronate available for absorption, and 2) performance differences between the DR and IR formulations (e.g., location of drug release). Bisphosphonate absorption is believed to occur mainly in the upper part of the small intestine. Since risedronate is though to be absorbed via the paracellular pathway and has low absolute oral bioavailability (<1%), the effect of EDTA on increasing risedronate's paracellular transport and bioavailability by 44% could be considered a worst case scenario for potential drug interactions.

Overall, an effect of EDTA in risedronate DR on increasing paracellular transport could not be ruled out. However, any effect on paracellular transport appears to be modest (44% increase with paracellular transport substrate risedronate). Effects on increasing paracellular transport should not significantly affect the bioavailability of drugs absorbed via transcellular pathway or drugs with high oral bioavailability. Narrow therapeutic drugs digoxin, warfarin, theophylline, and phenytoin have high oral bioavailability (>80%) and are not expected to be significantly affected by an increase in paracellular transport.

2.4.5 What is the effect of calcium intake on the bioavailability of risedronate DR? Does administering risedronate DR 35 mg with dinner alter bioavailability compared to administering with breakfast?

Calcium supplementation is recommended as part of treatment and prevention of osteoporosis. There is a concern that calcium coadministration would reduce the bioavailability of risedronate DR. Calcium presence in the gastrointestinal track (from food or calcium supplements) binds risedronate and reduces the risedronate available for absorption. The Sponsor conducted a PK study (Study 2008138) to assess the effect of calcium coadministration (600 mg elemental calcium/400 IU vitamin D tablet) on bioavailability of risedronate DR (as assessed by Ae). This was a randomized, open-label, single-dose, 3-treatment, 3-period crossover relative bioavailability study in 101 healthy women between 40 and 70 years of age. Treatment periods were separated by washout periods of 14 to 17 days. The 3 treatments were as follows:

- Treatment A (DRFB+Ca/vitD): risedronate 35 mg DR oral tablet administered after an overnight (10 hour) fast and within 5 minutes after completing a standard breakfast and taking 1 Caltrate® 600+D tablet (600 mg elemental calcium plus 400 IU vitamin D; (b) (4) . No additional food was allowed for at least 4 hours post-dose

- Treatment B (DR dinner): risedronate 35 mg DR oral tablet administered after a 6 hour fast and within 5 minutes after completing a standard dinner. No additional food was allowed for at least 4 hours post-dose

- Treatment C (DRFB): risedronate 35 mg DR oral tablet administered after an overnight (10 hour) fast and within 5 minutes after completing a standard breakfast. No additional food was allowed for at least 4 hours post-dose

The standard breakfast contained approximately 450 calories and 15 grams fat. The standard dinner contained approximately 900 calories and 34 grams of fat. The meals immediately preceding dosing contained approximately 300 mg calcium. For Treatment A (DRFB+Ca/vitD), the total amount of calcium provided in the pre-dose meal and the Caltrate 600+D tablets was approximately 900 mg.

Urinary risedronate excretion was measured for 72 hours post dosing. The results are shown in Table 13. They indicate that coadministration of 600 mg calcium supplement reduced risedronate bioavailability (as measured by risedronate Ae) by a mean of 38% (Table 14). This magnitude of change was based on the assumption that a typical meal contains 300 mg calcium. It should be noted that the magnitude of percent change may be lowered if the meal contained more than 300 mg calcium and may be higher if the meal contained less than 300 mg calcium. The chosen meal calcium content of 300 mg in this study appears reasonable given that the Recommended Daily Allowance (RDA) of calcium in adults is 1000 – 1200 mg day.

To reduce the potential for decreasing risedronate bioavailability, calcium supplements or antacids containing calcium or magnesium divalent cations should be taken at a different time of day relative to time of risedronate administration. Ideally, calcium supplement should be taken in the evening if risedronate is taken in the morning. This recommendation is based in part on a scintigraphy study of an early enteric coated risedronate DR formulation (Study 2004132) which showed that food delayed the mean time to initial disintegration of risedronate by about 8 hours. The mean (SD) time to initial disintegration of risedronate DR 35 mg tablet under fed conditions was estimated to be 10.1 (7.3) hours.

Risedronate DR administered after dinner provided greater exposure (approximately 87% increase in Ae) compared to administration following a breakfast (Table 14). The reason for higher bioavailability when risedronate DR is taken with dinner is not known. It was unlikely to be due to the differences in meal content of breakfast and dinner since a high fat, high calorie meal had been shown to cause a small (~30%) decrease in bioavailability of risedronate DR.

Table 13: Geometric mean risedronate urinary excretion over 72 hours (study 2008138)

PK Parameter	35 mg DRFB + Ca/vitD (n=87) (95% CI)	35 mg DR dinner (n=95) (95% CI)	35 mg DRFB (n=96) (95% CI)
Ae (ug)	74.244 (53.506, 103.019)	222.913 (166.810, 297.887)	120.198 (88.045, 164.093)
A'e (%)	0.212 (0.153, 0.294)	0.637 (0.477, 0.851)	0.344 (0.252, 0.469)

Table 14: Ratios of geometric mean risedronate urinary excretion over 72 hours (study 2008138)

PK Parameter	35 mg DRFB + Ca/vitD / 35 mg DRFB (90% CI)	35 mg DR dinner / 35 mg DRFB (90% CI)
Ae (ug)	0.6206 (0.4338, 0.8878)	1.8650 (1.3307, 2.6140)
A'e (%)	0.6204 (0.4337, 0.8874)	1.8644 (1.3304, 2.6128)

2.4.6 Do divalent and trivalent cations contained in commonly administered oral formulations have the potential to interfere with absorption of risedronate DR?

Divalent and trivalent cations could bind to risedronate and reduce its bioavailability. A concern was raised whether drugs commonly used by osteoporotic patients contain divalent or trivalent cations and whether they could interfere with risedronate absorption. To address this concern, the sponsor determined the amount of cations in drugs commonly used by patients in 2 of their clinical trials. The sponsor first compiled a list of common (top 50% or 75%) concomitant mediations reported in 2 Phase 3 studies with

risedronate (studies 2007008 and 2005032). Drugs that have labeled divalent and trivalent cation content exceeding that of the high fat meal (>400 mg calcium; e.g., calcium supplements and antacids) were excluded. The list of drugs considered is shown in Table 15.

Table 15: List of medications from studies 2007008 and 2005032

Acetylsalicylic acid	Enalapril maleate	Pantoprazole
Acyclovir	Glucosamine	Paracetamol
Alprazolam	Ibuprofen	Perindopril
Amlodipine besylate	Isosorbide mononitrate	Prednisone
Amoxicillin	Ketoprofen	Ramipril
Atenolol	Levothyroxine sodium	Ranitidine hydrochloride
Atorvastatin calcium	Lisinopril	Rosuvastatin calcium
Bisoprolol fumarate	Loratadine	Salbutamol
Bromazepam	Metoprolol succinate	Simvastatin
Budesonide	Metronidazole	Tetracycline hydrochloride
Ciprofloxacin	Mometasone furoate	Trimetazidine
Clarithromycin	Naproxen sodium	Ubidecarenone
Clonazepam	Norfloxacin	
Diclofenac	Omeprazole magnesium	

Following a review of the product label for each concomitant medication, those that had cations above trace levels (dyes, pigments, lubricants) were tested to determine calcium, magnesium, aluminum, and iron content. The drugs tested were amlodinpine besylate (Norvasc), atorvastatin calcium (Lipitor), bisoprolol fumarate (Zebeta), levothyroxine sodium (Levothyroid), lisinopril (Prinivil), rosuvastatin calcium (Crestor), and Coenzyme Q10 (ubidecarenone). Calcium carbonate (Os-cal) 500 mg was used as a positive control.

The results indicated that the amount of divalent and trivalent cations (magnesium, aluminum, iron, and calcium) in drugs commonly used in patients enrolled in risedronate Phase 3 studies were low except for calcium supplements or antacids. The highest cation content was about 100 mg calcium in atorvastatin 80 mg tablet. Data from study 2008138 showed that coadministration of 600 mg elemental calcium resulted in 38% decrease in bioavailability of risedronate DR tablet. The lower calcium content of 100 mg calcium in atorvastatin may potentially interfere with the bioavailability of risedronate DR but is likely to be much less than the 38% decrease seen with 600 mg calcium. The results suggested that cations content of drugs commonly used in the osteoporotic patients studied would not significantly affect the bioavailability of risedronate DR. Additionally, since risedronate DR formulation has higher bioavailability than the approved risedronate IR formulation, a small decrease in bioavailability should not affect the effectiveness of risedronate DR.

The sponsor only evaluated cation content of drugs administered in postmenopausal women enrolled in Phase 3 study for treatment of osteoporosis. It is not known if drugs used in other populations (e.g., men) that were not evaluated would contain a higher amount of cation that could potentially affect risedronate absorption.

2.5 General Biopharmaceutics

2.5.1 What were the formulations used in clinical studies supporting the NDA?

During development of risedronate DR 35 mg, 3 different formulations were administered in the relevant clinical studies. They were designated as formulations A, B, and C in this review (see Table 16). Phase 3 clinical study used mostly formulation A with some patients administered formulation B in the early part

of the study. Formulation A was also used in Phase 1 studies 2007120, 2008052, 2008119, and 2008138. Formulation B was used in the drug interaction study with esomeprazole (study 2007027). Formulation C was used in Phase 2 study 2005107.

The TBM (also denoted as formulation D) is identical to formulation A with the exception of the omission of (b) (4) color. A BE study was conducted to compare the relative bioavailability of these 2 formulations (see section 2.5.2). Formulation B has slightly different core than formulation A. However, the changes were determined to be minor (level 1 change) and no bridging studies are needed. Formulation C has a slightly different core (same core as Formulation B) as well as a slightly different enteric coating compared to Formulation A. These changes were considered minor and no bridging studies were needed. The compositions of these 4 formulations are shown in Tables 17 and 18.

Study 2004132 used several earlier pilot formulations (with a 240 mg core) that are not discussed here.

Table 16: Drug formulations used in the relevant clinical studies

Formulation	Material number	Clinical study(ies) that used the formulation	Important notes
A	(b) (4)	Phase 3 study 2007008, Phase 1 studies 2007120, 2008052, 2008119, and 2008138	Primary formulation used in Phase 3 study.
B		Small portion of Phase 3 study 2007008, Phase 1 study 2007027 (esomeprazole interaction)	Has same enteric coating as formulation A but a slightly different active core.
C		Phase 2 study 2005107	Has slightly different enteric coating and active core compared to formulation A. It has the same core as formulation B.
D		BE study 2008119	To-be-marketed formulation. Formulation D is identical to formulation A with the exception of no (b) (4) color. However, it is produced at a different manufacturing plant.

Table 17: Composition of formulation A (denoted as Phase III Clinical) and TBM formulation (denoted as Commercial)

Component	Unit Quantity (mg/tablet)		Function
	Phase III Clinical	Commercial	
(b) (4)			
Risedronate sodium	35.0 a	35.0 a	Active
ProSolv SMCC 90 b			(b) (4)
Edetate disodium, USP			
Sodium starch glycolate, NF			
Stearic acid, NF			
Magnesium stearate, NF			
(b) (4)			
(b) (4)			
Methacrylic acid copolymer			
(b) (4)			
Triethyl citrate, NF			
Talc, USP			
Ferric oxide, NF, yellow			
(b) (4)			
Simethicone, USP			
Polysorbate 80, NF			
(b) (4			
Total Tablet Weight	350.06	350.00	

a (b) (4)

b ProSolv SMCC 90 (b) (4)

(b) (4)

c (b) (4)

d (b) (4) Methacrylic Acid Copolymer (b) (4)

e (b) (4)

Table 18: Composition of formulations B and C

Dosage form	Formulation B	Formulation C
Ingredient	mg/tablet	mg/tablet
(b) (4) Risedronate sodium	35.0	35.0
ProSolv SMCC 90	(b) (4)	
Edetate disodium, USP		
Sodium starch glycolate, NF		
Stearic acid, NF		
Magnesium stearate, NF		
(b) (4)		
(b) (4)		
Methacrylic acid copolymer (b) (4)		
Triethyl citrate, NF		
Talc, USP		

Ferric oxide yellow, NF	(b) (4)	
(b) (4)		
Simethicone, USP		
Polysorbate 80, NF		
(b) (4)		
Typical total tablet weight	321 mg	319 mg

2.5.2 Is the to-be-marketed product identical to the phase 3 clinical trial product with respect to formulation, manufacturing process, and manufacturing site?

The Phase 3 study (study 2007008) administered 2 different risedronate DR 35 mg formulations, namely formulations A and B. Formulation A was used in the majority of patients. Formulation B was used in a small number of patients (n=91) for up to 16 weeks of the 1-year efficacy study. The Sponsor conducted sensitivity analysis by excluding these 91 patients from the ITT population, and indicated that similar lumbar spine BMD results were recorded with or without inclusion of these 91 patients. The sponsor also submitted data showing similar dissolution profiles for formulations A and B in pH 6.8, 0.05 M phosphate buffer at 10, 20, 30, and 45 minutes. The biopharmaceutics reviewer, Dr. Sandra Suarez, and the Chemistry, Manufacturing, and Controls reviewer, Dr. Caroline Strasinger, have determined that the difference between formulations A and B is considered minor and a bridging study is not needed (communicated via email on 4/20/2010).

The TBM formulation is identical to formulation A, except for the removal of a (b) (4) pigment that was used in the clinical tablet. The sourcing of the commercial tablet is from a manufacturing site that is different from the site at which the clinical formulation A was manufactured. Therefore, the Office of New Drug Quality Assessment recommended that a BE study be conducted to bridge the manufacturing changes.

The sponsor conducted BE study 2008119 to compare the bioavailability of the TBM formulation (test) to formulation A (reference). This was a 2-treatment, 2-period, single dose, crossover study under standard fasting conditions in healthy males and females (n=485 subjects were administered at least one treatment). The results from study 2008119 showed that the 90% CIs for test/reference ratio for risedronate C_{max} and AUCtlast were within the 80 – 125% BE limits (Table 19), indicating that the 2 formulations were BE under fasting conditions.

A fed BE study was not conducted. However, there was a small (about 30% decrease) effect of food on absorption of risedronate DR 35 mg tablets. In addition, the TBM formulation is identical in composition to the clinical trial formulation, except for a minor component (removal of (b) (4) pigment). Therefore, additional BE assessment under fed conditions was not requested.

Table 19: Results of BE analysis for risedronate from study 2008119 comparing formulation D (denoted as Commercial 35 mg DR) and formulation A (denoted as Phase III 35 mg DR)

PK Parameter	Phase III 35 mg DR (n=467) (95% CI)	Commercial 35 mg DR (n=471) (95% CI)	Commercial 35 mg DR/ Phase III 35 mg DR (90% CI)
Primary Parameters			
Cmax (ng/mL)	**14.094 (12.540, 15.839)**	**13.766 (12.251, 15.468)**	**0.977 (0.885, 1.079)**
AUCtlast (ng*h/mL)	**34.203 (30.289, 38.624)**	**34.248 (30.334, 38.666)**	**1.001 (0.904, 1.109)**
Secondary Parameters			
tmax (h)	2.983 (2.884, 3.085)	3.021 (2.921, 3.125)	1.013 (0.979, 1.049)
Ae (ug)	157.845 (140.349, 177.522)	162.671 (144.848, 182.687)	1.031 (0.933, 1.138)
A'e (%)	0.451 (0.401, 0.507)	0.465 (0.414, 0.522)	1.031 (0.933, 1.138)

Means are fitted geometric means from ANOVA model with fixed effects for treatment, treatment sequence, period, gender and study center.
Subject within treatment sequence is a random effect.
/RISEDRONATE/LIBERTAS/pk/2008119/ANAL/pkanal.sas; SAS 8.2 23JUN09 16:29 f09jun09 BQ7644.

2.5.3 Is the performance of risedronate DR 35 mg formulation likely to be affected by coadministration of alcohol?

The potential for dose-dumping due to alcohol coadministration was evaluated in vitro. Risedronate DR 35 mg tablets were tested with 20% ethanol in the acid and buffer phases during dissolution testing. Samples were obtained and the results compared to tablets tested without ethanol (control). The results for the acid phase showed no release of risedronate in either medium as the % risedronate dissolved for all tablets was (b) (4) For the buffer phase, there was an increase in dissolution of about (b) (4) at the early time point of 10 minutes with f2 testing applied to dissolution profiles showed a value less than 50. However, the average of percent risedronate dissolved at 30 minutes in buffer was similar between the two sets of tablets (n=12); (b) (4) for the control and (b) (4) for the tablets in 20% ethanol (Please see Biopharmaceutics review by Dr. Sandra Suarez for additional details).

The above results indicate that ethanol coadministration should not affect the delayed release property of risedronate DR in vivo. Since risedronate DR is not an extended release formulation and it has relatively rapid dissolution in the buffer stage ((b) (4) in 30 minutes), the increase in dissolution at 10 minutes in buffer is not considered clinically significant.

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess concentrations?

For all Phase 1 and 2 studies (i.e., studies 2004132, 2007120, 2008052, 2005107, 2007027, 2008076, 2008138, and 2008119), (b) (4) analyzed human urine specimens for concentrations of risedronate using a validated high performance liquid chromatography / tandem mass spectrometry method (HPLC/MS/MS method, Validation report 45034HAU). For the bioequivalence study (2008119), serum specimens were analyzed by (b) (4) for concentrations of risedronate using a validated HPLC/MS/MS (Validation report 77077QTP).

(b) (4)

(b) (4)

2.6.2 Were the bioanalytical methods adequately validated?

HPLC/MS/MS method for risedronic acid in human urine was validated in validation project number 45034HAU by (b) (4). The assay was initially validated for the range of 0.2 - 197.8 ng/mL, as reported on 8/16/2005. Subsequently, the assay range was extended to 0.2 - 302.4 ng/mL, as reported on 3/20/2008. The assay has within-run precision range of 1.49 – 7.28% and between-run precision of 1.64 – 11.46%. Accuracy ranged between 100.6 – 103.0%. Long-term storage stability at -20ºC was demonstrated for 511 days.

HPLC/MS/MS method for risedronic acid in human serum was validated in validation project number 77077QTP by (b) (4). The assay was validated for the range of 0.2 – 201.2 ng/mL, as reported on 4/21/2008. The assay has within-run precision range of 1.26 – 7.31% and between-run precision of 5.61 – 6.35%. Accuracy ranged between 102.3 – 104.3%. Long-term storage stability at -20ºC was demonstrated for 360 days.

Due to differences in the molecular weight for risedronic acid (molecular weight 283.11) and risedronate sodium (molecular weight 305.10), assay values (i.e., measured as risedronic acid) were multiplied by 1.078 (i.e., 305.10/283.11 = 1.078) to report concentrations in terms of risedronate sodium.

A Division of Scientific Investigation (DSI) consult was sent for inspection of the clinical study and bioanalytical sites for study 2008119. The results of the inspection have not yet been communicated to the review team.

3 Detailed Labeling Recommendations

The following labeling changes to sections 7 and 12 are recommended. Recommended changes to other sections will be communicated directly to the review team. Deletions are shown as ~~strikethrough~~ and additions are <u>double underlined</u>.

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4 Appendix

4.1 Individual study review

Review of study 2008119

Title of study: A Multi-center, Randomized, Double-blind, Two-treatment, Two-period, Two-sequence, Crossover Study to Assess the Bioequivalence of the Phase III and commercial Risedronate 35 mg Delayed-release Formulations in Healthy Male and Female Subjects.

Review note: The terms to-be-marketed (TBM) and commercial are used interchangeably in this study review and refer to formulation D or material number (b) (4) *The term Phase III formulation refers to the primary formulation used in Phase 3 study 2007008, namely formulation A or material number* (b) (4).

Objective: The objective of the study was to assess the BE between the to-be-marketed and the primary Phase 3 formulation (formulation A).

Design: This was a randomized, double-blind, 2-treatment, 2-period, 2-sequence, crossover study, with a 14- to 17-day washout period between treatment periods. Randomization was stratified by study center and sex. Each treatment was administered with at least 4 oz water. The 2 treatments were as follows:

- Treatment 1 (Reference Phase III clinical supply): one 35 mg DR tablet administered as a single oral dose after an overnight (10-hour) fast, followed by a 4-hour fast
- Treatment 2 (Test commercial tablets): one 35 mg DR tablet administered as a single oral dose after an overnight (10-hour) fast, followed by a 4-hour fast

During each period, subjects were admitted 1 day before administration of study drug and remained at the study center for 3 days following administration of study drug. Blood samples were collected for risedronate serum PK analysis during each treatment period at: 0 (pre-dose), 0.75, 1.5, 2.25, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 20, 24 and 30 hours after study drug administration. Urine was pooled for 12 hours pre-dose and 3 consecutive 24-hours periods starting at dosing (i.e., 0 to 24, 24 to 48, and 48 to 72 hours relative to dosing).

Number of subjects: 538 healthy male and female subjects 19 – 63 years of age were enrolled, of which 453 completed the study. Excluding 53 subjects enrolled at the Qualia Clinical Services (Qualia) site, which closed after dosing Period 1, 485 subjects received at least one treatment.

Test product: Risedronate 35 mg DR tablets; Material Number: (b) (4) (TBM formulation); Batch/Lot Number: 437373/08-000628; Batch Size (b) (4) tablets (actual).

Reference product: Risedronate 35 mg DR tablets; Material Number: (b) (4) (Phase III formulation); Batch/Lot Number: 07-000404/07-000404 Batch Size: (b) (4) tablets (actual).

Pharmacokinetics assessment: Serum concentration-time data was used to calculate AUCtlast, Cmax, and tmax. The cumulative Ae was assessed over 72 hours following administration of study drug and the percent of dose excreted in urine (A'e [%]) was estimated.

PK parameters were analyzed for subjects who had quantifiable levels of risedronate for at least 1 treatment period, except for subjects at the Qualia site. The 53 subjects at the Qualia site were only dosed in Period 1 and then the site closed.

An interim analysis, assessing only variability of PK parameters, for sample size re-estimation was planned and conducted after 169 subjects completed the study to determine the final sample size estimation. Based on the results of the interim analysis, the sample size was changed from 312 to 485 subjects.

Statistical Methods: Cmax and AUCtlast as well as Ae and A'e (%) (0-72 hours) were analyzed for subjects who had quantifiable levels of risedronate for at least 1 treatment period.
The 90% CIs were constructed for the ratios of least squares estimates of the PK parameters Cmax and AUCtlast obtained following administration of formulation D (Test) and formulation A (Reference). Bioequivalence of the Reference and Test tablets was to be concluded if the above 90% CIs for Cmax and AUCtlast fall within the interval of [0.80, 1.25].

If risedronate concentrations for a subject were not detectable in all 3 urine samples for a given treatment, the concentrations were set to ½ the lower limit of quantitation and the calculation of Ae and A'e (%) proceeded as usual. This procedure was specified to address the possibility of zero values for Ae and A'e (%), which would be problematic for using log transformation. Any subject with non-detectable risedronate levels in all samples for both treatments was not included in the BE analysis. An analogous procedure was used to calculate serum Cmax and AUCtlast in such cases, i.e., setting concentrations to ½ the lower limit of quantitation. Ae, A'e (%), Cmax, and AUCtlast were log transformed prior to the analysis. The linear statistical model for log-transformed parameters (Ae, A'e [%], Cmax, and AUCtlast) included treatment, treatment period, treatment sequence, gender, and study center as fixed effects. The subject nested within each treatment sequence was specified as a random effect. The CI of treatment difference (in log-scale) was constructed based on model fitted estimates.

Demographics: The mean age of the subjects was 40.2 years; 62% of the subjects were males and 38% were females. The mean age of the female subjects (47.0) was approximately 11 years older than the male subjects (36.0). The majority was Caucasian (82%) and of Hispanic or Latino origin (65%). Demographic stratified by sex for all enrolled subjects is shown in Table 1.

Table 1: Demographic and baseline characteristics be sex (intent to treat population)

Parameter Statistic/Category	Female (N=204)	Male (N=334)
Age		
n	204	334
Mean (SD)	47.1 (8.39)	35.3 (9.23)
Median	48	35
Min, Max	24.0, 63.0	19.0, 59.0
Race		
Indian (American)	1 (<1%)	2 (<1%)
Asian (Oriental)	0 (0%)	3 (<1%)
Black	21 (10%)	69 (21%)
Caucasian	179 (89%)	250 (75%)
Multi-Racial	1 (<1%)	8 (2%)
Hawaiian/Pacific Islander	0 (0%)	1 (<1%)
Ethnicity		
Hispanic or Latino	149 (73%)	169 (51%)
Not Hispanic or Latino	55 (27%)	165 (49%)
Baseline Weight (kg)		
n	204	334
Mean (SD)	68.9 (9.54)	80.6 (10.95)
Median	68	80
Min, Max	45.0, 97.4	57.0, 118.2
Baseline BMI		
n	204	334
Mean (SD)	26.8 (3.07)	26.4 (3.01)
Median	27	27
Min, Max	18.0, 32.0	19.0, 32.0
Creatinine Clearance		
n	204	334
Mean (SD)	118.2 (25.05)	129.9 (24.66)
Median	115	127
Min, Max	76.2, 217.1	66.3, 201.2

Subjects' disposition: Six subjects total (3 for each formulation) had non-detectable concentrations of risedronate; 4 subjects had non-detectable concentrations of risedronate in either their serum or urine and 2 subjects (1 for the Phase III tablet and 1 for the commercial tablet) had non-detectable concentrations of risedronate in both their serum and urine.

Pharmacokinetic Results:

Following single dose administration of the TBM formulation the mean (CV%) serum risedronate C_{max} and AUCtlast were 25.3 ng/mL (109.8%) and 63.5 ng*h/mL (106.5%), respectively. The median (range) T_{max} was 3 hours (0.75 – 12). The mean (CV%) Ae and Ae% for 72 hours post dose were 289.5 µg (109.6%) and 0.83% (109.6%), respectively (Tables 2 and 4).

Similar results were observed for the Phase III clinical formulation. Following single dose administration of the Phase III formulation the mean (CV%) serum risedronate C_{max} and AUCtlast were 25.6 ng/mL (115.7%) and 63.6 ng*h/mL (116.7%), respectively. The median (range) T_{max} was 3 hours (0.75 – 24).

The mean (CV%) Ae and Ae% for 72 hours post dose were -284.3 µg (108.5%) and 0.81% (108.5%), respectively (Tables 3 and 5).

The mean serum risedronate concentration-time profiles following single dose administration of either formulation are shown in figure 1. Measurable serum and urinary risedronate concentration were detected in all, except for 6 subjects. There was high variability in the exposure to risedronate between subjects within a formulation as well as between formulations within a subject.

Figure 1: Mean serum risedronate concentration-time profiles following administration of a single dose 35 mg delayed-release tablet.

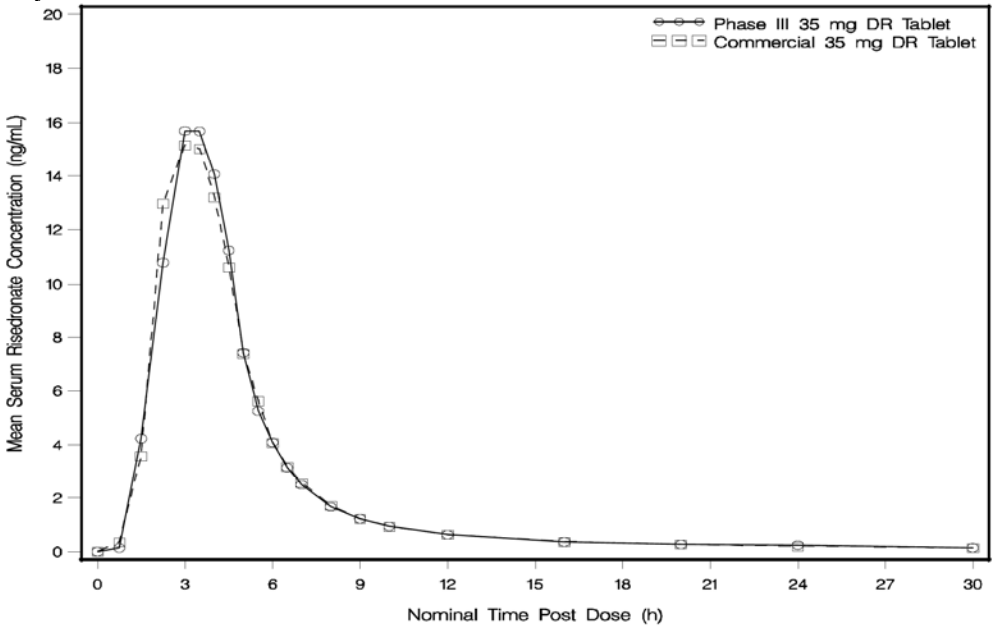


Table 2: Summary of risedronate serum PK parameters for subjects administered the <u>to-be-marketed formulation</u>. Results were reported for all and separated by sex.

Subject	C_{max} (ng/mL)	t_{max} (h)	$AUCt_{last}$ (ng•h/mL)
Overall			
N	468	468	468
Mean	25.3036	3.1974	63.488
CV%	109.8	33.3	106.5
Geometric Mean	14.1241	3.0231	34.991
CV% Geometric Mean	183.9	35.7	196.9
Median	15.6500	3.0000	42.990
Minimum	0.108	0.750	0.06
Maximum	203.000	12.117	554.93
Males			
N	290	290	290
Mean	21.6601	3.2524	54.893
CV%	109.2	34.8	102.7
Geometric Mean	12.2313	3.0705	30.453
CV% Geometric Mean	171.4	35.8	188.2
Median	13.1500	3.0000	35.680
Minimum	0.108	0.750	0.27
Maximum	139.000	12.117	283.37
Females			
N	178	178	178
Mean	31.2398	3.1079	77.492
CV%	104.5	30.5	104.5
Geometric Mean	17.8555	2.9474	43.879
CV% Geometric Mean	195.2	35.4	202.1
Median	21.7500	3.0000	52.905
Minimum	0.108	0.750	0.06
Maximum	203.000	5.500	554.93

C_{max} is the maximum serum analyte concentration; t_{max} is the time to maximum serum analyte concentration; and $AUCt_{last}$ is the area under the serum analyte concentration-time curve from time zero to the last quantifiable serum analyte concentration.

Subject listings for all parameters reported in Appendix 13.2.5.2, Tables 503-998.

Table 3: Summary of risedronate serum PK parameters for subjects administered the Phase III formulation. Results were reported for all and separated by sex.

Subject	C_{max} (ng/mL)	t_{max} (h)	$AUCt_{last}$ (ng•h/mL)
Overall			
N	464	464	464
Mean	25.6491	3.1776	63.573
CV%	115.7	44.1	116.7
Geometric Mean	14.5729	2.9875	35.230
CV% Geometric Mean	172.0	35.5	187.2
Median	16.2000	3.0000	40.040
Minimum	0.108	0.750	0.09
Maximum	236.000	24.000	644.52
Males			
N	285	285	285
Mean	23.4700	3.1520	56.599
CV%	125.3	34.3	122.3
Geometric Mean	13.3072	2.9825	31.685
CV% Geometric Mean	162.3	34.9	176.1
Median	13.5000	3.0000	35.350
Minimum	0.108	0.750	0.09
Maximum	236.000	12.000	611.10
Females			
N	179	179	179
Mean	29.1186	3.2183	74.678
CV%	102.5	55.9	107.7
Geometric Mean	16.8412	2.9956	41.711
CV% Geometric Mean	184.8	36.6	201.0
Median	19.9000	3.0000	51.780
Minimum	0.108	0.750	0.67
Maximum	211.000	24.000	644.52

C_{max} is the maximum serum analyte concentration; t_{max} is the time to maximum serum analyte concentration; and $AUCt_{last}$ is the area under the serum analyte concentration-time curve from time zero to the last quantifiable serum analyte concentration.

Subject listings for all parameters reported in Appendix 13.2.5.2, Tables 1-502.

Table 4: Summary of risedronate urinary recovery for subjects administered the to-be-marketed formulation. Results were reported for all and separated by sex.

	0 – 24 hours		24 – 48 hours		48 – 72 hours		0 – 72 hours	
Descriptive Statistic	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)
Overall								
N	468	468	468	468	465	465	468	468
Mean	260.4962	0.74428	17.8167	0.05090	11.2902	0.03226	289.5308	0.82723
CV%	111.5	111.5	99.8	99.8	108.3	108.3	109.6	109.6
Geometric Mean	144.6921	0.41349	11.0137	0.03147	7.2087	0.02060	164.9972	0.47145
CV% Geometric Mean	191.7	191.5	152.3	152.4	138.7	138.6	178.4	178.3
Median	168.3750	0.48105	12.8970	0.03685	7.6720	0.02190	191.2330	0.54635
Minimum	0.232	0.0007	0.000	0.0000	0.000	0.0000	0.621	0.0018
Maximum	2810.325	8.0295	130.750	0.3736	125.400	0.3583	3017.360	8.6210
Males								
N	289	289	289	289	286	286	289	289
Mean	239.8510	0.68529	16.4139	0.04690	10.3429	0.02955	266.5004	0.76143
CV%	108.4	108.4	98.9	98.9	102.7	102.7	106.6	106.6
Geometric Mean	133.8023	0.38234	10.1803	0.02908	6.7066	0.01918	152.3525	0.43531
CV% Geometric Mean	183.8	183.7	148.8	149.0	136.7	136.2	172.8	172.8
Median	149.9130	0.42830	11.4750	0.03280	7.0350	0.02010	166.6920	0.47630
Minimum	0.578	0.0017	0.000	0.0000	0.000	0.0000	1.494	0.0043
Maximum	1546.900	4.4197	96.140	0.2747	80.735	0.2307	1677.000	4.7914
Females								
N	179	179	179	179	179	179	179	179
Mean	293.8285	0.83951	20.0817	0.05738	12.8037	0.03658	326.7139	0.93347
CV%	113.0	113.0	99.0	99.0	111.9	111.9	110.8	110.8
Geometric Mean	164.1755	0.46922	12.5092	0.03575	8.0810	0.02308	187.6648	0.53626
CV% Geometric Mean	202.7	202.2	156.0	155.8	140.3	140.7	185.3	185.2
Median	208.5000	0.59570	13.7700	0.03930	8.6000	0.02460	230.2280	0.65780
Minimum	0.232	0.0007	0.000	0.0000	0.000	0.0000	0.621	0.0018
Maximum	2810.325	8.0295	130.750	0.3736	125.400	0.3583	3017.360	8.6210

A_e is the amount of drug excreted in urine over the stated time interval; and A'_e (%) is the amount of drug excreted in urine over the stated time interval, normalized for dose, and expressed as a percentage.

Data calculated using raw data contained in Appendix 13.2.5.2, Tables 1498-1993.

Table 5: Summary of risedronate urinary recovery for subjects administered the Phase III formulation. Results were reported for all and separated by sex.

Descriptive Statistic	0 – 24 hours		24 – 48 hours		48 – 72 hours		0 – 72 hours	
	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)	A_e (µg)	A'_e (%)
Overall								
N	451	451	451	451	447	447	451	451
Mean	255.0696	0.72877	18.1164	0.05176	11.2017	0.03201	284.2883	0.81225
CV%	109.8	109.8	113.0	113.0	101.5	101.5	108.5	108.5
Geometric Mean	142.2316	0.40635	11.3489	0.03242	7.4064	0.02117	162.9301	0.46553
CV% Geometric Mean	193.9	194.0	140.6	140.8	133.7	133.5	180.1	180.1
Median	171.1000	0.48890	12.2770	0.03510	7.8800	0.02250	193.7680	0.55360
Minimum	0.324	0.0009	0.000	0.0000	0.000	0.0000	0.718	0.0021
Maximum	2283.300	6.5237	192.675	0.5505	86.858	0.2482	2562.833	7.3224
Males								
N	271	271	271	271	268	268	271	271
Mean	235.9578	0.67417	16.3789	0.04680	10.1657	0.02905	262.3899	0.74968
CV%	108.2	108.2	110.9	110.9	107.3	107.3	107.6	107.6
Geometric Mean	131.7051	0.37626	10.3521	0.02957	6.6151	0.01891	150.3759	0.42967
CV% Geometric Mean	192.3	192.5	136.8	137.0	135.3	134.9	178.3	178.2
Median	158.5280	0.45290	10.9100	0.03120	7.1880	0.02050	174.8010	0.49940
Minimum	0.324	0.0009	0.000	0.0000	0.000	0.0000	0.718	0.0021
Maximum	1680.000	4.8000	123.950	0.3541	83.605	0.2389	1887.555	5.3930
Females								
N	180	180	180	180	179	179	180	180
Mean	283.8434	0.81099	20.7322	0.05924	12.7529	0.03644	317.2576	0.90645
CV%	110.0	110.0	112.6	112.6	93.2	93.2	108.0	108.0
Geometric Mean	159.6877	0.45627	13.0437	0.03727	8.7857	0.02510	183.8353	0.52523
CV% Geometric Mean	194.5	194.5	143.7	143.8	126.8	126.8	180.9	181.0
Median	191.4625	0.54700	14.2990	0.04085	9.4140	0.02690	220.9440	0.63130
Minimum	2.040	0.0058	0.000	0.0000	0.000	0.0000	2.040	0.0058
Maximum	2283.300	6.5237	192.675	0.5505	86.858	0.2482	2562.833	7.3224

A_e is the amount of drug excreted in urine over the stated time interval; and A'_e (%) is the amount of drug excreted in urine over the stated time interval, normalized for dose, and expressed as a percentage.

Data calculated using raw data contained in Appendix 13.2.5.2, Tables 999-1497.

Bioequivalence between the TBM and Phase III formulations:

The primary analysis for bioequivalence was based on serum risedronate C_{max} and AUCtlast. The results showed that the 90% CI for the C_{max} and AUCtlast ratios between the TBM formulation and the primary Phase III formulation was within the 0.80 – 1.25 range (Table 6). The mean (90% CI) ratios for C_{max} and AUCtlast were 0.977 (0.885, 1.079) and 1.001 (0.904, 1.109), respectively. Similar median T_{max} was observed for the 2 formulations. These data support that the TBM formulation is bioequivalent to the Phase III formulation A.

Table 6: BE analysis of PK parameters

PK Parameter	Phase III 35 mg DR (n=467) (95% CI)	Commercial 35 mg DR (n=471) (95% CI)	Commercial 35 mg DR/ Phase III 35 mg DR (90% CI)
Primary Parameters			
Cmax (ng/mL)	**14.094 (12.540, 15.839)**	**13.766 (12.251, 15.468)**	**0.977 (0.885, 1.079)**
AUCtlast (ng*h/mL)	**34.203 (30.289, 38.624)**	**34.248 (30.334, 38.666)**	**1.001 (0.904, 1.109)**
Secondary Parameters			
tmax (h)	2.983 (2.884, 3.085)	3.021 (2.921, 3.125)	1.013 (0.979, 1.049)
Ae (ug)	157.845 (140.349, 177.522)	162.671 (144.848, 182.687)	1.031 (0.933, 1.138)
A'e (%)	0.451 (0.401, 0.507)	0.465 (0.414, 0.522)	1.031 (0.933, 1.138)

Means are fitted geometric means from ANOVA model with fixed effects for treatment, treatment sequence, period, gender and study center.
Subject within treatment sequence is a random effect.
/RISEDRONATE/LIBERTAS/pk/2008119/ANAL/pkanal.sas; SAS 8.2 23JUN09 16:29 f09jun09 BQ7644.

PK analysis by sex:

Study 2008119 enrolled about 38% females and the data was used to assess the effect of sex on observed bioavailability. The analysis was performed for data from both formulations as well as for each formulation separately. Similar results (with slight differences) were observed for the 3 different analyses (Tables 7, 8, and 9). Since the formulations are considered bioequivalent and each subject received both

formulations in this study, the data from both formulations could be combined to assess the effect of gender on risedronate bioavailability. This larger dataset would offer the best statistical certainty of the estimates. The results of the combined dataset showed that the mean (90% CI) males to females ratios for C_{max}, AUC, and Ae were 0.825 (0.704, 0.968), 0.814 (0.689, 0.962), and 0.913 (0.778, 1.071), respectively. The mean ratio of T_{max} was 1.023.

Table 7: Analysis of PK parameters by sex for both treatments combined

PK Parameter	Males (n=298) (95% CI)	Females (n=184) (95% CI)	Males/Females (90% CI)
Cmax (ng/mL)	12.655 (11.278, 14.201)	15.331 (13.086, 17.961)	0.825 (0.704, 0.968)
tmax (h)	3.037 (2.945, 3.131)	2.968 (2.846, 3.095)	1.023 (0.981, 1.067)
AUCtlast (ng*h/mL)	30.883 (27.383, 34.829)	37.930 (32.153, 44.746)	0.814 (0.689, 0.962)
Ae (ug)	153.117 (136.222, 172.107)	167.694 (143.322, 196.212)	0.913 (0.778, 1.071)
A'e (%)	0.437 (0.389, 0.492)	0.479 (0.410, 0.561)	0.913 (0.778, 1.071)
Means are fitted geometric means from ANOVA model with fixed effects for treatment, treatment sequence, period, gender and study center. Subject within treatment sequence is a random effect. /RISEDRONATE/LIBERTAS/pk/2008119/ANAL/pkanal.sas; SAS 8.2 23JUN09 16:29 f09jun09 BQ7644.			

Table 8: Analysis of PK parameters by sex for to-be-marketed formulation

PK Parameter	Males (n=291) (95% CI)	Females (n=180) (95% CI)	Males/Females (90% CI)
Cmax (ng/mL)	12.148 (10.566, 13.967)	15.684 (12.940, 19.009)	0.775 (0.638, 0.940)
tmax (h)	3.085 (2.963, 3.212)	2.940 (2.781, 3.108)	1.049 (0.992, 1.110)
AUCtlast (ng*h/mL)	30.316 (26.215, 35.058)	38.916 (31.854, 47.543)	0.779 (0.637, 0.953)
Ae (ug)	154.572 (134.716, 177.355)	171.581 (142.315, 206.866)	0.901 (0.745, 1.089)
A'e (%)	0.442 (0.385, 0.507)	0.490 (0.407, 0.591)	0.901 (0.745, 1.089)
Means are fitted geometric means from ANOVA model with fixed effects for period, gender and study center. /RISEDRONATE/LIBERTAS/pk/2008119/ANAL/pkanal.sas; SAS 8.2 23JUN09 16:29 f09jun09 BQ7644.			

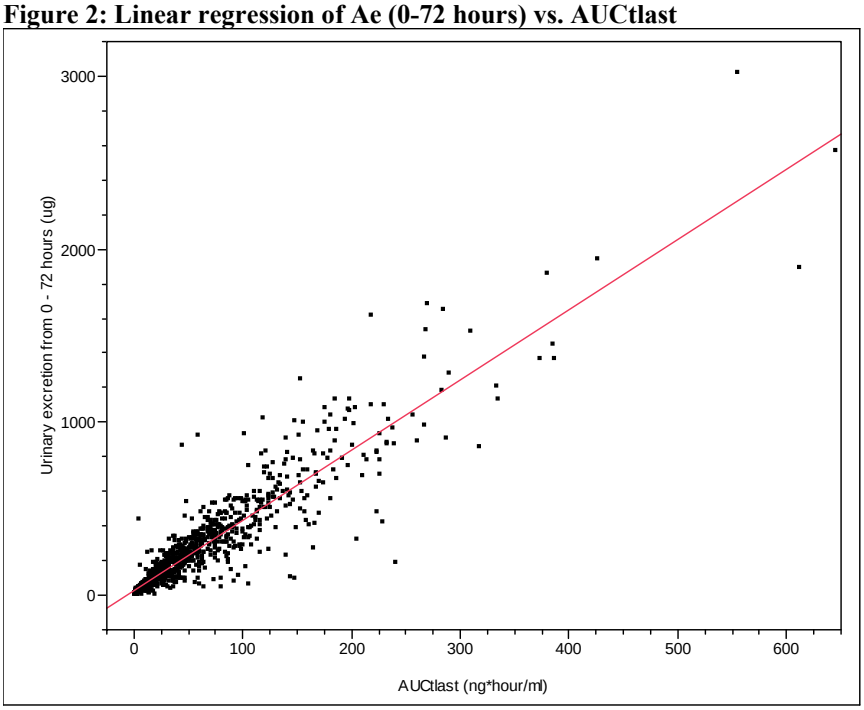
Table 9: Analysis of PK parameters by sex for Phase 3 clinical formulation

PK Parameter	Males (n=285) (95% CI)	Females (n=182) (95% CI)	Males/Females (90% CI)
Cmax (ng/mL)	13.051 (11.367, 14.983)	15.252 (12.629, 18.418)	0.856 (0.707, 1.035)
tmax (h)	2.991 (2.871, 3.116)	3.003 (2.839, 3.175)	0.996 (0.942, 1.054)
AUCtlast (ng*h/mL)	31.180 (26.998, 36.010)	37.641 (30.919, 45.824)	0.828 (0.679, 1.010)
Ae (ug)	150.111 (129.969, 173.374)	169.517 (140.170, 205.008)	0.886 (0.729, 1.075)
A'e (%)	0.429 (0.371, 0.495)	0.484 (0.400, 0.586)	0.886 (0.730, 1.075)
Means are fitted geometric means from ANOVA model with fixed effects for period, gender and study center. /RISEDRONATE/LIBERTAS/pk/2008119/ANAL/pkanal.sas; SAS 8.2 23JUN09 16:29 f09jun09 BQ7644.			

Correlation between risedronate urinary excretion and AUC:

The Sponsor has used Ae as an indirect measure of bioavailability for risedronate oral tablets. Since this study measured both Ae and serum AUC, a correlation analysis between Ae (measured for 72 hours post dose) and AUCtlast was performed. Data from both formulations and sexes were used. Figure 2 shows the linear regression. The fitted equation was Ae = 29.70 + 4.058 * AUCtlast. The results indicated that Ae and AUCtlast were highly correlated (r^2 = 0.845).

Figure 2: Linear regression of Ae (0-72 hours) vs. AUCtlast



4.2 Pharmacometrics Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 22,560
Submission Number (Date)	24 Sep 2009
Drug Name	Risedronate
Proposed Indication	• Treatment of postmenopausal osteoporosis [redacted] (b) (4)
Clinical Division	Division of Reproductive and Urologic Products
Primary CP Reviewer	Doanh Tran, Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Myong-Jin Kim, Pharm.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.
Sponsor	Warner Chilcott Pharmaceuticals, Inc.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does population PK/PD analysis support the 35 mg delayed-release (DR) weekly dosing regimen administered [redacted] (b) (4) after breakfast?

Yes. The final PK/PD analysis is generally acceptable based on the goodness of fits, known clearance pathway of risedronate, and good precision of parameter estimates (Table 1-Table 3). The population PK/PD model suggests:

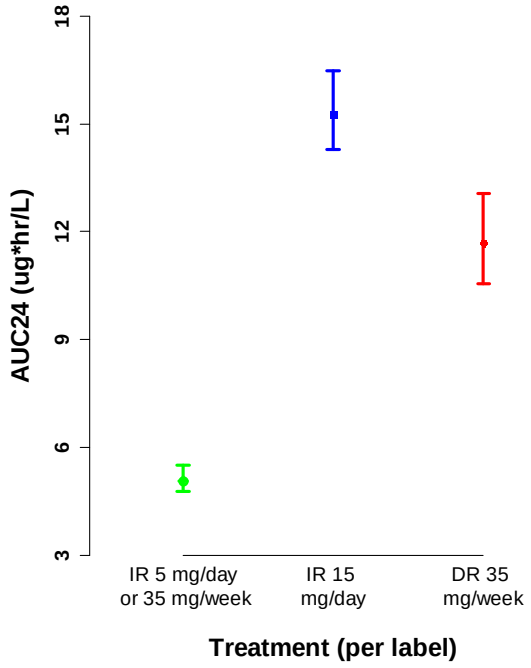
1. dose-proportionality of the DR formulation across the 20-100 mg dose range.
2. higher relative bioavailability (135% higher) of the DR formulation compared to the IR formulation if administered per label instructions (overnight fasted, 30-60 minutes before breakfast).
3. 38% reduction in bioavailability of the DR formulation upon concomitant administration of 40 mg esomeprazole.

The population PK analysis did not detect significant food effect on the bioavailability of the DR formulation across studies. Based on population PK/PD modeling and simulation, the 35 mg DR weekly dosing regimen administered [redacted] (b) (4) after breakfast is reasonable from clinical pharmacology perspective.

1. Efficacy: The efficacy of 35 mg DR weekly dosing regimen is well supported by the pivotal Phase 3 study (Study 2007008). The population PK/PD analysis supports the efficacy by matching exposures (AUC) and PD biomarker responses (measured as reduction in bone turnover markers [BTMs] from baseline) between DR and IR formulations. The 35 mg DR weekly dose results in similar or greater exposure and PD responses than the 5 mg/day or 35 mg/week IR dose and is more robust than 20 mg DR weekly dose especially under strict fasting conditions or in combination with esomeprazole. (b) (4) (b) (4) (b) (4) Therefore, we think the 35 mg DR weekly dosing regimen is reasonable based on the following safety discussion.

2. Safety: The drug exposure (based on AUC) after administration of 35 mg DR dose are higher than the 5 mg IR dose. However, the IR doses of 75 and 150 mg (given less frequently) result in higher C_{max} levels than that of the 35 mg DR dose. Moreover, 15 mg IR daily dose results in similar or greater average AUC_{24} than the 35 mg DR dose (Figure 1). Two-year, Phase III safety IR data of 150 mg OAM (Study 2005032 in women with PMO), 75 mg 2CDM (Study 2004012 in women with PMO), and 15 mg daily (Study 1998033 and Study 1998034 in women and men with knee osteoarthritis) were submitted. Therefore, exposures (Cmax and AUC) after 35 mg DR dosing regimen administered weekly before or after breakfast are reasonably similar or lower than other regimens or doses used clinically. At this time, medical reviewer (Dr. Stephen R Bienz) did not identify any major safety concerns that is likely to be dose limiting. The 35 mg DR dose administered weekly is reasonable.

Figure 1. Normalized average 24 hour AUC of risedronate at steady state simulated for 5 mg/day and 35 mg/week IR, 15 mg/day IR, and 35 mg/week DR when administered per label instructions (overnight fasted, 30-60 minutes before breakfast)



Points indicate the population means and the vertical bars are the 95% confidence intervals. Patient demographics in Study 2005032 were used for simulation. 300 trial replicates with 1000 subjects for each trial were simulated. The average AUC at steady state was calculated as $AUC_{24avg,ss} = \frac{Dose \bullet F}{\tau / 24 \bullet CL}$. The exposure of 15 mg IR daily dose was derived from the 5 mg IR daily dose assuming linear PK.

1.1.2 Is there a need to adjust dose of the 35 mg DR in renal impairment patients?

Risedronate is excreted unchanged primarily via the kidney. From the population PK model and previous studies, an approximately 2-3 fold elevation in risedronate systemic exposure is expected in patients with creatinine clearance of approximately 30 mL/min as compared to persons with normal renal function. Combined the 2-4 fold exposure elevation of DR formulation as compared to the IR formulation under per-label administration, a 4-12 fold exposure elevation in moderate renal impairment patients taking the 35 mg DR may be expected as compared to normal renal function patients taking the marketed 35 mg IR. In the current ACTONEL label and the proposed labeling text for the DR formulation, risedronate is not recommended for use in patients with severe renal impairment and no dosage adjustment is necessary in patients with mild and moderate renal impairment. However, the high exposure of risedronate of DR formulation in renal impairment patients raised a safety concern of applying 35 mg DR in the moderate renal impairment patients.

In the current Phase III DR study (Study 2007008) and previous 15 mg IR daily studies (Study 1998033 and Study 1998034 in women and men with knee osteoarthritis), 55 out of 615 patients and 12 out of 609 patients who had been exposed to the 35 mg DR weekly or 15 mg IR daily high exposure respectively had creatinine clearance ≤ 50 ml/min. At this time, no major safety problems were raised in these renal impairment patients. In Study 2007008, the clinical fracture incidence in patients with moderate renal impairment (3.64%) was not substantially different from patients without moderate impairment (3.04%).

1.2 Recommendations

The sponsor proposed 35 mg DR dosing regimen administered weekly (b) (4) after breakfast is acceptable from clinical pharmacology perspective.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 PERTINENT REGULATORY BACKGROUND

Risedronate sodium as an immediate-release formulation is currently approved by the FDA for postmenopausal osteoporosis (PMO) (5 mg/day, 35 mg/week, 75 mg/two consecutive days per month, 150 mg/month) and treatment to increase bone mass in men with osteoporosis (35 mg/week).

In this application, the sponsor submitted 7 Phase 1 studies, 1 Phase 2 study, and 1 Phase 3 non-inferiority efficacy and safety study to support the registration of the 35 mg delayed-release formulation of risedronate tablets administered weekly (b) (4) after breakfast for the treatment (b) (4) of PMO (b) (4) Additionally, the sponsor submitted 2-year safety data on unapproved higher doses from previous IR Phase III clinical studies to support the safety of the 35 mg DR formulation.

Population PK analysis was conducted to support the dose proportionality and to assess the effect of food and other intrinsic (e.g., sex) and extrinsic factors (e.g., co-medication of esomeprazole) on the exposure of risedronate DR across the doses tested (20, 35, 50, 75 and 100 mg). Population PK/PD modeling and simulation based on the bone turnover markers (BTM) was conducted to support the appropriateness of the 35 mg risedronate DR regimen.

3 RESULTS OF SPONSOR'S ANALYSIS

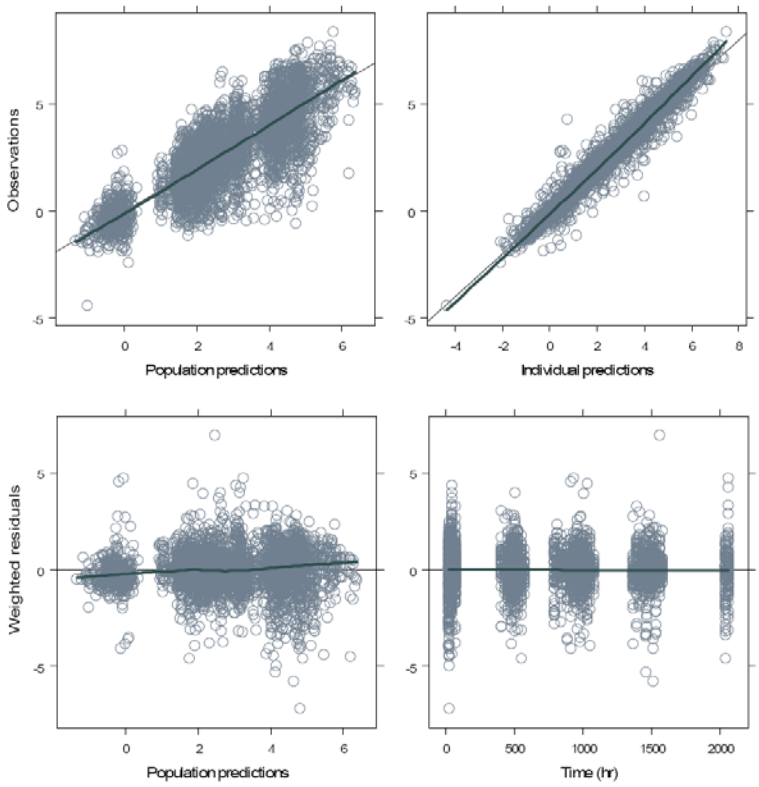
3.1 Population PK/PD analysis

Population PK analysis of the risedronate DR formulation was conducted on data obtained from six studies (five Phase I studies and one Phase II study) with a total of 478 subjects and 3830 observations. Only urine observations were available for the DR PK model. These studies examined single or multiple risedronate DR treatments with doses in the range of 20-100 mg.

- The population PK model of the DR formulation was built on the previous IR analysis (a three-compartment PK model with the first order process with a lag time in absorption and renal as well as non-renal clearance). The PK modeling of the DR formulation data focused on the absorption kinetics and bioavailability, and assumed that the distribution and elimination kinetics of the absorbed drug are independent of the formulation. Effects of the DR formulation on bioavailability, absorption rate and lag time were considered for the DR absorption model.
- The PK modeling was carried out using log-transformed observations. The additive error model adopted for the log-transformed observations corresponds to a multiplicative error model with log-normally distributed residuals for the non-transformed observations.
- Effects of food, dose and co-administration of esomeprazole on bioavailability and absorption lag were assessed by a forward inclusion and backward deletion algorithm. The statistical criteria were p=0.01 and p=0.001 for inclusion and deletion respectively. Co-medication of esomeprazole was found to reduce the bioavailability and a high-fat breakfast increased the lag time.

The goodness-of-fit plots for the final population PK model are displayed in Figure 2.

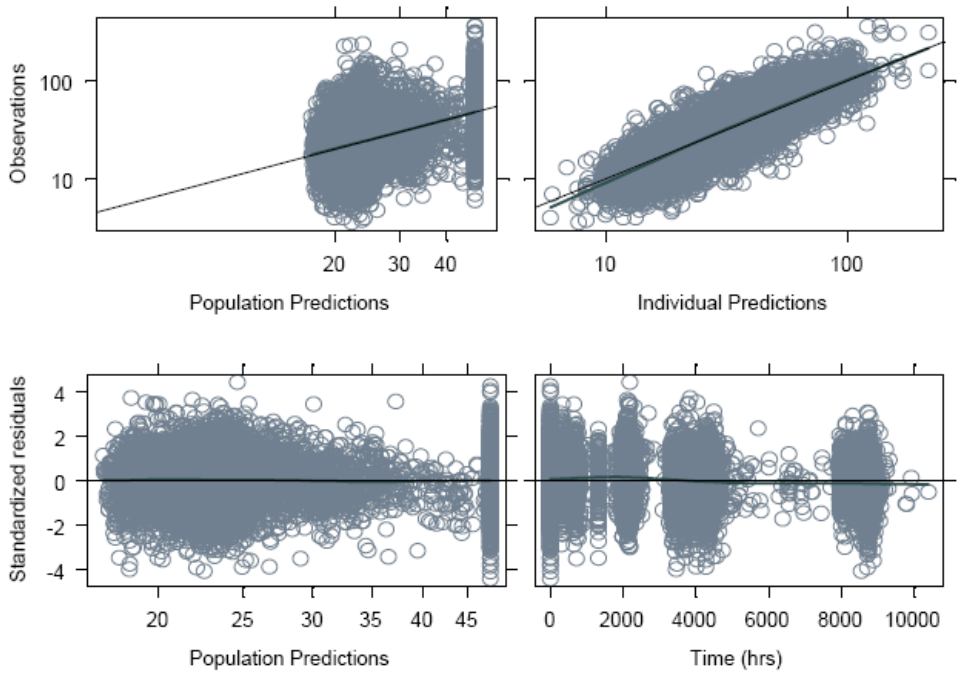
Figure 2. Goodness-of-fit plots for the final population pharmacokinetic model [line of unity (grey line) and trend line (black line)]



Source: Figure 8-9 Sponsor's Population PK Analysis Report: page 39

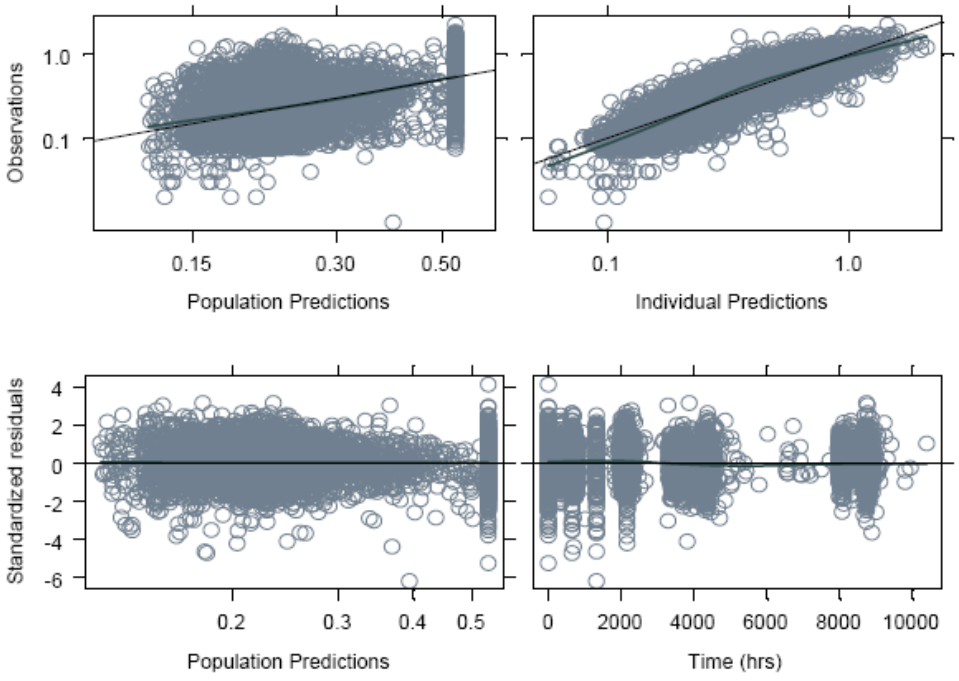
Pharmacodynamic data from 144 postmenopausal women in one DR Phase II study (2005107) were analyzed together with the three Phase III studies previously used in the IR analysis giving a total of 2066 subjects. Two bone turnover markers (BTMs) were studied in the PK/PD analysis: serum concentration of type 1 collagen crosslinked C-telopeptide (sCTX), and urine concentration of type 1 collagen cross-linked N-telopeptide (uNTX) giving a total of 16843 uNTX observations and 7781 sCTX observations. The effect site models for uNTX and sCTX with a proportional Emax-type response characteristic were based on the previous IR analysis (see appendix). The additive error model was adopted for the log-transformed observations. The goodness-of-fit plots for the final population PK/PD model are displayed in Figure 3 and Figure 4.

Figure 3. Goodness-of-fit plots for the final population uNTX model [line of unity (grey line) and trend line (black line)]



Source: Figure 15, Sponsor's Population PK Analysis Report: page 46

Figure 4. Goodness-of-fit plots for the final population sCTX model [line of unity (grey line) and trend line (black line)]



Source: Figure 20, Sponsor's Population PK Analysis Report: page 52

Reviewer's Comments:

The sponsor conducted a comprehensive population PK/PD analysis. The parameters of the final PK/PD model were estimated with good precision (Table 1-Table 3). From the goodness of fits plots and known clearance pathway of risedronate, the results and conclusions drawn from the analysis are generally acceptable.

1. *The DR formulation demonstrated dose-proportionality across the 20-100 mg dose range. The empirical analysis based on Phase 1 studies (see Clinical Pharmacology review) also supports dose proportionality.*
2. *Unlike the IR formulation, the population PK analysis did not detect significant food effect on the bioavailability of the DR formulation across studies; thus, administration of the risedronate DR formulation* (b) (4) *after breakfast will consequently have no effect on BTM reduction.*
3. *The relative bioavailability of the DR formulation is 135% higher compared to the IR formulation for per-label administration (overnight fasted, 30-60 minutes before breakfast).*
4. *The DR formulation was estimated to give 57% higher inter-dose variability magnitude giving it an approximate coefficient of variation of 116% compared to 74% for the IR formulation.*

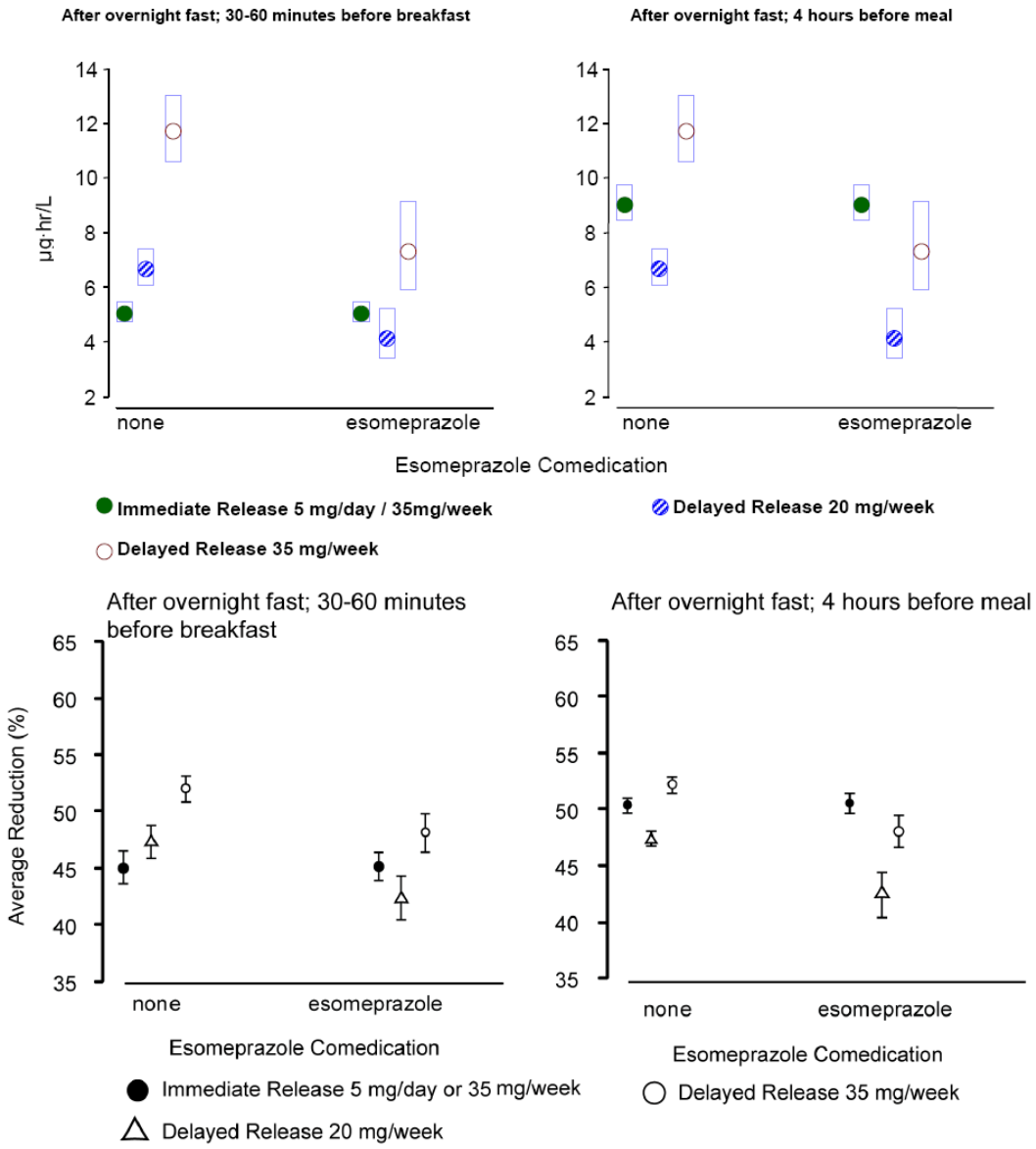
5. *Consistent with the delayed release characteristics, the DR formulation was found to have a longer delay (6.63 hrs) between administration of the dose and the onset of the absorption as compared to the IR model (0.15 hours). Administration of the DR formulation of risedronate after a high fat breakfast was estimated to increase the lag time further to 17.6 hours. These findings agree roughly with the time of complete disintegration of the DR tablets as shown by a scintigraphic study (2004132). Given the long time (3-4 months) needed to reach a steady state concentration at the effect sites, the impact of the longer lag time for the DR formulation is predicted to be minimal.*
6. *Concomitant medication with 40 mg esomeprazole was found to decrease the bioavailability of the DR formulation by 38%.*

3.2 Population PK analysis supports the 35 mg DR weekly dosing regimen administered before or after breakfast

In the population PK analysis focusing on the absorption kinetics, the 35 mg DR weekly dose was found to have 32% higher bioavailability as compared to the 35 mg IR weekly dose given after overnight fast and four hours before a meal. Unlike the IR formulation, the breakfast had no discernible effect on the absorption of risedronate in the DR formulation. For per-label administration, the 35 mg DR dose yields 135% higher exposure than the 35 mg IR dose. This is in line with the observations from study 2007120, where these differences were approximately 44% higher for the DR formulation compared to the IR formulation given after overnight fast and four hours before a meal and 120% higher for per-label administration, respectively.

Given the higher bioavailability of the DR formulation, a lower dose (20 mg/week) was evaluated pharmacokinetically and pharmacodynamically based on the simulation study. For per-label administration (overnight fasted, 30-60 minutes before breakfast) the 20 mg/week DR treatment is predicted to give an average steady state exposure that is comparable to the 5 mg/day and 35 mg/week IR treatments. However, given under the stricter fasting condition (overnight fasted, 4 hours before breakfast), the 20 mg/week DR simulation was not able to match the same levels of exposure as the IR treatments. Esomeprazole comedication is estimated to decrease the bioavailability by 38% for DR risedronate, but the uNTX reduction is predicted to decrease by much less for the two DR treatments (less than 10%). The 20 mg/week DR simulation with esomeprazole comedication had less exposure and reduction in the BTMs than 5 mg/day IR given under per-label food conditions (Figure 5).

Figure 5. Average 24 hour AUC (top) and uNTX reduction (bottom) of risedronate at steady state simulated for 5mg/day and 35mg/week IR and 20mg/week DR under per label administration (overnight fast – 30-60 minutes before breakfast) and fasted food conditions as well as with or without esomeprazole.



Points indicate the population expectations and the vertical bars the 95% confidence intervals.

Source: Figure 24 and 26, Sponsor's Population PK Analysis Report: page 57 and 59

Reviewer's comments:

1. *<u>Efficacy</u>: The efficacy of 35 mg DR weekly dosing regimen is well supported by the pivotal Phase 3 study (Study 2007008). The population PK/PD analysis supports the efficacy by matching exposures (AUC) and reduction in BTMs between DR and IR formulations. The 35 mg DR weekly dose results in similar or*

greater exposure and PD responses than the 5 mg/day or 35 mg/week IR dose and is more robust than 20 mg DR weekly dose especially under strict fasting conditions or in combination with esomeprazole. The data supports the proposed dosing regimen of 35 mg weekly DR formulation (b) (4) [redacted] *Therefore, we think the 35 mg DR weekly dosing regimen is reasonable based on the following safety discussion.*

2. *<u>Safety</u>: According to the population PK model and the simulation results, IR doses of 75 and 150 mg result in great C_{max} levels than the 35 mg DR dose. Moreover, 15 mg IR daily dose results in similar or greater AUC_{24} than the 35 mg DR dose (Figure 1). Two-year, Phase III safety IR data of 150 mg OAM (Study 2005032 in women with PMO), 75 mg 2CDM (Study 2004012 in women with PMO), and 15 mg daily (Study 1998033 and Study 1998034 in women and men with knee osteoarthritis) were submitted. Therefore, exposures (Cmax and AUC) after 35 mg DR dosing regimen administered weekly before or after breakfast are reasonably similar or lower than other regimens or doses used clinically. At this time, medical reviewer (Dr. Stephen R Bienz) did not identify any major safety concerns that could be dose limiting. The 35 mg DR dose administered weekly is reasonable.*

4 LISTING OF ANALYSES DATA SETS, CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews**
run24.mod	PPK analysis (final model)	\Risedronate_NDA22560_JL\PPK Analyses\Final Model
nmDR.csv	NONMEM dataset	\Risedronate_NDA22560_JL\PPK Analyses\Final Model
DRPK24.R	PPK diagnostic plot	Risedronate_NDA22560_JL\PPK Analyses\PPKplot

5 APPENDIX

The non-linear mixed effect PD model for the uNTX and sCTX responses

$$\log(BTM_{ij}) = \log(F_{ij}) + \varepsilon_{ij},$$

$$F_{ij} = BL_i \left[1 - Fmax_i \left(\frac{Ce_{ij}}{Ce_{ij} + EC_{50,i}} \right) \right],$$

$$BL_i = BL \; e^{\eta_{1i}},$$

$$Fmax_i = Fmax \; e^{\eta_{2i}},$$

$$EC_{50,i} = EC_{50} \; e^{\eta_{3i}},$$

where

BTM_{ij} is the j^{th} observation of uNTX or sCTX in the i^{th} subject

BL is the baseline BTM level,

F max is the maximum fractional BTM reduction,

EC_{50} is the concentration at which half of the maximum effect is achieved

Ce_{ij} is the effect compartment concentration,

$\eta \sim MVN(0, \Omega)$,

$\varepsilon_{ij} \sim N(0, \sigma^2)$,

$i = i^{th}$ subject,

$j = j^{th}$ observation.

Table 1. Parameter estimates for the Final PPK model

Parameter	Symbol	Estimate	RSE (%)
Structural Model Fixed Effects			
IR bioavailability (dimensionless)	F	0.0063	N/A
DR bioavailability (fractional increase rel. to IR F)	$\Theta_{F, DR}$	1.35	7.7
Renal clearance fraction (dimensionless)	Fr	0.756	N/A
Central clearance	Clc	6.72	N/A
Central volume of distribution (L)	Vc	27.5	N/A
Intercompartmental clearance I	Qc2	3.23	N/A
Peripheral volume of distribution I (L)	V2	62.6	N/A
Intercompartmental clearance II	Qc3	4.43	N/A
Peripheral volume of distribution II (L)	V3	1370	N/A
Absorption rate (1/hr)	Ka	4.16	N/A
IR Absorption time lag (hr)	IR.ALAG	0.152	N/A
DR absorption time lag (hr)	DR. ALAG	6.63	13.7
Covariate Effects			
Absorption time lag for DR.FOOD5	DR.ALAG5	1.66	22.2
Effect of DR.ESO on F	$\Theta_{F, DR.ESO}$	-0.376	18.2
Effect of IR DOSE ≥ 100 mg on F	$\Theta_{F, IR.DOSE}$	1.24	N/A
Effect of IR WH1 on F	$\Theta_{F, IR.WH.1}$	0.23	N/A
Effect of IR WH3 on F	$\Theta_{F, IR.WH.3}$	-0.17	N/A
Effect of IR WH4 on F	$\Theta_{F, IR.WH.4}$	-0.48	N/A
Effect of IR FOOD1 on F	$\Theta_{F, IR.FOOD.1}$	-0.14	N/A
Effect of IR FOOD3 on F	$\Theta_{F, IR.FOOD.3}$	0.78	N/A
Effect of CCL on Clc	$\Theta_{Cl, CCL}$	0.579	N/A
Effect of BMI on Clc	$\Theta_{Cl, BMI}$	-0.968	N/A
Effect of AGE on Clc	$\Theta_{Cl, Age}$	-0.44	N/A
Effect of WT on Clc	$\Theta_{Cl, Weight}$	0.45	N/A
Effect of WT on Vc	$\Theta_{V, Weight}$	1.28	N/A
Effect of BMI on Vc	$\Theta_{V, BMI}$	-1.13	N/A
Effect of SEX on Vc	$\Theta_{V, SEX}$	0.228	N/A
Effect of IR formulation on Inter-dose variability magnitude (log-scale)	$\Theta_{IDV,IR}$	-0.454[7]	19.7
Effect of overnight fasting on Inter-dose variability magnitude (log-scale)	$\Theta_{IDV,DR.FOOD23}$	-0.291[8]	25.8
Box-Cox shape parameter for inter-individual and inter-dose variability	λ	-0.23	14.2
Inter-individual Random Effects (given as variances)			
var(F)	ω_F	0.272	20.6
var(Cl_c)	Ω_{Cl}	0.0651	N/A
var(V_c)	Ω_V	0.114	N/A
Intra-Subject Inter-Dose Random Effects (given as variances)			
var(F)	π_F	1.36	8.0
Intra-Subject Inter-observation Random Effects (Residual Error - given as variances)			
Residual for urine compartment	ε_u	0.483	3.9

Source: Sponsor's Population PK Analysis Report: page 38

Table 2. Parameter estimates for the Final uNTX model

Parameter	Symbol	Estimate	Confidence Interval (95%)
Structural Model Fixed Effects			
Transition coefficient (1/hr)	Keo	0.00411	N/A
PD lag time (hr)	pdLag	23.6	N/A
Baseline uNTX (mmol BCE/nmol Creat)	BL	47.8	46.9 - 48.7
Max. fractional reduction (dimensionless)	Fmax	0.644	0.63 - 0.657
Concentration at half-maximal PD effect (ng/mL)	EC50	0.0578	0.0517 - 0.0647
Inter-individual Random Effects (given as standard deviation)			
sd(BL)	ω_{bl}	0.377	0.364 - 0.391
Intra-Subject Random Effects (given as standard deviation)			
Log of proportional error	log(σ)	0.342	0.338 - 0.346

Source: Sponsor's Population PK Analysis Report: page 48

Table 3. Parameter estimates for the Final sCTX model

Parameter	Symbol	Estimate	Confidence Interval (95%)
Structural Model Fixed Effects			
Transition coefficient (1/hr)	Keo	0.00394	N/A
PD lag time (hr)	pdLag	2.05	N/A
Baseline sCTX (ng/mL)	BL	0.533	0.518 - 0.547
Max. fractional reduction (dimensionless)	Fmax	0.783	0.765 - 0.801
Concentration at half-maximal PD effect (ng/mL)	EC50	0.0793	0.0711 - 0.0883
Inter-individual Random Effects (given as standard deviation)			
sd(BL)	ω_{bl}	0.461	0.443 - 0.479
Intra-Subject Random Effects (given as standard deviation)			
Log of proportional error	log(σ)	0.367	0.36 - 0.373

Source: Sponsor's Population PK Analysis Report: page 51

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22560	ORIG-1	WARNER CHILCOTT CO LLC	(b) (4)

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/s/

DOANH C TRAN
06/15/2010

JIANG LIU
06/15/2010

PRAVIN R JADHAV
06/15/2010

MYONG JIN KIM
06/15/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-560	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Procter & Gamble	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	(b) (4)	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Risedronate Sodium	**Date Assigned:**	Oct 26, 2009
Indication:	Osteoporosis	**Date of Review:**	March 26, 2010
Formulation	Delayed Released Tablets, 35 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Sep 24, 2009, Feb 25, 2010	Sep 24, 2009	Oct 26, 2009	July 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications		

REVIEW SUMMARY:

Risedronate sodium as an immediate-release formulation is currently approved for postmenopausal osteoporosis (PMO) (5 mg/day, 35 mg/week, 75 mg/two consecutive days per month, 150 mg/month), and other related bone disorders. The present submission seeks approval of the use of a novel 35 mg delayed-release formulation of risedronate sodium administered once-a-week for treatment (b) (4) of postmenopausal osteoporosis (b) (4) This new formulation was intended to minimize the impact of food and polyvalent cations on risedronate absorption, (b) (4) .

The development program for this new product consists of two Phase 3 clinical trials in postmenopausal women, together with a comprehensive pharmacokinetic data in men and women with the IR and DR products.

The risedronate sodium DR tablet was designed to protect the drug from release in stomach and allow release in the small intestine. Therefore, according to the sponsor, a physiologically relevant "two stage dissolution method" has been proposed for this product as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling Times (min)	Specification (Q)
Delayed release tablet	(b) (4)					

Risedronate 35 mg DR tablets for commercial use are planned to be manufactured at a different site from that at which the risedronate 35 mg DR clinical supply for the Phase III study was manufactured. In support of this change, the sponsor included the results of an in vivo BE study and dissolution profiles comparisons. The BE study is being reviewed by OCP. According to the sponsor, the formulations were bioequivalent. F2 similarity values were higher than 50. This indicates no significant difference in the in vitro/in vivo performance of the commercial scale and clinical formulation of risedronate 35 mg DR tablets.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 22-560(000) submitted on Sep 24, 2009. We found this NDA acceptable from biopharmaceutics perspective. The following comment should be conveyed to the sponsor:

1. The following dissolution specifications are recommended based on the mean dissolution values from clinical drug product release, clinical drug product pivotal stability, and commercial scale drug product release batches:

   - **Acid Stage:** No individual tablet exceeds (b) (4) dissolved at (b) (4) hours.
   - **Buffer Stage**: Not less than (b) (4) (Q) of the label amount of risedronate sodium is dissolved at (b) (4) minutes.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-560, JDavid, ADorantes, Dchristner, CStrasinger

INTRODUCTION
The Sponsor currently markets risedronate as an IR formulation. For PMO, risedronate 5 mg IR daily, 35 mg IR once a week, and 75 mg IR on 2 consecutive days per month regimens are currently approved by FDA, the European national agencies via the Mutual Recognition Procedure (MRP), and Health Canada; risedronate 150 mg IR once a month has also been approved by the FDA and Health Canada. For men with osteoporosis, risedronate 35 mg IR once a week is currently approved by the FDA, the European national agencies via the MRP, and Health Canada.

The present submission seeks approval of the use of a novel 35 mg delayed-release formulation of risedronate sodium administered once-a-week for treatment (b) (4) of postmenopausal osteoporosis (b) (4) This new formulation was intended to minimize the impact of food (b) (4)

This review of this NDA will focus on the acceptability of the proposed dissolution method and specifications.

CHEMISTRY

Formulation

The drug product is a yellow, oval-shaped, enteric coated tablet containing 35 mg of risedronate sodium on an anhydrous basis which is equivalent to 32.48 mg of risedronic acid. The tablet is engraved with "EC 35" on one side only. Tablets are packaged in blisters. According to the sponsor, the drug delivery concept of DR risedronate formulation was to separate the dosage form from the co-administered food, then bind free calcium from the co-administered meal with the use of a competitive chelating agent. Each weekly DR tablet contains 35 mg of risedronate sodium and (b) (4) of EDTA, and is enteric coated with a (b) (4) coating (b) (4) This enteric coating is resistant to gastric juice but dissolves readily above pH 5.5, protecting the tablet from releasing drug in the stomach and allowing release of the tablet contents in the small intestine.

The sponsor states that the core tablet formulation is identical between the Phase III clinical and commercial scales; except for the removal of (b) (4) from the coating (b) (4) the Phase III clinical and commercial coating formulations are the same. The components and composition of the product are summarized in Table 1.

Table 1. Components and composition for Risedronate Delayed Release tablets, 35 mg

Component	Unit Quantity (mg/tablet)		Function
	Phase III Clinical	Commercial	
(b) (4)			
Risedronate sodium	35.0 [a]	35.0 [a]	Active
ProSolv SMCC 90 [b]			(b) (4)
Edetate disodium, USP			
Sodium starch glycolate, NF			
Stearic acid, NF			
Magnesium stearate, NF			
(b) (4)			
(b) (4)			
Methacrylic acid copolymer			
(b) (4)			
Triethyl citrate, NF			
Talc, USP			
Ferric oxide, NF, yellow			
(b) (4)			
Simethicone, USP			
Polysorbate 80, NF			
(b) (4)			
Total Tablet Weight	350.06	350.00	

(b) (4)

b: ProSolv SMCC 90 (b) (4)
.
c: (b) (4)
d: (b) (4) (Methacrylic Acid Copolymer (b) (4)
(b) (4)

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS

DISSOLUTION METHOD

The risedronate sodium DR tablet was designed to protect the drug from release in stomach and allow release in the small intestine. Therefore, according to the sponsor, a physiologically relevant "two stage dissolution method" has been proposed for this product as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Sampling Times (min)
Delayed release tablet	(b) (4)				

Dissolution Robustness Testing

A dissolution study was conducted to simulate the effect of prolonged gastric retention on drug release since a potential concern with enteric-coated dosage forms is that drug will release in the stomach after prolonged gastric retention. For this purpose, tablets were placed separately in the dissolution vessel (USP, apparatus 2) for 16 hours at pH 1.2, 3, 4, and 5 and then transferred to a pH 6.8 medium; the amount of drug dissolved was analyzed by UV. For each pH, 12 tablets were analyzed. Figure 1 shows the mean dissolution in the pH 6.8 buffer after prolonged exposure for 16 hours at the various pHs. According to the sponsor, in 0.1 N HCl, no risedronate sodium was released over the 16-hour period.

Analytical Method Validation

The current dissolution procedure (b) (4) was implemented in March 2007. The following summarizes the results of the method validation:

Precision

Repeatability

An estimated precision of 1.2% (1σ) was determined over a range of 4.4-20.0% theory (1.5-7 mg risedronate sodium/tablet) for the acid stage and an estimated precision of 1.6% (1σ) was determined over a range of 17.4-120.0% theory (6-42 mg risedronate sodium/tablet) for the buffer stage.

Instrument Precision

One acid recovery sample (4.4%) and three buffer recovery samples (4.4%, 43.1%, and 87.0% nominal concentration) were each read ten times. Absorbance values were assessed to determine instrument precision. The RSD values ranged from .1% to 0.5%.

Linearity

Acid Stage

Seven solutions of risedronate sodium were prepared at concentrations ranging from 3.2-30.4 µg/mL representing 4.6-43.4% of the nominal concentration. The linear regression

analysis of the corrected absorbance (y) versus % nominal risedronate sodium concentration (x) gave an r square value of 0.99996.

Buffer Stage
Five solutions of risedronate sodium were prepared at concentrations ranging from about 3.5-84 µg/mL representing 5-120% of the nominal concentration. The linear regression analysis of the corrected absorbance (y) versus % nominal risedronate sodium concentration (x) gave an r square value of 0.99962.

Specificity
The excipient components do not interfere with quantitation for the dissolution procedure.

Lower Limit of Quantitation
For the 0.1 N hydrochloric acid stage of the test, the lowest value for which both linearity and precision have been demonstrated is 4.6% of the nominal risedronate sodium concentration (0.07 mg/mL).

Robustness
The following parameters were varied and found not to have an effect:

- Buffer concentration within ± 10% of target (0.05 M).
- Measurement wavelength within ± 2 nm of target (263 nm).
- Age of the buffer media up to 14 days.

Buffer pH was determined to be a critical parameter. If this parameter varies from the indicated value, uncharacteristic results may be obtained. In general, the following effect has been observed:

- Decreasing pH causes slower dissolution.

Solution Stability
The standard solutions were observed to be stable for at least 7 days.

Reviewer's Comments
The sponsor provided enough information to support the validity of the analytical method for determining dissolution.

SPONSOR'S PROPOSED DISSOLUTION SPECIFICATIONS
The proposed dissolution specifications for sodium delayed-release tablets, 35 mg is as follows:

(b) (4)

Buffer Stage: Not less than (b) (4)(Q) of the label amount of risedronate sodium is dissolved at (b) (4) minutes. Meets USP <711> acceptance table for delayed-release dosage forms.

Dissolution data were also drawn from the following sources for use in assessing an appropriate specification:

- Clinical drug product release test data (Tables 2 and 2a)
- Clinical drug product pivotal stability data (Tables 3 and 3a)
- Commercial scale drug product release test data (Tables 4 and 4a)

Descriptions of relevant batches used in clinical and stability studies are provided in the table below.

(b) (4)

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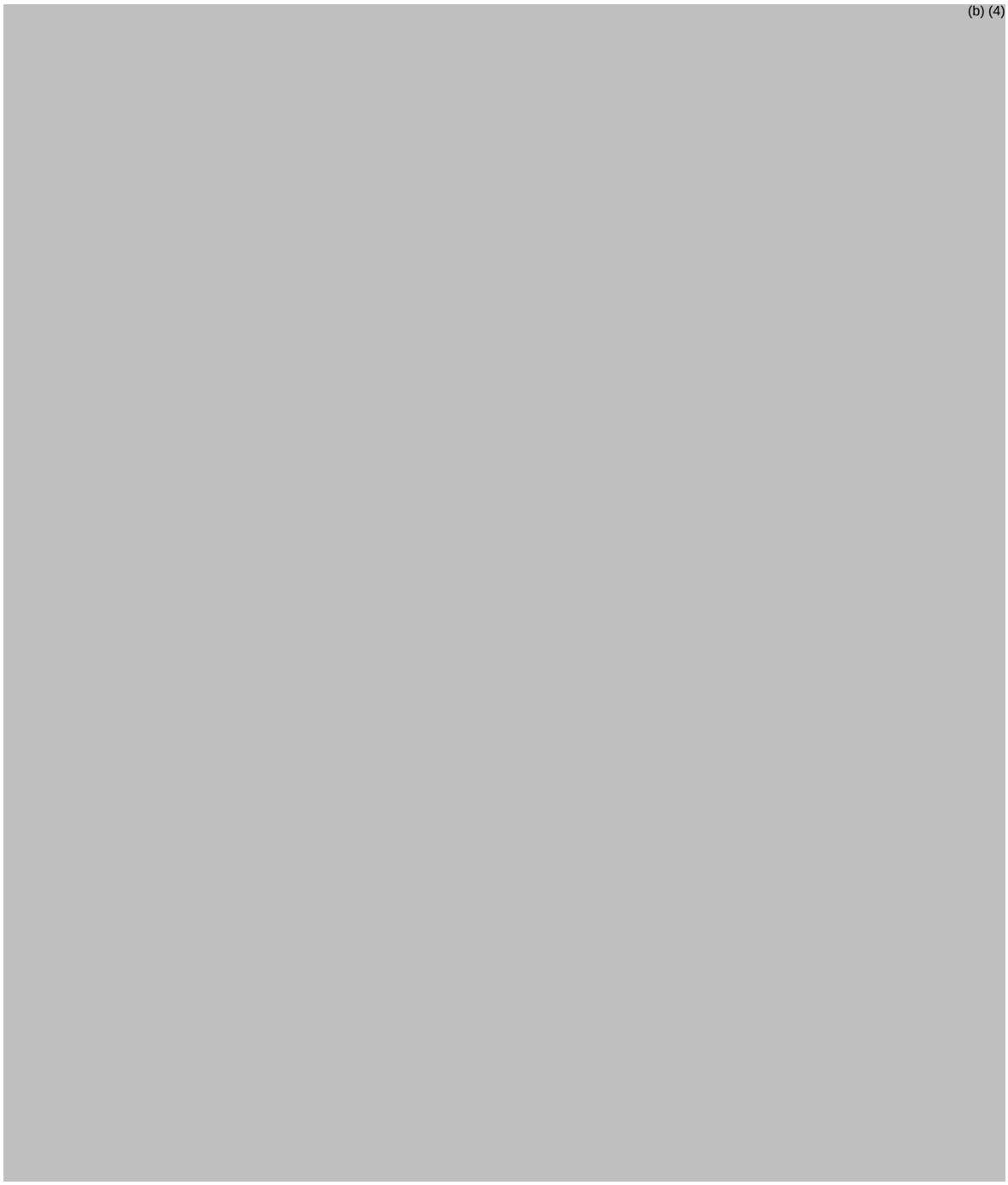

Reviewer's Comments
The following dissolution specifications are recommended based on the mean dissolution values shown in Tables 2 to 4 above:

Acid Stage: No individual tablet exceeds (b) (4) dissolved at (b) (4) hours. Meets USP <711> acceptance table for delayed-release dosage forms.

Buffer Stage: Not less than (b) (4) (Q) of the label amount of risedronate sodium is dissolved at (b) (4) minutes.

Commercial vs. Phase 3 Formulation Studies

A dissolution study was included comparing clinical and commercial scale risedronate 35 mg DR tablets. Dissolution time profiles were generated for one clinical batch and one commercial scale batch. For each batch, a multi-point dissolution profile was generated using the proposed dissolution method with buffer stage samples taken at 10, 15, 20, 25, 30, and 45 minutes. All method parameters were the same as the proposed dissolution procedure (b) (4) . Twenty-four tablets from each batch were tested. f2 similarity values were higher than 50. In addition, a BE study was conducted to determine similar in vivo performance of the two formulations. The studied is being reviewed by OCP. According to the sponsor, the formulations were bioequivalent. This indicates no significant difference in the in vitro/in vivo performance of the commercial scale and clinical formulation of risedronate 35 mg DR tablets.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22560	ORIG-1	WARNER CHILCOTT CO LLC	(b) (4)

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/s/

SANDRA SUAREZ
04/12/2010

PATRICK J MARROUM
04/12/2010

NDA/BLA Number: 22-560 **Applicant: Procter & Gamble Pharmaceuticals, Inc.** **Stamp Date: 9/24/2009**

Drug Name: Risedronate sodium delayed-release tablets **NDA/BLA Type: Original**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x		
2	Has the applicant provided metabolism and drug-drug interaction information?	x		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	x		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			N/A
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	x		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A
11	Is the appropriate pharmacokinetic information submitted?	x		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x		
	General			

13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	x		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	x		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x		
17	Was the translation from another language important or needed for publication?			N/A

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please see Comments for Sponsor section of at the end of the filing memo.

Doanh Tran, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Myong Jin Kim, Pharm.D.

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-560**	**Brand Name**	(b) (4)
OCP Division	**DCP3**	**Generic Name**	**Risedronate sodium**
Medical Division	**DRUP**	**Drug Class**	**Bisphosphonate**
OCP Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Indication(s)**	• **Treatment of postmenopausal osteoporosis** (b) (4)
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Delayed-release tablet**
		Dosing Regimen	**One tablet orally once a week**
Date of Submission	**9/24/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**5/10/2010**	**Sponsor**	**Procter & Gamble Pharmaceuticals, Inc.**
PDUFA Due Date	**7/24/2010**	**Priority Classification**	**Standard**
Division Due Date	**5/17/2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:	x	7		2004132, 2007120, 2008052, 2008119, 2008138, 2003066, 2004035
multiple dose:	x	1		2000009 (PK of 15 mg IR formulation)
Patients-				
single dose:				
multiple dose:	x			2005107
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		2007027
In-vivo effects of primary drug:				
In-vitro:	x	3		Cations, EDTA, alcohol
Subpopulation studies -				
ethnicity:				
gender:	x			2008119

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	1		2005107
Phase 3:	x	1		2007008
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	x			
Data rich:				
Data sparse:	x	2		Section 5.3.3.5 for IR and DR formulations
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		2008076
Bioequivalence studies -				
traditional design; single / multi dose:	x			2008119
replicate design; single / multi dose:				
Food-drug interaction studies:	x			2007120, 2008052, 2008138
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		17		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	x	Comments will be sent with Day 74 letter.
QBR questions (key issues to be considered)	**1. What is the relative exposure between 35 mg DR formulation, 35 mg IR formulation, and 20 mg DR formulation?** **2. Does the use of urinary excretion data alone (as was used in all PK studies other than the BE study) adequately describes the pharmacokinetics of risedronate DR and permits the assessment of food effects, effect of proton pump inhibitor, etc.?** **3. Is the instruction to take risedronate DR with at least 4 oz. of water (instead of 6 – 8 oz) appropriate?** **4. Is the instruction to take risedronate DR in the morning with or without food appropriate?** **5. Is the Phase 3 clinical product bioequivalent to the to-be-marketed product?** **6. How is the 2nd formulation (formulation (b) (4)) used in Phase 3 study 2007008 bridged to the to-be-marketed product? If it was not bridged, how the data from subjects using that formulation should be treated?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 22-560
Compound: **Risedronate sodium delayed-release tablets** (b) (4)
Sponsor: **Procter & Gamble Pharmaceuticals, Inc.**

Date: **10/15/2009**
Reviewer: Doanh Tran

Background: Risedronate is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. The sponsor currently markets risedronate as an immediate release (IR) formulation under the trade name Actonel. Actonel is available at tablet strengths of 5, 30, 35, 75, and 150 mg. Actonel is approved for the following indications: 1) treatment and prevention of postmenopausal osteoporosis, 2) treatment to increase bone mass in men with osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis, and treatment of Paget's disease.

The sponsor has developed an enteric coated risedronate 35 mg delayed release (DR) tablet with a pH trigger of 5.5 and contains (b) (4) of edetate disodium dihydrate (EDTA) for once weekly oral administration. The sponsor is seeking the following indications:

- Treatment of postmenopausal osteoporosis (PMO)

(b) (4)

The indication of treatment of PMO is supported directly by a Phase 3 non-inferiority study. (b) (4)

The NDA is primarily supported by 9 clinical studies (7 Phase 1 pharmacokinetic (PK)/safety/tolerability studies, 1 Phase 2 efficacy/safety/PK study, and 1 Phase 3 efficacy and safety study). The NDA also contains 2 population PK/Pharmacodynamic (PD) reports for the immediate release (IR) and delayed release (DR) formulation, respectively. Reports of in vitro studies on 1) potential effect of divalent and trivalent cations in other medications to interfere with risedronate DR absorption, 2) potential effect for EDTA (a component of the DR formulation) to cause change in absorption of other drugs, and 3) potential for alcohol to compromise the modified-release nature of the formulation were also provided. (b) (4) . Additional supporting data includes a PK

study of risedronate 15 mg IR formulation (Study 2000009) and 15 other safety and efficacy studies.

PK assessments of all studies, except the bioequivalence (BE) study, were done by measuring risedronate urinary excretion (Ae) instead of serum risedronate. The Division of Metabolism and Endocrinology Products has previously agreed to this method of PK assessment (End of Phase 2 meeting minutes, DARRTS 8/31/2007).

Absorption:

The primary bioavailability data for risedronate DR comes from BE study 2008119. This study was a single dose BE study conducted under fasting conditions that measured both serum concentration and urinary excretion for risedronate. Urinary excretion data (used as an indirect measure of the extent of risedronate absorption) following administration of single doses of risedronate DR are also available from several other Phase 1 studies. Steady state risedronate urinary excretion data are also available from Phase 2 study 2005107.

Intensive serum PK samplings were obtained in BE study 2008119 that evaluated the bioavailability of single doses of the Phase 3 clinical product and the to-be-marketed product. The summary of results is shown in Figure 1 and Table 1. The 35 mg risedronate DR tablet achieved T_{max} at ~3 hours when administered 4 hours prior to a meal.

Figure 1: Mean Serum Risedronate Concentration-Time Profiles Following Single Dose Administration of Risedronate 35 mg Delayed-Release Tablets (fasting conditions, study 2008119)

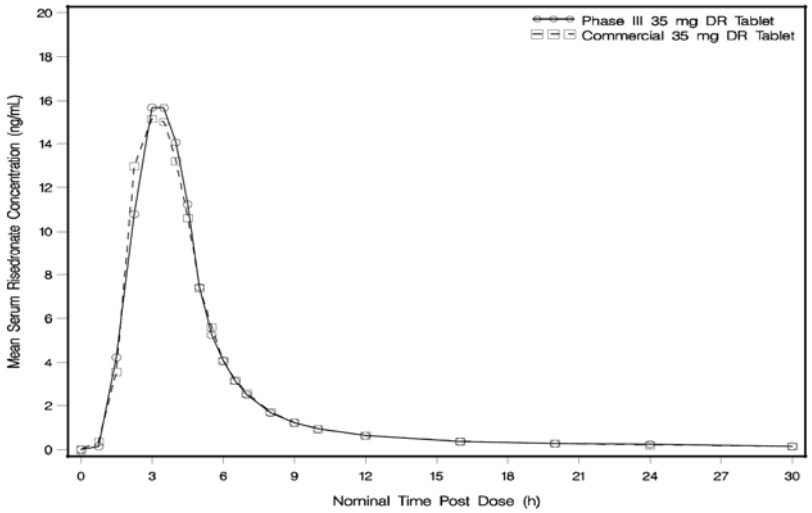

Table 1: Geometric mean PK parameters following single dose of 35 mg risedronate DR (study 2008119)

PK Parameter	Phase III 35 mg DR (n=467) (95% CI)	Commercial 35 mg DR (n=471) (95% CI)	Commercial 35 mg DR/ Phase III 35 mg DR (90% CI)
Primary Parameters			
Cmax (ng/mL)	**14.094 (12.540, 15.839)**	**13.766 (12.251, 15.468)**	**0.977 (0.885, 1.079)**
AUCtlast (ng*h/mL)	**34.203 (30.289, 38.624)**	**34.248 (30.334, 38.666)**	**1.001 (0.904, 1.109)**
Secondary Parameters			
tmax (h)	2.983 (2.884, 3.085)	3.021 (2.921, 3.125)	1.013 (0.979, 1.049)
Ae (ug)	157.845 (140.349, 177.522)	162.671 (144.848, 182.687)	1.031 (0.933, 1.138)
A'e (%)	0.451 (0.401, 0.507)	0.465 (0.414, 0.522)	1.031 (0.933, 1.138)

Food effect:
In a crossover pharmacokinetic study (study 2007120) that evaluated food effect, the bioavailability of risedronate DR 35 mg tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration of 4 hours before a meal. In the same study, the bioavailability of the 35 mg risedronate DR tablet administered after a high-fat breakfast was similar to the 35 mg risedronate IR tablet dosed 4 hours before a meal and was ~2-fold greater than the 35 mg risedronate immediate-release tablet administered 30 minutes prior to a high-fat breakfast. The highest extent of absorption was observed when risedronate DR was administered under fasting condition, which showed 44% higher bioavailability compared to when the same dose of risedronate IR was given under fasting conditions.

Risedronate DR administered after dinner provided greater exposure (approximately 87% increase in Ae) compared to administration following a breakfast (study 2008138).

Distribution, metabolism, and excretion:
No data were submitted. These sections of the label as primarily based on the approved label for Actonel.

Drug interactions:
Study 2008138 evaluated the effect of coadministration of a 600 mg elemental calcium/400 IU vitamin D tablet on the urinary excretion of risedronate DR. The addition of the calcium/vitamin D supplement resulted in an approximate 38% reduction in the amount of risedronate absorbed (as measured by risedronate Ae).

Study 2007027 evaluated the effect of coadministration of esomeprazole (40 mg for 8 days with a single dose risedronate DR given on day 6) on the bioavailability of risedronate DR. The extent of risedronate absorption was reduced by 32% to 48% depending on the time of esomeprazole administration (prior to the evening meal or prior to breakfast, respectively).

The sponsor provided a report indicating that the amount of divalent and trivalent cations (magnesium, aluminum, iron, and calcium) in drugs commonly used in patients enrolled in risedronate Phase 3 studies was low and they assert that it should not interfere with

absorption of risedronate DR tablets. The only exceptions were calcium supplements or antacids.

A report on the potential of EDTA contained in risedronate DR tablet to alter the solubility of other drugs was also provided. The sponsor stated that based on their analysis of the in vitro data, risedronate DR is not likely to result in changes in the absorption of concomitant medications.

Specific populations:
The effect of sex on PK of risedronate DR was assessed based on data from BE study 2008119, where single doses of risedronate DR were administered to healthy male (n=298) and female (n=184) volunteers. For Cmax and AUCtlast, the ratios for males to females were 0.825 and 0.814, respectively. The ratio of tmax for males to females was 1.023. The ratio of Ae for males to females for was 0.913. Similar results were obtained when data from each formulation (Phase 3 product and to-be-marketed product) were analyzed separately.

Pharmacodynamics:
Phase 2 study 2005107 and Phase 3 study 2007008 measured bone turnover markers urinary type-1 collagen cross-linked N-telopeptide corrected for creatinine clearance (NTX/Cr) and serum type-1 collagen cross-linked C-telopeptide (CTX) and the bone formation marker bone-specific alkaline phosphatase (BAP).

Population PK/PD:
The sponsor provided a population PK/PD analysis of pooled data across studies to assess the dose proportionality, effect of food, variability, and impact of covariates on exposure of risedronate DR as well as appropriateness of the 35 mg risedronate DR dose. The sponsor drew the following conclusions:

- The DR formulation demonstrated dose-proportionality across the 20-100 mg dose range.
- There is no evidence that food appreciably affects the bioavailability of the DR formulation; thus, administration of the risedronate DR formulation with food will consequently not have an effect on BTM reduction.
- Under strict fasting conditions (ie, given after an overnight fast and 4 hours before a meal), the model predicted exposure to be 32% higher for the DR formulation compared to the IR formulation. Results of Study 2007120 were similar to the predicted model (44% higher availability for DR compared to IR fasted).
- Like the risedronate IR formulation, variability in the exposure is large; the estimated coefficients of variation for the inter-dose (intra-patient) components were 116% for the DR formulation and 74% for the IR formulation ($p<0.05$).

The sponsor also used the population PK/PD model to simulate the PD (i.e., bone turnover markers) response for a 20 mg risedronate DR tablet to support that the 35 mg risedronate DR tablet is an appropriate dose for the DR formulation.

Clinical vs. to-be-marketed formulation:

The sponsor stated that the risedronate sodium 35 mg DR to-be-marketed (commercial) formulation is identical to the Phase 3 clinical tablet formulation (Material number (b) (4), denoted here as Formulation A) except for the removal of the (b) (4) pigment that was used in the clinical tablet. The core tablet manufacturing process at the clinical scale (b) (4) is representative of the process used for commercial core tablet manufacturing (b) (4) The enteric coating process at clinical scale (b) (4) is also representative of the commercial scale enteric coating process (b) (4) and the equipment used for manufacturing the clinical and commercial tablets is of the same design and operating principle. The sourcing of the commercial tablet is from a manufacturing site that is different from the site at which the clinical formulation was manufactured. The sponsor conducted a BE study which indicated that the to-be-marketed tablet is bioequivalent to the phase 3 clinical product Formulation A (see Table 1). Formulation A was also used in Phase 1 studies 2007120, 2008052, 2008119, and 2008138.

This reviewer noted that a small number of subjects (approximately 90) in the Phase 3 study (study 2007008) was administered a different risedronate 35 mg DR formulation (Material number (b) (4), denoted here as Formulation B) that has the same enteric coating but a slightly different core. This Formulation B was also used in the drug interaction study with esomeprazole (study 2007027). A request was made to the Physical Assessment Lead Dr. Donna Christner to give advice on whether or not Formulation A and Formulation B are similar. Dr. Christner stated that there was a change in the (b) (4) component of the core. This reviewer will request additional data from sponsor regarding which subjects were administered Formulation B in the Phase 3 study and for what duration. Additionally, the sponsor will be requested to provide any bridging data that they have between Formulation B and Formulation A or the to-be-marketed product.

A third formulation (Formulation C) with a slightly different core (same core as Formulation B) as well as a slightly different enteric coating compared to Formulation A was used in the Phase 2 study 2005107. A request was made to the Physical Assessment Lead Dr. Donna Christner to give advice on whether or not Formulation A and Formulation C are similar. Dr. Christner stated that the coating changes are minimal and do not need to be bridged. The core change was the same as in Formulation B and will be addressed as discussed above.

Method validation:
For all Phase 1 and 2 studies (i.e., studies 2004132, 2007120, 2008052, 2005107, 2007027, 2008076, and 2008138), (b) (4) analyzed human urine specimens for concentrations of risedronate using a validated high performance liquid chromatography / tandem mass spectrometry method. For the bioequivalence study (2008119), both human urine and serum specimens were analyzed by (b) (4) for concentrations of risedronate using a validated high performance liquid chromatography / tandem mass spectrometry method. Bioanalytical reports and method validation reports were submitted.

(b) (4)

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-560 is fileable.

Bioequivalence study 2008119 provides the primary link between the Phase 3 clinical trial product and the to-be-marketed product. This study utilized 6 clinical sites and 1 bioanalytical site. This reviewer recommends that a Division of Scientific Investigation (DSI) consult be sent for inspection of the clinical study and bioanalytical sites listed below that were used for this study.

Clinical study site:

Site 104970: Comprehensive Phase One Miramar

Principal investigator:
Dr. Maria Gutierrez
Sub-investigators:
(b) (4)

Address and contact information:
3400 Enterprise Way
Miramar, FL 33025
Phone: 954-266-1000

Bioanalysis site:
(b) (4)

(b) (4))

Comments for sponsor:

- Phase 3 study 2007008 administered 2 different risedronate delayed release tablet formulations (material number (b) (4)) that had different risedronate cores. Please provide the following information:

- A listing of all patients in the phase 3 study 2007008 that were administered the (b) (4) formulation and the start and stop time relative to the first dose that each patient used this formulation.
- Any information that was used to bridge between formulations (b) (4) and (b) (4).
- Proposal and rationale for how data from patients that were administered formulation (b) (4) should be treated.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22560	ORIG-1	PROCTER AND GAMBLE PHARMACEUTICALS INC	(b) (4)

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/s/

DOANH C TRAN
11/20/2009

MYONG JIN KIM
11/23/2009