CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022560Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 7, 2010
From	Theresa Kehoe, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 022560-1 (b) (4) 000
Applicant	Warner Chilcott
Date of Submission	September 24, 2009
PDUFA Goal Date	July 24, 2010, extended to October 24, 2010
Proprietary Name / **Established (USAN) names**	Atelvia risedronate sodium
Dosage forms / Strength	delayed release tablet, 35 mg once weekly
Proposed Indication(s)	022560-1: Treatment of postmenopausal osteoporosis (b) (4)
Recommended:	022560-1: Approve (b) (4)

1. Introduction

Warner Chilcott Pharmaceuticals, Inc has submitted this new drug application seeking approval of Atelvia, a novel delayed release formulation of risedronate sodium, for (b) (4) treatment of postmenopausal osteoporosis (b) (4)

Atelvia contains the bisphosphonate [1-hydroxy-2-(3-pyridinyl) ethylidene] bis[phosphonic acid] (risedronate), the active drug substance in Actonel, risedronate sodium, an approved oral bisphosphonate medication. Actonel 30 mg daily was approved for treatment of Paget's disease of bone in March, 1998. Actonel 5 mg daily was approved in April, 2000, for prevention of postmenopausal osteoporosis, for treatment of postmenopausal osteoporosis, for prevention of corticosteroid-induced osteoporosis, and for treatment of corticosteroid-induced osteoporosis. Actonel 35 mg once weekly was approved for the prevention and treatment of postmenopausal osteoporosis in May, 2002. The 35 mg once weekly dosing regimen was also approved for treatment to increase bone mass in men with osteoporosis in August, 2006. Actonel 75 mg per day for two consecutive days per month was approved for the prevention and treatment of postmenopausal osteoporosis in April, 2007. Actonel 150 mg once monthly was approved for the treatment of postmenopausal osteoporosis in April, 2008.

Current therapies available for the treatment of osteoporosis in postmenopausal women include Fosamax (alendronate) 10 mg daily and 70 mg weekly; Fosamax plus D (alendronate plus cholecalciferol) 70mg/2800 IU weekly or 70mg/5600 IU weekly; Actonel (risedronate) 5 mg daily, 35 mg weekly, 75 mg on two consecutive days monthly and 150 mg once monthly; Actonel and calcium (risedronate copackaged with calcium) 35 mg once weekly with calcium 1250 mg daily; Boniva (ibandronate) 2.5 mg daily oral, 150 mg once monthly oral or 3 mg intravenously every 3 months; Evista (raloxifene) 60 mg daily; Miacalcin (salmon calcitonin) nasal spray 200 IU daily; and Fortical (salmon calcitonin) nasal spray 200 IU daily. Forteo (teriparatide) 20 mcg daily by subcutaneous injection and Prolia (denosumab) 60 mg every 6 months by subcutaneous injection are indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture.

Bisphosphonates are incorporated into the hydroxyapatite crystals of bone and act by inhibition of osteoclasts. The result of osteoclast inhibition is decreased bone resorption and increased bone mass. Incorporation of the bisphosphonate into bone hydroxyapatite results in a long residency time in bone. In adults, oral bisphosphonates have been associated with a number of safety issues including upper gastrointestinal adverse events, osteonecrosis of the jaw, musculoskeletal adverse events related to pain, inflammatory eye events, and more recently, possible atypical fracture of the femur. This review will discuss these safety issues as they relate to the currently proposed product.

2. Background

Bisphosphonates administered orally have a very low bioavailability (<1%) which is further decreased in the presence of food. For this reason, all oral bisphosphonate products currently marketed are administered in the morning in the fasting state and patients must remain without food or drink for 30 – 60 minutes after administration. During Atelvia's development, the Applicant's objective was to develop a risedronate sodium delayed-release tablet to be administered once weekly, (b) (4) Atelvia was formulated to minimize the interaction of risedronate sodium with food, (b) (4) To achieve this, Atelvia is enteric coated to prevent tablet disintegration in the stomach and allow release in the small intestine. Drug release is controlled with a coating with a pH trigger of 5.5. In addition, a competitive chelating agent (edetate disodium dihydrate [EDTA], (b) (4)

The current application is supported by the dose finding trial 2005107 and the one year interim analysis of the clinical efficacy trial 2007008. Trial 2007008 is a 2-year, randomized, double-blind, double-dummy, active control, noninferiority trial evaluating the change from baseline in lumbar spine bone mineral density with 35 mg delayed

release risedronate weekly given either before or after breakfast compared to 5 mg immediate release risedronate daily. The 5 mg daily immediate release risedronate was chosen as the active comparator because this is the dose that was shown to be efficacious in reducing morphometric vertebral fractures.

After review of the findings from dose finding trial 2005107 presented in the briefing package for the June 28, 2007, End of Phase 2 meeting, the Division was concerned regarding the higher risedronate exposure and recommended that the Applicant consider the addition of a lower dose arm, such as a 20 mg delayed release dose, in the Phase 3 trial 2007008. The Applicant chose not to do this and only studied the 35 mg once weekly delayed release dose.

During the preNDA meeting held April 21, 2009, the Applicant was informed that

> *"As discussed at the end of phase 2 meeting, we continue to believe that additional safety data beyond one year of therapy are necessary, especially as the suggested lower dose delayed release tablet was not included in your phase 3 trial. Expected risedronate exposure with the 35 mg delayed release product is higher than that seen with the immediate release product. We are concerned that an increased number and severity of adverse events may result. We also continue to be highly concerned regarding the potential for altered calcium metabolism, which in combination with the increased risedronate exposure may result in impaired bone mineralization in at-risk patients. Bone histomorphometry data will be necessary to allow adequate safety review. We strongly encourage you to submit 2-year safety data including bone histomorphometry in your original NDA submission."*

The Applicant chose to submit the marketing application containing only the one year interim study report. During the review of the NDA, the clinical team determined that bone histomorphometry data would be required to adequately assure bone safety. The Applicant was informed on June 1, 2010. The bone biopsy report from the Year-2 Study of 2007008 was submitted on June 28, 2010. These clinical data were considered a major amendment and triggered a 3-month clock extension to allow adequate time for review.

3. CMC/Device

This NDA is recommended for approval from a CMC perspective. Please refer to Dr. Carolyn Strasinger's product quality review, and Dr. Sandra Suarez Sharp's biopharmaceutics review for complete details.

Drug Product: Atelvia (risedronate sodium) is a yellow, delayed-release, enteric coated tablet containing 35mg of drug substance on an anhydrous basis (equivalent to 32.48 mg of risedronic acid). Drug release is controlled with a 5.5 pH trigger methacrylic acid copolymer (b) (4). An additional competitive chelating agen (b) (4) EDTA) has been added (b) (4).

The quality of the tablets is controlled by tests for description, identification of risedronate sodium, content uniformity, assay, dissolution, and degradation products. No impurity specification has been set for the product. This is consistent with the currently approved Actonel immediate release tablet. Process impurities are monitored in the drug substance and no degradants have been observed under normal handling and storage. Degradation is monitored for stability, however, not at release because the substance is very stable and the product is manufactured in a way in which it is unlikely to cause formation of degradants.

The tablets are manufactured by Norwich Pharmaceuticals in North Norwich, NY for Warner Chilcott Pharmaceuticals Inc. The tablets are packaged in (b) (4) clear (b) (4) blister with aluminum foil lidding. Each package will contain (b) (4) four (b) (4) tablets. The Applicant proposed a three year expiration dating period with a storage statement of "Store at controlled room temperature 20˚-25˚C (68˚-77˚F) [see USP]." The applicant analyzed assay results using SAS® Stability macro as justification for their 36 month shelf life request. The applicant submitted updated stability data on April 23, 2010, indicating that that 35 mg risedronate sodium delayed-release tablets packaged in clear (b) (4) aluminum foil blisters are physically and chemically stable for 24 months at 25˚C/60%RH and 6 months at 40˚C/75%RH. The provided data allow extrapolation to 36 months of expiration dating period according to ICH Q1E as originally requested. Therefore, an expiration dating period of 36 months is granted.

Drug substance**:** No information has been submitted in the application for the drug substance as the drug substance information is unchanged from that previously provided in the approved NDA 20-835 (Actonel). This was previously discussed and agreed upon by the FDA in the Pre-NDA meeting dated May 20, 2009.

For the commercial product, all risedronate sodium drug substance will be sourced from the (b) (4). Annual reports indicate that the drug substance is stable for 48 months, and a 60 month time point for testing has been committed to. The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for the drug substance and drug product for assuring product quality of drug substance and drug product.

The ONDQA/biopharmaceutics team has reviewed the dissolution methods for Atelvia. Because Atelvia is designed to protect the drug from release in the stomach and allow release in the small intestine, the Applicant proposed a two stage dissolution method which they considered to be more physiologically relevant. The Applicant proposed the following dissolution specifications:

(b) (4)

(b) (4)

While the proposed dissolution method and specifications were found generally acceptable, after review of the mean dissolution values, the Buffer Stage dissolution specifications were recommended to be changed to: (b) (4)

The following comment was conveyed to the Applicant on May 11, 2010:

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 2 hours.
    - **Buffer Stage**: Not less than (b) (4) (Q) of the label amount of risedronate sodium is dissolved at 30 minutes.

The Applicant accepted these dissolution specifications in a letter dated June 23, 2010.

Facilities review/inspection: An overall "Acceptable" rating was provided by the Office of Compliance May 1, 2010. A categorical exclusion for an environmental assessment was granted on December 4, 2009.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. Gemma Kuijper's review for complete details. After early evaluations, the Applicant chose to go forward with development of a formulation containing 35 mg risedronate and 100 mg EDTA. A full nonclinical package (PD, PK, single and repeat-dose toxicity studies, reproductive toxicity, genotoxicity and carcinogenicity studies) for the drug substance, risedronate sodium, has previously been submitted and reviewed. Target organs of risedronate toxicity included liver, kidney, stomach, and lung in both rats and dogs, and testes, esophagus, intestine, pancreas, and lymph nodes only in dogs. Risedronate was not genotoxic, not teratogenic (rat, rabbit) and not carcinogenic (32 mg/kg/day in mice, 24 mg/kg/day in rats).

The qualification threshold for impurities in the drug substance (b) (4) for doses ≤ 2 g/day) has not been exceeded. For the drug product, there is no change in the impurity profile and the qualification threshold for degradation products (b) (4) for daily doses of 10-100 mg) is not exceeded for the delayed release drug product. The delayed release risedronate contains EDTA-disodium (b) (4). EDTA is not present as an excipient in approved oral drug products. EDTA (as Na_2EDTA and $CaNa_2EDTA$) is widely used and FDA-approved as a direct food additive as a preservative, processing aid, stabilizer and/or chelating agent (e.g. in

canned soft drinks, canned vegetables, margarine, pickles) at 25-800ppm ($CaNa_2EDTA$) or 36-500ppm (Na_2EDTA). EDTA and its salts are also used as chelating agents in cosmetic preparations at concentrations < 2%. As EDTA-calcium-disodium (Calcium Disodium Versenate) it is approved for the treatment of heavy metal poisoning, at an IV or IM dose of 1000 mg/m^2/day (ca. 2500 mg/day for an adult). EDTA-disodium (Endrate) is approved for emergency treatment of hypercalcemia and treatment of digitalis-induced arrhythmia, with IV doses of 50 mg/kg/day, up to a maximum of 3 grams/day, infused over ≥3h, daily for 5 days.

To support the use of this new formulation, the Applicant conducted a 13 week study in dogs comparing risedronate alone with risedronate plus EDTA. A total of 108 animals were studied and divided into 9 dose groups with 12 animals (6 male, 6 female) in each dose group. Each dose group received a combination of risedronate and EDTA = control, low dose (8 mg/kg), or high dose 916 mg/kg) risedronate with control, low dose (2.5 mg/kg) or high dose (12.5 mg/kg) EDTA. The 8 mg/kg risedronate dose yielded a 36-fold multiple of human exposure (AUC) and the 16 mg/kg dose a 430-fold multiple. The low dose of EDTA is equivalent to a 80 mg dose in humans, and the high dose to a 400 mg dose in humans (on mg/m^2 basis).

Risedronate effects at both 8 and 16 mg/kg doses were similar to those seen in prior risedronate studies. EDTA alone had no effects on any pharmacologic parameter, including bone morphology, and the addition of EDTA to risedronate did not cause any new toxicities beyond those already observed in the risedronate-only groups. EDTA did appear to increase risedronate exposure and exacerbate risedronate toxicities, including systemic and local gastric toxicity. The enhancement of toxicity, as well the increase in risedronate exposure by EDTA, was most prominent in the low 8 mg/kg risedronate dose group. The exacerbation of risedronate-induced toxicities was only seen with the high dose (12.5 mg/kg) EDTA group. The data suggest that EDTA in the DR tablet may enhance risedronate absorption and risedronate-related gastrointestinal and systemic toxicities.

As outlined in Dr. Kuijper's review, the Applicant did not conduct long term animal toxicity studies with oral EDTA. However, the NOAEL in a 2-year dietary rat study was used to define an acceptable daily intake (ADI) of 150 mg per day (JECFA, 1974). The addition of a weekly dose of (b) (4) to the maximum estimated intake of approximately 650 mg per week does not raise significant safety concerns. The (b) (4) EDTA dose in the DR tablet is unlikely to have a significant effect on bone and mineral metabolism and the EDTA-risedronate combination is unlikely to have adverse effects on bone. Nonclinical bone quality studies with the risedronate-EDTA combination have not been conducted since there is no significant cause for concern.

5. Clinical Pharmacology/Biopharmaceutics

Please see Dr. Doanh Tran's review for complete details.

General clinical pharmacology/biopharmaceutics: Atelvia is a delayed release risedronate product that is enteric coated with a pH trigger of 5.5. The formulation also contains EDTA. The goal of this new formulation is to decrease the food effect and improve the bioavailability of risedronate. Following single dose administration of risedronate delayed release 35 mg in healthy men and women under fasting conditions, the arithmetic mean (CV%) serum risedronate maximum concentration (Cmax) was 25.3 ng/mL (109.8%) and AUC from time 0 to time of last measurable concentration (AUC_{tlast}) was 63.5 ng*h/mL (106.5%). The median (range) Tmax was 3 hours (0.75 – 12). The mean (CV%) Ae for 72 hours post dose was 289.5 mcg (109.6%). There are limited data regarding multiple dose administration. When compared to the currently approved 35 mg immediate release risedronate formulation, the bioavailability (based on Ae) of the delayed release formulation is higher than immediate release 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). Risedronate has a long terminal t1/2 (~500 hours) that has been hypothesized to represent the dissociation of risedronate from the surface of bone.

Risedronate delayed release bioavailability was dose proportional or slightly more than dose proportional in the DR tablet strength range of 20 mg – 100 mg.

The effect of food on bioavailability of risedronate delayed release 35 mg was evaluated in a single dose, crossover study in 74 postmenopausal women (study 2007120). Overall, food decreased the bioavailability of the risedronate delayed release 35 mg tablet by approximately 30%, compared to an approximately 54% reduction of the immediate release tablet. Evaluation across tablet strengths of 20 – 100 mg support that the risedronate delayed release formulation is less sensitive to food effect than that observed for the immediate release formulation.

Bioequivalence of the clinical trial formulation and the to-be-marketed formulation: The to-be-marketed formulation of Atelvia will be manufactured by Norwich Pharmaceuticals (Norwich, NY), while the clinical trial formulation was manufactured by Procter and Gamble Pharmaceuticals (Norwich, NY). The Applicant conducted a single dose BE study to compare the bioavailability of the to-be-marketed formulation (test) to the primary Phase 3 formulation (reference) under a fasting state. The pharmacokinetics of this study were done using risedronate AUC instead of the urinary risedronate Ae, as was previously used. The results showed that the 90% CIs for test/reference ratio for risedronate Cmax and AUC_{tlast} were within the 80 – 125% BE limits indicating that the two formulations are bioequivalent.

Drug-drug interactions:

Effect of EDTA: There are two potential issues with EDTA that may lead to altered drug absorption: EDTA is a chelating agent that may alter the solubility of a drug, and EDTA has been shown to increase paracellular transport. Results of in vitro solubility studies indicated that the EDTA in the Atelvia tablet is not likely to have significant influence on solubility of several drugs. An effect on paracellular transport could not

be ruled out. However, when administered under fasting conditions, the bioavailability of delayed release 35 mg Atelvia tablet was approximately 44% higher than the immediate release 35 mg Actonel tablet. This suggests 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%, which would be considered a modest effect.

Effect of calcium co-administration or cations from other co-administered drugs: Co-administration of a 600 mg calcium supplement reduced risedronate bioavailability (based on Ae) by a mean of 38% (90% CI 11%, 57%) when risedronate delayed release was taken after breakfast.

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

Effect of esomeprazole administration: The effect of concomitant administration of esomeprazole magnesium (Nexium®) on the bioavailability of Atelvia was evaluated in study 2007027. Pharmacokinetic analyses were performed on urine samples (Ae). The extent of risedronate absorption (given after breakfast) was reduced by 32% if esomeprazole were administered prior to dinner and by 48% if esomeprazole were administered prior to breakfast. Assessment of the distribution of risedronate Ae did not reveal any apparent bimodal distribution that would be indicative of a complete failure of the enteric coating in the presence of esomeprazole.

Pathway of elimination: The Applicant is relying on prior data for risedronate metabolism and excretion. There is no evidence of systemic metabolism of risedronate and approximately half of the absorbed dose is excreted in the urine in the first 24 hours after ingestion.

Hepatic impairment: The sponsor did not conduct a study to evaluate the effect of hepatic impairment on the PK of risedronate delayed release. Prior review of risedronate immediate release data indicate that there is no evidence of systemic metabolism of risedronate. No dosage adjustment for hepatic impairment was recommended for Actonel (risedronate immediate release). A similar recommendation could be applied to Atelvia (risedronate delayed release).

Renal impairment: The sponsor did not conduct a study to evaluate the effect of renal impairment on the PK of Atelvia. Risedronate is excreted unchanged primarily via the kidney. The current label for Actonel (risedronate immediate release) 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. A review by Pharmacometric reviewer, Dr. Jiang Liu, indicated that due to higher exposure of the risedronate delayed release formulation compared to immediate release formulation, a 4 to 12 fold higher exposure may be expected in moderate renal impairment patients taking Atelvia when compared to normal renal function patients taking Actonel. The higher exposure raised concerns with regard to

whether the same recommendation of no dosage adjustment in patients with moderate renal impairment used for Actonel should apply for Atelvia. However, it was noted that the phase 3 clinical trial 2007008 did enroll subjects with creatinine clearance (CLcr) ≤50 ml/min and no safety concerns were raised. When comparing exposure for the delayed release formulation only, a 2 to 3-fold higher exposure may be present in patients with moderate renal impairment relative to patients with normal renal function. A specific evaluation of patients with moderate renal impairment (CLcr 30 – 60 mL/min) was conducted during the clinical review and no increase in the number of subjects with adverse events was noted in patients with moderate renal insufficiency. Of specific adverse events that are possibly related to increased systemic risedronate exposure due to renal function status, only "PTH increased" occurred consistently at a higher rate in subjects with moderate renal impairment. However, even moderate renal impairment is associated with alterations in mineral metabolism that may contribute to the elevated PTH seen in this population.

Effect of age: No study was conducted to evaluate the effect of age on bioavailability of Atelvia. Prior review of risedronate immediate release data have concluded that the bioavailability and disposition of risedronate are similar in elderly (>60 years of age) and younger subjects (current Actonel label).

Effect of gender: The effect of gender on the pharmacokinetics of Atelvia was assessed based on data from the bioequivalence study 2008119, where single doses of risedronate delayed release 35 mg were administered to healthy male (n=298) and female (n=184) volunteers. For Cmax and AUC_{tlast}, 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.

QT assessment: Risedronate's effect on QT was not assessed.

Other notable issues:

The clinical and bioanalytical sites for the bioequivalence (BE) study 2008119 were inspected by the Division of Scientific Investigation (DSI). For this bioequivalence study between the clinical trial formulation and the to-be-marketed formulation, there were minor deviations noted in the serum risedronate sample collection and assay. Therefore, the serum data, which provided the primary assessment of bioequivalence between the two formulations, was acceptable.

For the urine sample collection and assay, DSI noted that there were problems related to the incurred samples reproducibility (ISR), including a high ISR failure from a prior study (study 92058) using the same analytical method (b) (4) The reason for the failure is not known. Subsequently, a new analytical method has been developed (b) (4) DSI recommends that because the actual cause of the ISR failure of method in (b) (4) is not known, the measured concentration values for any given sample using this method may not be accurate. Therefore, any samples that were previously analyzed using (b) (4) should be reanalyzed using the new method, (b) (4).

However, further review of the ISR failure in study 92058 by Dr. Tran suggests that method (b) (4) was sufficiently robust with a consistency rate of 85% to the new method in (b) (4). 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 (b) (4) may not be reliable. The analyses of Ae data are important in the studies that assess changes in bioavailability of risedronate due to co-administration of food, calcium supplement, or esomeprazole.

- In the primary food effect study (Study 2007120) urine risedronate concentration was assayed using an older method (b) (4). The results achieved were consistent with the known effect of food on risedronate absorption. Therefore, the study results do not raise concern regarding the assay validity. In addition, given the two dosing arms in the Phase 3 trial (Atelvia given before and immediately following food), the safety and efficacy of this Atelvia has been adequately evaluated. Therefore, the DSI findings do not affect the overall conclusions and recommendations regarding food effect.

- In the study evaluating the effect of calcium co-administration on the bioavailability of risedronate delayed release 35 mg tablets (Study 2008138) urine risedronate concentration was assayed using method (b) (4). The results showed that co-administration 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 (b) (4) would not affect the overall conclusions and recommendations.

- In the study evaluating the effect of concomitant administration of esomeprazole on the bioavailability of risedronate delayed (Study 2007027) urine risedronate concentrations were assayed using an older method (b) (4). 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. In a worst case scenario, complete and immediate failure of the enteric coating may render the risedronate delayed release tablet to behave similar to an immediate release 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). Therefore, in the 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, Dr. Tran recommends that the sponsor reanalyze the samples from study 2007027 using the method in (b) (4) to confirm the results. Furthermore (b) (4) product label should specify that risedronate DR not be used in patients taking acid suppressants. Once the reanalysis of samples from study 2007027 is complete, the sponsor should submit the results (b) (4)

(b) (4) A postmarketing commitment requiring re-analysis of the urine samples from study 2007027 was discussed with the Applicant during a telephone conference on September 29, 2010. The Applicant informed the Division that stored urine samples from that study had been discarded. Therefore, the following postmarketing commitment was requested and agreed upon:

- 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.

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

6. Clinical Microbiology

There are no clinical microbiology issues associated with this oral bisphosphonate product.

7. Clinical/Statistical- Efficacy

Please refer to Dr. Stephen Bienz's clinical review and Dr. Xin Fang's statistical review for complete details. The Applicant seeks approval of (b) (4) treatment of postmenopausal osteoporosis, (b) (4)

7.1. Dose-finding

Trial 2005107 evaluated risedronate weekly dosing and compared the currently approved 35 mg immediate release tablet administered according to the labeled instructions (at least 30 minutes prior to breakfast under fasting conditions) with delayed release formulations of 35 mg and 50 mg risedronate. Both delayed release formulations contained (b) (4) edetate disodium dehydrate (EDTA) and an enteric coating which is designed to release the drug product at a pH of 5.5. Based on Phase 1 data, the Applicant believed that the 50 mg delayed release dose would be needed to achieve the systemic exposure seen with the approved weekly 35 mg immediate release risedronate dose.

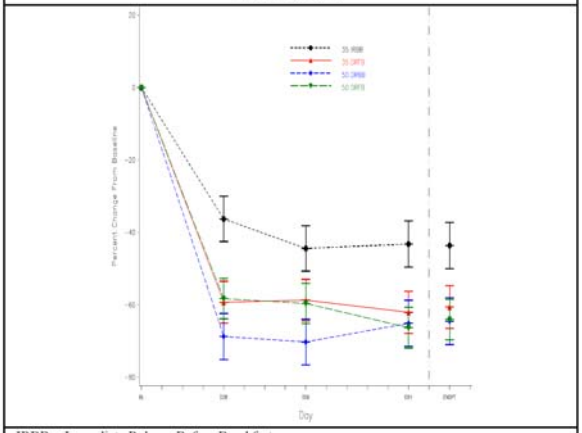
This trial is a randomized, double-blind, triple-dummy, active control, parallel-group study of 13 weeks duration. A total of 182 subjects were randomized into one of four treatment groups: 1) risedronate immediate release 35 mg taken prior to breakfast (35 mg IRBB, n = 37); 2) risedronate delayed release 35 mg taken immediately following breakfast (35 mg DRFB, n = 36); 3) risedronate delayed release 50 mg taken immediately following breakfast (50 mg DRFB, n = 72); or 4) risedronate delayed release 50 mg taken prior to breakfast (50 mg DRBB, n = 36). One enrolled subject did not receive a dose of study drug. Of the 181 subjects who received study drug, 168 (93%) completed the 13 week study. Ninety-five subjects participated in the pharmacokinetic analyses, 89 of which completed the study. Most subjects were compliant with ≥ 80% of study medication.

The study population was healthy postmenopausal women. The diagnosis of osteoporosis or low bone mass was not an entry requirement and bone mineral density was not evaluated. The mean age of enrollees was 60 years with a range of 45 – 79 years. Approximately 78% enrolled subjects were Caucasian race.

As outlined in Figure 1 below, all delayed release dose groups had significantly more suppression of serum carboxy-terminal collagen crosslinks (CTX) than the currently approved 35 mg immediately release group. At study Week 13, 35 mg once weekly immediate release resulted in a 43.2% least squares mean decrease in serum CTX (35 IRBB, black), compared to -62.1% for 35 mg delayed release following breakfast (35 DRFB, red), -66.3% for 50 mg delayed release following breakfast (50 DRFB, green), and -65.1% for 50 mg delayed release before breakfast (50 DRBB, blue).

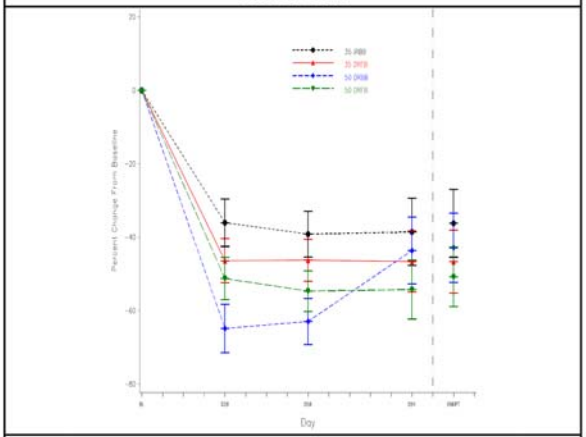
Similar results were also seen for cross-linked N-telopeptides of type I collagen (NTX, Figure 2). At week 13, the mean urine NTX/creatinine ratio was decreased 38.6% in the 35 mg immediate release group (35 IRBB, black), compared to -46.6% for 35 mg delayed release following breakfast (35 DRFB, red), -54.3% for 50 mg delayed release following breakfast (50 DRFB, green), and -46.3% for 50 mg delayed release before breakfast (50 DRBB, blue).

Figure 1
Serum CTX by Visit - Percent Change from Baseline (Least Squares Means +/- 1 SE)
Intent-to-Treat



IRBB = Immediate Release Before Breakfast
DRFB = Delayed Release Following Breakfast
DRBB = Delayed Release Before Breakfast
/RISEDRONATE/pk/2005107/graphs/figures.sas SAS 8.2 02MAR07:14:25 f28feb07 av6459

Figure 2
NTX/Cr by Visit - Percent Change from Baseline (Least Squares Means +/- 1 SE)
Intent-to-Treat



IRBB = Immediate Release Before Breakfast
DRFB = Delayed Release Following Breakfast
DRBB = Delayed Release Before Breakfast
/RISEDRONATE/pk/2005107/graphs/figures.sas SAS 8.2 02MAR07:14:25 f28feb07 av6459

Source: 2005107-report-body

Pharmacokinetic analyses were also conducted in a subset of subjects. As noted in the table below, all delayed release treatment groups had higher risedronate exposure when compared to the currently approved 35 mg once weekly immediate release risedronate.

Trial 2005107: Cumulative Amount of Risedronate Excreted in Urine (Ae)			
	N	Geometric LS Mean (95% CI)	Ratio vs 35 mg IRBB (95% CI)
Day 1			
35 mg IRBB	20	60.49 (30.78 , 118.87)	
35 mg DRFB	19	92.42 (46.26 , 184.64)	1.53 (0.583 , 4.007)
50 mg DRFB	38	140.21 (85.63 , 229.57)	2.32 (1.009 , 5.325)
50 mg DRBB	18	154.69 (75.78 , 315.79)	2.56 (0.962 , 6.800)
Day 85			
35 mg IRBB	17	60.00 (33.89 , 106.24)	
35 mg DRFB	18	182.58 (104.83 , 318.02)	3.04 (1.372 , 6.746)
50 mg DRFB	36	166.48 (112.20 , 247.00)	2.77 (1.387 , 5.549)
50 mg DRBB	18	118.06 (67.61 , 206.14)	1.97 (0.887 , 4.363)
Source: 2005107-report-body, Table 16			

Both the pharmacodynamic and pharmacokinetic evaluations indicate that both the 35 mg delayed release dose and the 50 mg delayed release dose result in higher

risedronate exposure and consequent suppression of bone resorption biomarkers when compared to the 35 mg once weekly immediate release risedronate dose. Based on the results achieved, the Applicant chose to take the 35 mg delayed release dose, rather than the 50 mg delayed release dose into the phase 3 trial.

It should be noted that after review of the findings from study 2005107 presented in the briefing package for the June 28, 2007, End of Phase 2 meeting, the Division was concerned regarding the higher risedronate exposure and recommended that the Applicant consider the addition of a lower dose arm, such as a 20 mg delayed release, in the Phase 3 trial. The Applicant chose not to do this and only studied the 35 mg once weekly delayed release dose.

7.2 Phase 3 Clinical Studies

7.2.1 Treatment of Postmenopausal Osteoporosis

The key efficacy trial supporting the treatment of postmenopausal osteoporosis indication is the one year interim analysis of Trial 2007008. Trial 2007008 is a 2-year, randomized, double-blind, double-dummy, active control, noninferiority trial evaluating the change from baseline in lumbar spine bone mineral density with 35 mg delayed release risedronate weekly given either before or after breakfast compared to 5 mg immediate release risedronate daily. The 5 mg daily immediate release risedronate was chosen as the active comparator because this is the dose that was shown to be efficacious in reducing morphometric vertebral fractures. Enrolled subjects were postmenopausal women aged 50 years or older with osteoporosis, defined as a lumbar spine bone mineral density (BMD) more than 2.5 standard deviations (SD) below the normal young adult mean (T score ≤ -2.5), OR a lumbar spine BMD more than 2.0 SD below the normal young adult mean (T score ≤ -2.0) with at least one prevalent vertebral fracture. Subjects were randomized 1:1:1 to receive immediate release risedronate 5 mg daily administered before breakfast (IRBB); or delayed release risedronate 35 mg once weekly, administered before breakfast (DRBB); or delayed release risedronate 35 mg once weekly, administered immediately following breakfast (DRFB). To maintain the blind, all patients received a daily tablet (drug or placebo) taken before 30 minutes before breakfast, a weekly tablet (drug or placebo) taken at least 30 minutes before breakfast, and a weekly tablet (drug or placebo) taken immediately following breakfast. In addition to study drug, all patients received 1000 mg calcium and 800 – 1000 IU vitamin D daily throughout the study period.

Disposition: A total of 922 subjects were enrolled into the study and received study drug (307 in the 5 mg daily immediate release, before breakfast group, 307 in the 35 mg weekly delayed release, following breakfast group, and 308 in the 35 mg weekly delayed release, before breakfast group). At Month 12, 50 (16%) subjects in the daily immediate release, before breakfast group, 55 (18%) subjects in the 35 mg weekly delayed release, following breakfast group and 49 (16%) subjects in the 35 mg weekly delayed release, before breakfast group had discontinued from the study. The most

common reason for discontinuation was voluntary withdrawal (22 (7%) immediate release, before breakfast, 25 (8%) delayed release, following breakfast, and 26 (8%) delayed release, before breakfast) followed by adverse event (25 (8%) immediate release, before breakfast, 28 (9%) delayed release, following breakfast, and 16 (5%) delayed release, before breakfast).

Demographics: All subjects enrolled in this study were women. The average age of enrollees was approximately 66 years with a range of 50 – 87 years. Overall, 44% of the population was age 65 to 75 years and 13% were over age 75 years. Approximately 99% of the enrolled population was Caucasian. The mean time since last menses was 18 years. The mean baseline 25 hydroxyvitamin D level was 70 nmol/L (28 ng/mL). The mean baseline lumbar spine T-score was -3.1. Overall, 29% of the enrolled population had at least one prevalent vertebral fracture at baseline.

Efficacy Measures: The primary endpoint was change in lumbar spine bone mineral density (BMD) at week 52. Bone mineral density measurements of the lumbar spine and hip were assessed using dual x-ray absorptiometry (DXA) at baseline and weeks 26, 52, and 104. Lateral spine x-rays were obtained at baseline and weeks 52 and 104 to assess for the presence of vertebral fractures. Changes in biochemical markers of bone turnover were assessed at baseline and weeks 13, 26, 52, and 104 as secondary endpoints.

> Lumbar spine BMD: The mean baseline lumbar spine T-score was -3.1 in all treatment groups. As outlined in the table below, the mean percent increase in lumbar spine BMD at week 52 (mITT, LOCF) was 3.1% in the 5 mg daily immediate release before breakfast group, 3.4% in the 35 mg weekly delayed release following breakfast group, and 3.4% in the 35 mg weekly delayed release before breakfast group. For both delayed release treatment groups, the upper bound of the 95% confidence interval for the difference in mean percent change from baseline was less than the pre-defined noninferiority limit of 1.5%. Therefore, both the 35 mg delayed release tablet administered once weekly following breakfast and the 35 mg delayed release tablet administered once weekly before breakfast can be considered noninferior to the 5 mg immediate release daily dosing regimen. Pooled analysis of the delayed release dose group did not demonstrate superiority to the once daily immediate release regimen.

Study 2007008: Percent Change in Lumbar Spine BMD at week 52 (mITT, LOCF)			
	5 mg IR daily before breakfast IRBB	**35 mg DR weekly after breakfast DRFB**	**35 mg DR weekly before breakfast DRBB**
N	307	307	308
n, mITT	270	261	271
Baseline (gm/cm2)	0.757	0.758	0.758
Week 52, LOCF			
LS mean percent change	3.118	3.352	3.414
95% CI	2.710 , 3.526	2.936 , 3.767	3.007 , 3.822
Treatment Difference			
LS mean difference		-0.233	-0.296
95% CI		-0.816 , 0.394	-0.873 , 0.281
Noninferiority Margin			
upper bound 95% CI		0.394	0.281
Source: 2007008-report-body, Table 11			

Hip BMD: Change in total hip, femoral neck and trochanter BMD at week 52 were secondary endpoints of the trial. As outlined Dr. Bienz's review, the mean percent increase in total hip BMD at week 52 (mITT, LOCF) was 1.8% in the 5 mg daily immediate release before breakfast group, 2.1% in the 35 mg weekly delayed release following breakfast group, and 2.1% in the 35 mg weekly delayed release before breakfast group.

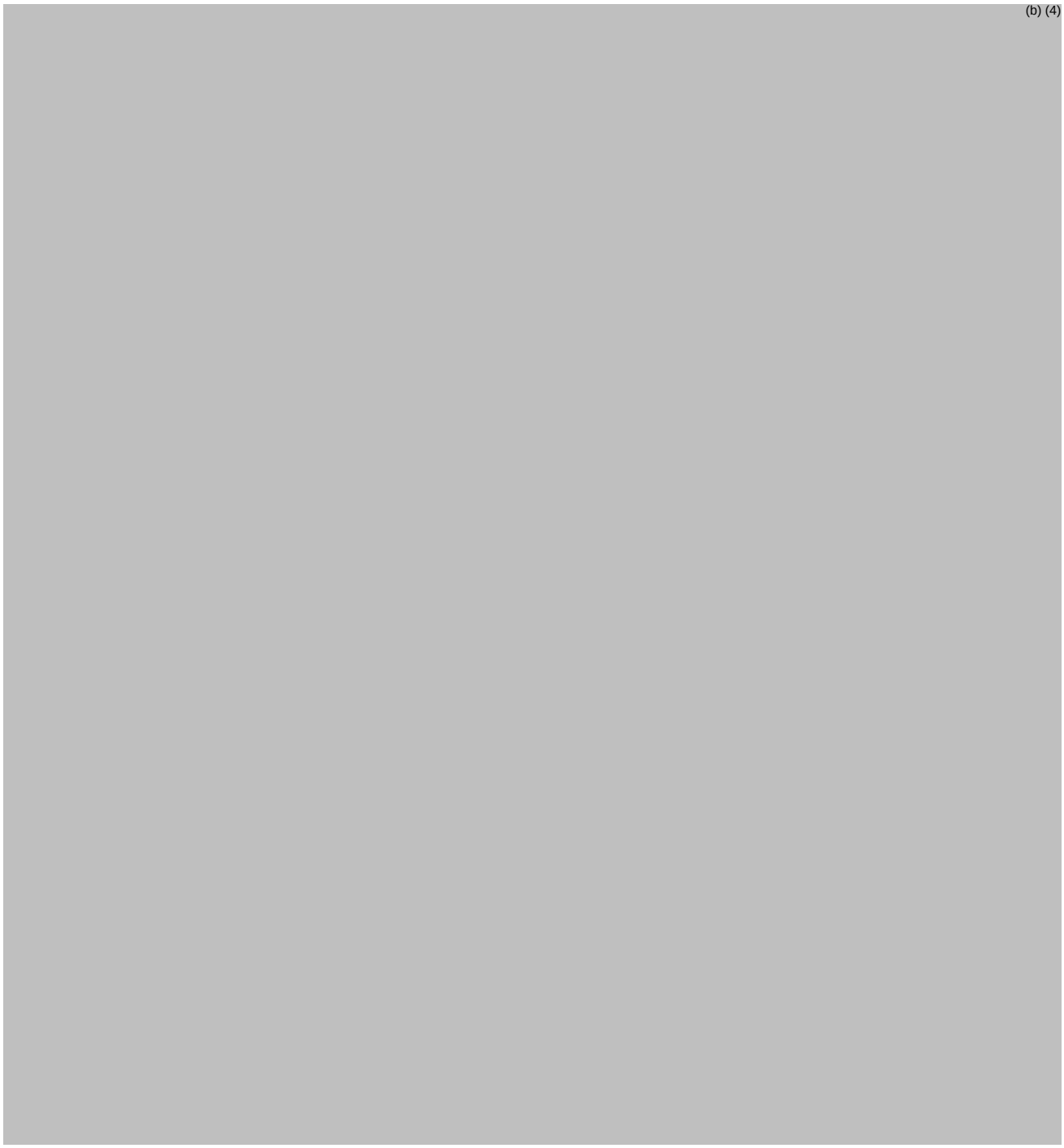
At the femoral neck, the mean percent increase in BMD at week 52 was 1.2% in the 5 mg daily immediate release before breakfast group, 1.5% in the 35 mg weekly delayed release following breakfast group, and 1.7% in the 35 mg weekly delayed release before breakfast group.

At the trochanter, the mean percent increase in BMD at week 52 was 2.2% in the 5 mg daily immediate release before breakfast group, 2.7% in the 35 mg weekly delayed release following breakfast group, and 2.8% in the 35 mg weekly delayed release before breakfast group.

Fracture: Spinal x-ray for evaluation of morphometric vertebral fractures were performed at baseline and week 52. The radiographs were sent to the central reading facility (b) (4) and interpreted using the semiquantitative Genant scoring method. At study initiation 70 (24%) subjects in the daily immediate release, before breakfast group, 81 (28%) subjects in the 35 mg weekly delayed release, following breakfast group and 87 (29%) subjects in the 35 mg weekly delayed release, before breakfast group had a prevalent morphometric vertebral fracture on baseline radiograph. At week 52, seven subjects had new morphometric vertebral fractures (2 in the daily immediate release, before breakfast group, 2 in the 35 mg weekly delayed release, following breakfast group and 3 in the 35 mg weekly delayed release, before breakfast group).

Clinical fractures, both non-vertebral and symptomatic vertebral fractures, were recorded as adverse events. A total of 27 subjects sustained a new clinical fracture during the first year of the study (6 (2%) in the 5 mg immediate release, before breakfast group, 9 (3%) in the delayed release, following breakfast group, and 12 (4%) in the delayed release, before breakfast group). When data from the 120 day safety update are included, clinical fractures reported as adverse events occurred in a total of 43 subjects (13 (4%) in the 5 mg immediate release, before breakfast group, 10 (3%) in the delayed release, following breakfast group, and 20 (6%) in the delayed release, before breakfast group).

Biochemical Markers of Bone Turnover: Biochemical markers of bone resorption (serum carboxy-terminal collagen crosslinks (CTX) and cross-linked N-telopeptides of type I collagen (NTX)) and bone formation (bone specific alkaline phosphatase (BAP)) were measured at baseline and weeks 13, 26, and 52. As outlined in Dr. Bienz's review, both weekly delayed release treatment groups had similar decreases in biochemical markers of bone turnover when compared to the daily immediate release group.



7.3 Summary of Efficacy

For the treatment of postmenopausal osteoporosis indication, I agree with Dr. Bienz that the efficacy of Atelvia has clearly been demonstrated, based on bone mineral density. At one year, the mean lumbar spine increase was 3.1% in the 5 mg daily

immediate release before breakfast group, 3.4% in the 35 mg weekly delayed release following breakfast group, and 3.4% in the 35 mg weekly delayed release before breakfast group. For both delayed release treatment groups, the upper bound of the 95% confidence interval for the difference in mean percent change from baseline was less than the pre-defined noninferiority limit of 1.5%. These findings allow an adequate bridge between the BMD increases noted with the delayed release risedronate formulations and the fracture risk reduction efficacy previously demonstrated with the 5 mg daily immediate release risedronate.

8. Safety

8.1 General Safety Considerations

Atelvia (delayed release risedronate) is in the pharmacologic class of bisphosphonates. Known safety signals with bisphosphonates include hypocalcemia, and upper gastrointestinal adverse events (with oral bisphosphonates). Safety signals that have become evident post marketing include osteonecrosis of the jaw, severe musculoskeletal bone pain, and ocular inflammation. In addition, there is an ongoing investigation regarding a potential safety signal of atypical fractures associated with bisphosphonate use.

8.2 Safety Findings from Submitted Clinical Trials

8.2.1 Treatment of Postmenopausal Osteoporosis

Safety Events and Exposure: As outlined in the table below, a total of 922 subjects were exposed to risedronate in this trial, with 615 exposed to the 35 mg delayed release formulation, administered either before breakfast or immediately following

breakfast. Eighty-three percent of the enrolled population completed the first year of the trial.

Trial 2007008: Percent Change in Lumbar Spine BMD at week 52 (mITT, LOCF)			
	5 mg IR daily before breakfast IRBB	**35 mg DR weekly after breakfast DRFB**	**35 mg DR weekly before breakfast DRBB**
N, treated	307	307	308
N, completed Month 12	257 (83.7)	252 (82.1)	258 (83.8)
Discontinued	50 (16.3)	55 (17.9)	49 (15.9)
Death	1 (0.3)	0	0
Serious Adverse Event	22 (7.2)	20 (6.5)	21 (6.8)
Adverse Event with Withdrawal	25 (8.1)	28 (9.1)	19 (6.2)
Adverse Event	211 (68.7)	222 (72.3)	238 (77.3)
Source: 2007008-report-body, Table 23			

Deaths: One death occurred in the first year of trial 2007008. A 68 year old woman in the 5 mg daily immediate release risedronate group suffered a myocardial infarction study day (b)(6) and died (b)(6) days later.

Serious Adverse Events: Serious adverse events (SAEs) were reported by 63 subjects in the first year of trial 2007008 (22 (7.2%) in the 5 mg daily immediate release, before breakfast group, 20 (6.5%) in the 35 mg weekly delayed release, following breakfast group, and 21 (6.8%) in the 35 mg weekly delayed release, before breakfast group). As outlined in Dr. Bienz's review, the incidence of SAEs was similar across treatment groups and the most common system organ classes for SAEs were Infections, Injury, and Gastrointestinal disorders.

An imbalance is noted in the SOC Reproductive and Breast disorders, with more events occurring in the 5 mg daily immediate release, before breakfast group (4 subjects in the 5 mg daily immediate release, before breakfast group, one subject in the 35 mg weekly delayed release, following breakfast group, and none in the 35 mg weekly delayed release, before breakfast group [p=0.0527]). As outlined in Dr. Bienz's review, the events in the IRBB group were individual events that are known to occur in the postmenopausal population and are likely not due to study drug.

Adverse Events Leading to Study Withdrawal: A total of 72 subjects experienced an adverse event leading to withdrawal from trial 2007008 (25 (8.1%) in the 5mg daily immediate release, before breakfast group, 28 (9.1%) in the 35mg weekly delayed release, following breakfast group, and 19 (6.2%) in the 35mg weekly delayed release, before breakfast group). Events were balanced between treatment groups. As outlined in Dr. Bienz's review, gastrointestinal adverse events were the most common adverse event reason for study withdrawal.

Adverse Events: Overall, 72.8% of subjects reported an adverse event during the first year of trial 2007008 (211 (68.7%) in the 5mg daily immediate release, before breakfast group, 222 (72.3%) in the 35mg weekly delayed release, following breakfast group, and 238 (77.3%) in the 35mg weekly delayed release, before breakfast group). An imbalance is noted, with more subjects in the 35 mg weekly delayed release, before breakfast group reporting events (77.3% in the 35 mg weekly DRBB group compared to 68.7% in the 5mg daily IRBB group, p=0.0572). This imbalance appears to be driven by gastrointestinal disorders with the main imbalance in the preferred term abdominal pain, upper (7 (2.3%) in the 5mg daily immediate release, before breakfast group, 9 (2.9%) in the 35mg weekly delayed release, following breakfast group, and 23 (7.5%) in the 35mg weekly delayed release, before breakfast group [p=0.0041]). The most common adverse event preferred terms were arthralgia, nasopharyngitis, diarrhea, back pain, and influenza.

Trial 2007008: Adverse Events by SOC (ITT, Month 12)

	5 mg IR daily before breakfast IRBB	35 mg DR weekly after breakfast DRFB	35 mg DR weekly before breakfast DRBB
N, treated	307	307	308
n (%), Overall	211 (68.7)	222 (72.3)	238 (77.3)
Gastrointestinal	85 (27.7)	101 (32.9)	105 (34.1)
Infections and infestations	89 (29.0)	100 (32.6)	94 (30.5)
Musculoskeletal	73 (23.8)	78 (25.4)	78 (25.3)
Injury	32 (10.4)	29 (9.4)	27 (8.8)
Nervous system	38 (12.4)	26 (8.5)	31 (10.1)
General	16 (5.2)	25 (8.1)	29 (9.4)
Skin and subcutaneous	16 (5.2)	21 (6.8)	21 (6.8)
Respiratory	17 (5.5)	17 (5.5)	20 (6.5)
Vascular	14 (4.6)	17 (5.5)	19 (6.2)
Investigations	12 (3.9)	16 (5.2)	24 (7.8)
Metabolism and nutrition	9 (2.9)	12 (3.9)	14 (4.5)
Cardiac	10 (3.3)	11 (3.6)	21 (6.8)
Blood and lymphatic	2 (0.7)	9 (2.9)	4 (1.3)
Psychiatric	8 (2.6)	9 (2.9)	12 (3.9)
Eye	12 (3.9)	8 (2.6)	9 (2.9)
Ear and labyrinth	12 (3.9)	7 (2.3)	7 (2.3)
Neoplasms	8 (2.6)	7 (2.3)	6 (1.9)
Renal	7 (2.3)	7 (2.3)	13 (4.2)
Endocrine	7 (2.3)	6 (2.0)	10 (3.2)
Reproductive	9 (2.9)	5 (1.6)	5 (1.6)

Source: 2007008-report-body, Table 24

Adverse Events of Special Interest:

Fractures: See the efficacy section for a discussion of fractures that occurred during the first year of trial 2007008. There were two reports of hip and/or femur fracture. A 78 year old subject in the 35mg weekly delayed release,

following breakfast group sustained a femoral neck fracture after falling on a slippery street, and a 73 year old subject in the 5mg daily immediate release, before breakfast group sustained a distal femur fracture that was located above the condyle after slipping in the shower and falling. No further details of the femur fracture are available to be able to determine if it could be considered atypical.

Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause upper gastroesophageal irritation. As outlined in the nonclinical section of this review, the addition of EDTA to risedronate did appear to increase risedronate exposure and exacerbate risedronate toxicities, including local gastric toxicity in animal studies. In the first year of trail 2007008, upper gastrointestinal adverse events occurred in 154 subjects (45 (14.7%) in the 5mg daily immediate release, before breakfast group, 48 (15.6%) in the 35mg weekly delayed release, following breakfast group, and 61 (19.8%) in the 35mg weekly delayed release, before breakfast group). More subjects in the 35mg weekly delayed release, before breakfast group experienced upper gastrointestinal AEs (19.8% in the 35 mg DRBB group, compared to 14.7% in the IRBB group). An imbalance was Also noted in the number of subjects reporting moderate to severe upper gastrointestinal adverse events (2.9% in the 5mg daily IRBB group compared to 7.5% in the 35mg weekly DRBB group [p=0.0430]). As outlined in Dr. Bienz's review, preferred terms associated with significantly higher numbers of patients reporting AEs were abdominal pain, upper (7 (2.3%) in the 5mg daily immediate release, before breakfast group, 9 (2.9%) in the 35mg weekly delayed release, following breakfast group, and 23 (7.5%) in the 35mg weekly delayed release, before breakfast group [p=0.0041]); and gastrointestinal pain (none in the 5mg daily immediate release, before breakfast group, none in the 35mg weekly delayed release, following breakfast group, and 4 (1.3%) in the 35mg weekly delayed release, before breakfast group [p=0.0366]). The number of subjects that used nonsteriodal anti-inflammatory products or had prior history of upper gastrointestinal disease appeared balanced between treatment groups and therefore, are not likely to be contributing to the imbalances noted.

Musculoskeletal Pain: An increased incidence of muscular and bone pain has been reported with bisphosphonate use. There was no significant difference in musculoskeletal adverse events, including arthralgia, back pain, musculoskeletal pain, myalgia, neck pain, bone pain and pain in extremity, between the treatment groups (52 (16.9%) in the 5mg daily immediate release, before breakfast group, 56 (18.2%) in the 35mg weekly delayed release, following breakfast group, and 57(18.5%) in the 35mg weekly delayed release, before breakfast group).

Osteonecrosis of the Jaw: Both intravenous and oral bisphosphonates have been associated with osteonecrosis of the jaw. No cases of osteonecrosis of the jaw were reported. Symptoms possibly related to osteonecrosis of the jaw,

including oral abscess, mouth ulceration, pain in jaw, tooth abscess, tooth infection, and toothache, were reported by 15 subjects (6 in the 5mg daily immediate release, before breakfast group, 2 in the 35mg weekly delayed release, following breakfast group, and 7 in the 35mg weekly delayed release, before breakfast group).

Atrial Fibrillation: An increased incidence of atrial fibrillation serious adverse events was noted in one trial with intravenous zoledronic acid and in one arm of the alendronate fracture intervention trial. As outlined in Dr. Bienz's review, six subjects had atrial fibrillation or atrial flutter noted at baseline in trial 2007008. In the first year of the trial, atrial fibrillation events were reported in 4 subjects, one of whom had a history at baseline.

Inflammatory Eye Disease: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Symptoms suggestive of inflammatory eye disease, including preferred terms conjunctivitis, eye irritation, eye inflammation, eye pain and iridocyclitis, were reported by 9 subjects (6 in the 5mg daily immediate release, before breakfast group, 2 in the 35mg weekly delayed release, following breakfast group, and 1 in the 35mg weekly delayed release, before breakfast group).

Acute Phase Reaction: Symptoms consistent with acute phase reaction have been reported with both intravenous and high dose oral bisphosphonate use. Symptoms considered possibly related to an acute phase reaction include flu-like symptoms such as fatigue, fever, chills, myalgia, arthralgia, pain and generalized body aches, occurring within 3 days of dosing and lasting less than 7 days. In the first year of trial 2007008, fifteen subjects reported at least one symptom consistent with acute phase reaction (4(1.3%) in the 5mg daily immediate release, before breakfast group, 7(2.3%) in the 35mg weekly delayed release, following breakfast group, and 4(1.3%) in the 35mg weekly delayed release, before breakfast group).

Laboratory Data: As outlined in Dr. Bienz's review, mean laboratory values remained in the normal range and no clinically significant mean changes in laboratory parameters were noted in trial 2007008.

Hypocalcemia: Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. The nadir in serum calcium historically occurs 7 – 10 days post dose. Hypocalcemia adverse events (preferred terms blood calcium decreased, hypocalcemia) were reported in 3 subjects (one in the 5mg daily immediate release, before breakfast group, two in the 35mg weekly delayed release, following breakfast group, and none in the 35mg weekly delayed release, before breakfast group). In trial 2007008, serum calcium was measured at baseline, day 14, and weeks 13, 26, and 52. Mean serum calcium levels remained within the normal range at all time points and the mean change in serum calcium remained small, with

the largest excursion occurring at day 14 (-0.02 to -0.04 mmol/L). The largest number of subjects shifted from normal to low calcium at day 14 (8 (2.8%) in the 5mg daily immediate release, before breakfast group, 9 (3.2%) in the 35mg weekly delayed release, following breakfast group, and 15 (5.1%) in the 35mg weekly delayed release, before breakfast group).

Parathyroid hormone: In trial 2007008, serum intact parathyroid hormone (iPTH) levels were measured at baseline, day 14, and weeks 13, 26, and 52. Hyperparathyroidism adverse events (preferred terms blood parathyroid hormone increased, hyperparathyroidism secondary, and hyperparathyroidism) were reported in 23 subjects (6 in the 5mg daily immediate release, before breakfast group, 4 in the 35mg weekly delayed release, following breakfast group, and 13 in the 35mg weekly delayed release, before breakfast group). Mean serum iPTH levels were within the normal range at all time points and similar across treatment groups. As outlined in Dr. Bienz's review, a large number of subjects had excursions of iPTH to above normal range (> 65 pg/mL) at some point during the trial (94 (30.6%) in the 5mg daily immediate release, before breakfast group, 101 (32.9%) in the 35mg weekly delayed release, following breakfast group, and 115 (37.3%) in the 35mg weekly delayed release, before breakfast group). However, it was also noted that a large number of subjects had elevated iPTH at baseline.

Elevated iPTH levels in subjects who were normal at baseline was further explored. The largest number of subjects with elevated iPTH occurred at day 14, as one would expect given the anticipated nadir in serum calcium. However, prolonged elevation was also noted in some subjects, predominantly in the 35mg weekly delayed release, before breakfast group. Some subjects had markedly elevated iPTH levels (≥98 pg/mL). As outlined in table 28 of Dr. Bienz's review, a total of 107 subjects with normal iPTH at baseline had elevated iPTH (>65 pg/mL) at week 26 or 52 (26 (8.5%) in the 5mg daily immediate release, before breakfast group, 33 (10.7%) in the 35mg weekly delayed release, following breakfast group, and 48 (15.6%) in the 35mg weekly delayed release, before breakfast group). Similarly, a total of 15 subjects with normal iPTH at baseline had markedly elevated iPTH (≥98 pg/mL) at week 26 or 52 (2 (0.7%) in the 5mg daily immediate release, before breakfast group, 5 (1.6%) in the 35mg weekly delayed release, following breakfast group, and 8 (2.6%) in the 35mg weekly delayed release, before breakfast group).

These findings cannot be adequately explained by changes in serum calcium or phosphorus levels and one questions whether there is an effect from the chelation effect of the EDTA component of Atelvia. I agree with Dr. Bienz that these findings should be labeled.

Bone Histomorphometry: The Applicant has submitted bone histomorphometry data from prior Actonel studies to support the bone safety of Atelvia. However, as previously noted, treatment with Atelvia increases the risedronate exposure 2 – 4

times that seen with immediate release Actonel. This raises concern regarding a potential compromise of bone quality. Of the bone histomorphometry data submitted, only the 15 mg daily immediate release risedronate dose from trial 1998033 approximates the anticipated risedronate exposure achieved with Atelvia. Trial 1998033 was a two year trial of risedronate 5 mg daily, 15 mg daily, 50 mg weekly, and placebo for the treatment of knee osteoarthritis with 1232 men and women age 40 to 80 years randomized. Unpaired, double tetracycline-labeled iliac crest bone biopsy specimens were obtained from 17 subjects in the 15 mg daily group at Month 24. Of the seventeen subjects, 10 were women, with 4 women classified as postmenopausal. Of the four biopsy samples from postmenopausal women, three were evaluable and two had full histomorphometry performed. In the three evaluable specimens, there was no evidence of pathologic changes. One subject that had full histomorphometry evaluated was noted to have an elevated mineralization lag time of 130 days. While prolonged mineralization lag time can be a harbinger of a mineralization defect, this subject's osteoid thickness was 5.2 mcm, which is in the normal range and does not elevate the concern for a mineralization defect.

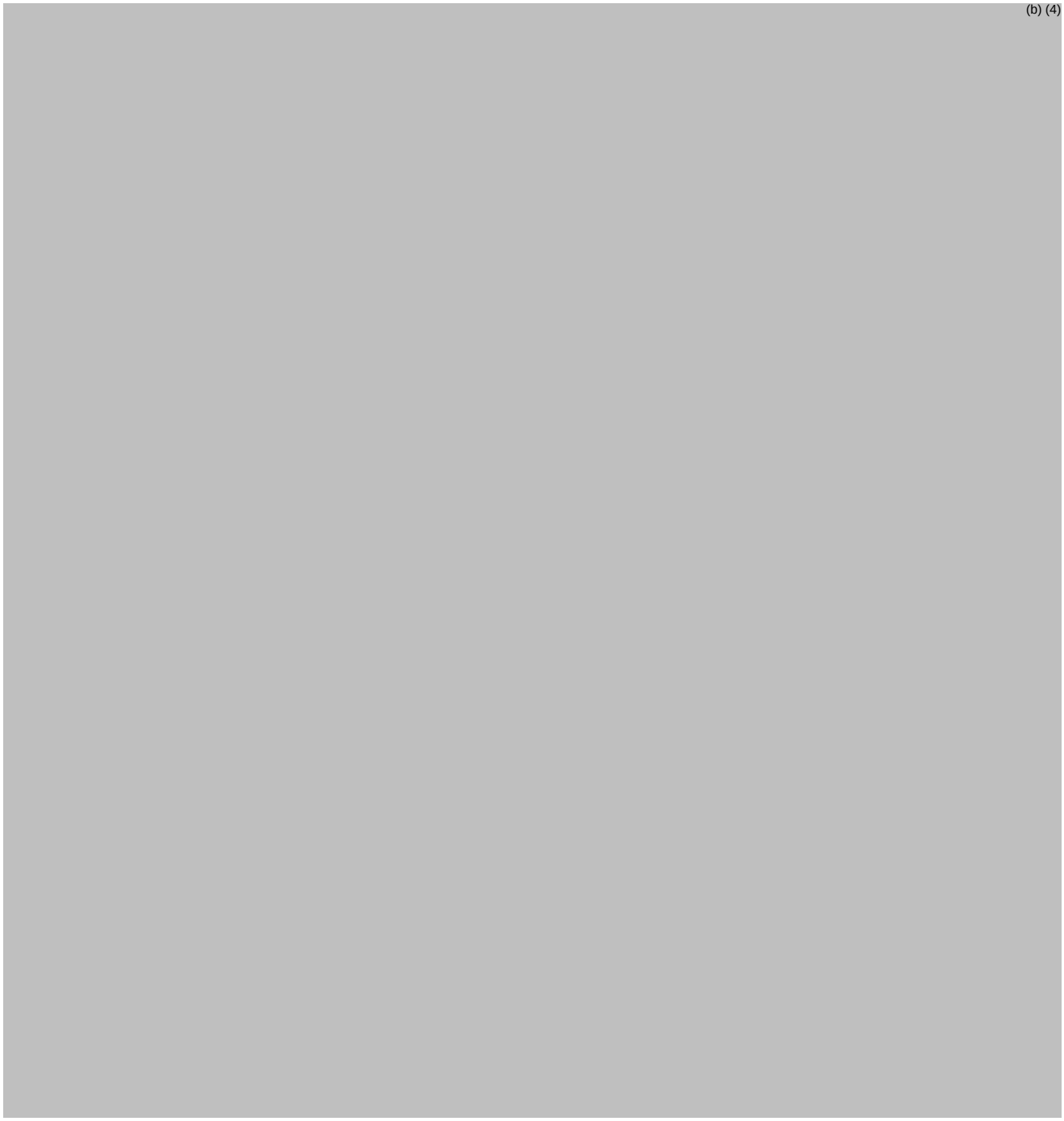
Given the small amount of available data on bone histomorphometry, the clinical team decided that the findings from trial 2007008 would need to be reviewed to adequately assure that the elevated risedronate exposure achieved with Atelvia would not have a negative effect on bone quality and specifically, mineralization. Bone histomorphometry results from trial 2007008 were submitted June 28, 2010. Unpaired, double tetracycline labeled, iliac crest bone biopsy specimens were obtained from 45 subjects at week 104 (18 in the 5mg daily immediate release, before breakfast group, 15 in the 35mg weekly delayed release, following breakfast group, and 12 in the 35mg weekly delayed release, before breakfast group). Demographics features were balanced across the treatment groups.

Of the 45 biopsies obtained, 44 were evaluable and double tetracycline labeling was evident in all biopsies. Full histomorphometric analysis was not possible in 5 subjects (one in the 5mg daily immediate release, before breakfast group, three in the 35mg weekly delayed release, following breakfast group, and one in the 35mg weekly delayed release, before breakfast group). Qualitative histology revealed no pathologic findings in any of the biopsy samples. As outlined in Table 53 of Dr. Bienz's review, activation frequency is suppressed in all treatment groups, which is expected given the known suppression of bone turnover seen with risedronate. Mineralization defects, a concern with bisphosphonates and of particular concern with Atelvia because of the increased risedronate exposure and the presence of the chelating agent EDTA, would present as an increase in mineralization lag time, and if severe enough an increase in osteoid thickness.

Mineralization lag time (MLT) represents the mean time interval between deposition of osteoid and its mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. The mean MLT was in the normal range for all treatment groups. However, outliers are also present. Overall, 16 subjects had a biopsy with a MLT greater than 100 days (5

in the 5mg daily immediate release, before breakfast group, 7 in the 35mg weekly delayed release, following breakfast group, and 4 in the 35mg weekly delayed release, before breakfast group). Two subjects, one in the 5mg daily immediate release, before breakfast group and one in the 35mg weekly delayed release, following breakfast group had a biopsy with a MLT greater than 250 days. No subjects with an elevated MLT had an osteoid thickness that was elevated. Therefore, while MLT is elevated in a number of subjects, there is no evidence of a mineralization defect.

(b) (4)



(b) (4)

8.3 Safety Update

The 120 safety update was submitted on January 22, 2010, and contains safety information from the ongoing trial 2007008 up to a cut-off date of November 19, 2009. The imbalance noted in the interim one year study report, namely more subjects in the 35 mg weekly delayed release, before breakfast group reporting adverse events continues to be present, now with a lower p-value = 0.0401. No new deaths have occurred in the trial and there is no new signal in serious adverse events or adverse events leading to withdrawal.

Gastrointestinal disorders: The imbalance noted in the preferred term "abdominal pain, upper" continues to be present in the 120 day safety update, with the number of patients in the immediate release risedronate group remaining stable and the number of subjects reporting symptoms in the delayed release groups increasing (7 (2.3%) in the 5mg daily immediate release, before breakfast group, 10 (3.3%) in the 35mg weekly delayed release, following breakfast group, and 26 (8.4%) in the 35mg weekly delayed release, before breakfast group [p=0.0009]). There were no new gastrointestinal pain adverse events reported.

There were no new safety signals or significant changes in other adverse events of interest as reported in the 120 day safety update.

8.4 Summary of Safety

The data supporting the safety of Atelvia is predominantly from the one year interim study report for Trial 2007008. Approximately 615 postmenopausal women with osteoporosis were exposed to Atelvia, once weekly 35 mg delayed release risedronate, taken either before breakfast or immediately following breakfast.

Overall, approximately 73% of the study population reported at least one adverse event during the first year of the trial. One death occurred during the first year of the trial, in the active comparator group. Serious adverse events occurred in approximately 7% of enrolled subjects and were generally balanced across the treatment groups. The most common system organ classes for SAEs were Infections, Injury, and Gastrointestinal disorders. Adverse events leading to withdrawal were reported in 8% of enrolled subjects and were generally balanced across the treatment groups with gastrointestinal adverse events the most common reason for withdrawal.

When comparing the currently approved active comparator, 5 mg daily immediate release risedronate to 35 mg once weekly delayed release risedronate given before breakfast, a significant imbalance is noted with significantly more subjects receiving delayed release risedronate before breakfast reporting adverse events. This imbalance appears to be driven primarily by gastrointestinal adverse events. This finding becomes notable because of the long history and relationship between oral bisphosphonates and upper gastrointestinal irritation. In fact, when evaluating upper

gastrointestinal adverse events specifically, several imbalances are noted. Treatment with Atelvia 35 mg before breakfast resulted in significantly more adverse event reports of upper abdominal pain 7.5% compared to 2.3% for the Actonel 5 mg daily (p=0.0041). This trend continued and strengthened when the 120 day safety data is added (8.4% compared to 2.3%, p=0.0009). An imbalance was also noted in the number of subjects reporting moderate to severe upper gastrointestinal adverse events 2.9% in the 5mg daily immediate release, before breakfast group compared to 7.5% in the 35mg weekly delayed release, before breakfast group (p=0.0430). Similar trends were not noted when Atelvia 35 mg was administered immediately following breakfast. These findings are highly concerning and raise questions regarding the risk benefit profile of Atelvia administered before breakfast. I agree with Dr. Bienz that Atelvia should only be approved if administered immediately following breakfast, not before breakfast.

Because of concerns regarding Atelvia's potential for altered calcium metabolism due to the combination of increased risedronate exposure, the presence of the chelating agent EDTA, and the effect such changes may have on bone mineralization in at-risk patients, bone histomorphometry results were carefully reviewed for mineralization defects. While approximately 2% of subjects had mineralization lag times greater than 100 days, no subject with an elevated MLT had an osteoid thickness that was elevated. Therefore, there is no evidence of a mineralization defect.

9. Advisory Committee Meeting

An Advisory Committee meeting was not conducted for this New Drug Application.

10. Pediatrics

The Applicant's request to waive the requirement to conduct pediatric studies in all age groups for delayed release risedronate was reviewed by the PeRC PREA subcommittee on February 17, 2010, and was granted. A full waiver for pediatric studies was recommended because studies would be impossible or highly impracticable and because the indications for this drug product (postmenopausal osteoporosis) do not occur in the pediatric population.

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): There are no AIP issues with this product or Applicant.

Exclusivity or patent issues: In this New Drug Application, the Applicant is relying on nonclinical, clinical, and clinical pharmacology data from immediate release

risedronate. However, they own this data and therefore, there are no issues regarding the right to reference the data.

Financial disclosure: Dr. Bienz has reviewed the financial disclosure statements for all investigators and sub-investigators. No financial relationships of concern were noted.

DSI audits: The Division of Scientific Investigations (DSI) conducted inspections of three clinical sites from the Phase 3 trial 2007008 to evaluate the conduct of the trial.

Dr. Artur Racewicz's site in Białystok, Poland was inspected because 24% of enrolled subjects at this site reported adverse events, compared to the trial average of 75%. Dr. Jose Zanchetta's site in Ciudad Autónoma de Buenos Aires, Argentina was inspected because of high enrollment (63 randomized subjects). Dr. Robert Recker's site at Creighton University Osteoporosis Research Center in Omaha, NE was inspected because of high enrollment (34 randomized subjects).

All three clinical sites were classified as NAI (no deviation from regulations) and the data appear acceptable.

12. Labeling

Proprietary name: The Applicant initially proposed the proprietary name (b) (4) After review and discussion between the clinical team and the Division of Medication Error Prevention and Analysis (DMEPA) these names were denied (b) (4)

(b) (4)

Subsequently, the Applicant submitted the proposed proprietary name Atelvia. After further analysis, both the clinical team and DMEPA agree that the proprietary name Atelvia. The Applicant was informed on June 23, 2010. Re-analysis of the proprietary

name Atelvia was performed within 90 days of approval and the name remains acceptable.

Physician labeling: The Applicant has based the full prescribing information on the currently approved Actonel label. With the exception of minor revisions to labeling language, the full prescribing information has been agreed upon. The main changes to the Applicant's proposed labeling include:

Indications statement: The Applicant proposed indications language for the treatment of postmenopausal osteoporosis (b) (4) In addition, the review team was concerned that given the increased risedronate exposure with the delayed release product, it should be made clear that the approval was based on noninferiority of bone mineral density, not fracture data. Therefore, the agreed upon indications statement is:

> ATELVIA is indicated for the treatment of osteoporosis in postmenopausal women. Bone mineral density increases achieved at one year with ATELVIA are non-inferior to increases seen with risedronate sodium 5 mg (immediate release) daily. Daily risedronate sodium 5 mg (immediate release) has been shown to reduce the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures.

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Dosage and Administration: The Applicant proposed (b) (4) the review team believes that Atelvia should only be taken following breakfast. The review team also believed it was important for prescribers to know that the gastrointestinal adverse event profile of Atelvia if taken before breakfast. Therefore, the agreed upon Dosage and Administration section will read.

> ATELVIA should be taken in the morning immediately following breakfast.
>
> When compared with immediate release risedronate, treatment with ATELVIA resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions. ATELVIA should be taken immediately following breakfast and not under fasting conditions.

Carton and immediate container labels: The Carton and Container labeling have been found acceptable by the CMC reviewer, the Division of Medication Error, Prevention and Analysis, and the Division of Drug Marketing, Advertising and Communication.

Patient labeling: The Applicant has submitted a patient package insert, which has been review by the Division of Risk Management's Patient Labeling Team and the

Division of Drug Marketing, Advertising and Communication. The applicant has accepted all of the recommended changes to the patient labeling.

13. Recommendations/Risk Benefit Assessment

13.1 Treatment of Postmenopausal Osteoporosis

Recommended Regulatory Action:

I recommend APPROVAL of Atelvia 35 mg once weekly, dosed immediately following breakfast, for the treatment of postmenopausal osteoporosis.

Risk Benefit Assessment:

I agree with Dr. Bienz that the efficacy of Atelvia has demonstrated a positive risk/ benefit profile when administered immediately following breakfast. At one year, the mean lumbar spine BMD increase was 3.1% in the 5 mg daily immediate release before breakfast group and 3.4% in the 35 mg weekly delayed release following breakfast group. The upper bound of the 95% confidence interval for the difference in mean percent change from baseline was less than the pre-defined noninferiority limit of 1.5%. These findings allow an adequate bridge between the BMD increases noted with the delayed release risedronate formulations and the fracture risk reduction efficacy previously demonstrated with the 5 mg daily immediate release risedronate. The safety profile of Atelvia administered immediately following breakfast is similar to the known safety profile of immediate release Actonel administered before breakfast.

Recommendation for Postmarketing Risk Evaluation and Management Strategies:

At this time, a Postmarketing Risk Evaluation and Management Strategy is not recommended.

Recommendation for other Postmarketing Requirements and Commitments:

I agree with the following Postmarketing Commitment proposed the Clinical Pharmacology team and agreed to by the Applicant:

> 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

Recommended Comments to Applicant:

No further comments need to be sent to the Applicant.

(b) (4)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA E KEHOE
10/08/2010

GEORGE S BENSON
10/08/2010