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APPLICATION NUMBER:

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SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	October 8, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA #	22-560
Applicant Name	Warner Chilcott
Date of Submission	September 24, 2009
PDUFA Goal Date	July 24, 2010 – PDUFA goal date extended to October 24, 2010
Proprietary Name / Established Name	Atelvia Risedronate sodium
Dosage Forms / Strength	Delayed-release tablet/35 mg to be taken once weekly
Proposed Indication(s)	1. Treatment of postmenopausal osteoporosis (b) (4)
Action	Approval of indication #1. (b) (4)

Medical Officer Review	Stephen Bienz, MD
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Gemma Kuijpers, PhD Lynnda Reid, PhD
CMC Review	Caroline Strasinger, PhD Moo Jhong Rhee, PhD
Biopharmaceutics Review	Sandra Suarez Sharp, PhD Patrick Marroum, PhD
Clinical Pharmacology Review	Doanh Tran, PhD Myong-Jin Kim, PharmD
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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
SEALD = Study Endpoints and Labeling Development

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1. Introduction

Risedronate sodium (Actonel), a bisphosphonate, was first approved in the United States in 1998 for the treatment of Paget's disease of bone. Actonel has subsequently been approved for the treatment and prevention of post-menopausal osteoporosis and to increase bone mass in men with osteoporosis. Doses for the treatment of osteoporosis include 5 mg/day, 35 mg/week, 75 mg two consecutive days/month, and 150 mg/month. All of these doses are immediate release tablet formulations which are to be taken with 6 to 8 oz. of water at least 30 minutes before the first food or drink of the day. Bisphosphonates, including risedronate, have poor bioavailability and must be taken under fasting conditions.

The sponsor has developed a delayed release formulation consisting of 35 mg risedronate sodium and (b) (4) edetate disodium dihydrate [EDTA] in an enteric coating designed to release the drug at a pH above 5.5. (b) (4)

NDA 22-560 requests (b) (4) indications for this new delayed release risedronate formulation. (b) (4)

- Treatment of post-menopausal osteroporosis (NDA 22-560/Original-1)

(b) (4)

2. Background

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, non-inferiority 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 and regimen that was shown to be efficacious in reducing morphometric vertebral fractures.

An End of Phase 2 meeting was held on June 28, 2007. The Division was concerned about the higher risedronate exposure seen with the delayed release formulation and recommended that the Sponsor consider the addition of a lower dose arm, such as a 20 mg delayed release dose, in Phase 3 trial 2007008. The Sponsor chose not to pursue this option and studied only the 35 mg once weekly delayed release dose.

A pre-NDA meeting was held on April 21, 2009. The sponsor was informed that, primarily because of the increased risedronate exposure seen with the delayed release tablet, bone histomorphometry would be necessary for an adequate safety review.

The Sponsor submitted NDA 22-560 on September 24, 2009. During the review of the NDA, the clinical team determined that bone histomorphometry data would be required to adequately assure bone safety. The Sponsor was informed of this requirement 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. The sponsor was notified of a 3-month clock extension on July 14, 2010. The revised PDUFA date is now October 24, 2010.

3. CMC/Device

The CMC reviewer concluded that "from the CMC perspective, this NDA is recommended for approval. No Phase 4 commitments are recommended."

The Chemistry review concluded that the NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An overall "Acceptable" recommendation has been made by the Office of Compliance. All labels and labeling have the required information. The ONDQA/biopharmaceutics team has reviewed the dissolution specifications for the Atelvia drug product. They found the data acceptable from a biopharmaceutics perspective.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that "from a pharmacology/toxicology perspective, this NDA can be approved. No additional nonclinical studies are needed."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. 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. When compared to the currently approved 35 mg immediate release risedronate formulation, the bioavailability (based on urinary levels) of the delayed release formulation is higher than the 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). 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.

The Sponsor 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 serum AUC instead of urinary risedronate levels which were determined in prior studies. The results showed that the 90% CIs for test/reference ratio for risedronate C_{max} and AUC_{tlast} were within the 80 – 125% BE limits indicating that the two formulations are bioequivalent.

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.

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. The Pharmacometric review 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 patients with normal renal function 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. The phase 3 clinical trial 2007008 did enroll subjects with a creatinine clearance (CLcr) ≤50 ml/min and no safety concerns were raised. 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.

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

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 C_{max} and AUC_{tlast}, the ratios for male to female were 0.825 and 0.814, respectively.

The initial Clinical Pharmacology review (June 15, 2010) stated that the "Acceptable" recommendation was contingent on a satisfactory inspection of the clinical and bioanalytical sites for bioequivalence study 2008119 by the Division of Scientific Investigation (DSI).

The clinical and bioanalytical sites for the bioequivalence (BE) study 2008119 were inspected by the Division of Scientific Investigation (DSI) and the DSI recommendations were included in a memorandum dated July 21, 2010. For the 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. The serum data, which provided the primary assessment of bioequivalence between the two formulations, are considered 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 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.

Further review of the ISR failure in study 2009003 (a phase two study of 75 and 100 mg strengths of a once per month DR formulation) by the clinical pharmacology review team concluded 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. However, since the actual cause for ISR failure in certain urine samples is not known, the absolute concentration values of any given urine sample measured by using (b) (4) may not be reliable. The clinical pharmacology reviewer concluded that analyses of urinary risedronate data are important in the studies that assess changes in bioavailability of risedronate due to co-administration of food, calcium supplementation, 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. The clinical pharmacology reviewer concluded that "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.

- 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 clinical pharmacology reviewer concluded that "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 (Study 2007027) evaluating the effect of concomitant administration of esomeprazole on the bioavailability of risedronate delayed release tablets, 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 for efficacy, the clinical pharmacology reviewer initially recommended that the sponsor reanalyze the urine samples from study 2007027 using the method in (b) (4) to confirm the results. "Furthermore, the current results of study 2007027 should not be included in the

product label and the 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 and the label could be revised accordingly." When this issue was discussed with the sponsor, the sponsor stated that urine samples to re-evaluate risedronate levels were not available.

Therefore, the following postmarketing commitment was requested and agreed upon by the sponsor:

"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

6. **Clinical Microbiology**

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

7. **Clinical/Statistical-Efficacy**

The efficacy data to support this NDA are derived primarily from the one year data of **Phase 3 trial 2007008**. Supporting data are contained in Phase 2 dose-finding trial 2005107.

Phase 3 trial 2007008 is a multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, non-inferiority trial in subjects with postmenopausal osteoporosis which is being conducted at 43 centers in 8 countries in North and South America and Europe. Lumbar spine bone mineral density (BMD) is the primary endpoint. Data from the first 52 weeks are reported in this NDA application. The second year of the trial is ongoing and continues to be double-blinded.

Nine hundred twenty-two (922) women at least 50 years of age, at least 5 years postmenopausal, and with confirmed osteoporosis (T-score at spine or total hip $\leq$ -2.5 or T-score $\leq$ -2.0 with a prevalent vertebral fracture) were randomized to risedronate 35 mg DR weekly either immediately following breakfast (FB) or at least 30 minutes before breakfast (BB), or to risedronate 5 mg IR daily. Patients were instructed not to lie down for at least 30 minutes after dosing. All subjects are supplemented with 1000 mg of elemental calcium and 800-1000 IU vitamin D daily throughout the trial.

Demographic and baseline characteristics for Trial 2007008 were balanced across treatment groups. Fifteen percent of subjects were enrolled at US sites. Overall, 99.5% of patients were Caucasian including the 31.3% who were Hispanic (in this trial Hispanic was considered an ethnicity within the Caucasian race), the mean age at screening was 66

years, and the mean number of years since menopause was 18. The mean baseline BMD T score was -3.11 for the lumbar spine and -2.95 for the total hip. Approximately 27% of the study population had a vertebral fracture at baseline.

A total of 1859 subjects were screened and 923 subjects were randomized. Of the subjects randomized, 922 received at least one dose of study drug and constitute the ITT population. One subject randomized to the 5 mg IRBB group did not take any study drug. Overall, 17% of subjects discontinued from the study. The percent of subjects who dropped out on or prior to Week 52 was similar across the 3 groups (16 to 18%). The most common reasons for discontinuation were AE (8%, 5 mg IR daily; 9%, 35 mg DRFB; 5%, 35 mg DRBB) and voluntary withdrawal (7%, 5 mg IR daily; 8%, 35 mg DRFB; 8%, 35 mg DRBB).

Endpoints: The primary efficacy endpoint was the change in lumbar spine BMD from baseline to 52 weeks comparing risedronate 35 mg DR weekly (following breakfast and then, if successful, before breakfast) to 5 mg IR daily (before breakfast) with last observation carried forward (LOCF) for non-inferiority.

For the primary analysis, in hierarchal order, the percent change from baseline in lumbar spine BMD of the 35 mg DRFB (following breakfast) regimen was compared to the 5 mg IRBB (before breakfast) regimen. If non-inferiority were demonstrated, the 35 mg DRBB regimen was compared to the 5 mg IRBB regimen. Analysis of variance (ANOVA) was performed with treatment, anti-coagulation medication use (warfarin, heparin), and pooled centers as fixed effects, baseline lumbar spine BMD as a covariate, and percent change from baseline in lumbar spine BMD at Endpoint as the response variable.

If the upper limit of the 95% 2-sided confidence interval (CI) for the treatment difference obtained from the model above were less than the pre-defined non-inferiority margin of 1.5%, the 35 mg DR once-a-week regimen was declared non-inferior to the 5 mg IR daily regimen.

Fracture reduction is the efficacy measure desired for agents to treat osteoporosis. As large and long trials are generally required to show fracture efficacy, once that has been shown for a drug, the Agency usually requires comparable BMD change for other doses and formulations of the drug to "bridge" to the fracture efficacy. For risedronate, fracture efficacy has been shown for the 5 mg immediate release dose.

Secondary endpoints included: 1) BMD increases at other sites being comparable for the 35 mg DR formulation and the 5 mg IR formulation and 2) Bone turnover markers (BTMs) serum type-1 collagen C-telopeptide (CTX), urine type-I collagen N-telopeptide (NTX), and bone specific alkaline phosphatase (BSAP) in the various treatment groups.

Efficacy results:

The mean percent change from baseline in lumbar spine BMD was the primary efficacy outcome. All three dosing regimens increased lumbar spine BMD significantly from

baseline to Endpoint in the primary efficacy population (Table 1). The mean percent change from baseline in lumbar spine BMD was 3.1% for the 5 mg IR group and 3.4% for both the 35 mg DRFB group and 35 mg DRBB group.

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 IR 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 1. Trial 2007008 Lumbar Spine BMD, % Change from Baseline, PE Population

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

The BMD changes in the two 35 mg DR groups were higher than that of the 5 mg IR group. The LS mean differences for the two DR groups shown in Table 1 is a negative number because the statistical analysis plan called for subtracting the 35 DR groups from the 5 mg IR group.

The lumbar spine BMD increase achieved in the 5 mg IR group (3.1%) is less than the BMD increases seen in prior 5 mg daily risedronate trials where the change in BMD at 52 weeks ranged from +3.4% to +4.0%. Trial population differences may explain the lower BMD change. Hispanic subjects exceed 31% in this trial, but ranged from 2 to 5 % in the earlier trials.

Superiority to the 5 mg Daily Regimen:
As both DR weekly dosing regimens were shown to be non-inferior to the 5 mg IR daily regimen based on lumbar spine BMD at Week 52, the DR results were pooled and the superiority of the DR once-a-week regimen to the 5 mg IR daily regimen assessed based on percent change from baseline in lumbar spine BMD at Week 52. The 95% confidence interval of the difference crosses zero (-0.766, 0.236), indicating that the DR regimens do not improve BMD statistically more than the IR regimen. The p-value for the difference is 0.2992.

Secondary endpoints:

BMD measurements of the lumbar spine and proximal femur (total hip, femoral neck, and trochanter) acquired at baseline and at Weeks 26, 52, and Endpoint (Week 52 with LOCF) were compared for all treatment groups for the ITT population. Statistically significant BMD increases are noted at all post-baseline time-points for all sites in all treatment groups. At the femoral neck in the 35 mg DRBB group at 52 Weeks and Endpoint, BMD was increased statistically more than the IR regimen. Numerically, however, the DR regimens increased BMD more than the IR regimens in 23 of 24 comparisons; only the 35 mg DRBB group at 26 Weeks at the lumbar spine increased numerically in BMD less than the corresponding IR group and by 52 Weeks and Endpoint that had numerically reversed. This is consistent with the known higher absorption of the DR formulations, and is supportive of efficacy of the 35 mg DR formulation.

Vertebral Fractures in Trial 2007008:

A total of 7 subjects experienced at least 1 new vertebral fracture (2 in the 5 mg IRBB group, 2 in the 35 mg DRFB group, and 3 in the 35 mg DRBB group). The number and percent of patients with radiographically detectable (morphometric) new vertebral fractures over the 52 weeks of the trial was small and similar across all treatment groups. This trial was not powered for fracture endpoints.

Markers of Bone Turnover in Trial 2007008:

All bone turnover markers (BTMs) (serum type-1 collagen C-telopeptide (CTX), urine type-I collagen N-telopeptide (NTX), and bone specific alkaline phosphatase (BSAP)) were significantly reduced from baseline for all treatment groups at all post-baseline time points tested.

Statistical review:

The statistical reviewer noted that “the efficacy results from one multi-regional study (2007008) support that risedronate sodium 35 mg delayed-release (DR) weekly dose was as effective as risedronate sodium 5 mg immediate-release (IR) before breakfast daily dose in the increase of lumbar spine bone mineral density (BMD) in postmenopausal

women at Week 52. From a statistical perspective, this application provided adequate data to support the non-inferiority of risedronate 35 mg DR weekly dose to risedronate 5 mg IR daily dose. However, the number of subjects who reported treatment emergent adverse events (TEAE) in the 35 mg DR before breakfast dose group was statistically higher than subjects reported in the 5 mg IR dose group."

Efficacy summary:

For the treatment of postmenopausal osteoporosis indication, the Cross-Discipline Team Leader, primary Medical Officer, and the Statistical reviewers believe that the efficacy of Atelvia, based on bone mineral density, has been demonstrated. At one year, the mean lumbar spine increase in BMD 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 non-inferiority 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**

The primary safety data source for this NDA is the 52 week data from Phase 3 trial 2007008 (n=922 randomized to three groups – 5 mg risedronate before breakfast daily, 35 mg before breakfast weekly, and 35 mg following breakfast weekly). This is the longest duration trial with the risedronate DR formulation (52 weeks of data submitted from a 2 year trial) and the only trial in one of the populations for which a treatment indication is sought.

Exposure:

Although days of exposure are similar (Table 2), PK data suggest increased total exposure to risedronate with the DR formulation.

Table 2. Trial 2007008 Extent of Exposure, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Subject-days of Exposure n Mean (SD) Min Max	307 322.5 (101.6) 1 381	307 318.1 (110.3) 2 380	307 324.3 (102.6) 1 389
Duration of Treatment > 90 Days > 180 Days > 270 Days > 360 Days	 282 (91.9%) 270 (87.9%) 258 (84.0%) 245 (79.8%)	 275 (89.6%) 264 (86.0%) 258 (84.0%) 249 (81.1%)	 281 (91.2%) 271 (88.0%) 264 (85.7%) 250 (81.2%)
Source: Study 2007008 Year 1 Final Report, Table 22			

Demographics:

Demographic and baseline characteristics for Phase 3 trial 2007008 were balanced across treatment groups. Fifteen percent of subjects were enrolled at US sites. Overall, 99.5% of patients were Caucasian including the 31.3% who were Hispanic (Hispanics were listed as an ethnicity within the Caucasian race for this trial), the mean age at screening was 66 years, and the mean number of years since menopause was 18. The mean baseline BMD T score was -3.11 for the lumbar spine and -2.95 for the total hip. Approximately 27% of the study population had a vertebral fracture at baseline.

Deaths:

One death was reported in the Phase 3 trial 2007008. A 68-year-old Caucasian woman in the 5 mg IRBB group with a history of tobacco use, COPD, and hypertension suffered cardiac arrest on study day 31. She was successfully resuscitated but remained in a coma and died 11 days later.

There were no deaths reported in the Phase 2 trial 2005107 or any of the Phase 1 trials.

Nonfatal Serious Adverse Events (SAEs):

A total of 63 subjects experienced a serious adverse event (SAE) in Trial 2007008 (22 (7.2%) in the 5mg daily IR group, 20 (6.5%) in the 35mg weekly DRFB group, and 21 (6.8%) in the 35mg weekly DRBB group). Serious adverse events, grouped by system organ class and preferred term, occurring in two or more subjects in any treatment group

are shown in Table 3. Infections and infestations, injury, poisoning and procedural complications, and gastrointestinal disorders were the system organ classes with the most SAEs recorded. The incidence of SAEs was similar across all treatment groups. No patterns were observed for any treatment group as to any specific SAE.

Numerically more subjects (4) in the 5 mg IRBB group experienced reproductive and breast disorder SAEs, compared to one subject in the DR groups. One of these subjects had an ovarian cyst, one breast dysplasia, one uterine prolapse, and one female genital tract fistula as SAEs. In the DR groups, one subject in the 35 mg DRFB group suffered an SAE of ovarian cyst in this SOC.

Table 3. Trial 2007008 Serious Adverse Events in ≥ 2 Subjects 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	p-value
Overall	22 (7.2%) 24	20 (6.5%) 24	21 (6.8%) 25	0.9594
Infections and infestations	3 (1.0%) 3	5 (1.6%) 5	2 (0.6%) 2	0.4518
Injury, poisoning and procedural complications	3 (1.0%) 4	4 (1.3%) 5	2 (0.6%) 3	0.6557
Radius fracture	1 (0.3%) 1	2 (0.7%) 2	1 (0.3%) 2	0.8510
Gastrointestinal	2 (0.7%) 2	3 (1.0%) 3	3 (1.0%) 3	1.0000
Neoplasms	2 (0.7%) 2	2 (0.7%) 2	0 (0.0%) 0	0.4056
Cardiac	1 (0.3%) 1	1 (0.3%) 1	3 (1.0%) 4	0.6280
Nervous system	1 (0.3%) 1	1 (0.3%) 1	2 (0.6%) 2	1.0000
Reproductive and breast	4 (1.3%) 4	1 (0.3%) 1	0 (0.0%) 0	0.0527
Endocrine disorders	2 (0.7%) 2	0 (0.0%) 0	1 (0.3%) 1	0.5541
Hyperparathyroidism	2 (0.7%) 2	0 (0.0%) 0	1 (0.3%) 1	0.5541
Musculoskeletal	2 (0.7%) 2	0 (0.0%) 0	3 (1.0%) 3	0.3808
Osteoarthritis	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Vascular	1 (0.3%) 1	0 (0.0%) 0	3 (1.0%) 3	0.3319

n (%) = number (percent) of subjects within specified category and treatment
nAE = number of adverse events within the specified category and treatment
P-value from Fisher's Exact Test (no adjustment for multiple comparisons)
Source: Study 2007008 Year 1 Final Report, Table 26

Two subjects in Phase 2 trial 2005107 had a total of 3 serious adverse events. A 60-year-old woman in the 35 mg DRFB group was hospitalized for appendicitis on study day 22. She recovered after a laparoscopic appendectomy and continued in the trial. A 61-year-old woman in the 50 mg DRFB group was hospitalized on study day 8 with chest pain and cholelithiasis. She recovered following laparoscopic cholecystectomy. She withdrew from the trial.

One SAE occurred during Trial 2008119, the bioequivalence trial. A 45-year-old man fractured his right ankle while playing basketball during the washout period 11 days after receiving the Phase three 35 mg DR treatment. The subject withdrew from the trial.

There were no SAEs reported in Phase I trials 2004132, 2007027, 2007120, 2008052, 2008138, and 2008076.

Study Withdrawal/Discontinuation:

Adverse events leading to withdrawal in Trial 2007008 were balanced between treatment groups. A total of 72 subjects experienced an adverse event leading to withdrawal (25 (8.1%) in the 5 mg daily IRBB group, 28 (9.1%) in the 35 mg weekly DRFB group, and 19 (6.2%) in the 35 mg weekly DRBB group). Gastrointestinal adverse events were the most common reason for withdrawal, and accounted for 41 of 72 (57%) of the study withdrawals.

Adverse events:

Adverse Events: Overall, 72.8% of subjects reported an adverse event during the first year of trial 2007008. An imbalance is noted, with more subjects in the 35 mg weekly delayed release, before breakfast group reporting events (Table 4). 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.

Table 4. Adverse Events in Trial 2007008

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:

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.

Fractures: 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 in 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 an "atypical fracture."

Gastrointestinal disorders: In the first year of trail 2007008, upper gastrointestinal adverse events occurred in 154 subjects with more subjects experiencing upper gastrointestinal AEs in the 35 mg weekly delayed release, before breakfast group. An imbalance was noted in the number of subjects reporting moderate to severe upper gastrointestinal adverse events (9 (2.9%) in the 5 mg daily immediate release, before breakfast group, 15 (4.9%) in the 35 mg weekly delayed release, following breakfast group, and 23 (7.5%) in the 35 mg weekly delayed release, before breakfast group [p=0.0430]). Preferred terms associated with significantly higher numbers of patients reporting AEs were abdominal pain, upper (7 (2.3%) in the 5 mg daily immediate release, before breakfast group, 9 (2.9%) in the 35 mg weekly delayed release, following breakfast group, and 23 (7.5%) in the 35 mg 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]).

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.

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.

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. 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 5 mg daily immediate release, before breakfast group, 7(2.3%) in the 35 mg weekly delayed release, following breakfast group, and 4(1.3%) in the 35 mg weekly delayed release, before breakfast group).

Laboratory Data: 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 5 mg daily immediate release, before breakfast group, two in the 35 mg weekly delayed release, following breakfast group, and none in the 35mg weekly delayed release, before breakfast group).

Bone Histomorphometry: The Sponsor submitted bone histomorphometry data from prior Actonel studies to support the bone safety of Atelvia. Treatment with Atelvia, however, increases the risedronate exposure 2 – 4 times that seen with immediate release Actonel. This raises concern regarding a potential compromise of bone quality. Given the small amount of available data on bone histomorphometry, the clinical team determined that the histomorphometry 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 5 mg daily immediate release, before breakfast group, 15 in the 35 mg weekly delayed release, following breakfast group, and 12 in the 35 mg weekly delayed release, before breakfast group).

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 5 mg daily immediate release, before breakfast group, three in the 35 mg weekly delayed release, following breakfast group, and one in the 35 mg weekly delayed release, before breakfast group). Qualitative histology revealed no pathologic findings in any of the biopsy samples. Activation frequency was 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 (MLT), and if severe enough an increase in osteoid thickness.

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 5 mg daily immediate release, before breakfast group, 7 in the 35 mg weekly delayed release, following breakfast group, and 4 in the 35mg weekly delayed release, before breakfast group). Two subjects, one in the 5 mg daily immediate release, before breakfast group and one in the 35 mg 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) The average age of enrollees in trial 2007008 was approximately 66 years with a range of 50 – 87 years. Overall, 10% of the enrolled study population was age 55 years or less and 24% were age 60 years or less. All subjects in trial 2007008 had a diagnosis of osteoporosis, either by BMD or by the presence of an osteoporotic fracture, at study entry.

(b) (4) .

(b) (4)

Safety Update:

The 120 day 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]).

Safety Summary:

The data supporting the safety of Atelvia are predominantly from the one year interim study report for Trial 2007008. Approximately 600 postmenopausal women with osteoporosis were exposure 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. 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 5 mg daily immediate release, before breakfast group compared to 7.5% in the 35 mg weekly delayed release, before breakfast group (p=0.0430)]. Similar trends were not noted when Atelvia 35 mg was administered immediately following breakfast. I agree with the Cross

Discipline Team Leader and the primary Medical officer that Atelvia should only be approved if administered immediately following breakfast, not before breakfast.

9. **Advisory Committee Meeting**

No Advisory Committee meeting was held. Atelvia (risedronate delayed release tablet) is a new formulation of an approved drug. No new safety concerns were identified during the review.

10. **Pediatrics**

The sponsor requested a full waiver for pediatric studies under PREA and their request was reviewed by the Pediatric Review Committee (PeRC). DRUP had recommended that a full waiver be granted because the disease/condition does not exist in children. "PeRC agreed with the Division to grant a full waiver for this product."

11. **Other Relevant Regulatory Issues**

Division of Scientific Investigations:

Three clinical sites were inspected and the data generated from these sites was considered acceptable.

Financial Disclosure:

Financial disclosure statements for investigators and sub-investigators for all required trials in the development program were submitted and reviewed by the primary medical officer who concluded that "the Sponsor appears to have adequately complied with the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators." No financial arrangements whereby the value of the compensation could be influenced by the outcome of the study, no significant payments of other sorts from the sponsor, excluding the costs of conducting the study or other clinical studies, no proprietary or financial interest in the test product, and no significant equity interest in the sponsor of the study for themselves, spouses, or dependent children were found. Financial statements were missing for two sub-investigators for the Phase 2 trial 2005107. One of these left employment before screening for the study began and the other left employment and could not be located.

Division of Risk Management (DRISK):

DRISK reviewed the Patient Package Insert and their recommendations were incorporated into the labeling.

Division of Drug Marketing, Advertising and Communications (DDMAC):

DDMAC reviewed the Package Insert (PI) and the Patient Package Insert (PPI) and their recommendations were considered and incorporated into the labeling. DDMAC also reviewed the carton and container labeling.

Division of Medication Error Prevention and Analysis Labeling (DMEPA):

DMEPA found the proposed proprietary name, Atelvia, to be acceptable. The Container and Carton labels were also found to be acceptable.

12. Labeling

Proprietary name: The Sponsor initially proposed the proprietary name (b) (4) with an alternate of (b) (4) After review and discussion between the clinical team and the Division of Medication Error Prevention and Analysis (DMEPA) these names were denied because the data submitted did not provide sufficient evidence (b) (4)

(b) (4)

Subsequently, the Applicant submitted the proposed proprietary name Atelvia. Both the clinical team and DMEPA agree that the proprietary name Atelvia is acceptable.

Physician labeling:

(b) (4)

(b) (4), the review team believed that, given the increased risedronate exposure with the delayed release product, it should be made clear in labeling that the approval was based on non-inferiority 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: (b) (4) . The gastrointestinal adverse events

profile of Atelvia when taken before breakfast is significantly worse than the currently approved Actonel taken before breakfast. For this reason, the review team believes that Atelvia should only be taken following breakfast. The review team also believes it is important for prescribers to know 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.

13. Decision/Action/Risk Benefit Assessment

Decision:

The Cross Discipline Team Leader, primary Medical Officer, and the Statistical, Clinical Pharmacology, and Pharmacology/toxicology reviewers all believe that Atelvia should be approved for the indication "treatment of postmenopausal osteoporosis" (NDA 22-560/Original 1). (b) (4)

I agree with these recommendations. NDA 22-560/Original-1 will be approved (b) (4)

Risk/Benefit Determination [NDA 22-560/Original-1: Treatment of postmenopausal osteoporosis indication].

The efficacy of Atelvia for the treatment of postmenopausal osteoporosis has been adequately demonstrated. In a well controlled Phase 3 trial (2007008), at one year, the mean lumbar spine increase in BMD was 3.1% in the fisedronate 5 mg daily immediate release before breakfast group and 3.4% in the risedronate 35 mg weekly delayed release tablet following breakfast group. The upper bound of the 95% confidence interval for the difference in mean percent change from baseline in BMD was less than the pre-defined non inferiority limit of -1.5%. These findings allow an adequate bridge between the BMD increases noted with the delayed release risedronate formulation 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. I believe that Atelvia has demonstrated a positive risk/ benefit profile when administered immediately following breakfast for the treatment of postmenopausal osteoporosis indication and an approval letter will be sent to the sponsor.

Recommendations for Risk Evaluation and Mitigation Strategies (REMS)/Post Marketing Requirement (PMR) [NDA 22-560/Original 1: Treatment of postmenopausal osteoporosis indication].

None

Post-marketing commitment [NDA 22-560/Original-1: Treatment of postmenopausal osteoporosis indication]:

The clinical pharmacology review team has recommended that the following post-marketing commitment is necessary to assure efficacy in patients taking both Atelvia and a proton pump inhibitor. I concur with this recommendation. The sponsor has agreed to conduct this 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


(b) (4)

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/s/

GEORGE S BENSON
10/08/2010