

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022560Orig1s000

MEDICAL REVIEW(S)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-560

Applicant: Procter and Gamble Pharmaceuticals

Stamp Date: September 24, 2009

Drug Name: (b) (4)
(Risedronate sodium delayed release)

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			(b) (4)
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?		X		The application is missing 2.6.2 Pharmacology written summary, 2.6.3 Pharmacology tabulated summary, 2.6.4 Pharmacokinetic written summary, and 2.6.5 Pharmacokinetic tabulated summary. The clinical reviewer defers to ClinPharm and PharmTox on filability. The reviewers from those disciplines have been advised.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If				505(b)(1)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Application is a 505(b)(2) and if appropriate, what is the reference drug?				
DOSE					
13.	<p>If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i>, appropriately designed dose-ranging studies)?</p> <p>Study Number: 2005107</p> <p>Study Title: A Multicenter, Double Blind, Active-controlled, Parallel Design Study to Assess the Efficacy, Safety and Pharmacokinetics of Risedronate Upon Multiple Dose Oral Administration of a 35 mg Delayed-Release, a 50 mg Delayed-Release or a 35 mg Immediate-Release Formulation Administered Weekly for 13 Weeks to Postmenopausal Women</p> <p>Sample Size: 181</p> <p>Arms: 35 mg IR (approved) weekly 35 mg DR weekly following breakfast 50 mg DR weekly following breakfast 50 mg DR weekly before breakfast</p> <p>Location in submission: 5.3.4.1</p>	X			<p>Exposure from the 35 mg and 50 mg DR formulations appeared to be greater than that of the 35 mg IR (approved) formulation. Exposure in trial 2008052, a phase 1 single dose 4 period crossover trial, from a 20 mg DR formulation was also higher than from the 35 mg IR formulation. It appears systemic exposure with the 35 mg DR formulation is 2-4 times higher than the 35 mg IR formulation. High dose risedronate bone histomorphometry data included in this application:</p> <p>1. Trial 1998033, both genders for OA with biopsy at 24 months, 15 at 15 mg IR daily (10 female, some may be premenopausal), 17 at 50 mg IR weekly.</p> <p>2. Trial HMR4003E/3001 for PMO with 22 paired biopsies at 24 months on 50 mg IR weekly. PK Trial 2000009 indicates dose-proportional steady state pharmacokinetics between 5 mg and 15 mg daily doses.</p> <p><i>Note: It is not clear that risedronate exposure achieved with these "high" doses approximate the exposure achieved with the proposed DR formulations</i></p>
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: A Non-inferiority Comparison of 35 mg Delayed-release Risedronate, Administered Once-weekly Either Before or After Breakfast, and 5 mg Immediate-release Risedronate, Administered Once-daily Before Breakfast, in the Treatment of Postmenopausal Osteoporosis as Assessed Over 2 Years; a Phase III, Multicenter, Double-blind, Double-dummy, Randomized, Active-controlled, Parallel-group Study Indication: PMO Pivotal Study #2: None Indication:	X			Submitted based on year one data of a two year trial
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary endpoint of lumbar spine BMD for the Phase 3 trial
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Not found (15% of subjects in the Phase 3 trial are from the US)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Not found (15% of subjects in the Phase 3 trial are from the US)
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Found for all trials except RRF008593, conducted in 1993

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement (b) (4)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes (see question 8)

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. NA

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

1. Insufficient information is available to assure adequate bone safety for the level of risedronate exposure achieved with the proposed product (35 mg DR formulation). As outlined in the preNDA meeting minutes, this safety issue, which requires adequate bone histomorphometry data at the anticipated drug exposure levels, remains a concern for the Division.
 - a. Provide the tables referenced in sections 4.3.5.1 and 4.3.5.2 of Clinical Report 1998033 regarding bone histopathology and histomorphometry (Appendix 3.16 Tables 1 and 2 and Appendix 5.18 Table 1) and any other tables, figures, or listings related to bone histopathology or histomorphometry from Clinical Report 1998033 not included in your NDA submission.
 - b. Provide justification for why the bone histomorphometry data provided in the submission should be adequate to demonstrate the bone safety of the proposed product. This discussion should include an in depth analysis of the risedronate exposures achieved or anticipated for each histomorphometry study submitted. Pharmacokinetic data should be submitted in support of your discussion.
2. Submit a rationale for assuming the applicability of foreign data in the NDA submission to the U.S. population or provide the location of this rationale in the submission. This discussion should include an in-depth analysis of the calcium and vitamin D status in various populations enrolled.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22560

ORIG-1

PROCTER AND
GAMBLE
PHARMACEUTICA
LS INC

 (b) (4)

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

/s/

STEPHEN R BIENZ
11/18/2009

THERESA E KEHOE
11/19/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-560
Priority or Standard	Standard
Submit Date(s)	September 24, 2009
Received Date(s)	September 24, 2009
PDUFA Goal Date	July 24, 2010
Division / Office	Division of Reproductive and Urologic Products / Office of Drug Evaluation III
Reviewer Name(s)	Stephen R. Bienz, MD
Review Completion Date	June 30, 2010
Established Name	Risedronate Sodium
Proposed Trade Name	Atelvia
Therapeutic Class	Bisphosphonate
Applicant	Warner Chilcott
Formulation(s)	Delayed-release Tablet
Dosing Regimen	35 mg Orally Weekly in the Morning (b) (4)
Indication(s)	• Treatment of Postmenopausal Osteoporosis (b) (4)
Intended Population(s)	Postmenopausal Women with Osteoporosis (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Treatment of Osteoporosis in Postmenopausal Women: Based on my review of the clinical data submitted for Atelvia, I recommend that Atelvia be approved to be taken following breakfast for treatment of postmenopausal osteoporosis.

- Atelvia 35 mg weekly has been shown to be non-inferior to risedronate immediate release 5 mg daily to increase bone mineral density at the lumbar spine over one year.
- Adverse events with Atelvia dosed immediately following breakfast appear similar to immediate release risedronate.
- Atelvia should not be taken before breakfast. In the Phase 3 trial, an 8 to 9% increase in subjects with adverse events was shown when Atelvia was dosed at least 30 minutes before breakfast. In the 120 Day Safety Update, this was statistically significant. The increase was especially concentrated in gastrointestinal and abdominal pain categories.

(b) (4)

(b) (4)

1.2 Risk Benefit Assessment

Atelvia consists of 35 mg risedronate sodium with (b) (4) of disodium EDTA and an enteric coating designed to release the drug above pH 5.5. Bisphosphonates, including risedronate, have very poor oral bioavailability and must be taken under fasting conditions. (b) (4)

Risedronate is currently approved as an immediate release product in doses of 5 mg daily, 35 mg once weekly, 75 mg two consecutive days once monthly, and 150 mg once monthly. Fracture efficacy was demonstrated with the 5 mg daily dose. All immediate release risedronate doses are to be taken with 6 to 8 oz. of plain water at least 30 minutes before the first food or drink of the day. Patients are not to lie down for 30 minutes after dosing. In the Phase 3 trial, Atelvia was taken with at least 4 oz. of plain water at least 30 minutes before or immediately after breakfast and subjects were instructed not to lie down for 30 minutes after dosing.

The efficacy of Atelvia was demonstrated in the first year of the two year Phase 3 trial 2007008, which is ongoing. Lumbar spine BMD increase with 35 mg weekly Atelvia taken either at least 30 minutes before or immediately after breakfast was not inferior to immediate release risedronate 5 mg daily. The upper limit of the 95% two-sided CI for the difference in mean percent change from baseline in lumbar spine BMD between the 5 mg IRBB group and the 35 mg DRFB group was less than the pre-defined non-inferiority margin of 1.5% (mean difference -0.233 [CI: -0.816, 0.349]), as was the upper limit of the 95% two-sided CI comparing the 5 mg IRBB group and the 35 mg DRBB regimen (mean difference -0.296 [CI: -0.873, 0.281]). This was confirmed in trial 2007008 by comparable BMD increases at other sites and comparable drops in bone turnover markers CTX, NTX, and bone specific alkaline phosphatase.

Disodium EDTA is considered an excipient in Atelvia. Preclinical data suggest, however, that EDTA may enhance absorption of risedronate, at least partially, through mechanisms other than the chelation (b) (4) and may potentiate risedronate toxicity, including toxicity in the gastrointestinal tract.

Pharmacokinetic (PK) comparisons in the Atelvia (risedronate DR) development program indicate risedronate from Atelvia is absorbed systemically from 2.1 to 4.2 times the extent the absorption from a 35 mg immediate release risedronate (see Section 6.1.8).

Absorption of the DR formulation is similar whether taken 30 minutes before or immediately after breakfast. In the only direct comparison of absorption of the DR formulation at those times a 50 mg risedronate was used.

With the higher mean absorption concerns arise with safety generally. As EDTA may potentiate GI adverse events (AEs), this becomes a particular area of concern. Also, bone safety, particularly with regard to bone formation and apposition, is an issue.

Bone safety at high systemic absorption had been inadequately studied (see Appendix 9.5). Late in the review cycle, Sponsor submitted 2 year bone histomorphometry data from the Phase 3 trial 2007008 which does appear to show bone safety with Atelvia (see Section 7.4.5.1).

More subjects with AE are seen with the Atelvia taken at least 30 minutes before breakfast. This reaches statistical significance in the 120 Day Safety Update with about 8 % more subjects having AEs compared to the approved 5 mg immediate release formulation (subjects with AE, 231 (75%) for 5 mg IRBB, 241 (78%) for 35 mg DRFB, and 257 (83%) for 35 mg DRBB regimens, $p=0.0401$. If subjects with AE are compared for 35 mg DRFB to 5 mg IRBB, the p -value is 0.3891. If subjects with AE are compared for 35 mg DRBB to 5 mg IRBB, the p -value is 0.0128. See Section 7.7). The increase was especially concentrated in gastrointestinal and abdominal pain categories.

Bisphosphonates are widely used and available for osteoporosis and Paget's disease. The advantage with Atelvia is the ability to take it with food which is a convenience; there does not appear to be an efficacy advantage or disadvantage, nor is there a safety advantage. Moderate safety issues should therefore preclude approval of the application or any part of the application for which safety and efficacy have not been shown or can be reasonably assumed. On this basis:

- Approval for treatment of postmenopausal osteoporosis is recommended only for Atelvia dosed immediately after breakfast with at least 4 oz. of plain water. Other bisphosphonates, including immediate release risedronate, continue to be available for dosing at least 30 or 60 minutes before breakfast.

(b) (4)



1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant will need to provide a final report for the 2 year Phase 3 trial 2007008.

2 Introduction and Regulatory Background

2.1 Product Information

- Atelvia (proposed trade name) is risedronate sodium (established name) 35 mg and disodium EDTA (b) (4) in an enteric coated tablet designed to release contents above pH 5.5. Inactive ingredients include ferric oxide yellow, magnesium stearate, methacrylic acid copolymer, polysorbate 80, silicified microcrystalline cellulose (ProSolv SMCC90), simethicone, sodium starch glycolate, stearic acid, talc, and triethyl citrate.
- Risedronate is a pyridinyl bisphosphonate. The chemical name is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. Atelvia is a new combination of risedronate with the inactive ingredient disodium ethylenediaminetetraacetic acid (EDTA) (b) (4).
- Risedronate is a bone antiresorptive agent.
- The Sponsor proposes Atelvia to be taken 35 mg orally weekly in the morning (b) (4) for treatment (b) (4) of postmenopausal osteoporosis (b) (4).

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple drugs are currently approved for the treatment of postmenopausal osteoporosis, including multiple bisphosphonates, teriparatide, the estrogen agonist/antagonist raloxifene, and calcitonin. (b) (4)

(see Table 1).

Table 1, Approved Drugs for Osteoporosis

Drug	Dose	Route	Treatment of PMO
Bisphosphonates			
Atelvia (Proposed)	35 mg	PO	X
Risedronate	5 mg	PO	X
	35 mg	PO	X
	75 mg	PO	X
	150 mg	PO	X
Alendronate	5 mg	PO	
	10 mg	PO	X
	35 mg	PO	
	70 mg	PO	X
Ibandronate	3 mg	IV	X
	150 mg	PO	X
Zoledronate	5 mg	IV	X
PTH			
Teriparatide	20 mcg	SC	X
Estrogens			
Estrogen, various	various		
Estrogen agonist/antagonist			
Raloxifene	60 mg	PO	X
Calcitonin			
Calcitonin	200 IU	SC, nasal	X
PMO = postmenopausal osteoporosis, OP = osteoporosis			
(b) (4)			
Source: Package inserts			

2.3 Availability of Proposed Active Ingredient in the United States

Risedronate is approved for marketing in the United States for the following indications (NDA 20-835 except as noted):

- 03/27/1998, approved at 30 mg per day to treat Paget's disease of the bone
- 04/14/2000, approved at 5 mg per day to treat and prevent post menopausal osteoporosis and glucocorticoid-induced osteoporosis
- 05/17/2002, approved at 35 mg per week to treat and prevent post menopausal osteoporosis
- 08/12/2005, approved at 35 mg per week with calcium (separate tablets) to treat and prevent post menopausal osteoporosis (NDA 21-823)
- 08/11/2006, approved at 35 mg per week to increase bone mass in men with osteoporosis

- 04/16/2007, approved at 75 mg two consecutive days per month to treat and prevent (prevention per approval letter, caveat language in labeling) postmenopausal osteoporosis
- 04/22/2008, approved at 150 mg per month to treat postmenopausal osteoporosis (caveat language in labeling for prevention)

These are all oral tablet formulations; there is no liquid oral or IV preparation.

All of the currently approved doses are immediate release. To facilitate delivery of the tablet to the stomach, reduce upper GI adverse effects, and improve bioavailability, it is recommended that the tablet be swallowed before breakfast on an empty stomach with the patient in an upright position and with a full glass of plain water (6 to 8 oz.) Patients should then remain upright and refrain from any other oral intake for the next 30 minutes. Adequate intake of calcium and vitamin D is important in all patients. Risedronate is not recommended for patients with severe renal impairment (creatinine clearance <30 ml/min).

2.4 Important Safety Issues With Consideration to Related Drugs

Oral and intravenous bisphosphonates are approved for the treatment and/or prevention of postmenopausal osteoporosis (PMO) and glucocorticoid-induced osteoporosis, osteoporosis in men, Paget's disease of bone, hypercalcemia of malignancy, multiple myeloma, and bony metastases. Safety concerns with bisphosphonates include:

- **Gastrointestinal irritation, including dysphagia, esophagitis, and esophageal and gastric ulcers** can occur with oral bisphosphonates, particularly if not taken correctly.
- **Hypocalcemia:** Due to their mechanism of action, bisphosphonates prevent mobilization of calcium from bone. As bone is the major reservoir of calcium in the body, hypocalcemia may occur or worsen with bisphosphonate use, especially if taken without calcium and vitamin D supplementation.
- **Severe and occasionally incapacitating bone, joint and muscle pain** has been reported with bisphosphonate use. The etiology of the pain is not clear and in most cases, resolves with drug discontinuation.
- **Ocular inflammation, such as uveitis and scleritis**, occurred in as many as 0.1% of patients treated with risedronate.
- **Osteonecrosis, primarily of the jaw.** This has occurred most commonly in cancer patients treated with intravenous bisphosphonates, especially after undergoing dental procedures. However, some spontaneous cases have been reported in patients with PMO taking oral bisphosphonates, mainly with long-term use.
- **Renal damage:** Deterioration of renal function was observed with high dose Zometa (8 mg) and when zoledronic acid was infused over 5 minutes rather than the approved 15 minute time frame. A direct correlation of bisphosphonate dosing and deterioration of renal function has not been observed with any other

bisphosphonate product. Minimal data exists, however, in patients with a creatinine clearance <30 ml/min.

- **Harm to fetal skeleton:** As bisphosphonates are incorporated into bone, there is a theoretical risk if taken at any time before or during pregnancy, since bisphosphonates have a very long half-life in bones and are available for release back into the systemic circulation. Animal experiments have documented adverse effects on fetal skeletons; information in humans is extremely limited. Class labeling for all bisphosphonates was implemented for this potential concern in 2004.
- **Delayed fracture healing** due to suppression of osteoclast function is a theoretical, but unproven, risk.
- **Atypical fractures** of the femur have been reported and this safety issue is currently undergoing further evaluation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Risedronate delayed release IND 74,086 selected events:

- Pre-IND 74,086 was filed 12/19/2005. Earlier, input had been sought from the Division by a submission to IND 31,029 Serial No. 652, letter date June 14, 2005 mostly regarding EDTA (b) (4) with risedronate in a weekly formulation being considered an inactive excipient and its GRAS status.
- A pre-IND meeting was held 02/15/2006. Major applicable discussion includes:
 - From a CMC perspective, "edetate disodium dihydrate USP" is acceptable for use in the IND studies, and compendial requirements are applicable. Whether or not it is considered to be an active ingredient will be a clinical determination. (b) (5)
 - Doses of EDTA above (b) (4) needed to be supported by safety data.
- On 05/26/2006, after an exchange of e-mails and letters the following was sent to Sponsor: *The Division concurs with your request that edetate disodium dihydrate USP (b) (4) be categorized as an excipient. Edetate disodium dihydrate USP (b) (4) will not be considered to be an active ingredient.*
- IND 74,086 was filed on 06/14/2006
- An end of phase 2 meeting was held 06/28/2007. Issues included:
 - The apparent doubling of risedronate exposure with the delayed release product with possible effects on safety. The Agency recommended an additional lower dose, such as 20 mg, be studied in Phase 3.
 - The Sponsor agreed the phase 3 trial would be extended to 2 years for further safety information, but the Sponsor would submit one year data for approval of the NDA. Bone biopsies, clinical chemistries including calcium, phosphorus, magnesium, and PTH, and urinary calciums were to be included.

- [REDACTED] (b) (4)
- Pharmacokinetic data could be based on urine data alone. Later serum PK data was requested with the Phase 3 to commercial bioequivalence trial.
- A pre-NDA meeting was held 04/21/2009.
 - [REDACTED] (b) (4)
 - [REDACTED]
 - Sponsor was told bone histomorphometry data would be necessary to allow adequate safety review.
 - Sponsor was told approvability based on one year data would be a review issue.

2.6 Other Relevant Background Information

Sponsor originally requested [REDACTED] (b) (4) as the trade name for this product. After Agency objections, primarily for safety concerns [REDACTED] (b) (4), Sponsor withdrew that request and, on 4/12/2010, submitted Atelvia as the proposed trade name with [REDACTED] (b) (4) as an alternative. Atelvia has been found tentatively acceptable by DMEPA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is well organized with adequate datasets except for older trials. Information was generally easily found.

Pharmacokinetic information for the higher doses of immediate release risedronate did need to be requested and/or searched for in old submissions. This information was needed to compare risedronate absorption to allow comparison of bone histomorphometry, but PK data for the high dose risedronate were in separate trials from the histomorphometry.

3.2 Compliance with Good Clinical Practices

All trials in the risedronate DR development program were reportedly performed in compliance with Good Clinical Practice (GCP).

DSI conducted inspections of 3 sites from the Phase 3 trial 2007008.

- Dr. Artur Racewicz, Bialystok – Poland (low proportion of subjects with adverse events)
- Dr. Jose Zanchetta, Ciudad Autónoma de Buenos Aires – Argentina (high enrollment)
- Robert Recker, MD, Creighton University Osteoporosis Research Center, Omaha, NE (high enrollment)

Based on preliminary information, no significant regulatory violations were observed at these three sites. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

3.3 Financial Disclosures

Financial disclosure statements for investigators and sub-investigators for all required trials in the development program were submitted and reviewed. 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.

The Sponsor appears to have adequately complied with the FDA Guidance for Industry on Financial disclosure by Clinical Investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry review concludes 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 (Description and How Supplied sections) have the required information.

From the CMC perspective, this NDA is recommended for approval. No Phase 4 commitments are recommended.

The ONDQA/biopharmaceutics team has reviewed the dissolution specifications for the Atelvia drug product. They found the data acceptable from biopharmaceutics perspective. The following comment was conveyed to the sponsor:

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

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

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Pharmacology/Toxicology reviewed a 13 week dog study utilizing high dose risedronate and EDTA, in addition to studies previously reviewed. The Pharm/Tox reviewer has no concerns which affect approvability.

The Pharm/Tox reviewer reports the following: *To support the use of the delayed-release (DR) tablet containing 35 mg risedronate and (b) (4) EDTA, the sponsor conducted a 13-week dog study with weekly doses of risedronate (8 or 16 mg/kg) with or without EDTA (2.5 or 12.5 mg/kg). 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/m² basis).*

Risedronate effects at both 8 and 16 mg/kg doses included decreases in body weight and food consumption (in males), persistence/hypertrophy of primary spongiosa (pharmacologic effect), serum Ca and P decreases, ALT and AST increases, kidney weight increase, and histopathological changes in kidney (de/regeneration, cell enlargement, inflammation), liver (atrophy) and stomach (cell necrosis, regenerative hyperplasia, inflammation). At 16 mg/kg, additional effects included hematology and clinical chemistry changes (RBC decrease, increase in globulin, decrease in albumin, increase in bile acid), liver effects (vacuolation and glycogen decrease), stomach mineralization, and changes in lymph nodes, abdominal vein, testis and aorta. The effects have been observed previously in risedronate oral toxicity studies in the dog.

The main effect of EDTA was to increase risedronate exposure and exacerbate risedronate toxicities, including systemic and local gastric toxicity. 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. The enhancement of toxicity, as well the increase in

risedronate exposure by EDTA, was most prominent at the low 8 mg/kg dose of risedronate. The exacerbation of risedronate-induced toxicities was seen with the 12.5 mg/kg dose of EDTA only. The increase in local gastric toxicity was seen only in females. The NOAEL for risedronate was less than 8mg/kg (<36x human AUC) and the NOAEL for the EDTA-induced exacerbation of local and systemic toxicity was 2.5 mg/kg (0.8x human (b) (4) dose). The data suggest that EDTA in the DR tablet may enhance risedronate absorption and risedronate-related gastrointestinal and systemic toxicities.

Long term animal toxicity studies with oral EDTA have shown low toxicity and suggest no issues with a weekly dose of (b) (4). 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.

In the pivotal Phase 3 study, BMD increase and bone turnover suppression were observed that were slightly larger with the 35mg DR than with the 5mg IR product. Also, in clinical studies with the DR formulation an increase in urine Ae (amount excreted) of risedronate of 2x-4x, probably reflecting an increase in absorption and systemic exposure, has been observed. Based on adequate safety margins derived from nonclinical studies, such an increase in risedronate exposure is unlikely to cause an impairment of bone mineralization or an overt deterioration of bone quality. However, it may be associated with an increased risk for drug-related adverse events in all organ systems including the skeleton.

Conclusions

- *Based on toxicology data obtained with EDTA alone, the (b) (4) Na₂EDTA dose in the DR product is acceptable.*
- *Based on data from a 13-week dog study, the EDTA in the DR tablet may enhance risedronate absorption and risedronate-related systemic toxicities. The EDTA in the DR tablet may also exacerbate risedronate-related GI toxicity.*
- *The EDTA in the DR tablet may increase paracellular permeability to risedronate as well as co-administered drugs. This issue is addressed by the Clinical Pharmacology Reviewer.*
- *Increased risedronate exposure with the DR product is unlikely to cause impairment of bone mineralization or overt deterioration of bone quality.*
- *Increased risedronate exposure with the DR product may lead to a higher risk for drug-related adverse events including skeletal events.*

No new pharm/tox studies related to carcinogenicity and reproductive toxicology were performed to support this NDA. It is recommended that sections on carcinogenicity and

reproductive toxicology are continued from the current Actonel label with minimal change.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Risedronate has an affinity for hydroxyapatite crystals (b) (4)
At the cellular level, risedronate is an anti-resorptive agent and acts by inhibiting osteoclast function.

4.4.2 Pharmacodynamics

In clinical trials, treatment with risedronate results in decreases in biochemical markers of bone turnover. Markers of bone resorption are decreased with risedronate therapy. Because of the normal coupling of bone turnover, markers of bone formation are also decreased to a lesser degree. BMD typically increases, although over time the rate decreases.

4.4.3 Pharmacokinetics

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

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

Available data indicated that bioavailability (based on A_e) of the DR formulation is higher than IR formulation by approximately 2- to 4-fold under the most likely dosing conditions (i.e., risedronate DR immediately after breakfast and IR under per-label condition of at least 30 minutes before breakfast).

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

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2, Trials and Studies in the Risedronate 35 mg DR Development Program

Study ID	Design, Control Type	Arms Dose (mg) n enter/complete	Indication or Population	Mean Age, Yrs. (Range)	Duration
Phase 3 Trial					
2007008 (report 1 year of 2)	Multi-center, double-blind, randomized, active control, non-inferiority Phase 3 (1° endpoint L spine BMD)	5 qd IRBB 307/257 35 qwk DRBB 308/258 35 qwk DRFB 307/252	PMO	65.7 (50-87)	12 months of 24 completed
Phase 2 Trial					
2005107	Multi-center, double blind, randomized, active control Phase 2 (1° endpoint CTX)	35 qwk IRBB 37/33 35 qwk DRFB 36/35 50 qwk DRFB 72/65 50 qwk DRBB 36/35	Healthy PM females	59.9 (45-79)	13 weeks
Phase 1 Trials					
2008076	Phase 1 multicenter randomized, partially blinded, single rising dose monthly dosing (1° endpoint risedronate in urine in 72°)	75 DR 4° BB 16/16 75 DR FB 32/32 100 DR 4° BB 16/16 100 DR FB 32/32 150 IR BB 16/16	Sterile or PM females	56.8 (40-70)	Single dose
2008119	Phase I multicenter, randomized, double blind, crossover PK bioequivalence trial	35 DR 4° BB, commercial or phase 3 product (538/453)	Male (62%), sterile or PM females (38%)	40.2 (19-63)	Two doses. 18- 21 days between
2008138	Phase I multicenter randomized, open-label, 3- period crossover trial of food and calcium/vit. D effect (1° endpoint risedronate in urine in 72°)	35 DRFB 35 DRFB and calcium 35 DR Following dinner (101/94)	Sterile or PM females	58.3 (40-70)	Three doses separated by 18-21 days
2007027	Phase I multicenter randomized, open-label, 3- period, crossover PK trial of esomeprazole (Eso) effect on risedronate 35 mg DR (1° endpoint risedronate in urine in 72°)	All 35 DRFB D 6 placebo D 1-8 Eso 1 hr before dinner D 1-8 Eso 1 hr before brkfst D 1-8 (87/83)	Sterile or PM females	55.4 (40-69)	24 days as 3-8day periods
2008052	Phase I randomized, open- label, multicenter, single dose, 4-period crossover food effect trial (1° endpoint risedronate in urine in 72°)	20 DR 4° BB 20 DRFB 35 DRFB 35 IRBB (94/92)	Sterile or PM females	55.1 (41-69)	Four doses separated by 18-21 days

Study ID	Design, Control Type	Arms Dose (mg) n enter/complete	Indication or Population	Mean Age, Yrs. (Range)	Duration
2007120	Phase I randomized, open-label, multicenter, crossover PK trial of food effect (1° endpoint risedronate in urine in 72°)	35 DR 4° BB 35 DR FB 35 IR 4° BB 35 IR BB (76/74)	Sterile or PM females	53.6 (41-68)	Four doses separated by 18-25 days
2004132	Phase I two center, randomized, open-label single dose PK trial assessing four 35 mg risedronate/ (b) (4) EDTA delayed release formulations	35 IR fasted 20/19 35 DR fasted low-coat pH 5.5 18/18 35 DR fed low-coat pH 5.5 18/18 35 DR fasted high-coat pH 5.5 18/18 35 DR fed high-coat pH 5.5 17/17 35 DR fasted high-coat pH 5.5 SR 16/16 35 DR fed high-coat pH 5.5 SR 19/18 35 DR fasted high-coat pH 7.0 18/18 35 DR fed high-coat pH 7.0 16/16	Healthy male (75%) or female (25%) 40-70 years of age	50.4 (40-70)	Single dose
In vitro Studies					
In vitro Study	A study of the potential for medications containing divalent or trivalent cations to interfere with risedronate DR absorption.				
In vitro Study	A study of the potential for EDTA to cause a change in absorption of narrow therapeutic index and antiviral drugs.				
DR = delayed release, IR = immediately release, FB = following breakfast, BB = before breakfast Source: NDA 22-560 2.7.3.6.1 Tables 1, 2, 3					

5.2 Review Strategy

Extensive reviews were done of the Phase 3 trial 2007008 and the Phase 2 trial 2005107. The Phase 3 trial has by far the most extensive efficacy and safety data, although some efficacy and safety data is found in the Phase 2 trial, along with some PK data.

Brief reviews were done on the Phase 1 trials. None of these involves more than a few doses of the risedronate DR product.

5.3 Discussion of Individual Studies/Clinical Trials

See Appendix 9.4 for individual trial reviews. The Phase 2 dose finding trial, 2005107, efficacy, is also reviewed in abbreviated form below. Safety for Trial 2005107 is reviewed in Section 7. Efficacy for Trial 2008119, the bioequivalence trial between the Phase 3 and commercial DR product, is also reviewed in abbreviated form below, mostly for male to female PK parameters needed for the male indication. Safety for that trial may be found in the trial review in Appendix 9.4. The Phase 3 trial, 2007008, is reviewed in abbreviated form in Sections 6 and 7.

Phase 2 Trial 2005107 efficacy summary: Trial 2005107 showed greater reduction in the bone resorption marker CTX with risedronate delayed release (DR) 50 mg dosed at least 30 minutes prior to breakfast and immediately following breakfast and risedronate DR 35 mg immediately following breakfast weekly compared to approved risedronate immediate release (IR) 35 mg tablet dosed per label. PK studies in a subset of the population demonstrated about twice the urinary excretion (and therefore absorption) with all DR doses and timing compared to the IR dose.

Phase 2 Trial 2005107 was a 13-week, randomized, double-blind, triple-dummy, multiple-dose, active-controlled, multi-center (6 centers in the United States), parallel-group study in healthy post-menopausal women. Serum CTX was the primary endpoint. Subjects were randomly assigned to risedronate using a 1:1:1:2 ratio, respectively to one of the following 4 treatment groups:

- 35 mg IR weekly, at least 30 minutes prior to breakfast (IRBB)
- 35 mg DR weekly, immediately following breakfast (DRFB)
- 50 mg DR weekly, at least 30 minutes prior to breakfast (DRBB)
- 50 mg DR weekly, immediately following breakfast (DRFB)

Tablets taken before breakfast were to be taken with plain water (240 ml) and with the subject in an upright position. Subjects were to remain upright for at least 30 minutes following dosing. Tablets taken after breakfast were also to be taken with plain water (240 ml) but the subject was not restricted from lying down following dosing after breakfast.

All subjects received oral supplements of 1000 mg/day elemental calcium and 400 IU/day vitamin D throughout the treatment period. Calcium supplements were to be ingested at a different time of day than the study drug.

Subjects were female, from 45 to 80 years old, at least 2 years postmenopausal, and in generally good health. Subjects must not have a significant illness or condition which would prevent them from finishing the trial. Medical conditions other than osteoporosis which might affect bone were exclusions, as were most bone active agents in the 3 to 6 months before entering the trial and GI problems requiring use of prescription PPIs or H2 antagonists or frequent OTC antacid, stool softener, or laxative use.

Demographics, Trial 2005107: The treatment groups in Trial 2005107 were similar for demographic and baseline characteristics. Most subjects were Caucasian non-Hispanic or Hispanic. Mean age was 60 years with an age range of 45 to 79 years. Subjects in the PK subset and the per-protocol population were similar to those in the ITT population for demography and baseline characteristics. Table 3 shows demographic and baseline characteristics for the ITT population.

Table 3, Trial 2005107 Demographic and Baseline Characteristics, ITT Population

Parameter Statistic/Category	35 mg IRBB (N=37)	35 mg DRFB (N=36)	50 mg DRBB (N=36)	50 mg DRFB (N=72)	Overall (N=181)	p-value*
Age (years)						0.5993
Mean (SD)	61.1 (6.2)	58.9 (6.7)	60.0 (6.1)	59.7 (7.8)	59.9 (7.0)	
Min, Max	52, 78	45, 74	51, 74	45, 79	45, 79	
Race						0.5032
Asian (Oriental)	6 (16.2%)	6 (16.7%)	3 (8.3%)	10 (13.9%)	25 (13.8%)	
Black	0 (0.0%)	1 (2.8%)	3 (8.3%)	2 (2.8%)	6 (3.3%)	
Caucasian Non-Hispanic	17 (45.9%)	20 (55.6%)	12 (33.3%)	33 (45.8%)	82 (45.3%)	
Hispanic	13 (35.1%)	9 (25.0%)	14 (38.9%)	23 (31.9%)	59 (32.6%)	
Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.6%)	
Multi-Racial	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.6%)	
Other	1 (2.7%)	0 (0.0%)	4 (11.1%)	2 (2.8%)	7 (3.9%)	
Height (cm)						0.5422
Mean (SD)	159.2 (6.0)	159.7 (6.9)	161.4 (6.7)	160.5 (7.5)	160.2 (6.9)	
Min, Max	148, 172	144, 174	145, 173	142, 182	142, 182	
Weight (kg)						0.5320
Mean (SD)	67.9 (10.3)	66.2 (11.3)	69.8 (9.4)	68.5 (10.8)	68.2 (10.5)	
Min, Max	48.3, 91.1	41.6, 86.0	50.9, 90.3	44.3, 92.0	41.6, 92.0	
Tobacco Use						0.7360
Currently	4 (10.8%)	2 (5.6%)	1 (2.8%)	6 (8.3%)	13 (7.2%)	
Never	26 (70.3%)	23 (63.9%)	28 (77.8%)	49 (68.1%)	126 (69.6%)	
Previously	7 (18.9%)	11 (30.6%)	7 (19.4%)	17 (23.6%)	42 (23.2%)	
Alcohol Use						0.4050
Currently	20 (54.1%)	21 (58.3%)	13 (36.1%)	34 (47.2%)	88 (48.6%)	
Never	15 (40.5%)	15 (41.7%)	20 (55.6%)	34 (47.2%)	84 (46.4%)	
Previously	2 (5.4%)	0 (0.0%)	3 (8.3%)	4 (5.6%)	9 (5.0%)	
*Categorical p-values are Fisher's Exact and continuous p-values are one-way ANOVA						
Source: Study Number: 2005107, Final Report, Table 6						

Disposition, Trial 2005107: A total of 398 subjects were screened, 182 subjects were randomized, and 181 subjects received at least 1 dose of study drug and were included in the ITT population in Trial 2005107. One subject was withdrawn by the investigator before dosing for lymphocytosis. Overall, 168 subjects completed the study and 13 subjects were prematurely withdrawn.

No statistically significant differences between groups are noted in disposition Table 4 for proportion of subjects dropping out or for proportion of subjects dropping out for any major reason.

Table 4, Trial 2005107 Intent to Treat Population Disposition

	35 mg IRBB (N=37) n (%)	35 mg DRFB (N=36) n (%)	50 mg DRBB (N=36) n (%)	50 mg DRFB (N=72) n (%)	Fisher's Exact p-value
Completed Trial	33 (89.2%)	35 (97.2%)	35 (97.2%)	65 (90.3%)	0.3658
Did not Complete	4 (10.8%)	1 (2.8%)	1 (2.8%)	7 (9.7%)	0.3658
Adverse Events	2 (5.4%)	1 (2.8%)	0 (0.0%)	4 (5.6%)	0.6514
Lost to Follow-up	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0.3978
Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1.0000
Subject Decision	2 (5.4%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	0.4560

Source: Study Number: 2005107, Final Report, Table 4

Primary endpoint, Trial 2005107: In Trial 2005107, change in the BTM CTX over 13 weeks was the primary efficacy measure. As noted in Table 5 below, the mean percent decrease in serum CTX was greater than 60% for all delayed release formulations, compared to a 43% decrease with the currently marketed immediate release formulation. All decreases from baseline were significant (see CIs in Table 5).

The ratio of the mean percent change from baseline in CTX for the 50 mg DRFB regimen to the 35 mg IRBB regimen at Week 13 (the primary efficacy outcome, **bolded** in Table 5) was 1.54 with the 90% confidence interval not crossing 1.00 (90% CI = 1.18, 2.09) in the ITT population, indicating that this DR regimen suppressed CTX to a greater extent than the 35 mg IRBB regimen. The results of the analysis in the PP population were consistent with the primary analysis.

The 35 mg DRFB regimen and 50 mg DRBB regimen also suppressed CTX to a greater extent than the 35 mg IRBB regimen, with ratios of percent change from baseline at 13 weeks compared to the 35 mg IRBB regimen of 1.44 and 1.51 respectively, and the 90% confidence intervals not crossing 1.00 (see Table 5). Thus, all tested DR formulations suppress CTX to a greater extent than the approved 35 mg IR formulation. These results are supportive of the effectiveness of the risedronate 35 mg DR formulation.

The percent change from baseline in serum CTX at Week 13 comparing the 50 mg DRFB group to the 50 mg DRBB group and the 35 mg DRFB group gives ratios of 1.02 and 1.07 with the 90% confidence interval crossing 1.00 in both cases (90% CI = 0.82,

1.27 and 0.87, 1.32 respectively) (see Table 5). Within the limits of this trial, no difference in the effect of various DR formulations and dose times on CTX is found. The comparability of the 50 mg DRBB and 50 mg DRFB dosing in effect on CTX supports lack of food effect on the DR formulation.

Table 5, Trial 2005107 Mean Percent Change from Baseline to Week 13 of CTX, ITT Population

Treatment Group	N	LS Mean	95% Confidence Interval	Ratio vs. 35 mg IRBB (90% Confidence Interval)*	Ratio vs. 35 mg DRFB (90% Confidence Interval)*	Ratio vs. 50 mg DRBB (90% Confidence Interval)*
35 mg IRBB	34	-43.2	-55.8, -30.6			
35 mg DRFB	35	-62.1	-73.6, -50.6	1.44 (1.09, 1.96)		
50 mg DRBB	35	-65.1	-77.7, -52.5	1.51 (1.14, 2.07)		
50 mg DRFB	65	-66.3	-77.4, -55.2	1.54 (1.18, 2.09)	1.07 (0.87, 1.32)	1.02 (0.82, 1.27)
IRBB = Immediate Release Before Breakfast, DRFB = Delayed Release Following Breakfast, DRBB = Delayed Release Before Breakfast *90% confidence interval for ratios is protocol specified Source: Study Number: 2005107, Final Report, Table 8						

Secondary endpoints:

Change in Urine NTX in Trial 2005107:

As noted in Table 6 below, the mean percent decrease in urine type-1 collagen cross-linked N-telopeptide (NTX) corrected for creatinine clearance was greater than 43% for all delayed release formulations, compared to a 39% decrease with the currently marketed immediate release formulation. In all treatment groups, the decreases from baseline were statistically significant.

The ratios of the DR regimens to 35 mg IRBB reference treatment, as well as the ratios of the 50 mg DRFB group to the 50 mg DRBB group and the 35 mg DRFB group, at Week 13 for change in urine NTX from baseline are summarized in Table 6. All of the DR regimens suppress NTX to a similar degree as the immediate release formulation as the 90% confidence intervals for the ratios cross 1.00, but numerically all reduce NTX to a greater extent than the immediate release formulation. The 50 mg DRFB regimen reduces NTX to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens based on the ratio 90% confidence intervals crossing 1.00.

This is supportive of efficacy of the 35 mg DR formulation.

Table 6, Trial 2005107 Mean Percent Change from Baseline to Week 13 of Urine NTX Corrected for Creatinine Clearance, ITT Population

Treatment Group	N	LS Mean	(95% Confidence Interval)	Ratio vs. 35 mg IRBB (90% Confidence Interval)	Ratio vs. 35 mg DRFB (90% Confidence Interval)	Ratio vs. 50 mg DRBB (90% Confidence Interval)
35 mg IRBB	34	-38.6	(-56.6, -20.5)			
35 mg DRFB	35	-46.6	(-63.0, -30.2)	1.21 (0.75, 2.10)		
50 mg DRBB	35	-43.7	(-61.6, -25.7)	1.13 (0.67, 2.00)		
50 mg DRFB	65	-54.3	(-70.1, -38.4)	1.41 (0.91, 2.40)	1.17 (0.80, 1.75)	1.24 (0.83, 1.99)

Source: Study Number: 2005107, Final Report, Table 9

Change in Bone Specific Alkaline Phosphatase in Trial 2005107:

As noted in Table 7 below, all treatment groups showed statistically significant decrease in BSAP over 13 weeks. The mean percent decrease in serum bone alkaline phosphatase (BSAP) at Week 13 was numerically greater for the 50 mg delayed release formulation compared to the 35 mg DR and IR formulations, but only the 50 mg DRBB treatment regimen was statistically greater using the 95% confidence interval. The ratios of the DR regimens to 35 mg IRBB reference treatment for change in serum BSAP from baseline all show suppression of BSAP to a similar degree as the immediate release formulation as the 90% confidence intervals (protocol specified) of the ratios cross 1.00. The 50 mg DRFB regimen reduces BSAP to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens based on the ratio 90% confidence intervals crossing 1.00.

This is supportive of efficacy of the 35 mg DR formulation.

Table 7, Trial 2005107 Mean Percent Change from Baseline to Week 13 of Serum Bone Alkaline Phosphatase, ITT Population

Treatment Group	N	LS Mean	(95% Confidence Interval)	Ratio vs. 35 mg IRBB (90% Confidence Interval)	Ratio vs. 35 mg DRFB (90% Confidence Interval)	Ratio vs. 50 mg DRBB (90% Confidence Interval)
35 mg IRBB	34	-11.0	(-19.6, -2.4)			
35 mg DRFB	35	-10.4	(-18.3, -2.5)	0.95 (0.32, 2.99)		
50 mg DRBB	35	-20.0	(-28.6, -11.4)	1.82 (0.93, 5.43)		
50 mg DRFB	65	-17.4	(-25.0, -9.8)	1.58 (0.80, 4.72)	1.67 (0.86, 4.67)	0.87 (0.50, 1.49)

Source: Study Number: 2005107, Final Report, Table 10

The mean percent changes from baseline for all the BTMs in Trial 2005107 (CTX, NTX, and BSAP) seen in the 50 mg DRBB regimen were similar to those seen in the 50 mg DRFB regimen, suggesting no food effect.

Pharmacokinetics in Trial 2005107:

The amount of risedronate recovered in urine within 48 hours of dosing on Day 1 and Day 85 was determined in the PK subset of subjects and is given in Table 8. The geometric least square mean of the Day 85 35 mg DRFB group is considerably higher than the Day 1 value (182.6 µg vs. 92.4 µg) with the Day 1 value falling outside the 95% confidence interval for the Day 85 value. This does not occur for any of the other dosing regimens. In addition, the Day 85 35 mg DRFB value is higher than either of the 50 mg DR regimens at either time point. None of the other regimens show a marked tendency for considerably higher values at Day 85 over Day 1. Sponsor reports no consistent change was noted over time for urinary excretion, as an equal number of subjects had increases and decreases in risedronate urinary excretion (Ae) at Day 85. This reviewer has doubts about the reproducibility of the Day 85 35 mg DRFB geometric mean data.

It would appear, from the means and ratio calculations in Table 8, that all of the DR formulations result in roughly twice the risedronate absorption as the approved IR formulation. Similar trends are seen both at Day 1 and Day 85. There is little difference between the 50 mg DR dose given 30 minutes before or immediately following breakfast. This supports lack of food effect. There also appears to be little difference in absorption between the 35 mg DR dose immediately following breakfast and the two 50 mg DR regimens. Sponsor reports this 2-fold increase in absorption for the DR formulations is similar to the increase observed when the 35 mg IR dose is given followed by a 4 hour instead of 30 minute fast. Sponsor contends the comparability of absorption for the 35 mg IR dose followed by a 4 hour fast and the 35 mg DRFB dose also argues for a lack of food effect.

Table 8, Trial 2005107 Risedronate Urinary Excretion over 48 Hours (Ae), Geometric Mean

Visit Treatment	N	Geometric LS Means (Ae, µg)	%CV	95% Confidence Interval	Ratio vs. 35 mg IRBB (95% Confidence Interval)	Ratio vs. 50 mg DRBB (95% Confidence Interval)
Day 1						
35 mg IRBB	20	60.5	118	30.8, 118.9		
35 mg DRFB	19	92.4	594	46.3, 184.6	1.53 (0.58, 4.01)	
50 mg DRBB	18	154.7	349	75.8, 315.8	2.56 (0.96, 6.80)	
50 mg DRFB	38	140.2	288	85.6, 229.6	2.32 (1.01, 5.33)	0.91 (0.38, 2.14)
Day 85						
35 mg IRBB	17	60.0	99	33.9, 106.2		
35 mg DRFB	18	182.6	130	104.8, 318.0	3.04 (1.37, 6.75)	
50 mg DRBB	18	118.1	128	67.6, 206.1	1.97 (0.89, 4.36)	
50 mg DRFB	36	166.5	264	112.2, 247.0	2.77 (1.39, 5.55)	1.41 (0.72, 2.78)
Avg of Days 1 & 85						
35 mg IRBB	20	63.5		38.7, 104.2		
35 mg DRFB	19	134.1		80.7, 222.8	2.11 (1.04, 4.29)	
50 mg DRBB	18	135.3		80.2, 228.3	2.13 (1.04, 4.37)	
50 mg DRFB	38	143.7		100.1, 206.3	2.26 (1.23, 4.17)	1.06 (0.57, 2.00)
%CV=coefficient of variation for the geometric mean						
Source: Study Number: 2005107, Final Report, Table 16						

Trial 2008119 was the bioequivalence trial between the Phase 3 and commercial risedronate DR 35 mg tablets. It was a 2 period, crossover, single dose trial. Dosing occurred after an overnight (10-hour) fast and was followed by a 4-hour fast. Subjects remained at the study center for 3 days following administration. Urine for 72 hours and blood samples for 30 hours were collected for risedronate PK analysis. Treatment periods were separated by washout periods lasting 14 to 17 days.

Healthy males and surgically sterile or postmenopausal females age 18 to 65 were eligible to participate. Mean age of the subjects was 40 years with 62% males and 38% females. Mean age of female subjects (47) was older than male subjects (36). The majority of subjects were Hispanic (65%).

There were 579 subjects randomized and 538 dosed. Thirty seven subjects were not dosed as exclusionary criteria were met prior to dosing. The additional 4 subjects were alternates that were not needed.

A site with 53 subjects closed after period 1 dosing. These data could not be verified via the standard query process therefore, these PK data were not included in the PK analyses.

Of the 538 subjects dosed, 85 withdrew and 453 completed the trial. The majority of the withdrawals were from the closed site. Other reasons given for withdrawal are similar for

the two treatment groups and include 16 voluntary withdrawals, 9 for AEs (2 of these from the closed site), 3 for protocol violations, 3 lost to follow up, 2 investigator discretion, and 1 “unable to meet protocol criteria”.

Brief summary of pharmacokinetics: For the primary PK parameters of C_{max} and AUC, the commercial risedronate 35 mg DR tablet was bioequivalent to the Phase III risedronate 35 mg DR tablet as demonstrated by the 90% CIs of the ratios that were within the 0.80 – 1.25 range (see Table 9).

Table 9, Trial 2008119 Pharmacokinetic Parameters

	Phase 3 Risedronate 35 mg DR (N=467) (95% CI)	Commercial Risedronate 35 mg DR (N=471) (95% CI)	Commercial/Phase 3 Ratio (90% CI)
C _{max} (ng/ml)	14.1 (12.5, 15.8)	13.8 (12.3, 15.5)	0.98 (0.88, 1.08)
AUC (ng*h/ml)	34.2 (30.3, 38.6)	34.2 (30.3, 38.7)	1.00 (0.90, 1.11)
t _{max} (h)	3.0 (2.9, 3.1)	3.0 (2.9, 3.1)	1.01 (0.98, 1.05)
A _e (µg)	158 (140, 178)	163 (145, 183)	1.03 (0.93, 1.14)
A'e (%)	0.451 (0.401, 0.507)	0.465 (0.414, 0.522)	1.03 (0.93, 1.14)

Source: Study Report 2008119, Table 3

PK data for the Phase 3 and commercial tablets were combined and evaluated by gender (Table 10). For C_{max} and AUC, the ratio of each parameter for males to females was approximately 0.8 and the ratio of t_{max} for males to females was approximately 1.0. For A_e and A'e, the ratio of each parameter for males to females was approximately 0.9. When the PK parameters of the 2 formulations were separately analyzed by gender, similar results were observed.

Table 10, Trial 2008119 Combined PK Parameters by Gender

	Males (N=298) (95% CI)	Females (N=184) (95% CI)	Male/Female Ratio (90% CI)
C _{max} (ng/ml)	12.7 (11.3, 14.2)	15.3 (13.1, 18.0)	0.82 (0.70, 0.97)
AUC (ng*h/ml)	30.9 (27.4, 34.8)	37.9 (32.2, 44.7)	0.81 (0.69, 0.96)
t _{max} (h)	3.0 (2.9, 3.1)	3.0 (2.8, 3.1)	1.02 (0.98, 1.07)
A _e (µg)	153 (136, 172)	168 (143, 196)	0.91 (0.78, 1.07)
A'e (%)	0.437 (0.389, 0.492)	0.479 (0.410, 0.561)	0.91 (0.78, 1.07)

Source: Study Report 2008119, Table 4

6 Review of Efficacy

Efficacy Summary

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.

The risedronate 35 mg delayed release (DR) formulation taken weekly either at least 30 minutes before breakfast or immediately following breakfast is shown in 52 week data from the Phase 3 trial 2007008 to be non-inferior to the approved 5 mg immediate release (IR) formulation taken daily per label for increasing lumbar spine BMD in a postmenopausal osteoporosis (PMO) population (3.4% increase for both DR regimens, 3.1% for the IR regimen). This efficacy is confirmed by BMD increases at other sites being comparable for the 35 mg DR formulation and the 5 mg IR formulation. 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 also reduced similarly by the 35 mg DR formulation and the 5 mg IR formulation.

Further confirmation of the efficacy of the 35 mg DR formulation was seen in the 13 week Phase 2 trial 2005107, where BTMs CTX, NTX, and BSAP were reduced at least as much by the DR regimen given weekly immediately following breakfast compared to the approved 35 mg IR formulation given per label to a healthy postmenopausal population (see Section 5.3). A subset of subjects in that trial had urinary pharmacokinetic measurements done showing mean excretion, and therefore presumed absorption, of 2.1 times the risedronate following the DR formulation compared to the IR formulation. Other PK trials have shown as much as a 4.2 times increased urinary excretion of risedronate following a 35 mg DR dose compared to the 35 mg IR dose (Trial 2008052).

6.1 Indication: Treatment of postmenopausal osteoporosis

6.1.1 Methods

The Phase 3 trial 2007008 and the Phase 2 trial 2005107 are the two trials which provide efficacy data for the risedronate 35 mg DR formulation. Other brief PK, bioequivalence, and drug interaction trials are listed in Table 2 in Section 5.1. Full reviews of Trials 2005107 and 2007008, along with brief reviews of the PK, bioequivalence, and drug interaction studies, are found in Appendix 9.4. Only the Phase 3 trial 2007008 is in an osteoporotic population. An abbreviated review of Trial 2007008 is found in this section, and of Trial 2005107 in Section 5.3.

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 the European Union. Lumbar spine BMD is the primary endpoint. The first 52 weeks are reported in this NDA application. The second year of the trial is ongoing and continues to be double-blinded.

Female subjects at least 50 years old, at least 5 years postmenopausal, and with confirmed osteoporosis (T-score at spine or total hip ≤ -2.5 or T-score ≤ -2.0 with a prevalent vertebral fracture) were randomized to risedronate 35 mg DR weekly either immediately following breakfast or at least 30 minutes before breakfast, or to risedronate 5 mg IR daily. All subjects are supplemented with 1000 mg of elemental calcium and 800-1000 IU vitamin D daily throughout the trial. These are not to be taken at the same time of day as study medications.

All tablets were taken with at least 4 oz/120 ml plain water per tablet with the subject in an upright position. The patient was instructed not to lie down for at least 30 minutes after dosing.

Reviewer comment: Sponsor desires this water and positioning information in the label. Current IR label states 6-8 oz. of water. As the 4 oz. of water is used in the Phase 3 trial, inclusion of that amount in labeling is acceptable.

Subjects must not have a significant illness or condition which would prevent them from finishing the trial or prevent evaluation of spine by radiograph or DXA or the hip by DXA. Medical conditions other than osteoporosis which might affect bone were exclusions, as were most bone active agents in the 3 to 12 months before entering the trial.

6.1.2 Demographics

Trial 2007008: Demographic and baseline characteristics for Trial 2007008 were balanced across treatment groups and are shown for the ITT population in Table 11. 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 25-hydroxy vitamin D level was 69.8 nmol/L (28 ng/mL). 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.

Table 11, Trial 2007008 Demographic and Baseline Characteristics, ITT Population

Parameter Statistic/Category	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)	Overall (N=922)	p- value
Age (years) at Screening Mean (SD) Min, Max	65.3 (7.4) 50.0, 84.0	65.8 (7.4) 50.0, 87.0	66.0 (7.5) 50.0, 83.0	65.7 (7.4) 50.0, 87.0	0.4818
Race					0.8512
Asian (Oriental)	1 (0.3%)	1 (0.3%)	0 (0.0%)	2 (0.2%)	
Caucasian	306 (99.7%)	305 (99.3%)	306 (99.4%)	917 (99.5%)	
Hispanic	97 (31.6%)	96 (31.3%)	96 (31.2%)	289 (31.3%)	
Multi-Racial	0 (0.0%)	1 (0.3%)	2 (0.6%)	3 (0.3%)	
Years Since Menopause Mean (SD) Min, Max	17.5 (8.6) 5.0, 49.0	18.2 (8.0) 5.0, 52.0	18.8 (8.5) 5.0, 46.0	18.2 (8.4) 5.0, 52.0	0.1931
Body Mass Index (kg/m ²) Mean (SD)	25.5 (3.4)	25.0 (3.5)	25.3 (3.4)	25.3 (3.4)	0.2879
Creatinine Clearance Mean (SD) Min, Max	73.0 (18.7) 39.6, 142.0	71.2 (17.2) 34.0, 135.5	70.4 (16.3) 22.4, 142.4	71.6 (17.4) 22.4, 142.4	0.1600
Serum 25(OH) Vitamin D Mean (SD) (nmol/L) Min, Max	69.8 (24.0) 17.5, 162.2	70.4 (26.7) 15.0, 257.1	69.3 (24.4) 15.0, 172.2	69.8 (25.0) 15.0, 257.1	0.8568
Height (cm) Mean (SD)	157.3 (6.1)	156.6 (6.3)	156.8 (6.2)	156.9 (6.2)	0.3913
T-score for Lumbar Spine n Mean (SD) Min, Max	273 -3.12 (0.52) -4.9, -1.7	268 -3.11 (0.58) -4.7, 1.0	262 -3.11 (0.56) -4.8, -1.6	803 -3.11 (0.56) -4.9, 1.0	0.9723
T-score for Proximal Femur n Mean (SD) Min, Max	307 -2.96 (1.44) -5.7, 0.6	307 -2.95 (1.32) -6.2, 0.1	308 -2.94 (1.39) -6.0, 0.9	922 -2.95 (1.38) -6.2, 0.9	0.9873
Known Fracture Status n At Least 1 Prevalent Vertebral Fracture	291 70 (24.1%)	287 81 (28.2%)	299 87 (27.1%)	877 238 (27.1%)	0.3396
Source: Study 2007008 Year 1 Final Report, Tables 5, 6, and 7					

Reviewer comment: A total of 119 subjects did not have a baseline lumbar spine BMD listed because “The calculation of lumbar spine T-score was only applied when all 4 lumbar spine vertebrae were intact.” Only T-scores for lumbar spines with all vertebrae 1 to 4 evaluable (e.g., without fracture, marked sclerosis) are listed in Table 11.

Subjects with unknown fracture status (N=45) are those who’s baseline spinal radiographs were read as indeterminate as to fracture status.

6.1.3 Subject Disposition

Trial 2007008: A total of 1859 subjects were screened and 923 subjects were randomized into Trial 2007008. Of the subjects randomized, 922 received at least one dose of study drug and constitute the ITT population, as outlined in Table 12. 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%, 5 mg IRBB daily; 18%, 35 mg DRFB; 16%, 35 mg DRBB). The most common reasons for discontinuation were AE (8%, 5 mg IRBB daily; 9%, 35 mg DRFB; 5%, 35 mg DRBB) and voluntary withdrawal (7%, 5 mg IRBB daily; 8%, 35 mg DRFB; 8%, 35 mg DRBB). Of the subjects who withdrew voluntarily, 10 in the 5 mg IRBB daily group (3%), 6 in the 35 mg DRFB group (2%), and 12 in the 35 mg DRBB group (4%) had an ongoing adverse event at the time of withdrawal.

Table 12, Trial 2007008 Subject Disposition, ITT Population

Parameter Category	5 mg IRBB Daily (N=307) n (%)	35 mg DRFB Weekly (N=307) n (%)	35 mg DRBB Weekly (N=308) n (%)	p-value*
Status				
Completed Week 52	257 (83.7%)	252 (82.1%)	258 (83.8%)	0.8361
Continued in Study, No Week 52 Visit	0 (0.0%)	0 (0.0%)	1 (0.3%)	1.0000
Discontinued on/prior to Week 52	50 (16.3%)	55 (17.9%)	49 (15.9%)	0.7735
Discontinuation Reason				
Adverse Events	25 (8.1%)	28 (9.1%)	16 (5.2%)	0.1450
Investigator Discretion	0 (0.0%)	0 (0.0%)	3 (1.0%)	0.1104
Lost to Follow-up	3 (1.0%)	2 (0.7%)	4 (1.3%)	0.9138
Voluntary Withdrawal	22 (7.2%)	25 (8.1%)	26 (8.4%)	0.8634
(Voluntary WD with ongoing AE)	10 (3.3%)	6 (2.0%)	12 (3.9%)	
Analysis Populations				
Intent-to-treat	307	307	308	
Primary Efficacy (MITT)	270 (87.9%)	261 (85.0%)	271 (88.0%)	
Per-protocol	222 (72.3%)	217 (70.7%)	213 (69.2%)	
* Fisher's Exact Test				
Source: Study 2007008 Year 1 Final Report, Tables 2, 3, and datasets				

6.1.4 Analysis of Primary Endpoint(s)

Trial 2007008: The mean percent change from baseline in lumbar spine bone mineral density as assessed by dual x-ray absorptometry and read at a central reading facility was the primary efficacy outcome. All three dosing regimens increased lumbar spine BMD significantly from baseline to Endpoint (52 weeks, LOCF) in the primary efficacy population, as shown in Table 13. The mean percent change from baseline in lumbar spine BMD was 3.1% for the 5 mg IRBB group and 3.4% for both the 35 mg DRFB group and 35 mg DRBB group.

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

Supportive analyses for percent change from baseline in lumbar spine BMD using a PP population and Week 52 time point were consistent with the primary analysis.

Table 13, 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	270	261	271
Least Squares Mean (g/cm ²)	0.757	0.758	0.758
Endpoint (52 weeks, LOCF)			
n	270	261	271
LS Mean (%Δ from baseline)	3.118*	3.352*	3.414*
95% CI	2.710, 3.526	2.936, 3.767	3.007, 3.822
LS Mean Difference Compared to 5 mg IRBB		-0.233	-0.296
95% CI		-0.816, 0.349	-0.873, 0.281
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. P-values are not given by the Sponsor Source: Study 2007008 Year 1 Final Report, Table 11			

It should be noted that the lumbar spine BMD increase achieved in the 5 mg IRBB 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.

Reviewer comment: The various intermittently dosed risedronate IR formulations (35 mg weekly, 75 mg two consecutive days per month, 150 mg monthly) have been approved based on non-inferiority trials with 52 week data from 2 year trials with lumbar spine BMD as the primary efficacy measure. Sponsor has submitted this DR formulation with 52 week data from a 2 year trial also, but this formulation differs from the IR formulations by the EDTA and enteric coating.

6.1.5 Analysis of Secondary Endpoints(s)

Bone Mineral Density in Trial 2007008:

Table 14 compares DXA measurements of lumbar spine and proximal femur (total hip, femoral neck, and trochanter) acquired at baseline with Weeks 26, 52, and Endpoint (Week 52 with LOCF) 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.

Table 14, Trial 2007008 BMD, % Change from Baseline, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Lumbar Spine			
Baseline n	304	304	308
LS Mean (g/cm ²)	0.757	0.759	0.758
Week 26 n	265	257	267
LS Mean (% change from baseline)	2.751*	2.854*	2.566*
95% CI	2.364, 3.139	2.460, 3.248	2.180, 2.952
LS Mean Difference from IR		-0.102	0.185
95% CI		-0.655, 0.451	-0.362, 0.733
Week 52 n	253	247	254
LS Mean (% change from baseline)	3.169*	3.359*	3.470*
95% CI	2.751, 3.586	2.937, 3.781	3.053, 3.887
LS Mean Difference from IR		-0.190	-0.301
95% CI		-0.784, 0.404	-0.891, 0.290
Endpoint (52 weeks, LOCF) n	270	261	271
LS Mean (% change from baseline)	3.118*	3.352*	3.414*
95% CI	2.710, 3.526	2.936, 3.767	3.007, 3.822
LS Mean Difference from IR		-0.233	-0.296
95% CI		-0.816, 0.349	-0.873, 0.281
Total Hip			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.760	0.761	0.762
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.613*	1.748*	1.685*
95% CI	1.354, 1.872	1.486, 2.010	1.426, 1.943
LS Mean Difference from IR		-0.135	-0.072
95% CI		-0.504, 0.234	-0.437, 0.294
Week 52 n	258	256	258
LS Mean (% change from baseline)	1.872*	2.201*	2.160*
95% CI	1.589, 2.154	1.917, 2.485	1.878, 2.443
LS Mean Difference from IR		-0.329	-0.289
95% CI		-0.730, 0.071	-0.688, 0.111

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Endpoint n	279	274	280
LS Mean (% change from baseline)	1.785*	2.073*	2.075*
95% CI	1.508, 2.062	1.793, 2.352	1.799, 2.352
LS Mean Difference from IR		-0.288	-0.290
95% CI		-0.682, 0.106	-0.681, 0.101
Femoral Neck			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.687	0.687	0.689
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.120*	1.385*	1.246*
95% CI	0.792, 1.447	1.053, 1.716	0.920, 1.572
LS Mean Difference from IR		-0.265	-0.126
95% CI		-0.731, 0.201	-0.588, 0.336
Week 52 n	258	256	258
LS Mean (% change from baseline)	1.215*	1.554*	1.779*
95% CI	0.876, 1.554	1.214, 1.895	1.440, 2.118
LS Mean Difference from IR		-0.339	-0.563
95% CI		-0.820, 0.142	-1.043, -0.083
Endpoint n	279	274	280
LS Mean (% change from baseline)	1.180*	1.507*	1.717*
95% CI	0.853, 1.507	1.177, 1.838	1.390, 2.044
LS Mean Difference from IR		-0.327	-0.537
95% CI		-0.793, 0.138	-1.000, -0.074
Trochanter			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.597	0.595	0.598
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.900*	2.148*	2.164*
95% CI	1.470, 2.329	1.713, 2.583	1.736, 2.592
LS Mean Difference from IR		-0.249	-0.265
95% CI		-0.860, 0.363	-0.871, 0.342
Week 52 n	258	256	258
LS Mean (% change from baseline)	2.358*	2.925*	2.880*
95% CI	1.917, 2.800	2.482, 3.368	2.439, 3.322
LS Mean Difference from IR		-0.566	-0.522
95% CI		-1.192, 0.059	-1.147, 0.103
Endpoint n	279	274	280
LS Mean (% change from baseline)	2.186*	2.732*	2.764*
95% CI	1.746, 2.625	2.288, 3.175	2.326, 3.203
LS Mean Difference from IR		-0.546	-0.579
95% CI		-1.170, 0.078	-1.199, 0.042
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons			
Source: Study 2007008 Year 1 Final Report, Tables 13, 15, 16, and 17			

Superiority to the 5 mg Daily Regimen in Trial 2007008:

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 with LOCF. Results are shown in Table 15. 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. A p-value for the difference (0.2992) which is not significant confirms statistical equality given the limits of this trial.

Table 15, Trial 2007008 Lumbar Spine BMD, % Change from Baseline, Combined DR Treatment Groups, PE Population

	5 mg IRBB Daily (N=307)	35 mg DRFB+DRBB Weekly (N=615)
Baseline		
n	270	532
Least Squares Mean (g/cm ²)	0.757	0.758
Endpoint (52 weeks, LOCF)		
n	270	532
Least Squares Mean (%)	3.118*	3.383*
95% CI	2.710, 3.526	3.093, 3.674
LS Mean Difference		-0.265
95% CI		-0.766, 0.236
P-value		0.2992
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons		
Source: Study 2007008 Year 1 Final Report, Table 12		

Treatment Responders in Trial 2007008:

Approximately 82-87% of subjects were considered as treatment responders with a positive change from baseline in lumbar spine BMD at Week 52 and Endpoint, as shown in Table 16. Although slightly higher percentages responded in the DR treatment groups as compared to the IR group, the differences were not statistically significant.

This is supportive of efficacy of the 35 mg DR formulation.

Table 16 Trial 2007008 Response to Treatment (> 0% Change from Baseline in Lumbar Spine BMD), ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Week 52 n	253	247	254
Responder	208 (82.2%)	216 (87.4%)	218 (85.8%)
Non-responder	45 (17.8%)	31 (12.6%)	36 (14.2%)
Relative Risk (95%CI)		1.06 (0.99, 1.15)	1.04 (0.97, 1.13)
p-value		0.1072	0.2777
Endpoint n	270	261	271
Responder	221 (81.9%)	228 (87.4%)	231 (85.2%)
Non-responder	49 (18.1%)	33 (12.6%)	40 (14.8%)
Relative Risk (95%CI)		1.07 (0.99, 1.15)	1.04 (0.97, 1.12)
p-value		0.0926	0.2989
Source: Study 2007008 Year 1 Final Report, Table 14			

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, as indicated in Table 17. All 7 patients experienced only 1 new vertebral fracture. This trial was not powered for fracture endpoints.

Table 17, Trial 2007008 Incidence of New Morphometric Vertebral Fractures, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Week 52 n	254	253	257
≥ 1 New Fractured Vertebra	2 (0.8%)	2 (0.8%)	3 (1.2%)
No New Fractured Vertebra	252 (99.2%)	251 (99.2%)	254 (98.8%)
Relative Risk (95%CI)		1.00 (0.14, 7.07)	1.48 (0.25, 8.80)
p-value		1.0000	1.0000
Endpoint n	270	261	271
≥ 1 New Fractured Vertebra	2 (0.7%)	2 (0.8%)	3 (1.1%)
No New Fractured Vertebra	268 (99.3%)	259 (99.2%)	268 (98.9%)
Relative Risk (95%CI)		1.03 (0.15, 7.29)	1.49 (0.25, 8.87)
p-value		1.0000	1.0000

Source: Study 2007008 Year 1 Final Report, Table 21

Clinical Fractures Reported as Adverse Events: Clinical fractures reported as AEs included all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures and are shown in Table 18. A total of 27 subjects reported clinical fractures as AEs (6 [2.0%] subjects, 5 mg IRBB; 9 [2.9%] subjects, 35 mg DRFB; 12 [3.9%] subjects, 35 mg DRBB, p=0.3799). Although numerically more subjects in the DR regimens suffered clinical fractures, this difference did not reach statistical significance. Numerically more subjects in the DR regimens suffered radial fractures but again this did not reach statistical significance (1 [0.3%] subject, 5 mg IRBB; 5 [1.6%] subjects, 35 mg DRFB; 4 [1.3%] subjects, 35 mg DRBB, p=0.3024). Overall, fracture types appear similar between groups.

Reviewer comment: Even though not statistically significant, greater numbers of clinical fractures in the DR regimens concern this reviewer about disordered bone apposition with the higher risedronate exposure. Adequate bone biopsy information is needed.

The left distal femur fracture (above the condyle, also above a knee “prosthesis replacement”) in the IRBB group was suffered by a 73 year old Caucasian female in a fall in the shower on study day (b) (6).

Table 18, Trial 2007008 All Clinical Fractures Reported as AEs, ITT Population

All Fractures 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
All Fractures	6 (2.0%) 7	9 (2.9%) 11	12 (3.9%) 15	0.3799
Radius fracture	1 (0.3%) 1	5 (1.6%) 5	4 (1.3%) 5	0.3024
Hip fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Humerus fracture	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Patella fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Pelvic fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Rib fracture	0 (0.0%) 0	1 (0.3%) 1	2 (0.6%) 2	0.7771
Ulna fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Ankle fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Clavicle fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Femur fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Fibula fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hand fracture	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2	1.0000
Spinal compression fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Stress fracture	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2	1.0000
Thoracic vertebral fracture	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Tibia fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659

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 33

Clinical Fractures Reported as Adverse Events, 120 Day Safety Update: Since 52 week data 7 new subjects in the 5 mg IRBB group, 1 subject in the 35 mg DRFB group, and 8 subjects in the 35 mg DRBB group suffered a clinical fracture. A total of 43 subjects reported clinical fractures as AEs (13 [4.2%] subjects, 5 mg IRBB; 10 [3.3%] subjects, 35 mg DRFB; 20 [6.5%] subjects, 35 mg DRBB, p=0.1634). Numerically more subjects in the DR regimens suffered radial fractures but this did not reach statistical significance (1 [0.3%] subject, 5 mg IRBB; 5 [1.6%] subjects, 35 mg DRFB; 5 [1.6%] subjects, 35 mg DRBB, p=0.2527). Overall, fracture types appear similar between groups (see 120 Day Safety Update, Section 7.7).

Reviewer comment: Nearly as many fractures occurred between 52 weeks and the 120 Day Safety Update in the 5 mg IRBB group as the 35 mg DRBB group, and more than the 35 mg DRFB group. This is reassuring regarding disordered bone apposition with the DR formulation.

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, as shown in Table 19. Statistically several of the DR regimens and time points were reduced to a greater extent than the corresponding IR regimen as

indicated by the 95% CI of the difference not crossing zero. Numerically, however, every comparison between the DR regimens and the IR regimen at every post-baseline time point showed a greater drop for all BTMs in the DR treatment groups. These findings are consistent with the known higher absorption of risedronate from the DR formulation, and are supportive of efficacy of the 35 mg DR formulation.

Table 19, Trial 2007008 Bone Turnover Markers, % Change from Baseline, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Serum CTX			
Baseline n	307	306	307
Least Squares Mean (ng/mL)	0.64	0.64	0.67
Week 13 n	280	275	277
LS Mean	-42.3*	-46.8*	-46.1*
95% CI	-45.6, -39.0	-50.1, -43.4	-49.4, -42.7
LS Mean Difference from IR		4.5	3.7
95% CI		-0.3, 9.2	-1.0, 8.4
Week 26 n	274	265	273
LS Mean	-44.4*	-49.2*	-49.4*
95% CI	-47.9, -40.9	-52.7, -45.6	-52.9, -45.9
LS Mean Difference from IR		4.8	5.0
95% CI		-0.2, 9.8	0.0, 9.9
Week 52 n	258	256	258
LS Mean	-44.4*	-49.2*	-50.0*
95% CI	-48.1, -40.7	-52.9, -45.4	-53.8, -46.3
LS Mean Difference from IR		4.8	5.6
95% CI		-0.5, 10.1	0.36, 10.9
Endpoint n	281	275	279
LS Mean	-42.2*	-48.7*	-47.7*
95% CI	-46.0, -38.4	-52.6, -44.9	-51.5, -43.9
LS Mean Difference from IR		6.6	5.5
95% CI		1.2, 11.9	0.2, 10.9
Urine NTX/Cr			
Baseline n	305	305	306
LS Mean (nmol BCE/mmol Creatinine)	76.0	74.6	73.0
Week 13 n	278	273	275
LS Mean	-42.6*	-46.4*	-45.4*
95% CI	-45.9, -39.3	-49.7, -43.1	-48.7, -42.1
LS Mean Difference from IR		3.8	2.8
95% CI		-0.9, 8.4	-1.8, 7.5
Week 26 n	271	265	272
LS Mean	-43.1*	-45.7*	-47.7*
95% CI	-46.4, -39.7	-49.1, -42.3	-51.1, -44.3
LS Mean Difference from IR		2.6	4.6
95% CI		-2.2, 7.4	-0.2, 9.4

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Week 52 n	256	253	257
LS Mean	-42.2*	-47.3*	-46.9*
95% CI	-45.7, -38.7	-50.8, -43.8	-50.3, -43.4
LS Mean Difference from IR		5.0	4.6
95% CI		0.1, 10.0	-0.3, 9.6
Endpoint n	279	274	278
LS Mean	-40.2*	-46.6*	-44.6*
95% CI	-43.8, -36.7	-50.2, -43.0	-48.2, -41.1
LS Mean Difference from IR		6.4	4.4
95% CI		1.3, 11.4	-0.6, 9.4
Serum BSAP			
Baseline n	307	306	307
LS Mean (U/L)	28.6	27.3	27.5
Week 13 n	280	275	277
LS Mean	-23.4*	-25.1*	-25.2*
95% CI	-25.4, -21.3	-27.2, -23.1	-27.2, -23.1
LS Mean Difference from IR		1.8	1.8
95% CI		-1.1, 4.7	-1.1, 4.7
Week 26 n	274	265	273
LS Mean	-31.3*	-33.7*	-32.6*
95% CI	-33.3, -29.2	-35.8, -31.6	-34.6, -30.5
LS Mean Difference from IR		2.4	1.3
95% CI		-0.5, 5.3	-1.6, 4.2
Week 52 n	258	256	258
LS Mean	-31.9*	-33.5*	-33.5*
95% CI	-34.1, -29.7	-35.7, -31.2	-35.7, -31.3
LS Mean Difference from IR		1.6	1.6
95% CI		-1.6, 4.7	-1.6, 4.8
Endpoint n	281	275	279
LS Mean	-31.4*	-32.8*	-32.8*
95% CI	-33.5, -29.2	-35.0, -30.6	-35.0, -30.7
LS Mean Difference from IR		1.4	1.5
95% CI		-1.7, 4.5	-1.6, 4.5
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. Source: Study 2007008 Year 1 Final Report, Tables 18, 19, and 20			

6.1.6 Other Endpoints

Effect of Anti-acid Preparations in Trial 2007008:

Atelvia has a pH sensitive coat that releases drug above pH 5.5, a theoretical concern exists that proton pump inhibitors (PPIs) and, to a lesser extent, H2 blockers (H2) could induce early drug release and reduce absorption and efficacy. This is a concern especially when dosing of the DR formulation occurs with food.

Percent change from baseline in lumbar spine BMD at Endpoint was analyzed using the covariance model to assess the effects of PPI use (see Table 20). PPI use was defined

as any PPI use (≥ 1 day) during the trial. A statistically significant interaction was observed between treatment group and PPI use for lumbar spine BMD ($p=0.0047$, see notes following table), however, the number of subjects who used PPI during the study is small (31 subjects, 5 mg IRBB; 32 subjects, 35 mg DRFB; 36 subjects, 35 mg DRBB). When comparing the treatment groups individually, changes in lumbar spine BMD between PPI non-users and users were not statistically significant for the 5 mg IRBB and 35 mg DRFB groups, although both groups had less increase in BMD numerically in PPI users. A significant increase of lumbar spine BMD was seen in the 35 mg DRBB PPI users compared to non-users. This difference is not explained.

To the extent the small numbers here allow the conclusion, PPIs do not appear to negatively affect the efficacy of the risedronate DR formulation.

Additional analysis was performed to assess the effect of PPI or H2 Blocker use and the corresponding interaction with treatment on the percent change from baseline in lumbar spine BMD at Endpoint. PPI/H2 use was defined as use of a PPI and/or an H2 blocker for any duration (≥ 1 day) during the trial. Numbers of subjects were slightly larger; there were 50 subjects in the 5 mg IRBB group, 52 subjects in the 35 mg DRFB group, and 52 subjects in the 35 mg DRBB group that were PPI/H2 users. The effect of PPI/H2 Blocker use on percent change from baseline in lumbar spine BMD was not statistically significant ($p=0.7651$). When individual treatment groups were considered, there were also no statistically significant differences between users and non-users ($p=0.5749$ for 5 mg IRBB, $p=0.9096$ for 35 mg DRFB and $p=0.2364$ for 35 mg DRBB). Furthermore, there was no significant interaction between treatment group and PPI/H2 blocker ($p=0.4318$).

Table 20, Trial 2007008 Lumbar Spine BMD, % Change from Baseline to Endpoint, PE PPI and H2 Non-users vs. Users

	5 mg IRBB Daily	35 mg DRFB Weekly	35 mg DRBB Weekly
PPI Use			
PPI Non-users Endpoint n	242	236	239
Mean (%) (SD)	3.231 (3.462)	3.415 (3.171)	3.202 (3.422)
Min, Max	-5.54, 15.29	-6.60, 13.87	-8.97, 18.60
PPI Users Endpoint n	28	25	32
Mean (%) (SD)	2.080 (3.593)	2.938 (3.096)	4.917 (4.649)
Min, Max	-6.76, 9.08	-2.77, 9.80	-5.69, 17.43
Difference of Means* (Non-users – Users)	1.151	0.477	-1.715
P-value	0.0668	0.4661	0.0101
PPI/H2 Use			
PPI/H2 Non-users Endpoint n	225	220	228
Mean (%) (SD)	3.155 (3.478)	3.373 (3.229)	3.287 (3.337)
Min, Max	-5.54, 15.29	-6.60, 13.87	-8.40, 18.60
PPI/H2 Users Endpoint n	45	41	43
Mean (%) (SD)	2.895 (3.563)	3.348 (2.809)	4.023 (4.864)
Min, Max	-6.76, 12.23	-2.77, 9.80	-8.97, 17.43
Difference of Means** (Non-users – Users)	0.260	0.025	-0.736
P-value	0.5749	0.9096	0.2364
*Significant at p=0.0047 using analysis of covariance			
**Not significant (p=0.4318)			
Source: Study 2007008 Year 1 Final Report, Section 11 Tables 18-21 and Appendix 13.1.9.3, Listings 7 and 10			

6.1.7 Subpopulations

In Phase 3 trial 2007008 there were no treatment by pooled center (centers were pooled by country), or treatment by age interactions noted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Phase 3 trial 2007008 compares BMD and bone turnover marker (BTM) changes for risedronate DR 35 mg with the approved risedronate 5 mg IR formulation and is discussed above. The Phase 2 trial 2005107 compares BTM changes for risedronate DR 35 mg and DR 50 mg to the approved risedronate 35 mg IR formulation and is discussed in Section 5.3, although PK measurements from Trial 2005107 are included in Table 21.

Table 21 shows trials in the DR development program which compare urinary excretion, and therefore presumably absorption, of the DR formulation to approved IR formulations. An early prototype trial (2004132) is not shown as several DR formulations were evaluated and the IR formulation was given with continued 4 hours of fasting beyond dosing, which is known to increase IR risedronate absorption. As noted in the table, where the DR formulation contains the same risedronate amount as the IR formulation, risedronate urinary excretion ranges from 2.1 to 4.2 times that of the IR formulation. Results with other DR doses confirm increased absorption with the DR formulation.

At the end of Phase 2 meeting, based on some of these results, Sponsor was encouraged to study a lower DR formulation dose in Phase 3 but declined to do so, opting instead to study a 20 mg DR formulation in Phase 1 trial 2008052.

Table 21, Risedronate DR Urinary PK Comparisons

Study/type Dose	Dosing Condition	N	Population/ Regimen	Ae (µg)	Ae Ratio ¹
2008052/Ph 1 X-over 20 mg DR 20 mg DR 35 mg DR 35 mg IR	Fasted Fed Fed 30-min	93 94 90 93	PM female/	75 93 197 47	1.6 2.0 4.2
2007120/Ph 1 X-over 35 mg DR 35 mg DR 35 mg IR	Fasted Fed 30-min	75 72 73	PM female/	180 126 58	3.1 2.2
2005107/Ph 2 13 week 35 mg DR 50 mg DR 50 mg DR 35 mg IR	FB FB Label Label	19 38 18 20	PM female/ OAW OAW OAW OAW	134 144 135 64	2.1 2.3 2.1
2008076/ Ph 1 Single dose 75 mg DR 75 mg DR 100 mg DR 100 mg DR 150 mg IR	Fasted Fed Fasted Fed Label	16 32 16 32 16	PM female/	409 348 583 508 339	1.2 1.0 1.7 1.5
Label = at least 30 minutes before breakfast; 30-min = 30 minutes before a high-fat meal; fasted = after an overnight fast that was continued for additional 4 hours; fed = immediately after a high-fat meal; FB = immediately following breakfast; PM = postmenopausal; OAW = once a week; Ae = urinary excretion 1 Ae ratios are relative to reference dose (IR dose) within each study Source: Individual study reports					

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance in this NDA were not evaluated beyond 52 weeks. BMD continued at least a trend to increasing from Week 26 to Week 52 and BTMs

remained low from the first post-baseline measurement at Week 13 in all treatment groups in the Phase 3 trial 2007008.

6.1.10 Additional Efficacy Issues/Analyses

A single Phase 3 trial has been agreed to as risedronate is an approved product. The enteric coating and EDTA are new with the risedronate DR formulation. Sponsor was informed at the pre-NDA meeting that approvability based on 52 week data would be a review issue.

(b) (4)



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7 Review of Safety

Safety Summary

Risedronate 35 mg DR has an adverse event profile similar to the approved risedronate IR dosages, except for an increased number or proportion of subjects experiencing adverse events, especially when the risedronate DR is dosed 30 minutes or more before breakfast (DRBB). When compared to risedronate 5 mg daily, this difference reaches statistical significance using log transformed total number of AEs for the DRBB treatment group using the 52 week data of the Phase 3 trial 2007008 (35 mg DRBB to 5 mg IRBB, $p=0.0227$), and with subjects with AE for the DRBB group (without log transformation) using the 120 day safety update data (35 mg DRBB to 5 mg IRBB, $p=0.0128$). The difference between the 35 mg DRBB group and the other 2 groups in the number of subjects reporting AEs was mostly due to higher incidences of AEs in the SOCs gastrointestinal disorders, general disorders and administration site conditions, investigations, and cardiac disorders. Abdominal pain upper, hiatal hernia, and increased PTH were the preferred terms that contributed to increased AEs in the DRBB group, while vomiting was increased in the DRFB group. By the 120 Day Safety Update, abdominal pain upper and other abdominal pain categories were contributing mostly to that AE difference. Deaths, serious adverse events, and withdrawal for adverse events are balanced between groups in the Phase 3 trial.

Elevated PTH occurs in more subjects in the DRBB treatment group in the Phase 3 trial, and in some cases this is a prolonged and/or marked elevation. The elevated PTH level does not appear to result in a significant impact on other measures of mineral metabolism. The effect of the prolonged PTH elevation on bone is unknown, although one could postulate that effects similar to primary hyperparathyroidism may be seen.

Also of concern are numerically more clinical fractures with the DR formulation, especially in the DRBB group, in the first 52 weeks of the Phase 3 trial. However, this difference became less extreme after inclusion of data from the 120 Day Safety Update.

Bone biopsy and histomorphometry was submitted late in the review cycle but does show bone safety of the DR formulation.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data source for this NDA is the 52 week data from the Phase 3 trial 2007008. 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 (postmenopausal osteoporosis, see Table 22). A thorough review of this study is located in the appendix (see Appendix 9.4).

The only trial from secondary safety data sources which represents more than a few doses of risedronate DR is the 13 week Phase 2 trial 2005107. Healthy postmenopausal women were treated primarily with a 50 mg risedronate DR formulation, although one arm used the 35 mg DR formulation. A thorough review is located in the appendix.

Brief reviews are in the appendix for other trials listed as secondary safety data sources, (b) (4). These trials use at most a few doses of the DR formulation in populations for which indications are not sought. Most of these are PK trials comparing DR formulations to IR formulations. Other trials include a bioequivalence trial for the Phase 3 and commercial 35 mg DR tablets, a time of day and calcium effect PK trial, and an esomeprazole effect PK trial.

(b) (4)
 Trials 1998033 and 1998034. That dose is expected to provide safety data at a risedronate exposure similar to the 35 mg DR risedronate weekly, although the population differs from an osteoporosis population. Review of safety data from those trials is in Section 7.4.5.2.

Brief reviews are also in the appendix for two early development PK trials using (b) (4) capsules, electronically opened at various intestinal sites, which are not listed in Table 22. These are Trials 2003066 and 2004035.

Table 22, Safety Data Sources

Study ID	Design, Control Type	Arms Dose (mg) n enter/complete	Indication or Population	Mean Age, Yrs. (Range)	Duration
Primary Safety Data Source, Phase 3 Trial					
2007008 (report 1 year of 2)	Multi-center, double-blind, randomized, active control, non-inferiority Phase 3 (1° endpoint L spine BMD)	5 qd IRBB 307/257 35 qwk DRBB 308/258 35 qwk DRFB 307/252	PMO	65.7 (50-87)	12 months of 24 completed
Secondary Safety Data Source, Phase 2 Trial					

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Stephen R. Bienz, MD
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Study ID	Design, Control Type	Arms Dose (mg) n enter/complete	Indication or Population	Mean Age, Yrs. (Range)	Duration
2005107	Multi-center, double blind, randomized, active control Phase 2 (1° endpoint CTX)	35 qwk IRBB 37/33 35 qwk DRFB 36/35 50 qwk DRFB 72/65 50 qwk DRBB 36/35	Healthy PM females	59.9 (45-79)	13 weeks
Secondary Safety Data Sources, Phase 1 Trials with DR to IR PK Comparisons					
2008076	Phase 1 multicenter randomized, partially blinded, single rising dose monthly dosing (1° endpoint risedronate in urine in 72°)	75 DR 4° BB 16/16 75 DR FB 32/32 100 DR 4° BB 16/16 100 DR FB 32/32 150 IR BB 16/16	Sterile or PM females	56.8 (40-70)	Single dose
2008052	Phase I randomized, open-label, multicenter, single dose, 4-period crossover food effect trial (1° endpoint risedronate in urine in 72°)	20 DR 4° BB 20 DRFB 35 DRFB 35 IRBB (94/92)	Sterile or PM females	55.1 (41-69)	Four doses separated by 18-21 days
2007120	Phase I randomized, open-label, multicenter, crossover PK trial of food effect (1° endpoint risedronate in urine in 72°)	35 DR 4° BB 35 DR FB 35 IR 4° BB 35 IR BB (76/74)	Sterile or PM females	53.6 (41-68)	Four doses separated by 18-25 days
2004132	Phase I two center, randomized, open-label single dose PK trial assessing four 35 mg risedronate (b) (4) EDTA delayed release formulations	35 IR fasted 20/19 35 DR fasted low-coat pH 5.5 18/18 35 DR fed low-coat pH 5.5 18/18 35 DR fasted high-coat pH 5.5 18/18 35 DR fed high-coat pH 5.5 17/17 35 DR fasted high-coat pH 5.5 SR 16/16 35 DR fed high-coat pH 5.5 SR 19/18 35 DR fasted high-coat pH 7.0 18/18 35 DR fed high-coat pH 7.0 16/16	Healthy male (75%) or female (25%) 40-70 years of age	50.4 (40-70)	Single dose
Secondary Safety Data Sources, Phase 1 Bioequivalence and Other Trials					
2008119	Phase I multicenter, randomized, double blind, crossover PK bioequivalence trial	35 DR 4° BB, commercial or phase 3 product (538/453)	Male (62%), sterile or PM females (38%)	40.2 (19-63)	Two doses. 18-21 days between
2008138	Phase I multicenter randomized, open-label, 3-period crossover trial of food and calcium/vit. D effect (1° endpoint risedronate in urine in 72°)	35 DRFB 35 DRFB and calcium 35 DR Following dinner (101/94)	Sterile or PM females	58.3 (40-70)	Three doses separated by 18-21 days

Study ID	Design, Control Type	Arms Dose (mg) n enter/complete	Indication or Population	Mean Age, Yrs. (Range)	Duration
2007027	Phase I multicenter randomized, open-label, 3-period, crossover PK trial of esomeprazole (Eso) effect on risedronate 35 mg DR (1° endpoint risedronate in urine in 72°)	All 35 DRFB D 6 placebo D 1-8 Eso 1 hr before dinner D 1-8 Eso 1 hr before brkfst D 1-8 (87/83)	Sterile or PM females	55.4 (40-69)	24 days as 3-8day periods
Secondary Safety Data Sources, Osteoarthritis Trials with Males and High Risedronate Exposure					
1998033	Phase 3 multicenter, double blind, randomized, placebo controlled, North American (1° endpoints, OA progression by JSN, WOMAC, & pt. gl. assess.)	Placebo 310/255 5 qd IRBB 306/252 15 qd IRBB 302/240 50 qwk IRBB 314/247	Mild to moderate knee OA. male 39% female 61%	60.5 (39-80)	24 months
1998034	Phase 3 multicenter, double blind, randomized, placebo controlled, European (1° endpoints, OA progression by JSN, WOMAC, & pt. gl. assess.)	Placebo 313/290 5 qd IRBB 322/299 15 qd IRBB 309/288 35 qwk IRBB 311/283	Mild to moderate knee OA. male 21% female 79%	63.6 (40-80)	24 months
DR = delayed release, IR = immediately release, FB = following breakfast, BB = before breakfast Source: NDA 22-560 2.7.3.6.1 Tables 1, 2, 3, 4					

7.1.2 Categorization of Adverse Events

Adverse events were characterized using MedDRA coding. Verbatim term to preferred term coding was reviewed and appears to have been appropriately applied.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data was not done as most safety data and all data in a postmenopausal osteoporosis population was from the Phase 3 trial 2007008

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure: The extent of exposure to study drug in the Phase 3 postmenopausal osteoporosis trial for the ITT population is shown in Table 23. About 80% of each treatment group received study drug for the 52 weeks. Mean subject-days of study drug

exposure was similar across groups at approximately 320. Exposure to the proposed dose of the DR formulation for 52 weeks was seen in 499 subjects and for 26 weeks in 535 subjects.

Although days of exposure are similar, PK data suggests increased total exposure to risedronate with the DR formulation.

Table 23, 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	307	307	307
Mean (SD)	322.5 (101.6)	318.1 (110.3)	324.3 (102.6)
Min	1	2	1
Max	381	380	389
Duration of Treatment			
> 90 Days	282 (91.9%)	275 (89.6%)	281 (91.2%)
> 180 Days	270 (87.9%)	264 (86.0%)	271 (88.0%)
> 270 Days	258 (84.0%)	258 (84.0%)	264 (85.7%)
> 360 Days	245 (79.8%)	249 (81.1%)	250 (81.2%)

Source: Study 2007008 Year 1 Final Report, Table 22

Duration of exposure to study drug in the Phase 2 trial in postmenopausal females is summarized in Table 24. More than 88% of subjects took study drug for the duration of the trial in all treatment groups. Exposure to the DR formulation for 3 months was seen in 135 subjects.

Table 24, Trial 2005107 Extent of Exposure, ITT Population

Parameter Statistic	35 mg IRBB (N=37)	35 mg DRFB (N=36)	50 mg DRBB (N=36)	50 mg DRFB (N=72)
Subject-days of exposure Mean (SD)	82.2 (9.4)	84.6 (2.3)	82.7 (14.0)	78.6 (21.3)
Min	43	71	1	1
Max	85	85	85	86
Duration of Treatment				
> 0 Weeks	37 (100%)	36 (100%)	36 (100%)	72 (100%)
> 4 Weeks	37 (100%)	36 (100%)	35 (97%)	67 (93%)
> 8 Weeks	35 (95%)	36 (100%)	35 (97%)	66 (92%)
> 12 Weeks	33 (89%)	35 (97%)	35 (97%)	65 (90%)

Source: Study Number: 2005107, Final Report, Table 11

Exposure in Phase 1 trials is summarized in Table 25. These trials were single dose or single dose crossover trials with at most 4 arms with the exception of Trial 2007027, which was of crossover design with three 8 day treatment periods. Populations varied but none were osteoporotic. Brief exposure to varying doses of DR formulations was seen in 991 subjects in these trials.

Table 25, Phase 1 Risedronate Brief Exposure

Trial	Risedronate IR Tablets			Risedronate DR Tablets							
	35 mg IR		150 mg IR	20 mg DR		35 mg DR		75 mg DR		100 mg DR	
Dosing Conditions	Fast	30-min	30-min	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed
2007027 ^a							86				
2007120 ^a	75	75				76	75				
2008052 ^a		94		93	94		93				
2008119 ^a						538					
2008138 ^a							101				
2008076			16					16	32	16	32
Total ^b		1	16		1	539	355	16	32	16	32

Fast = fasted overnight (at least 8 hours) and continued to fast for 4 hours post-dose, 30-min = fasted overnight (at least 8 hours) with dose given 30 minutes before breakfast, Fed= dosed after breakfast (1 of the doses in crossover Trial 2008138 was after dinner)
 a Crossover study; subjects may have received more than one dose of risedronate
 b Subject listed only once at highest DR dose taken

For products intended for long-term treatment of non-life-threatening conditions, the ICH has generally recommended that 1500 subjects be exposed to the investigational product, with 300 to 600 exposed for 26 weeks, and 100 exposed for 52 weeks (Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions). Risedronate DR exposure meets the guideline.

Demographics: See Section 6.1.2.

Trial 2007008: 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 25-hydroxy vitamin D level was 69.8 nmol/L (28 ng/ml). 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.

Trial 2005107: The treatment groups in Phase 2 trial 2005107 were similar for demographic and baseline characteristics. Most subjects were Caucasian non-Hispanic or Hispanic. Mean age was 60 years with an age range of 45 to 79 years.

7.2.2 Explorations for Dose Response

Adverse events in Trial 2007008, the Phase 3 trial, were evaluated overall by day of study onset. There appeared to be an expected tendency for more adverse events for

all treatment groups (5 mg IRBB, 35 mg DRFB, 35 mg DRBB) in the first month, but later no particular pattern was discernable. There did not appear to be increasing AEs at the end of the trial.

Trial 2005107 was a Phase 2, 13 week, randomized, double blind, triple dummy, active control trial conducted in a healthy postmenopausal population. Trial arms compared weekly 50 mg DRFB, 50 mg DRBB, and 35 mg DRFB to 35 mg IRBB (per label). This was a small study, with 36 to 72 subjects per treatment arm.

The most common adverse events in Trial 2005107 are listed in Table 33. There was a statistically significant increased incidence of diarrhea in the 50 mg groups (16.7% of subjects in DRBB and 9.7% in DRFB regimens) compared to the 35 mg groups (2.7% in IRBB and 0% in DRFB regimens, $p=0.0258$), and a trend toward increased incidence of AEs in abdominal pain and abdominal pain upper in the DR regimens, especially the 50 mg DRFB regimen, compared to the 35 mg IRBB regimen.

The excess noted under adverse event rates in the mean number of AEs per enrolled subject and mean number of AEs per subject with AEs for the 50 mg DRFB regimen (AEs per subject, 35 mg IRBB, 1.5; 50 mg DRFB, 2.4, AEs per subject with AE, 35 mg IRBB, 2.0; 50 mg DRFB, 3.3) appear to come primarily from the gastrointestinal disorders and nervous system disorders SOCs.

7.2.3 Special Animal and/or In Vitro Testing

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

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

Potential for EDTA to alter the absorption of coadministered drugs: To evaluate the potential for EDTA to directly solubilize or precipitate co-administered drugs the sponsor evaluated the effect of EDTA on the solubility of several soluble and poorly soluble drugs with a narrow therapeutic index. The sponsor also evaluated the specific drugs requested by the FDA at the End-of- Phase II meeting held on June 28, 2007. The

apparent solubility experiments were conducted in water alone and in the presence of predissolved EDTA at concentrations of 10 mM, 25 mM, and 100 mM. These EDTA concentrations are higher than the intestinal concentration expected in vivo (estimated to be ≤ 1.5 mM) following administration of risedronate DR.

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

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

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

7.2.4 Routine Clinical Testing

Safety measures to 52 weeks for the Phase 3 trial 2007008 include:

- Physical examination at Screening and 52 weeks
- Vital signs at each visit (Screening, Baseline, Day 14, Weeks 13, 26, 39, and 52)
- Safety laboratory data including CBC with differential, glucose, creatinine, creatinine clearance, calcium, phosphate, albumin, alkaline phosphatase, bilirubin, ALT, AST, sodium, magnesium, potassium, chloride, bicarbonate, and coagulation at Screening, Baseline, Weeks 13, 26, and 52 with an additional chemistry at Day 14
- iPTH at Baseline, Day 14, Week 26, and 52
- TSH and 25-OH vitamin D at Screening
- Urinalysis at Screening and Week 52
- Fecal blood at Baseline and Week 26
- ECG at baseline and Week 52

- DXA at Screening and Weeks 26 and 52
- Spine x-rays at Screening and Week 52
- AEs assessed at each visit and by phone at Day 28
- Bone biopsy is scheduled for the end of the trial at 2 years

Blood urea nitrogen is missing from the usual chemistry. As creatinine is evaluated, this is not felt to represent a serious deficiency. Total protein was also missing from the usual chemistry but this is also not felt to be a serious deficiency as albumin is evaluated and serum protein has not been an issue with risedronate IR. Routine clinical testing appears to be adequate for the Phase 3 trial. It also appears to be adequate for the Phase 2 trial 2005107

7.2.5 Metabolic, Clearance, and Interaction Workup

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

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Sponsor has adequately evaluated risedronate DR 35 mg for upper GI, musculoskeletal, acute phase reaction, and atrial fibrillation adverse events. Ocular adverse events, although not specifically addressed by the Sponsor, are adequately evaluated. See Section 7.3.5.

7.3 Major Safety Results

7.3.1 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 (b) (6). She was successfully resuscitated but remained in a coma and died (b) (6) days later.

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

7.3.2 Nonfatal Serious Adverse Events

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 26. 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 suffered 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 26, 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 (b) (6). 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 (b) (6) 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 (b) (6) 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.

7.3.3 Dropouts and/or Discontinuations

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 5mg daily IRBB group, 28 (9.1%) in the 35mg weekly DRFB group, and 19 (6.2%) in the 35mg weekly DRBB group). As outlined in Table 27, gastrointestinal adverse events were the most common reason for withdrawal, and accounted for 41 of 72 (57%) study withdrawals.

Of subjects who withdrew voluntarily, 10 in the 5 mg IRBB daily group (3%), 6 in the 35 mg DRFB group (2%), and 12 in the 35 mg DRBB group (4%) had an ongoing adverse event at the time of withdrawal. Adding these numbers to those withdrawing for an adverse event would not change conclusions regarding balanced numbers from each treatment group withdrawing for an adverse event.

Table 27, Trial 2007008 Adverse Events Leading to Withdrawal 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*	25 (8.1%) 38	28 (9.1%) 43	19 (6.2%) 32	0.3567
Gastrointestinal disorders	11 (3.6%) 17	17 (5.5%) 24	13 (4.2%) 20	0.5127
Abdominal pain	2 (0.7%) 2	4 (1.3%) 4	4 (1.3%) 4	0.7845
Diarrhea	2 (0.7%) 2	4 (1.3%) 4	0 (0.0%) 0	0.0932
Vomiting	1 (0.3%) 1	3 (1.0%) 3	0 (0.0%) 0	0.1346
Abdominal pain upper	0 (0.0%) 0	2 (0.7%) 2	4 (1.3%) 4	0.1752
Abdominal pain lower	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Constipation	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Musculoskeletal and connective tissue disorders	2 (0.7%) 2	4 (1.3%) 6	2 (0.6%) 3	0.6774
Myalgia	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Nervous system disorders	2 (0.7%) 2	3 (1.0%) 3	0 (0.0%) 0	0.2161
Headache	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Skin and subcutaneous tissue disorders	1 (0.3%) 1	3 (1.0%) 3	2 (0.6%) 2	0.7101
Eye disorders	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
General disorders and administration site conditions	2 (0.7%) 2	2 (0.7%) 2	2 (0.6%) 2	1.0000
Ear and labyrinth disorders	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Vertigo	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Endocrine disorders	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Hyperparathyroidism	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Injury, poisoning and procedural complications	2 (0.7%) 3	0 (0.0%) 0	0 (0.0%) 0	0.2213
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) *Includes adverse events in 3 subjects with onset date in Year 1 that eventually led to withdrawal after Month 12. This causes a discrepancy between this table and the Subject Disposition Table 70. Source: Study 2007008 Year 1 Final Report, Table 27				

Seven subjects in Trial 2005107 prematurely withdrew from the trial because of adverse events (2/37 (5.4%) in the 35mg weekly IRBB group, 1/36 (2.8%) in the 35mg weekly DRFB group, 0/36 (0%) in the 50 mg weekly DRBB group, and 4/72 (5.6%) in the 50mg weekly DRFB group).

- 35 mg IRBB group, 2 subjects
 - A 55 year old woman withdrew from the trial on study day 91 for upper respiratory tract infection which developed on study day 69. The event outcome is unknown.
 - A 74 year old woman withdrew from the trial on study day 47 due to neck, shoulder, and back pain which developed on study day 13. The pain resolved on day 78, 35 days after study drug cessation.
- 35 mg DRFB group, 1 subject

- A 52 year old woman withdrew from the trial on study day 84 for heartburn which developed on study day 73. This may have been occurring post-dose for a month. The event resolved.
- 50 mg DRBB group, no subjects
- 50 mg DRFB group, 4 subjects
 - A 61 year old woman withdrew from the trial on study day 16 for cholelithiasis. See SAEs above.
 - A 64 year old woman withdrew from the trial on study day 39 for bilateral leg pain which developed on study day 19. The pain resolved.
 - A 65 year old woman withdrew from the trial on study day 8 for loss of appetite which developed on study day 1. The event resolved.
 - A 73 year old woman withdrew from the trial on study day 18 for a second episode of gastroenteritis which developed on study day 16. Both episodes occurred about 1 day after study drug. EGD 14 days after the last dose demonstrated “lesions and inflammation in the antrum”. The event resolved.

Phase1 trial withdrawals for AEs included:

- Trial 2004132 – none
- Trial 2007027
 - 44 year old woman with upper abdominal pain a day after her first risedronate DR dose. The event resolved in 1 day.
 - 46 year old woman with nausea, vomiting, diarrhea, and flu-like symptoms 3 days after her second risedronate DR dose. The event resolved in 2 days.
- Trial 2007120 – none
- Trial 2008052
 - 60 year old woman withdrew with pyrexia and cough 18 days after dosing in Treatment Period 3 with 20 mg DR Fasted. The event was reported as ongoing.
- Trial 2008119
 - Withdrew during or after the Phase III 35 mg DR treatment period:
 - 50 year old woman withdrew due to gastritis the day after dosing. The event resolved in 4 days.
 - 20 year old man withdrew due to gastro esophageal reflux disease the day after dosing. The event was reported as ongoing.
 - 25 year old man withdrew due to elevated blood pressure the day after dosing. The event resolved in 7 days.
 - 59 year old woman withdrew due to worsening of cephalgia the day of dosing. The event resolved in 1 day.
 - 45 year old man withdrew due to a right ankle fracture (b) (6) days after dosing. The event was reported as ongoing.
 - Withdrew during or after the Commercial 35 mg DR treatment period:

- 28 year old man withdrew due to emesis the day of dosing. The event resolved the same day.
- 40 year old man withdrew due to myalgia the day after dosing. The event resolved in 3 days.
- 32 year old man withdrew due to influenza 20 days after dosing. The event was reported as ongoing.
- 25 year old man withdrew due to nausea and loose stool 16 days after dosing. The event resolved in 2 days.
- Trial 2008138
 - 42 year old woman withdrew due to strep pharyngitis during the DRFB+Ca/vitD period. The event resolved in 4 days.
 - 68 year old woman withdrew due to a tooth abscess during the DRFB+Ca/vitD period. The event resolved in 8 days.
 - 64 year old woman female withdrew due to intestinal flu during the DR dinner period. The event resolved in 3 days.
- Trial 2008076 - none

7.3.4 Significant Adverse Events

Adverse events in the Phase 3 trial 2007008 were reviewed for concerning unexpected events. No new safety signals were identified, particularly considering the demographics of the population.

Adverse events characterized as severe in intensity without reaching serious adverse event in the Phase 3 trial 2007008 were analyzed. Thirty three such events (1.5% of 2198 AEs) in 21 subjects (2.3% of 922 subjects) were found. No pattern was observed in severe non-serious adverse events which are outlined below.

- In the 5 mg IR treatment group 10 severe non-serious adverse events were found in 6 subjects. Two of these subjects had upper abdominal severe non-serious AEs (nausea; abdominal pain lower, abdominal pain, rectal hemorrhage, and abdominal distention). One of the subjects in the upper abdominal group also had back pain.
- In the 35 mg DRFB treatment group 13 severe non-serious adverse events were found in 10 subjects. Four of these subjects had abdominal severe non-serious AEs, but only one of those was upper abdominal (constipation; constipation; abdominal pain lower; vomiting). Four subjects, including the subject with the upper abdominal AE, had severe non-serious musculoskeletal AEs (back pain; musculoskeletal pain; arthralgia; myalgia).
- In the 35 mg DRBB treatment group 10 severe non-serious adverse events were found in 5 subjects. Two subjects had severe non-serious abdominal adverse events but only one of these was upper abdominal (fecal incontinence; constipation and GERD). Two subjects, including the subject with the upper

abdominal AE, had severe non-serious musculoskeletal AEs (pain in jaw; arthralgia).

7.3.5 Submission Specific Primary Safety Concerns

Elevated PTH: Parathyroid hormone (PTH) is one of the major hormonal regulators of calcium. Bone is the main reservoir for calcium replenishment in the body and bisphosphonates, like risedronate, act by inhibiting bone resorption which is the mechanism for calcium release from bone. Mild, transient elevations in PTH generally occur with bisphosphonate use.

Evaluation of PTH data from Trial 2007008 datasets was performed and results for protocol time points are shown in Table 28. As noted, 115 subjects (37.3%) in the DRBB treatment group had an elevated PTH (>65 pg/ml) at some point during the trial, compared to 101 subjects (32.9%) in the DRFB group and 94 subjects (30.6%) in the IR group. However, it should also be noted that a large number of subjects had abnormally elevated PTH at baseline. The diagnosis of hyperparathyroidism was an exclusionary criterion, but subjects with high PTH were not specifically excluded.

PTH changes in subjects with normal baseline PTH levels were further explored. High PTH values in subjects with normal values at baseline tended to be present in large numbers at day 14 for all treatment groups (32 subjects [12.7%], 5 mg IRBB; 44 subjects [17.7%], 35 mg DRFB; 50 subjects [19.1%], 35 mg DRBB, from shift tables), but this tendency lessened later in the trial (at Week 52, 18 subjects [8.0%], 5 mg IRBB; 19 subjects [8.6%], 35 mg DRFB; 25 subjects [10.9%], 35 mg DRBB, from shift tables). The time point with the most subjects with elevated levels was Day 14 for all treatment groups. Prolonged elevation was present in a number of subjects, especially in the DRBB group. In that group, 48 subjects (15.6%) had a high PTH at week 26 or 52 after a normal baseline measurement compared to 26 (8.5%) in the IR group.

Markedly high PTH (≥ 98 pg/ml) and shifts of PTH from normal to markedly high were also assessed. At Day 14, 3 subjects (1.2%) in the 5 mg IRBB group, 7 subjects (2.8%) in the 35 mg DRFB group, and 13 subjects (5.0%) in the 35 mg DRBB group had developed markedly high PTH values (from shift tables). Markedly elevated PTH was noted at some point during the trial in 37 subjects (12.0%) in the DRBB treatment group compared to 19 subjects (6.2%) in the DRFB group and 20 subjects (6.5%) in the IR group. The time point with the most subjects with markedly elevated levels was again 2 weeks for all treatment groups. Prolonged elevation was present in a greater number of subjects in the DRBB group with 8 subjects (2.6%) having a high PTH at week 26 or 52 after a normal baseline measurement compared to 5 subjects (1.6%) in the DRFB group and 2 subjects (0.7%) in the IR group.

Table 28, Trial 2007008 Serum PTH from Datasets

	5 mg IR Daily	35 mg DRFB Wkly	35 mg DRBB Wkly
N	307	307	308
High PTH at screening ¹ or baseline	43 (14.0%)	38 (12.4%)	36 (11.7%)
High PTH at 2 weeks	58 (18.9%)	68 (22.1%)	70 (22.7%)
High PTH at 26 weeks	29 (9.4%)	30 (9.8%)	47 (15.3%)
High PTH at 52 weeks	35 (11.4%)	30 (9.8%)	42 (13.6%)
High PTH at any protocol time	94 (30.6%)	101 (32.9%)	115 (37.3%)
High PTH at 26 or 52 weeks with normal at baseline and screening ¹	26 (8.5%)	33 (10.7%)	48 (15.6%)
Very high PTH at screening ¹ or baseline	9 (2.9%)	4 (1.3%)	9 (2.9%)
Very high PTH at 2 weeks	14 (4.6%)	13 (4.2%)	23 (7.5%)
Very high PTH at 26 weeks	6 (2.0%)	3 (1.0%)	13 (4.2%)
Very high PTH at 52 weeks	5 (1.6%)	7 (2.3%)	11 (3.6%)
Very high PTH at any protocol time	20 (6.5%)	19 (6.2%)	37 (12.0%)
Very high PTH at 26 or 52 weeks with normal at baseline and screening ¹	2 (0.7%)	5 (1.6%)	8 (2.6%)
DRFB = delayed release formulation immediately following breakfast weekly DRBB = delayed release formulation at least 30 minutes before breakfast weekly High PTH ≥ 66 pg/ml Very high PTH ≥ 98 pg/ml 1 Screening PTH only done in Argentine subjects Source: Trial 2007008 datasets			

The mean values for serum calcium, phosphorus, and magnesium were within the normal range at all time points and similar across treatment groups. At Day 14, the mean change in serum calcium from baseline was -0.08 mg/dl for the 5 mg IRBB group, -0.12 mg/dl for the 35 mg DRFB group, and -0.16 mg/dl for the DRBB group, with no large or clinically important mean changes at any time point. Shifts in phosphorus and magnesium were small and not clinically meaningful. Shift to hypocalcemia was slightly more prevalent at day 14, especially in the DRBB group (8 subjects [2.8%], 5 mg IRBB; 9 subjects [3.2%], 35 mg DRFB; 15 subjects [5.1%], 35 mg DRBB) than later in the trial, when shift to hypocalcemia was about equal between groups (at Week 52, 7 subjects [2.8%], 5 mg IRBB; 5 subjects [2.0%], 35 mg DRFB; 7 subjects [2.8%], 35 mg DRBB). Few markedly abnormal calcium or phosphorus levels were noted on treatment, with no more than 2 subjects a category from any treatment group.

A subset of 356 subjects underwent 24 hour urine collection for calcium excretion and creatinine clearance at baseline and Week 52. Mean urinary calcium excretions were normal and similar between treatment groups at baseline and 52 weeks (for 5 mg IRBB 164 and 188 mg, for 35 mg DRFB 175 and 169 mg, for 35 mg DRBB 179 and 176 mg). No pattern of change from baseline to Week 52 was observed.

If PTH is increased for prolonged periods, increased urinary calcium excretion is expected. Subjects in Trial 2007008 who had 24 hour urine collections at baseline and 52 weeks and had elevated PTH (> 65 pg/ml) at Week 26 or 52 after a normal baseline

PTH were examined for increased urinary calcium excretion at Week 52 compared to Baseline. Increased urinary excretion of calcium at Week 52 was seen in 3 of 7 subjects in the 5 mg IRBB treatment group, 6 of 13 subjects in the 35 mg DRFB group, and 7 of 22 subjects in the 35 mg DRBB group. If only subjects with normal baseline and elevated Week 52 PTH are considered, increased urinary excretion of calcium at Week 52 was seen in 2 of 4 subjects in the 5 mg IRBB treatment group, 4 of 6 subjects in the 35 mg DRFB group, and 2 of 12 subjects in the 35 mg DRBB group. This data does not support the supposition that the PTH elevation measured at Weeks 26 and 52 in Trial 2007008 is prolonged in duration.

Reviewer comment: There appears to be more PTH elevation in the DRBB treatment group which, in some subjects, is measured at several post-Baseline time points, but this appears not to be associated with major effects on mineral levels or urinary calcium excretion with only the slight shift to hypocalcemia at Day 14 noted. From pharmacokinetic studies, the risedronate exposure is similar regardless of whether the drug was administered 30 minutes before or following breakfast. Therefore, the exact etiology of the effect on PTH is unknown and it may be that the EDTA component of the drug product, although an excipient, plays a role. Perhaps increased absorption of EDTA occurs with an empty stomach but absorption is reported as < 5% of an oral dose. The EDTA used in the DR formulation is edetate disodium, which will cause hypocalcemic tetany with rapid IV infusion, rather than edetate calcium disodium, which would likely cause problems with risedronate absorption.

Various risedronate IR strengths have not shown PTH elevation relative to risedronate 5 mg. There appears to have been some mean PTH elevation with risedronate for a prolonged period of time, as much as 36 months, in the initial Phase 3 risedronate vs. placebo trials.

The Sponsor, in response to an information request, reports bisphosphonates and all anti-resorptive agents can cause PTH elevation, presumably by decreasing mobilization of calcium into the bloodstream. The larger dose would be expected to produce a larger effect. Doses after an overnight fast, when serum calcium is at a minimum, may produce more of a response than a dose after breakfast. The Sponsor also attributes much of the variability of PTH levels to diurnal variation and pulsatile release. The Sponsor argues insufficient EDTA is absorbed to expect an effect on calcium and PTH. Sponsor's explanation is rational and does explain the data.

Upper Gastrointestinal AEs: Irritation of the upper gastrointestinal mucosa is a well described adverse effect of oral bisphosphonates. The EDTA in the DR formulation may enhance risedronate related GI toxicity, based on non-clinical data.

The incidence of UGI AEs in Trial 2007008 is given in Table 29. The preferred terms of abdominal pain, dyspepsia, and upper abdominal pain are the most common AEs in this grouping.

There were numerically more subjects in the 35 mg DRBB group that had AEs in this category (61, 19.8%) than in the 35 mg DRFB group (48, 15.6%) or 5 mg IRBB group (45, 14.7%). Preferred term categories with statistically significant differences in numbers of subjects were abdominal pain upper (5 mg IRBB group, 7 subjects; 35 mg DRFB group, 9 subjects, 35 mg DRBB group, 23 subjects; $p=0.0041$) and gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; $p=0.0366$). Other preferred terms which are associated with pain or discomfort (abdominal pain, dyspepsia, abdominal discomfort, abdominal tenderness, epigastric discomfort, and chest pain) either had higher numbers of subjects in the DR groups, especially the 35 mg DRBB group, without reaching statistical significance, or were neutral. In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat) 19 (6.2%) subjects in the 5 mg IRBB group, 29 (9.4%) subjects in the 35 mg DRFB group and 40 (13.0%) subjects in the 35 mg DRBB group reported AEs ($p=0.0164$) (Study 2007008 Year 1 Final Report, Section 11 Table 49).

The AE of esophagitis was equal across treatment groups with one per group. Only one subject in the trial had erosive esophagitis (35 mg DRFB group).

Table 29, Trial 2007008 Upper GI AEs, 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	45 (14.7%) 54	48 (15.6%) 65	61 (19.8%) 106	0.2054
Gastrointestinal disorders	43 (14.0%) 52	48 (15.6%) 63	60 (19.5%) 104	0.1732
Abdominal pain	9 (2.9%) 10	16 (5.2%) 18	15 (4.9%) 18	0.3417
Dyspepsia	12 (3.9%) 14	12 (3.9%) 15	12 (3.9%) 14	1.0000
Abdominal pain upper	7 (2.3%) 8	9 (2.9%) 13	23 (7.5%) 31	0.0041
Gastritis	3 (1.0%) 3	3 (1.0%) 3	4 (1.3%) 4	1.0000
Gastroesophageal reflux disease	5 (1.6%) 5	3 (1.0%) 3	8 (2.6%) 9	0.3383
Abdominal discomfort	1 (0.3%) 1	2 (0.7%) 2	5 (1.6%) 6	0.2928
Hyperchlorhydria	6 (2.0%) 7	2 (0.7%) 2	5 (1.6%) 6	0.4183
Dysphagia	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Erosive esophagitis	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastric ulcer	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastritis atrophic	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Gastritis erosive	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Melena	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Esophagitis	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Abdominal tenderness	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Epigastric discomfort	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Gastrointestinal inflammation	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Gastrointestinal pain	0 (0.0%) 0	0 (0.0%) 0	4 (1.3%) 8	0.0366
Esophageal disorder	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Esophageal ulcer	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
General disorders and administration site conditions	1 (0.3%) 1	1 (0.3%) 1	2 (0.6%) 2	1.0000
Chest pain	1 (0.3%) 1	1 (0.3%) 1	2 (0.6%) 2	1.0000
Infections and infestations	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Helicobacter gastritis	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
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 28				

The influence of NSAIDs and/or aspirin on the incidence of UGI AEs was evaluated. Subjects were classified as users or non-users based on concomitant medication usage reported with any use leading to classification as a user. The number of users was similar across treatment groups. More subjects who used NSAIDs/aspirin reported UGI AEs than non-users (users: 26/147 [17.7%], 5 mg IRBB; 28/152 [18.4%], 35 mg DRFB; 34/132 [25.8%], 35 mg DRBB; non-users: 19/160 [11.9%], 5 mg IRBB; 20/155 [12.9%], 35 mg DRFB; 27/176 [15.3%], 35 mg DRBB) (Study 2007008 Year 1 Final Report, Section 11 Table 60). Among users, the difference between the 35 mg DRBB group and the other 2 groups was mainly due to AEs of abdominal pain upper (3 patients, 5 mg IRBB; 6 patients, 35 mg DRFB; 14 patients, 35 mg DRBB) (Study 2007008 Year 1 Final Report, Text p. 90).

Subjects were identified using MedDRA preferred terms as having a medical history of UGI disorders. Not surprisingly, a higher percentage of subjects with a medical history of UGI disorders experienced UGI AEs during the study than subjects without a medical history of upper GI disorders. The percentage of subjects with a medical history of UGI disorders was 30.9% in the 5 mg IRBB group, 32.6% in the 35 mg DRFB group, and 29.2% in the 35 mg DRBB group. In subjects with a medical history of UGI disorders, the incidence of UGI AEs was similar between the 5 mg IRBB group (19/95, 20.0%) and the 35 mg DRFB group (19/100, 19.0%); the incidence of UGI AEs was higher in the 35 mg DRBB group (28/90, 31.1%), mostly due to events of abdominal pain upper. In subjects without a medical history of upper GI disorders, the incidence of upper GI TEAEs were generally similar across treatment groups (26/212 or 12.3%, 5 mg IRBB; 29/207 or 14.0%, 35 mg DRFB, 33/218 or 15.1%, 35 mg DRBB) (Study 2007008 Year 1 Final Report, Section 11 Table 61).

Endoscopy or other appropriate GI diagnostic procedures were to be offered to all patients who developed a moderate or severe upper GI symptom. Only endoscopies were performed. Findings presented in Table 30 are for all patients who underwent endoscopy, including those who had it for reasons other than a moderate or severe GI symptom. A total of 31 patients (8 [2.6%], 5 mg IRBB; 10 [3.3%], 35 mg DRFB; 13 [4.2%], 35 mg DRBB) underwent an endoscopy procedure. Abnormal findings were similar across all 3 treatment groups. Five (1.6%) in the 5 mg IRBB group, 5 (1.6%) in the 35 mg DRFB group, and 7 (2.3%) in the 35 mg DRBB had at least 1 abnormal mucosal finding. Two patients had ulcers (1 stomach, 35 mg DRFB; 1 esophageal, 35 mg DRBB), and no patients had perforations. One patient in the 5 mg IRBB group had bleeding in the stomach, but no ulcer.

Table 30, Trial 2007008 Abnormal Endoscopy Inflammatory Findings

Treatment GI Site	Inflamm n (%) nAB	Erosion n (%) nAB	Bleeding n (%) nAB	Ulcerat. n (%) nAB	Perforat. n (%) nAB	Total n (%) nAB
5 mg IRBB (N = 307) Subjects with EGD = 8						
Esophagus	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1
Stomach	3 (1.0%) 3	2 (0.7%) 2	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 6
Duodenum	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2
Total	3 (1.0%) 5	2 (0.7%) 3	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 9
35 mg DRFB (N = 307) Subjects with EGD = 10						
Esophagus	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1
Stomach	3 (1.0%) 3	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	4 (1.3%) 5
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	3 (1.0%) 3	2 (0.7%) 2	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	5 (1.6%) 6
35 mg DRBB (N = 308) Subjects with EGD = 13						
Esophagus	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	2 (0.6%) 2
Stomach	4 (1.3%) 4	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 5
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	5 (1.6%) 5	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	7 (2.3%) 7

n (%) = number (percent) of patients with abnormality: (%) = (n/Patients within specified treatment)x100%.
 nAB = number of abnormal findings.
 Source: Study 2007008 Year 1 Final Report, Table 30

Musculoskeletal AEs: Increased musculoskeletal pain has been reported with multiple bisphosphonates including risedronate. Selected musculoskeletal AEs were reviewed in Trial 2007008 for potential differences between treatment groups (arthralgia, back pain, musculoskeletal pain, myalgia, neck pain, and bone pain), as shown in Table 31. Arthralgias (7%) and back pain (6%) were the most common of these AEs. Similar numbers and percents were found for all treatment groups for these selected adverse events.

Table 31, Trial 2007008 Selected Musculoskeletal AEs, ITT Population

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	46 (15.0%) 61	48 (15.6%) 71	53 (17.2%) 64	0.7561
Arthralgia	24 (7.8%) 29	21 (6.8%) 30	19 (6.2%) 23	0.7087
Back pain	18 (5.9%) 19	21 (6.8%) 24	19 (6.2%) 20	0.8870
Musculoskeletal pain	5 (1.6%) 5	6 (2.0%) 6	8 (2.6%) 8	0.7727
Myalgia	3 (1.0%) 3	4 (1.3%) 6	4 (1.3%) 4	1.0000
Neck pain	3 (1.0%) 3	3 (1.0%) 3	4 (1.3%) 4	1.0000
Bone pain	2 (0.7%) 2	2 (0.7%) 2	5 (1.6%) 5	0.5272

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 35

Acute Phase Reactions: Acute phase reactions have been reported with higher doses of risedronate used for intermittent dosing. Sponsor reports no cases of influenza-like illness or pyrexia within 3 days after study drug administration and lasting 7 days or less in Trial 2007008.

Sponsor also evaluated MedDRA preferred terms which have been associated with acute phase reactions beginning within 3 days after study drug administration and lasting 7 days or less (Acute phase reaction, Arthralgia, Asthenia, Back pain, Burning sensation, Chest wall pain, Chills, Dizziness, Fatigue, Feeling hot, Fibromyalgia, Headache, Hot flush, Influenza like illness, Joint stiffness, Malaise, Muscle spasms, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myofascial pain syndrome, Nausea, Neck pain, Pain, Pain in extremity, Paraesthesia, Pyrexia, Vertigo, and Vomiting). At least one such AE was present in 4 subjects (1.3%) in the 5 mg IRBB group, 7 subjects (2.3%) in the 35 mg DRFB group, and 4 subjects (1.3%) in the 35 mg DRBB group. In the 5 mg IRBB group, 1 subject (0.3%) had 2 associated AEs; in the 35 mg DRFB group, 2 subjects (0.7%) had 2 AEs; in the 35 mg DRBB, no subjects had 2 AEs. No subject had more than 2 such AEs. AEs associated with acute phase reactions in the expected time frame do not appear to be increased with the DR formulation.

As renal insufficiency may increase systemic risedronate exposure, estimated creatinine clearance was found for the 15 subjects with at least one AE compatible with an acute phase reaction. Only two of these subjects, both from the 5 mg IRBB treatment group, and both with a single associated AE, had creatinine clearances < 60 ml/min. Overall, about 25% of each treatment group had creatinine clearances < 60 ml/min.

Atrial Fibrillation: Increased atrial fibrillation with bisphosphonates has been reported in some trials and patient series. ECGs were performed on all subjects at baseline and Week 52 in Trial 2007008. In addition, patients at sites in Argentina had an ECG at screening. If the screening ECG showed previously undiagnosed atrial fibrillation, atrial flutter, or tachyarrhythmias, the patient also had an ECG at Week 26.

Atrial fibrillation or flutter was present in 6 subjects at baseline (1 subject, 5 mg IRBB; 5 subjects, 35 mg DRFB). Of the subjects in normal sinus rhythm at baseline who had repeat ECGs at Week 52 or study exit, none had atrial fibrillation or atrial flutter. Treatment emergent adverse events of atrial fibrillation were reported for four subjects, one of whom had atrial fibrillation at baseline and one of whom had a history of paroxysmal atrial fibrillation.

- 77 year old female in the 35 mg DRFB group with hypertension had atrial fibrillation on the baseline ECG.
- 74 year old female in the 35 mg DRBB group with a history of paroxysmal atrial fibrillation, supraventricular tachycardia, and ischemic heart disease was hospitalized on study day (b) (6) with paroxysmal supraventricular tachycardia and treated with carvediol.

- 70 year old female in the 35 mg DRBB group with hypertension and hypercholesterolemia with an MI on study day (b) (6) followed by triple bypass and several adverse events, including atrial fibrillation. At the time of study withdrawal on day 295 she was in normal sinus rhythm.
- 73 year old female in the 35 mg DRBB group with hypertension, hypercholesterolemia, and a history of an unspecified arrhythmia developed atrial fibrillation on study day (b) (6) treated with cardioversion on day (b) (6)

Ocular AEs: Inflammatory eye diseases, such as uveitis and scleritis, have been reported with bisphosphonate use. Ocular AEs in Trial 2007008 were uncommon and balanced across treatment groups (12 subjects (3.9%), 5 mg IRBB; 8 subjects (2.6%), 35 mg DRFB; 9 subjects (2.9%), 35 mg DRBB). The only preferred terms occurring in more than 1 subject per treatment group were cataract (5 subjects (1.6%), 5 mg IRBB; 2 subjects (0.7%), 35 mg DRFB; 1 subject (0.3%), 35 mg DRBB) and conjunctivitis (3 subjects (1.0%), 5 mg IRBB; 1 subject (0.3%), 35 mg DRFB; 1 subject (0.3%), 35 mg DRBB). One case of iridocyclitis was reported in the 35 mg DRFB treatment group.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Trial 2007008: Adverse events which occurred in 2% or more of any treatment group in the Phase 3 trial 2007008 are listed in Table 32. Overall, 69 to 77 % of subjects suffered at least one AE. Of note is a trend toward more subjects with adverse events with the DR formulation, especially with the DRBB regimen (subjects with AE, 211 for 5 mg IRBB, 222 for 35 mg DRFB, and 238 for 35 mg DRBB regimens, $p=0.0572$). If total AEs are analyzed (660 for 5 mg IRBB, 734 for 35 mg DRFB, and 804 for 35 mg DRBB regimens) the p-value by the Fisher's Exact Test is 0.0076, a moderately significant difference. Also noted are more AEs per enrolled subject and more AEs per subject with AEs in the DR regimens.

A comparison of the log transformed number of AEs among the three treatment groups was conducted. The transformation of number of AEs is $\ln(1+\text{number of AEs})$, which is monotone transformation and makes the distribution of number of AEs more like normal distribution. When comparing 35 mg DRFB to 5 mg IRBB, the p-value is 0.2277. When comparing 35 mg DRBB to 5 mg IRBB, the p-value is 0.0227.

Reviewer comment: A concern is raised by this data about more AEs with the 35 mg DR regimens, especially the prior to breakfast regimen, compared to the 5 mg IRBB regimen.

System organ classes (SOC) with the most reported AEs across all treatment groups were gastrointestinal disorders (32%), infections and infestations (31%), and

musculoskeletal and connective tissue disorders (25%). Preferred terms with the most AEs across treatment groups were arthralgia (7%), nasopharyngitis (7%), diarrhea (7%), back pain (6%), and influenza (6%).

No system organ classes had statistically significant differences between treatment groups for AEs. Preferred terms with statistically significant differences between treatment groups for AEs were abdominal pain upper (5 mg IRBB with 7 subjects (2.3%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 23 subjects (7.5%), $p=0.0041$) and osteoarthritis (5 mg IRBB with 8 subjects (2.6%), 35 mg DRFB with 5 subjects (1.6%), 35 mg DRBB with 1 subject (0.3%), $p=0.0388$). If SOCs significant at < 0.1 are considered, more cardiac disorders in the DRBB group were reported (5 mg IRBB with 10 subjects (3.3%), 35 mg DRFB with 11 subjects (3.6%), 35 mg DRBB with 21 subjects (6.8%), $p=0.0807$), and more blood and lymphatic disorders in the DRFB group (5 mg IRBB with 2 subjects (0.7%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 4 subjects (1.3%), $p=0.0899$). Additional preferred terms with significance at the 0.1 level include vomiting (5 mg IRBB with 5 subjects (1.6%), 35 mg DRFB with 15 subjects (4.9%), 35 mg DRBB with 8 subjects (2.6%), $p=0.0589$) and hiatal hernia (5 mg IRBB with 1 subject (0.3%), 35 mg DRFB with 2 subjects (0.7%), 35 mg DRBB with 8 subjects (2.6%), $p=0.0516$).

No single preferred term seemed to contribute markedly to the excess of AEs over subjects with AEs (i.e., subjects appear to mostly have had multiple AEs with different preferred terms). It appears much more common that a subject would have several AEs within the same SOC and seems especially common with the gastrointestinal disorders SOC where, in the 35 mg DRBB group, AEs are more than double subjects with AE (AEs 214, subjects with AE 105).

The difference between the 35 mg DRBB group and the other 2 groups in the number of subjects reporting AEs was mostly due to higher incidences of AEs in the SOCs gastrointestinal disorders, general disorders and administration site conditions, investigations, and cardiac disorders. The gastrointestinal disorders SOC is discussed in greater detail in Section 7.3.5.

In the general disorders and administration site conditions SOC, 16 (5.2%) subjects in the 5 mg IRBB group, 25 (8.1%) subjects in the 35 mg DRFB group and 29 (9.4%) subjects in the 35 mg DRBB group reported AEs. The difference between the 35 mg DRBB group and the 5 mg IRBB group was mostly due to TEAEs of pain (0 subjects, 5 mg IRBB; 4 subjects, 35 mg DRBB), edema peripheral (2 subjects, 5 mg IRBB; 5 subjects, 35 mg DRBB), and drug intolerance (2 subjects, 5 mg IRBB; 5 subjects, 35 mg DRBB). Per the Sponsor, based on verbatim terms, the AEs of drug intolerance were related to calcium intolerance, and none were related to the use of risedronate.

In the investigations SOC, 12 (3.9%) subjects in the 5 mg IRBB group, 16 (5.2%) subjects in the 35 mg DRFB group and 24 (7.8%) subjects in the 35 mg DRBB group

reported AEs. The most notable difference was observed in AEs of blood parathyroid hormone increased (3 subjects in 5 mg IRBB; 2 subjects, 35 mg DRFB; 7 subjects, 35 mg DRBB, see Section 7.3.5).

As mentioned above, in the cardiac disorders SOC, 10 (3.3%) subjects in the 5 mg IRBB group, 11 (3.6%) subjects in the 35 mg DRFB group and 21 (6.8%) subjects in the 35 mg DRBB group reported AEs. The difference between the 35 mg DRBB group and the 5 mg IRBB group was due to small differences in a variety of preferred terms, with no apparent pattern. A low number of serious cardiac events were reported in all treatment groups (1 subject, 5 mg IRBB; 1 subject, 35 mg DRFB; 3 subjects, 35 mg DRBB).

Table 32, Trial 2007008 Most Common Adverse Events (≥2% in any Treatment Group), ITT Population

System Organ Class Preferred Term	5 mg IRBB Daily (N=307) n (%) nAE	35 mg DRFB Weekly (N=307) n (%) nAE	35 mg DRBB Weekly (N=308) n (%) nAE	p-value
Overall	211 (68.7%) 660	222 (72.3%) 734	238 (77.3%) 804	0.0572
Gastrointestinal disorders	85 (27.7%) 142	101 (32.9%) 185	105 (34.1%) 214	0.1905
Diarrhea	15 (4.9%) 21	27 (8.8%) 29	18 (5.8%) 21	0.1366
Abdominal pain	9 (2.9%) 10	16 (5.2%) 18	15 (4.9%) 18	0.3417
Constipation	9 (2.9%) 10	15 (4.9%) 15	16 (5.2%) 16	0.3552
Vomiting	5 (1.6%) 5	15 (4.9%) 18	8 (2.6%) 11	0.0589
Dyspepsia	12 (3.9%) 14	12 (3.9%) 15	12 (3.9%) 14	1.0000
Nausea	12 (3.9%) 12	11 (3.6%) 14	10 (3.2%) 11	0.8813
Abdominal pain upper	7 (2.3%) 8	9 (2.9%) 13	23 (7.5%) 31	0.0041
Gastroesophageal reflux disease	5 (1.6%) 5	3 (1.0%) 3	8 (2.6%) 9	0.3383
Hiatus hernia	1 (0.3%) 1	2 (0.7%) 2	8 (2.6%) 8	0.0516
Infections and infestations	89 (29.0%) 125	100 (32.6%) 149	94 (30.5%) 145	0.6349
Influenza	19 (6.2%) 21	22 (7.2%) 24	18 (5.8%) 20	0.7892
Nasopharyngitis	16 (5.2%) 18	21 (6.8%) 23	26 (8.4%) 33	0.3022
Urinary tract infection	8 (2.6%) 9	15 (4.9%) 18	11 (3.6%) 12	0.3310
Bronchitis	13 (4.2%) 15	12 (3.9%) 15	13 (4.2%) 13	1.0000
Upper respiratory tract infection	8 (2.6%) 8	11 (3.6%) 11	9 (2.9%) 11	0.7895
Cystitis	7 (2.3%) 8	7 (2.3%) 8	5 (1.6%) 5	0.8075
Pharyngitis	3 (1.0%) 3	4 (1.3%) 4	9 (2.9%) 9	0.2097
Musculoskeletal and connective tissue disorders	73 (23.8%) 105	78 (25.4%) 115	78 (25.3%) 107	0.8786
Arthralgia	24 (7.8%) 29	21 (6.8%) 30	19 (6.2%) 23	0.7087
Back pain	18 (5.9%) 19	21 (6.8%) 24	19 (6.2%) 20	0.8870
Pain in extremity	7 (2.3%) 7	12 (3.9%) 12	8 (2.6%) 10	0.5213
Musculoskeletal pain	5 (1.6%) 5	6 (2.0%) 6	8 (2.6%) 8	0.7727
Osteoarthritis	8 (2.6%) 8	5 (1.6%) 5	1 (0.3%) 1	0.0388
Muscle spasms	7 (2.3%) 7	3 (1.0%) 3	9 (2.9%) 13	0.2089
Injury, poisoning and procedural complications	32 (10.4%) 46	29 (9.4%) 41	27 (8.8%) 40	0.7725
Fall	9 (2.9%) 10	12 (3.9%) 12	4 (1.3%) 4	0.1002
Contusion	10 (3.3%) 10	7 (2.3%) 8	6 (1.9%) 8	0.5620

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
Nervous system disorders	38 (12.4%) 49	26 (8.5%) 35	31 (10.1%) 34	0.2816
Dizziness	10 (3.3%) 10	8 (2.6%) 8	8 (2.6%) 9	0.8802
Headache	15 (4.9%) 15	8 (2.6%) 8	14 (4.5%) 14	0.3143
General disorders and administration site conditions	16 (5.2%) 18	25 (8.1%) 35	29 (9.4%) 39	0.1165
Skin and subcutaneous tissue disorders	16 (5.2%) 18	21 (6.8%) 23	21 (6.8%) 24	0.6646
Respiratory, thoracic and mediastinal disorders	17 (5.5%) 21	17 (5.5%) 21	20 (6.5%) 23	0.8929
Cough	7 (2.3%) 8	7 (2.3%) 7	5 (1.6%) 5	0.8075
Vascular disorders	14 (4.6%) 18	17 (5.5%) 17	19 (6.2%) 21	0.6956
Hypertension	11 (3.6%) 12	8 (2.6%) 8	10 (3.2%) 10	0.7956
Investigations	12 (3.9%) 17	16 (5.2%) 19	24 (7.8%) 27	0.1129
Blood parathyroid hormone increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7	0.2626
Metabolism and nutrition disorders	9 (2.9%) 9	12 (3.9%) 16	14 (4.5%) 14	0.6016
Hypercholesterolemia	2 (0.7%) 2	7 (2.3%) 7	6 (1.9%) 6	0.2261
Cardiac disorders	10 (3.3%) 10	11 (3.6%) 11	21 (6.8%) 28	0.0807
Blood and lymphatic system disorders	2 (0.7%) 2	9 (2.9%) 9	4 (1.3%) 4	0.0899
Psychiatric disorders	8 (2.6%) 9	9 (2.9%) 9	12 (3.9%) 17	0.7054
Eye disorders	12 (3.9%) 17	8 (2.6%) 11	9 (2.9%) 9	0.6677
Ear and labyrinth disorders	12 (3.9%) 14	7 (2.3%) 7	7 (2.3%) 7	0.4038
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.6%) 8	7 (2.3%) 7	6 (1.9%) 7	0.8246
Renal and urinary disorders	7 (2.3%) 7	7 (2.3%) 8	13 (4.2%) 16	0.3114
Endocrine disorders	7 (2.3%) 8	6 (2.0%) 6	10 (3.2%) 12	0.6466
Reproductive system and breast disorders	9 (2.9%) 10	5 (1.6%) 5	5 (1.6%) 6	0.4402
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 24				

Trial 2005107: Trial 2005107 was a 13 week, randomized, double blind, triple dummy, active control trial conducted in a healthy postmenopausal population as opposed to a population of women with postmenopausal osteoporosis, as was done in the Phase 3 trial.

The most common adverse events in Trial 2005107 are listed in Table 33. Headache was the most frequently reported AE in all treatment groups. Other frequently reported AEs were gastrointestinal (nausea, abdominal pain, abdominal pain upper, diarrhea, dyspepsia) or musculoskeletal (back pain) in nature. There was a statistically significant increased incidence of diarrhea in the 50 mg groups (DRBB and DRFB regimens) compared to the 35 mg groups (IRBB and DRFB regimens), and a trend toward

increased incidence of AEs in abdominal pain and abdominal pain upper in the DR regimens, especially the 50 mg DRFB regimen, compared to the 35 mg IRBB regimen.

The excess noted under adverse event rates in the mean number of AEs per enrolled subject and mean number of AEs per subject with AEs for the 50 mg DRFB regimen (AEs per subject, 35 mg IRBB, 1.5; 50 mg DRFB, 2.4, AEs per subject with AE, 35 mg IRBB, 2.0; 50 mg DRFB, 3.3) appear to come primarily from the gastrointestinal disorders and nervous system disorders SOCs.

Table 33, Trial 2005107 Most Common Adverse Events, ITT Population (> 7% in any Treatment Group)

System Organ Class Preferred Term	35 mg IRBB (N=37) n (%) nAE	35 mg DRFB (N=36) n (%) nAE	50 mg DRBB (N=36) n (%) nAE	50 mg DRFB (N=72) n (%) nAE	p-value
Overall	27 (73.0%) 55	19 (52.8%) 44	24 (66.7%) 55	51 (70.8%) 170	0.2397
Musculoskeletal and connective tissue disorders	8 (21.6%) 12	9 (25.0%) 13	7 (19.4%) 8	18 (25.0%) 28	0.9325
Back pain	3 (8.1%) 3	4 (11.1%) 4	0 (0.0%) 0	3 (4.2%) 3	0.1313
Gastrointestinal disorders	12 (32.4%) 15	8 (22.2%) 11	13 (36.1%) 23	26 (36.1%) 69	0.5078
Abdominal pain upper	0 (0.0%) 0	3 (8.3%) 3	1 (2.8%) 1	8 (11.1%) 11	0.0972
Abdominal pain	1 (2.7%) 1	2 (5.6%) 2	2 (5.6%) 4	6 (8.3%) 9	0.7440
Dyspepsia	4 (10.8%) 4	2 (5.6%) 3	0 (0.0%) 0	4 (5.6%) 4	0.2726
Nausea	3 (8.1%) 3	2 (5.6%) 2	4 (11.1%) 4	9 (12.5%) 13	0.7503
Vomiting	2 (5.4%) 2	1 (2.8%) 1	3 (8.3%) 3	2 (2.8%) 2	0.6202
Diarrhea	1 (2.7%) 1	0 (0.0%) 0	6 (16.7%) 6	7 (9.7%) 14	0.0258*
Nervous system disorders	11 (29.7%) 13	8 (22.2%) 13	10 (27.8%) 11	19 (26.4%) 39	0.9116
Headache	7 (18.9%) 9	8 (22.2%) 11	10 (27.8%) 10	16 (22.2%) 26	0.8506
Infections and infestations	6 (16.2%) 6	3 (8.3%) 3	3 (8.3%) 3	7 (9.7%) 10	0.6910
Upper respiratory tract infection	3 (8.1%) 3	0 (0.0%) 0	1 (2.8%) 1	2 (2.8%) 3	0.3567
Respiratory, thoracic and mediastinal disorders	1 (2.7%) 2	3 (8.3%) 3	3 (8.3%) 3	5 (6.9%) 7	0.7376

*Significant at the p < 0.05 level (treatment difference using Fisher's Exact Test)
 Source: Study Number: 2005107, Final Report, EoT Table 32

Phase 1 trials with the 35 mg DR formulation and an IR comparator group:

Trial 2004132 was a single dose parallel group trial comparing PK for 4 different 35 mg DR formulations fasted and fed to 35 mg IR fasted. For the DR formulation carried forward, 2 subjects (11%) fasted and 6 (33%) fed had 6 and 13 AEs. For the IR group, 5 subjects (25%) had 8 AEs. A large number GI SOC AEs were noted in the DR formulation to be carried forward compared to the IR formulation (1 for IR, 4 and 10 respectively for the DR fasted and fed).

Trial 2007120 was a 4 period single dose PK crossover trial in postmenopausal women to assess absorption of risedronate IR and DR under fasted and fed/label conditions. Total subjects with AE were similar between groups (35 mg IR per label, 15 (20%), 35 mg IR fasted, 21 (28%), 35 mg DR fed 20 (27%), 35 mg DR fasted, 16 (21%).

Numerically more musculoskeletal and CTD SOC AEs were seen with the DR formulation (5 after 35 mg IR per label, 2 after 35 mg IR fasted, 6 after 35 mg DR fed, and 8 after 35 mg DR fasted groups) and more headaches with the 35 mg IR fasted dose (5 after 35 mg IR per label, 15 after 35 mg IR fasted, 7 after 35 mg DR fed, and 6 after 35 mg DR fasted groups).

Trial 2008052 was a 4 period single dose PK crossover trial in postmenopausal women to assess absorption of risedronate 35 mg IR and 20 mg DR under fasted and fed/label conditions with a 35 mg DR fed arm. In this trial, more subjects had AEs after the 35 mg DR formulation following a high fat breakfast (26 (28%)) than after the 35 mg IR per label (21 (22%)). Many more total AEs were reported after the 35 mg DR formulation (77 vs. 32).

A review of adverse event differences after the 35 mg IR and 35 mg DR treatments showed substantially more after the DR formulation in the following SOCs:

- GI SOC (8 subjects with 9 AEs after IR, 14 subjects with 30 AEs after DR and especially more diarrhea, abdominal pain, and nausea after DR)
- General disorders SOC (3 subjects with 4 AEs after IR, 7 subjects with 8 AEs after DR and especially more chills after DR)
- Musculoskeletal and CTD SOC (5 subjects with 6 AEs after IR, 10 subjects with 13 AEs after DR and especially more in HLT MS and CTD signs and symptoms after DR)
- Nervous system SOC (6 subjects with 6 AEs after IR, 13 subjects with 18 AEs after DR and especially more headaches after DR)
- Skin and subcutaneous tissue SOC (1 subject with 1 AE after IR, 4 subjects with 5 AEs after DR)

Given that this is a crossover trial, more credibility may be given to the increased number of adverse events, as that increase is greater than the increase in subjects with adverse events.

Reviewer comment: The trend in the Phase 3 trial toward more subjects with adverse events with the 35 mg DR formulation, especially the DRBB dosing, is not confirmed by the Phase 2 trial, although a 35 mg DRBB group was not present in that trial and numerically more adverse events are present in Phase 2 with 50 mg DRFB dosing. Statistically more adverse events with 35 mg DRBB dosing in Phase 3 with a trend for 35 mg DRFB has some support from Phase 1 trials 2008052 and 2004132. GI and musculoskeletal SOC adverse events are common throughout trials.

7.4.2 Laboratory Findings

Adverse Events, Trial 2007008: Table 34 lists all laboratory values reported as AEs in the Phase 3 trial 2007008. Most laboratory values as AEs occurred in only one or two cases. The only difference between treatment groups to reach statistical significance in

this category was anemia, which was more common in the 35 mg DRFB group (6 subjects, compared to 1 in the 35 mg DRBB group and none in the 5 mg IRBB group). PTH increased and secondary hyperparathyroidism were more common in the 35 mg DRBB group, and hyperparathyroidism was more common in the 5 mg IRBB group, but these differences did not meet statistical significance. Sponsor reports 6 of 7 subjects diagnosed with secondary hyperparathyroidism are from a single site in Estonia, and 3 of the six had an onset date of Day 1 before they had taken study medication. Only one subject of these had sustained hypocalcemia.

Table 34, Trial 2007008 Laboratory Values as AEs, ITT Population

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
Blood cholesterol increased	1 (0.3%) 1	2 (0.7%) 2	1 (0.3%) 1	0.8510
Blood PTH increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7	0.2626
Urinary sediment abnormal	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Urine analysis abnormal	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Blood calcium decreased	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Blood glucose increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
aPTT prolonged	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
INR increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Prothrombin time prolonged	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Occult blood	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Occult blood positive	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
ALT increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
AST increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Transaminases increased	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Platelet count decreased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood creatinine increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood urea increased	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Cr clearance decreased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood alk. phos. increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Hypercholesterolemia	2 (0.7%) 2	7 (2.3%) 7	6 (1.9%) 6	0.2261
Hypercalcemia	0 (0.0%) 0	1 (0.3%) 1	2 (0.6%) 2	0.7771
Hypoglycemia	0 (0.0%) 0	1 (0.3%) 2	0 (0.0%) 0	0.6659
Hyponatremia	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Vitamin D deficiency	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Hyperlipidemia	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Dyslipidemia	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Hypokalemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hyperuricemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Anemia	0 (0.0%) 0	6 (2.0%) 6	1 (0.3%) 1	0.0137
Leukopenia	2 (0.7%) 2	2 (0.7%) 2	1 (0.3%) 1	0.7517
Thrombocythemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hematuria	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Leukocyturia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Renal failure acute	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Renal failure chronic	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hyperparathyroidism, 2°	0 (0.0%) 0	2 (0.7%) 2	5 (1.6%) 6	0.0769
Hyperparathyroidism	3 (1.0%) 3	0 (0.0%) 0	1 (0.3%) 1	0.2329

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
Hypothyroidism	3 (1.0%) 3	2 (0.7%) 2	1 (0.3%) 1	0.5449
Hypoparathyroidism	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Hyperbilirubinemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000

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, Section 11 Table 49

Marked Laboratory Abnormalities: Markedly abnormal laboratory values post baseline in Trial 2007008 were relatively uncommon and fairly equally spread across treatment groups except for PTH (≥ 98 ng/l) (16 subjects [5.3%], 5 mg IRBB; 19 subjects [6.3%], 35 mg DRFB; 38 subjects [12.5%], 35 mg DRBB). This is evaluated further in Section 7.3.5.

Table 35, Trial 2007008 Markedly Abnormal Lab Values Post Baseline, ITT Population

Lab Test	5 mg IRBB Daily (N=307)		35 mg DRFB Weekly (N=307)		35 mg DRBB Weekly (N=308)	
	n (%)	N	n (%)	N	n (%)	N
Hematocrit < 28%	0	293	1 (0.3%)	300	1 (0.3%)	301
Hemoglobin < 9.3 g/dl	0	293	1 (0.3%)	300	1 (0.3%)	301
Platelets < $112 \times 10^3/\text{mm}^3$	2 (0.7%)	292	2 (0.7%)	299	1 (0.3%)	300
Leukocytes < $3.3 \times 10^3/\text{mm}^3$	2 (0.7%)	293	4 (1.3%)	300	5 (1.7%)	301
Neutrophils < $1.43 \times 10^3/\text{mm}^3$	2 (0.7%)	293	1 (0.3%)	299	1 (0.3%)	301
Lymphs < $0.72 \times 10^3/\text{mm}^3$	2 (0.7%)	293	4 (1.3%)	299	1 (0.3%)	301
Lymphs > $5.04 \times 10^3/\text{mm}^3$	0	293	1 (0.3%)	299	0	301
Eosinophils > $1.12 \times 10^3/\text{mm}^3$	5 (1.7%)	293	3 (1.0%)	299	2 (0.7%)	301
Basophils > $0.25 \times 10^3/\text{mm}^3$	0	293	1 (0.3%)	299	0	301
Calcium < 7.6 mg/dl	1 (0.3%)	303	1 (0.3%)	303	1 (0.3%)	305
Calcium > 11.3 mg/dl	2 (0.7%)	303	0	303	0	305
Phosphate < 1.9 mg/dl	1 (0.3%)	303	2 (0.7%)	303	0	305
Phosphate > 6.1 mg/dl	0	303	0	303	1 (0.3%)	305
Alk Phos > 150 U/l	7 (2.3%)	303	4 (1.3%)	303	6 (2.0%)	305
Bilirubin > 1.5 mg/dl	3 (1.0%)	303	1 (0.3%)	303	3 (1.0%)	305
ALT > 111 U/l	2 (0.7%)	303	1 (0.3%)	303	1 (0.3%)	305
AST > 108 U/l	0	303	0	303	1 (0.3%)	305
Potassium < 3.2 mEq/l	0	303	0	303	2 (0.7%)	305
Potassium > 6.0 mEq/l	0	303	2 (0.7%)	303	1 (0.3%)	305
iPTH > 97 pg/ml	16 (5.3%)	302	19 (6.3%)	302	38 (12.5%)	305

N=Number of subjects with post-baseline measurement within specified treatment.
 Subjects with multiple high/low values were counted only once.
 Source: Study 2007008 Year 1 Final Report, Section 11 Tables 78 and 83

Mean Change from Baseline: The mean values for all hematology parameters (hemoglobin, red blood cell count, hematocrit, platelet count, white blood cell (WBC))

count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were within the normal range at all time points for all treatment groups and were similar across treatment groups in Trial 2007008. The mean changes from baseline at all time points were reviewed and were very small for each hematology parameter.

The mean values for all chemistry parameters (glucose, creatinine, creatinine clearance, calcium, phosphate, albumin, alkaline phosphatase, bilirubin, ALT, AST, sodium, magnesium, potassium, chloride, bicarbonate, and iPTH) were within the normal range at all time points for all treatment groups except iPTH was high for the 35 mg DRBB group at week 13 (67 pg/ml, not a protocol time for measurement, only 14 subjects measured). The mean changes from baseline to each post-baseline time point were generally small. An expected fall in alkaline phosphatase in all treatment groups was noted by week 13 which persisted through the rest of the reported period. There were no clinically important differences across groups for any chemistry parameter.

Urinalysis (pH, ketones, protein, glucose, blood, and bilirubin) was performed by dipstick at baseline, Week 52, and/or exit. Microscopy was performed only in subjects with abnormal urinalysis. A review of the urinalysis data showed no clinically relevant signals.

Prothrombin time, INR, and partial thromboplastin times were checked at baseline and weeks 13, 26, and 52 in Trial 2007008. For subjects not on anticoagulation with heparin or a vitamin K antagonist, mean values at all time points for all treatment groups were normal with no significant changes between time points. Individual values for the 18 subjects on anticoagulation therapy were reviewed, with no pattern of change noted.

Shifts: Shift tables for all hematology parameters were reviewed for Trial 2007008. A very slight predilection towards baseline leukocytopenia normalizing was noted in all treatment groups. No significant shifts were noted.

Shift tables for all chemistry parameters were reviewed. These were remarkable for the number of elevated alkaline phosphatase values at baseline which normalized during the trial. Hypocalcemia in subjects normocalcemic at baseline was slightly more prevalent at day 14, especially in the DRBB group, than later in the trial, when shift to hypocalcemia was about equal between groups. This is further discussed in Section 7.3.5. High iPTH values in subjects with normal values at baseline tended to be present in large numbers at day 14 for all treatment groups, but this tendency lessened later in the trial. The 35 mg DRBB group may have shown a greater tendency for iPTH increase (see Section 7.3.5).

Laboratory Adverse Events in Trial 2005107: Few lab abnormalities were reported as adverse events in Trial 2005107. In the 35 mg IRBB group, one adverse event was reported for each of blood glucose increased, blood cholesterol increased, and blood triglyceride increased. These were all in the same subject. Another AE of

hypercholesterolemia was reported. One subject in the 50 mg DRBB group had elevated ALT and AST reported as an AE. Another in the same group had hyponatremia. One subject in the 50 mg DRFB group had hypertriglyceridemia reported as an adverse event.

Marked Laboratory Abnormalities in Trial 2005107: Seven subjects reportedly had markedly abnormal laboratory which first occurred after study drug was administered for alkaline phosphatase (ALP), ALT, calcium, or potassium. The three for alkaline phosphatase all were in the 50 mg DRFB group. No narratives or CRFs are provided.

- A 52 year old Caucasian female had ALP values that were high at screening (133 U/L) and markedly high on Day 14 (151 U/L) but decreased to 102 U/L on Day 91, which was still above the normal range. ALT and AST values remained within the normal range throughout the study.
- A 60 year old Caucasian female had high ALP values at screening (123 U/L) and Day 14 (134 U/L) and a markedly high ALP on Day 91 (179 U/L). This subject also had elevated ALT values on Days 14 and 91, although AST values remained within the normal range.
- A 58 year old Asian female had high ALP values at screening (147 U/L) and admission (139 U/L) and a markedly high ALP on Day 14 (160 U/L). This subject's ALP value decreased to 104 U/L on Day 91, which was still above the normal range. ALT and AST values remained within the normal range throughout the study.

None of the above-mentioned subjects had relevant medical history or concomitant medications use.

Other extreme values following study medicine use are:

- A 57 year old Caucasian female in the 35 mg IRBB group with normal potassium at screening, admission, and Day 91 had a value of 6.3 mEq/l on Day 14.
- A 71 year old multiracial female in the 50 mg DRFB group with normal potassium at admission and Day 91 and 5.9 mEq/l at screening had a value of 6.5 mEq/l on Day 14.
- A 64 year old Caucasian female in the 50 mg DRBB group had normal transaminases at screening, admission, and Day 14. At Day 91 ALT was 160 U/l. AST was more mildly elevated at 59 U/l on Day 91.
- A 71 year old Caucasian female in the 50 mg DRBB group had a calcium level of 11.5 mg/dl on Day 14 with normal values at screening and Day 91.

Concomitant medications were reviewed and are unlikely to have caused any of these abnormal values. All abnormalities normalized by end of study except the ALT value found at end of study.

Mean Change from Baseline in Trial 2005107: Mean change from baseline for hematologic (hematocrit, hemoglobin, MCH, MCV, MCHC, platelet count, RBC count, and WBC count) and coagulation (PT, aPTT, INR) parameters by treatment groups

were reviewed. All mean values were within normal range at all time points. No clinically important differences were noted from baseline to 13 weeks.

Mean change from baseline for serum chemistries were reviewed, including creatinine, BUN, calcium, phosphorus, magnesium, ALT, AST, ALP, bilirubin, albumin, protein, carbon dioxide, sodium, potassium, chloride, cholesterol, triglycerides, and glucose. All mean values were within normal range at all time points except cholesterol. Calcium decreased a mean of 0.29 mg/dl and phosphorus a mean of 0.34 mg/dl between baseline and week 13, but these changes were similar between treatment groups, including the approved 35 mg IRBB group. No clinically important differences were noted in any parameter from baseline to 13 weeks.

Twenty four hour urine calcium was performed for subjects in the PK subset only (N=95). An increase was noted in all treatment groups from baseline to Week 12, with the most marked increase of 31% in the approved 35 mg IRBB group, but mean values remained in the normal range.

Shifts in Trial 2005107: Shift tables were reviewed for hematology, coagulation, and chemistry parameters. No obvious clinically relevant patterns were observed. In the PK subset, 24 hour urinary calcium excretion was > 300 mg at 12 weeks after a normal value at baseline in 4 of 17 subjects in the 35 mg IRBB group, 1 of 18 subjects in the 35 mg DRFB group, 0 of 18 subjects in the 50 mg DRBB group, and 4 of 36 subjects in the 50 mg DRFB group. The DR formulation does not appear to be associated with increased urinary calcium beyond that experienced with the approved IR formulation (note calcium and vitamin D supplementation in all groups).

7.4.3 Vital Signs

Mean vital sign values in the Phase 3 trial 2007008 were normal at all time points for all vital signs tested (BP, HR, and T) in all treatment groups. No clinically significant changes from baseline were seen. BMI for all treatment groups was at or slightly above 25.0 kg/m² and stable.

Shift tables for systolic blood pressure showed perhaps increased subjects in the DR regimens who were normotensive at baseline and then high (>140) especially at 52 weeks or endpoint (at Week 52, 23 subjects [10.4%], 5 mg IRBB; 31 subjects [14.0%], 35 mg DRFB; 40 subjects [17.8%], 35 mg DRBB). For diastolic blood pressure the increase (considered high at >89) was more equal across treatment groups (at Week 52, 31 subjects [13.7%], 5 mg IRBB; 29 subjects [13.3%], 35 mg DRFB; 28 subjects [12.1%], 35 mg DRBB). How much of this increase is from the common increase of blood pressure with age is unknown. A similar trend was not found in other risedronate trials for which shift tables were available. Markedly high blood pressures were uncommon. For systolic blood pressure 5 subjects (1.8%) in the 5 mg IRBB group at week 26 and 6 (2.3%) in the 35 mg DRFB group at week 39 were markedly high (> 200

mmHg or ≥ 180 mmHg and increase since baseline ≥ 30 mmHg). No other treatment group and time point had more than 2 subjects in this category. For diastolic blood pressure, at no time point did more than 2 subjects in a treatment group have a markedly high measurement (> 115 mmHg or ≥ 105 mmHg and increase since baseline ≥ 20 mmHg).

In Trial 2005107 mean vital sign values were normal at all time points for all vital signs tested (BP, HR, and T) in all treatment groups. No clinically significant changes from baseline were seen.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed on all patients at baseline and Week 52. In addition, patients at sites in Argentina had an ECG at screening; if the screening ECG showed previously undiagnosed atrial fibrillation, atrial flutter, or tachyarrhythmias, the patient also had an ECG at Week 26.

At baseline, over 80% of each treatment group was in normal sinus rhythm with most of the rest in sinus bradycardia (about 10% per group) or “other” (6 – 8% per group). A few subjects were in sinus arrhythmia or sinus tachycardia. One subject in the IRBB group was in accelerated idioventricular rhythm and another in that group in a paced rhythm. Little change in rhythm was seen at Week 52 or Endpoint.

Atrial fibrillation or flutter was present in 6 subjects at baseline (1 subject, 5 mg IRBB; 5 subjects, 35 mg DRFB). Of the subjects in normal sinus rhythm at baseline who had repeat ECGs at Week 52 or study exit, none had atrial fibrillation or atrial flutter. Treatment emergent adverse events of atrial fibrillation were reported for four subjects (1 subject in the DRFB group, 3 in DRBB), one of whom had atrial fibrillation at baseline (DRFB group) and one of whom had a history of paroxysmal atrial fibrillation (DRBB group). See Section 7.3.5.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Bone Histomorphometry

Bone histomorphometry results from Trial 2007008, the Phase 3 trial for Atelvia, were submitted June 28, 2010. Unpaired transiliac crest bone biopsies were obtained at Week 104 from subjects at 9 study sites. A total of 45 volunteers underwent biopsies; 18 of 307 subjects in the 5 mg daily group, 15 of 307 subjects in the 35 mg DRFB weekly group, and 12 of 308 subjects in the 35 mg DRBB weekly group.

Prior to the bone biopsy procedure, subjects were administered tetracycline (1000 mg daily) or demeclocycline (600 mg daily) for two 3-day periods, separated by a 14-day

interval. The bone biopsy samples were collected 5 to 14 days after the last dose of tetracycline or demeclocycline. Biopsies were processed at a central lab.

Although not randomly selected, demographic features, such as age (mean 64), race (predominantly Caucasian), ethnicity (about 35% Hispanic), and years since menopause (mean 17), were balanced between treatment groups. Baseline BMD was mostly balanced between groups; trochanter density in the 5 mg IRBB group was statistically lower in those subjects measured on Lunar densitometers compared to other treatment groups. Some differences in the baseline bone turnover markers CTX, NTX, and BSAP were noted, although the only one to reach statistical significance was a lower BSAP in the 35 mg DRBB group. In general, demographic features were similar to the ITT population.

Of the 45 biopsy samples, 44 were evaluable for histomorphometry. The non-evaluable sample (5 mg IRBB group) was crushed, although double tetracycline label was seen in the cortices. Double tetracycline label was seen in 44 out of the 45 biopsies in the field of view of standard sections in trabecular or cortical bone. One biopsy from the 5 mg IRBB group did not show double tetracycline label in the field of view of the standard sections reviewed; however, upon additional search, double label was found. Histomorphometry data for some dynamic bone formation parameters are unavailable due to lack of double tetracycline label in the standard sections analyzed (1 in the 5 mg IRBB group; 2 in the 35 mg DRFB group; 1 in the 35 mg DRBB group). An additional sample (35 mg DRFB group) had a fragmented cortex; therefore data are not available for cortical porosity and cortical thickness.

Normal lamellar bone, normal osteoid, and normal mineralization were found in all subjects in whom these were evaluable, and there was no evidence of woven bone or osteomalacia. None of the subjects had cortical trabecularization, marrow dyscrasia, marrow fibrosis, or other pathologic findings.

In Table 36 mean values of several histomorphometric parameters are compared for risedronate 5 mg IRBB daily subjects, 35 mg DRFB weekly subjects, and 35 mg DRBB weekly subjects.

Osteoid thickness: Osteoid thickness can be used a marker of bone formation. Increases in osteoid thickness would be expected in the setting of a mineralization defect. Osteoid thickness in DRFB treated subjects was statistically less than IRBB (approved) treated subjects (IRBB 5.8 μm vs. DRFB 5.2 μm , $p=0.034$, and DRBB 5.3 μm , $p=0.222$).

Osteoid volume (OV/BV): Osteoid volume represents the percentage of bone volume that is non-mineralized osteoid. A clear increase in OV/BV would support the hypothesis of impaired mineralization. The mean osteoid volume in the risedronate DR groups was

not different from the IRBB group (IRBB 0.81% vs. DRFB 0.99%, $p=0.610$, and DRBB 0.97%, $p=1.000$).

Osteoid surface (OS/BS): The osteoid surface/bone surface ratio reflects bone remodeling. The mean osteoid surface in the DR groups was similar to the IRBB group (IRBB 6.38% vs. DRFB 8.69%, $p=0.865$, and DRBB 9.21%, $p=0.690$).

Adjusted apposition rate (Aj.AR): The adjusted apposition rate represents the mineral apposition rate or the bone formation rate averaged over the entire osteoid surface. A decrease could indicate impairment of mineralization and the potential of the drug to induce osteomalacia. Adjusted apposition rate in risedronate DR treated subjects was not statistically different from the IRBB group (IRBB 0.12 $\mu\text{m}/\text{d}$ vs. DRFB 0.08 $\mu\text{m}/\text{d}$, $p=0.194$, and DRBB 0.10 $\mu\text{m}/\text{d}$, $p=0.553$).

Mineralization lag time (Mlt): Mineralization lag time (Mlt) is the interval between osteoid formation and mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. Mineralization lag time in risedronate DR treated subjects was not statistically different from the IRBB group (IRBB 92 days vs. DRFB 108 days, $p=0.456$ and DRBB 132 days, $p=0.693$).

Activation frequency (Ac.f): The activation frequency represents the probability that a new cycle of remodeling will be initiated at any point of the bone surface. The activation frequency in the risedronate DR groups was similar to the IRBB group (IRBB 0.09/yr vs. DRFB 0.08/yr, $p=0.201$, and DRBB 0.09/yr, $p=0.785$).

Bone formation rate/surface referent (BFR/BS): Mean bone formation rate/bone surface in the risedronate DR groups was similar to the IRBB group (IRBB 0.0072 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$ vs. DRFB 0.0059 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$, $p=0.148$, and DRBB 0.0070 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$, $p=0.921$).

Reviewer comment: In these histomorphometric values no concerning difference is seen between the approved 5 mg IR risedronate and the 35 mg DRFB and DRBB groups.

Table 36, Trial 2007008 Bone Histomorphometry Results

Biopsy Measurement Unit Statistics	5 mg IRBB QD (N = 18)	35 mg DRFB Qwk (N = 15)	35 mg DRBB Qwk (N = 12)	Wilcoxon p-value	
				35 mg DRFB - 5 mg IRBB	35 mg DRBB - 5 mg IRBB
Osteoid Thickness (um)					
n	17	15	12		
Mean (SD)	5.8 (0.9)	5.2 (0.8)	5.3 (0.6)	0.0337	0.2221
Min, Max	5.0, 8.0	4.1, 6.9	4.1, 6.2		
Osteoid Volume/ Bone Volume (%)					
n	17	15	12		
Mean (SD)	0.81 (0.63)	0.99 (1.22)	0.97 (0.96)	0.6101	1.0000
Osteoid Surface/ Bone Surface (%)					
n	17	15	12		
Mean (SD)	6.38 (3.54)	8.69 (8.62)	9.21 (7.60)	0.8651	0.6902
Adj. Appositional Rate (um/day)					
n	16	13	11		
Mean (SD)	0.12 (0.08)	0.08 (0.05)	0.10 (0.09)	0.1942	0.5529
Mineralization Lag Time (Days)					
n	16	13	11		
Mean (SD)	92 (85)	108 (91)	132 (173)	0.4560	0.6930
Min, Max	23, 325	25, 373	18, 618		
Activation Frequency (/Year)					
n	16	13	11		
Mean (SD)	0.09 (0.07)	0.08 (0.11)	0.09 (0.06)	0.2010	0.7854
Bone Form Rate-Tot Surf Ref					
n	16	13	11		
Mean (SD)	0.0072 (0.0055)	0.0059 (0.0076)	0.0070 (0.0043)	0.1476	0.9214

Source: Trial 2007008 Report of Bone Histology/Histomorphometry Results

7.4.5.2 Adverse Events at High Risedronate Absorption in Men

As previously discussed, of risedronate immediate release doses studied, only the risedronate 15 mg daily dose provides comparable absorption to the risedronate DR 35 mg weekly dose. No efficacy trials for the DR formulation have been conducted in men and, although men were included in some of the Phase 1 DR formulation trials, none of these were large enough or dosed for long enough to provide adequate information on any difference between adverse events at high risedronate absorption between men and women.

Two moderately large 2 year trials have been done with the risedronate immediate release 15 mg daily dose in men and women. These were both for mild to moderate medial knee osteoarthritis. Trial 1998033 was a placebo-controlled, double blind, randomized North American study in 763 women and 479 men, of whom 198 women and 107 men took 15 mg risedronate daily. Trial 1998034 was a placebo-controlled, double blind, randomized European study in 994 women and 261 men, of whom 237 women and 72 men took 15 mg risedronate daily.

Adverse events overall and by body system separated by dose and gender for these osteoarthritis trials are shown in Table 37. For the 15 mg treatment group, adverse events generally appear similar between males and females and also similar to the other treatment groups. For Trial 1998033 body as a whole adverse events for the male subjects at 15 mg daily appear more frequent than for males in other treatment groups, but this was not confirmed by Trial 1998034. Generally, body as a whole and digestive AEs appeared to be more frequent in females in most treatment groups in both studies. Respiratory and urogenital AEs appeared to be more frequent in females than males in Trial 1998033, but not 1998034.

Preferred terms benign prostatic hypertrophy, nephrolithiasis, and arrhythmia were identified in the male osteoporosis trial of the 35 mg immediate release risedronate against placebo as being possibly increased in males compared to females and placebo (benign prostatic hyperplasia placebo 3%; risedronate IR 35 mg 5%, nephrolithiasis placebo 0%; risedronate IR 35 mg 3%, and arrhythmia placebo 0%; risedronate IR 35 mg 2%). The higher absorption with the DR formulation raises concerns that these AEs could be higher with that formulation. Evaluation of these preferred terms or closely related terms in Trials 1998033 and 1998034 (COSTART rather than MedDRA coding used) indicate that numbers of these AEs are small and not clearly related to risedronate dose (see Table 37).

Table 37, Male vs. Female AEs at High Risedronate Absorption, Osteoarthritis Trials

Trial 1998033	15 mg QD		5 mg QD		50 mg QWk		Placebo	
	F	M	F	M	F	M	F	M
Gender								
Body System	N=198	N=107	N=191	N=119	N=194	N=120	N=180	N=133
Overall	191(96%)	102(95%)	183(96%)	110(92%)	189(97%)	117(98%)	173(96%)	124(93%)
AEs/subject	13.0	11.4	14.2	9.1	13.6	11.4	14.0	10.9
Whole Body	165(83%)	89(83%)	162(85%)	92(77%)	162(84%)	94(78%)	149(83%)	96(72%)
Cardiovascular	48(24%)	24(22%)	48(25%)	24(20%)	48(25%)	35(29%)	56(31%)	41(31%)
Digestive	75(38%)	28(26%)	77(40%)	29(24%)	90(46%)	45(38%)	77(43%)	47(35%)
Endocrine	6(3%)	3(3%)	3(2%)	0(0%)	4(2%)	0(0%)	4(2%)	2(2%)
Hemic & Lymph	13(7%)	5(5%)	13(7%)	7(6%)	19(10%)	14(12%)	11(6%)	9(7%)
Metab. & Nutrit.	62(31%)	23(21%)	54(28%)	25(21%)	47(24%)	32(27%)	54(30%)	36(27%)
Musculoskeletal	167(84%)	93(87%)	167(87%)	95(80%)	166(86%)	104(87%)	155(86%)	107(80%)
Nervous	55(28%)	28(26%)	59(31%)	30(25%)	65(34%)	37(31%)	51(28%)	34(26%)
Respiratory	68(34%)	31(29%)	56(29%)	23(19%)	62(32%)	32(27%)	67(37%)	31(23%)
Skin & Append.	46(23%)	28(26%)	46(24%)	28(24%)	44(23%)	31(26%)	46(26%)	30(23%)

Trial 1998033	15 mg QD		5 mg QD		50 mg QWk		Placebo	
Gender	F	M	F	M	F	M	F	M
Body System	N=198	N=107	N=191	N=119	N=194	N=120	N=180	N=133
Special Senses	26(13%)	20(19%)	24(13%)	15(13%)	28(14%)	17(14%)	26(14%)	13(10%)
Urogenital	38(19%)	10(9%)	35(18%)	13(11%)	35(18%)	9(8%)	36(20%)	14(11%)
Preferd. Term								
Prostat. Dis.		3(3%)		3(3%)		0(0%)		8(6%)
Kidney Calc.	1(1%)	1(1%)	2(1%)	2(2%)	1(1%)	3(2%)	3(2%)	0(0%)
Arrhythmia	4(2%)	5(5%)	2(1%)	2(2%)	2(1%)	4(3%)	2(1%)	2(2%)
Trial 1998034	15 mg QD		5 mg QD		35 mg QWk		Placebo	
Body System	N=237	N=72	N=254	N=68	N=244	N=67	N=259	N=54
Overall	211(89%)	65(90%)	235(93%)	58(85%)	217(89%)	57(85%)	237(92%)	42(78%)
AEs/subject	8.2	6.6	8.9	7.0	8.8	5.5	9.4	4.8
Whole Body	153(65%)	39(54%)	166(65%)	37(54%)	156(64%)	32(48%)	178(69%)	27(50%)
Cardiovascular	75(32%)	23(32%)	88(35%)	21(31%)	85(35%)	22(33%)	85(33%)	21(39%)
Digestive	51(22%)	18(25%)	70(28%)	10(15%)	59(24%)	15(22%)	73(28%)	7(13%)
Endocrine	8(3%)	0(0%)	9(4%)	3(4%)	6(2%)	2(3%)	16(6%)	2(4%)
Hemic & Lymph	10(4%)	3(4%)	7(3%)	3(4%)	3(1%)	1(1%)	9(3%)	0(0%)
Metab. & Nutrit.	35(15%)	6(8%)	35(14%)	8(12%)	26(11%)	7(10%)	38(15%)	6(11%)
Musculoskeletal	178(75%)	53(74%)	200(79%)	48(71%)	192(79%)	39(58%)	200(77%)	32(59%)
Nervous	35(15%)	14(19%)	44(17%)	11(16%)	46(19%)	7(10%)	52(20%)	5(9%)
Respiratory	31(13%)	7(10%)	42(17%)	13(19%)	36(15%)	9(13%)	34(13%)	5(9%)
Skin & Append.	24(10%)	8(11%)	23(9%)	8(12%)	22(9%)	7(10%)	33(13%)	5(9%)
Special Senses	15(6%)	4(6%)	13(5%)	8(12%)	20(8%)	4(6%)	22(8%)	7(13%)
Urogenital	25(11%)	9(12%)	26(10%)	5(7%)	27(11%)	8(12%)	42(16%)	5(9%)
Preferd. Term								
Prostat. Dis.		4(6%)		4(6%)		4(6%)		2(4%)
Kidney Calc.	2(1%)	0(0%)	1(0%)	0(0%)	0(0%)	2(3%)	1(0%)	0(0%)
Arrhythmia	4(2%)	0(0%)	2(1%)	1(1%)	3(1%)	0(0%)	3(1%)	1(2%)

n(%) = number (percent) of subjects within specified category and treatment
COSTART dictionary used for AEs
Source: Datasets for Trials 1998033 and 1998034

Conclusions: In a male osteoarthritis population, a dose of immediate release risedronate (15 mg daily) with comparable absorption to the risedronate 35 mg DR formulation for 2 years does not appear to cause increased adverse events compared to females, or compared to males treated with placebo or lower doses of risedronate.

7.4.6 Immunogenicity

Risedronate, as a non-peptide, is not expected to elicit an immune response in humans.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Data available in NDA 22-560 related to dose dependency for adverse events is limited. The best pertinent data is from the Phase 2 trial 2005107 (see Table 33). In this 13 week trial in healthy postmenopausal women more adverse events were reported in the 50 mg DRFB treatment group (51 of 72 subjects (70.8%) with 170 AEs) than the 35 mg DRFB group (19 of 36 subjects (52.8%) with 44 AEs). In comparing SOCs GI disorders stands out with more AEs reported in the 50 mg DRFB treatment group (26 subjects (36.1%) with 69 AEs) than the 35 mg DRFB group (8 subjects (22.2%) with 11 AEs). Abdominal pain upper, abdominal pain, nausea, and diarrhea were particularly more common in the 50 mg DRFB group.

7.5.2 Time Dependency for Adverse Events

Adverse events in Trial 2007008, the Phase 3 trial, were evaluated overall by day of study onset. There appeared to be an expected tendency for more adverse events for all treatment groups (5 mg IRBB, 35 mg DRFB, 35 mg DRBB) in the first month, but later no particular pattern was discernable. There did not appear to be increasing AEs at the end of the trial.

7.5.3 Drug-Demographic Interactions

Percentage of subjects with an AE by age was calculated and is shown in Table 38. Although there may be a slight trend to higher percentages of subjects with AEs at older ages, this is not surprising and not prominent and appears to be at least as marked in the approved IRBB treatment group as in the DR groups. As noted previously, overall, more subjects in the DRBB group had AEs.

Table 38, Trial 2007008 Subjects with AE by Age

Age	5 mg IRBB		35 mg DRFB		35 mg DRBB	
	N	n (%)	N	n (%)	N	n (%)
< 65	140	93 (66%)	127	97 (76%)	133	100 (75%)
65 - 74	129	90 (70%)	141	95 (67%)	133	104 (78%)
≥ 75	38	28 (74%)	39	30 (77%)	42	34 (81%)

n (%) = number (percent) of subjects with AE
 Source: Datasets

7.5.4 Drug-Disease Interactions

AEs in the Phase 3 trial 2007008 were evaluated for subjects with moderate renal insufficiency (estimated creatinine clearance of 30 to 60 ml/min.) at baseline compared

to subjects with mild or no renal insufficiency with results shown in Table 39. Subjects with moderate renal insufficiency are expected to have higher serum risedronate levels.

For the DR formulation no increase in the proportion of subjects with adverse events was noted with moderate renal insufficiency (for the DRFB group, 68.8% of subjects with moderate renal insufficiency with AEs, 73.5% without moderate renal insufficiency, for the DRBB group 74.7% and 78.0% respectively). For subjects with moderate renal insufficiency, there appears to be little difference in AEs between treatment groups, including the 5 mg IRBB group. For subjects with mild or no renal insufficiency, the majority of subjects, more subjects with AEs are noted with the DR formulation. This excess is discussed extensively for Trial 2007008 in Section 7.4.1.

Table 39, Trial 2007008 AEs by Renal Status

	5 mg IRBB Daily		35 mg DRFB Weekly		35 mg DRBB Weekly	
	N	n (%) nAE	N	n (%) nAE	N	n (%) nAE
Cr. Cl. < 30 ml/min					1*	1 (100%) 7
Cr. Cl. ≥ 30, < 60 ml/min	80	59 (73.8%) 202	77	53 (68.8%) 178	75	56 (74.7%) 168
Cr. Cl. ≥ 60 ml/min	227	152 (67.0%) 458	230	169 (73.5%) 556	232	181 (78.0%) 629
n (%) = number (percent) of subjects with AE nAE = number of adverse events * This subject was a protocol violation for Cr. Cl. < 30 ml/min Source: Study 2007008 Year 1 Final Report datasets						

Adverse events which might be related to increased systemic risedronate exposure and which showed higher rates with expected higher risedronate levels were sought and compared by renal status. From the Phase 3 trial 2007008 pain (general disorders SOC) and blood PTH increased were found. Arthralgias, back pain, and musculoskeletal pain are analyzed as they are common and presumably due to systemic absorption, although no increase with the higher absorption with the DR formulation was noted. Abdominal pain upper, abdominal pain, nausea, and diarrhea were noted to be more common at higher absorptions in the Phase 2 trial 2005107, and also vomiting in the Phase 3 trial, but these may be local irritation rather than systemic absorption. Results are shown in Table 40.

Over the AEs analyzed, only PTH increased occurred consistently at a higher rate in subjects with moderate renal insufficiency.

Table 40, Trial 2007008 Selected AEs by Renal Status

	5 mg IRBB Daily		35 mg DRFB Weekly		35 mg DRBB Weekly	
	N	n (%) nAE	N	n (%) nAE	N	n (%) nAE
Pain						
Cr. Cl. ≥ 30, < 60 ml/min	80	0 (0%) 0	77	1 (1.3%) 1	75	0 (0%) 0
Cr. Cl. ≥ 60 ml/min	227	0 (0%) 0	230	2 (0.9%) 2	232	4 (1.7%) 4
PTH increased						
Cr. Cl. ≥ 30, < 60 ml/min	80	2 (2.5%) 2	77	1 (1.3%) 2	75	4 (5.3%) 4
Cr. Cl. ≥ 60 ml/min	227	1 (0.4%) 1	230	1 (0.4%) 1	232	3 (1.3%) 3
Arthralgias						
Cr. Cl. ≥ 30, < 60 ml/min	80	5 (6.2%) 6	77	5 (6.5%) 6	75	4 (5.3%) 5
Cr. Cl. ≥ 60 ml/min	227	19 (8.4%) 23	230	16 (7.0%) 24	232	15 (6.5%) 18
Back pain						
Cr. Cl. ≥ 30, < 60 ml/min	80	6 (7.5%) 7	77	7 (9.1%) 9	75	4 (5.3%) 5
Cr. Cl. ≥ 60 ml/min	227	12 (5.3%) 12	230	14 (6.1%) 15	232	14 (6.0%) 14
Musculoskeletal pain						
Cr. Cl. ≥ 30, < 60 ml/min	80	1 (1.2%) 1	77	2 (2.6%) 2	75	2 (2.7%) 2
Cr. Cl. ≥ 60 ml/min	227	4 (1.8%) 4	230	4 (1.7%) 4	232	5 (2.2%) 5
Abdominal pain upper						
Cr. Cl. ≥ 30, < 60 ml/min	80	3 (3.8%) 4	77	2 (2.6%) 3	75	4 (5.3%) 4
Cr. Cl. ≥ 60 ml/min	227	4 (1.8%) 4	230	7 (3.0%) 10	232	18 (7.8%) 26
Abdominal pain						
Cr. Cl. ≥ 30, < 60 ml/min	80	1 (1.2%) 1	77	3 (3.9%) 3	75	1 (1.3%) 1
Cr. Cl. ≥ 60 ml/min	227	8 (3.5%) 9	230	13 (5.7%) 15	232	14 (6.0%) 17
Nausea						
Cr. Cl. ≥ 30, < 60 ml/min	80	4 (5.0%) 4	77	0 (0%) 0	75	2 (2.7%) 2
Cr. Cl. ≥ 60 ml/min	227	8 (3.5%) 8	230	11 (4.8%) 14	232	8 (3.4%) 9
Diarrhea						
Cr. Cl. ≥ 30, < 60 ml/min	80	7 (8.8%) 9	77	6 (7.8%) 6	75	6 (8.0%) 8
Cr. Cl. ≥ 60 ml/min	227	8 (3.5%) 12	230	21 (9.1%) 23	232	12 (5.2%) 13
Vomiting						
Cr. Cl. ≥ 30, < 60 ml/min	80	2 (2.5%) 2	77	1 (1.3%) 1	75	1 (1.3%) 2
Cr. Cl. ≥ 60 ml/min	227	3 (1.3%) 3	230	14 (6.1%) 17	232	7 (3.0%) 9
n (%) = number (percent) of subjects with AE						
nAE = number of adverse events						
Source: Study 2007008 Year 1 Final Report datasets						

As PTH elevation reported as an AE in Trial 2007008 was proportionately more common in subjects with moderate renal insufficiency, measured PTH elevation at 26 or 52 weeks with normal baseline, which has been noted to be more common especially in the 35 mg DRBB treatment group, was compared for subjects with moderate to severe renal insufficiency (RI) to subjects with mild or no RI. The only subject in the trial with severe RI did have normal PTH at baseline and marked elevation at week 26 or 52, and is included in Table 41.

Little difference was noted in the proportion of subjects with elevated (>65 pg/ml) or markedly elevated (>97 pg/ml) PTH compared by renal status.

Table 41, Trial 2007008 PTH Elevation at 26 and 52 Weeks by Renal Status

	5 mg IRBB Daily		35 mg DRFB Weekly		35 mg DRBB Weekly	
	N	n (%)	N	n (%)	N	n (%)
Elevated PTH (>65 pg/ml) at Week 26 or 52 Following a Normal Baseline						
Cr. Cl. < 60 ml/min	80	5 (6.2%)	77	7 (9.1%)	76	11 (14.5%)
Cr. Cl. ≥ 60 ml/min	227	21 (9.3%)	230	26 (11.3%)	232	37 (15.9%)
Very Elevated PTH (>97 pg/ml) at Week 26 or 52 Following a Normal Baseline						
Cr. Cl. < 60 ml/min	80	1 (1.2%)	77	2 (2.6%)	76	3 (3.9%)
Cr. Cl. ≥ 60 ml/min	227	1 (0.4%)	230	3 (1.3%)	232	5 (2.2%)
n (%) = number (percent) of subjects with elevated PTH						
Source: Study 2007008 Year 1 Final Report datasets						

No studies have been performed to assess risedronate’s safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

7.5.5 Drug-Drug Interactions

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

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

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

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no apparent association between the risedronate DR formulation and cancer. Although this conclusion is limited by the exposure database (499 subjects have been treated with this formulation for 1 year), the lack of genotoxicity in standard *in vitro* assays, the negative carcinogenicity studies testing doses 6.4-7.7x the human 30 mg/day dose for up to 104 weeks, and the lack of a cancer signal in the postmarketing database for risedronate and other bisphosphonates are reassuring.

7.6.2 Human Reproduction and Pregnancy Data

All risedronate clinical trials for both DR and IR formulations have excluded women who were pregnant or lactating. No data exists on fetal risk in humans, but a theoretical risk exists for the fetus of a woman becoming pregnant after a course of risedronate, as risedronate is incorporated into bone and may be gradually released for years following a course of treatment. It is unknown if risedronate is excreted in human milk.

All approved risedronate IR doses are classified as pregnancy category C.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Pediatric Review Committee Pediatric Research Equity Act (PeRC PREA) Subcommittee reviewed the risedronate DR request for a full waiver on February 17, 2010. As the condition for which treatment indication is sought does not exist in children (postmenopausal osteoporosis), a full waiver of the requirement to study the drug in children was granted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Substantial overdoses of risedronate 35 mg DR may cause decreases in serum calcium and phosphorus in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium, magnesium, and aluminum may be given to bind risedronate IR and reduce absorption of the drug. The impact of this intervention for risedronate 35 mg DR has not been evaluated. The risedronate 35 mg DR formulation is expected to be less sensitive to the binding effects of divalent cations.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore

physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

Drug abuse potential, withdrawal, and rebound are not applicable to risedronate DR. No abuse potential or withdrawal phenomena have been described for any of the bisphosphonates.

7.7 Additional Submissions / Safety Issues

120 Day Safety Update:

The 120 Day safety update was submitted electronically on 22 January, 2010, as sequence 0004 to NDA 22-560. It contains safety information from the only ongoing study in the development program, Phase 3 trial 2007008. Data tables present cumulative data from the beginning of the study to a cut-off date of 19 November 2009, using the same format as in the Year 1 report for Trial 2007008. Narratives are provided for patients who reported serious AEs, withdrawals due to AEs, and deaths that occurred between completion of the first year of treatment and the safety cut-off date. No datasets are provided.

No new IND safety reports were generated during the safety update period.

Phase 3 trial 2007008 is a multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, non-inferiority trial in subjects with postmenopausal osteoporosis. Arms include 35 mg risedronate DR formulation taken at least 30 minutes before breakfast (DRBB) and immediately following breakfast (DRFB) taken weekly are compared to a 5 mg immediate release (approved) risedronate taken per label daily (IRBB). All subjects are supplied with daily supplements of calcium equivalent to elemental calcium 1000 mg and 800-1000 IU vitamin D. Lumbar spine BMD is the primary endpoint. The first 52 weeks are reported in the NDA application. The second year of the trial is ongoing and continues to be double-blinded.

Risedronate 35 mg DR has an adverse event profile similar to the approved risedronate IR dosages, except for an increased number or proportion of subjects experiencing adverse events, especially when the risedronate DR is dosed 30 minutes or more before breakfast (DRBB). When compared to risedronate 5 mg daily, this difference reaches statistical significance for the DRBB regimen ($p=0.0128$) with about 8% more subjects with an AE in the DRBB group compared to the IRBB group. The difference between the 35 mg DRBB group and the other 2 groups in the number of subjects reporting AEs was mostly due to higher incidences of AEs in the SOC's gastrointestinal disorders and musculoskeletal and connective tissue disorders, with lesser increases in infections and infestations, general disorders and administrative site conditions, investigations, and cardiac disorders. The preferred term abdominal pain upper contributed most markedly to the excess of subjects with AE in the 35 mg DRBB group

(16 more than 35 mg DRFB, 19 more than 5 mg IRBB). In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat), 19 (6.2%) subjects in the 5 mg IRBB group, 31 (10.1%) subjects in the 35 mg DRFB group and 45 (14.6%) subjects in the 35 mg DRBB group reported AEs.

Deaths, serious adverse events, and withdrawal for adverse events are generally balanced between groups in the Phase 3 trial.

Events Rates: Adverse event rates are given in Table 42. Overall, 75 to 83% of subjects suffered at least one AE. Statistically more subjects had adverse events with the DR formulation, especially with the DRBB regimen (p=0.0401). The number of additional subjects reporting AEs after 52 weeks was similar across treatment groups 20 in the 5 mg IRBB group and 19 each in the 35 mg DRFB and DRBB groups)

Only one death is reported in the trial which is in the 5 mg IRBB group and is unchanged from 52 week data. Serious adverse events (SAEs) (about 9% of subjects) appear balanced between groups. Withdrawals due to AEs appear to show a slight trend towards more subjects in the DRFB group (IRBB 9%, DRFB 11%, DRBB 7%). The number of additional subjects withdrawing due to AE after 52 weeks was numerically higher in the DRFB group (2 in the 5 mg IRBB group, 5 in the 35 mg DRFB group, and 3 in the 35 mg DRBB group).

Table 42, Trial 2007008 Adverse Event Rates, ITT Population, 120 Day Safety Update

	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
AEs	231 (75.2%) 881	241 (78.5%) 967	257 (83.4%) 1037	0.0401
Serious AEs	26 (8.5%) 32	29 (9.4%) 45	28 (9.1%) 36	0.9170
Deaths	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Withdrawn due to AEs	27 (8.8%) 40	33 (10.7%) 48	22 (7.1%) 36	0.3102
Mean Number of AEs per Enrolled Subject	2.9	3.1	3.4	
Mean Number of AEs per Subject with AEs	3.8	4.0	4.0	
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, 120 Day Safety Update, Table 3				

Exposure: The extent of exposure to study drug in the Phase 3 postmenopausal osteoporosis trial for the ITT population is shown in Table 43. From 78 to 82% of each treatment group received study drug for at least 78 weeks. Beyond 52 weeks, a slight trend is noted towards more dropout for AE in the DR formulation arms which is more prominent in the DRFB arm. Mean subject-days of study drug exposure was slightly reduced in the DRFB arm, probably reflecting the dropout (IRBB group 482 days, DRFB

470 days, DRBB 479 days). This is changed from the 52 week report when mean subject-days of study drug exposure was similar across groups at approximately 320 (IRBB group 322 days, DRFB 318 days, DRBB 324 days).

Table 43, Trial 2007008 Extent of Exposure, ITT Population, 120 Day Safety Update

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Subject-days of Exposure n	307	307	308
Mean (SD)	482.2 (172.0)	469.7 (180.1)	478.8 (170.1)
Min	1	2	1
Max	666	666	652
Duration of Treatment			
> 90 Days	282 (91.9%)	275 (89.6%)	282 (91.6%)
> 180 Days	270 (87.9%)	264 (86.0%)	272 (88.3%)
> 270 Days	258 (84.0%)	258 (84.0%)	265 (86.0%)
> 360 Days	257 (83.7%)	256 (83.4%)	260 (84.4%)
> 450 Days	256 (83.4%)	246 (80.1%)	250 (81.2%)
> 540 Days	251 (81.8 %)	238 (77.5%)	244 (79.2%)
> 630 Days	23 (7.5%)	15 (4.9%)	18 (5.8%)

Source: Study 2007008, 120 Day Safety Update, Table 1

Deaths: No additional deaths were reported. One subject in the 5 mg IRBB group died in the first 52 weeks of the trial.

Non-fatal Serious Adverse Events: A total of 20 subjects experienced a serious adverse event (SAE) in Trial 2007008 from 52 weeks through the 120 Day Safety Update cutoff (4 in the 5mg daily IR group, 9 in the 35mg weekly DRFB group, and 7 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 44. 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 experienced infection and infestation SOC SAEs in the DRFB group (3 subjects in the 5 mg IRBB group, 10 subjects in the 35 mg DRFB group, and 3 subjects in the 35 mg DRBB group). These SAEs did not show further pattern as to type or area involved.

Numerically more subjects (4) in the 5 mg IRBB group experienced reproductive and breast disorder SAEs, compared to 2 subjects in the DR groups, both DRFB. One of these IRBB subjects suffered 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 and another suffered a cystocele in this SOC.

Table 44, Trial 2007008 Serious Adverse Events in ≥ 2 Subjects in any Treatment Group, ITT Population, 120 Day Safety Update

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	26 (8.5%) 32	29 (9.4%) 45	28 (9.1%) 36	0.9170
Infections and infestations	3 (1.0%) 3	10 (3.3%) 12	3 (1.0%) 3	0.0689
Appendicitis	0 (0.0%) 0	2 (0.7%) 2	0 (0.0%) 0	0.2213
Pneumonia	0 (0.0%) 0	2 (0.7%) 2	0 (0.0%) 0	0.2213
Injury, poisoning and procedural complications	4 (1.3%) 5	5 (1.6%) 6	4 (1.3%) 5	0.9426
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	6 (1.9%) 6	0.4088
Constipation	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Neoplasms	3 (1.0%) 3	2 (0.7%) 2	1 (0.3%) 1	0.5449
Cardiac	2 (0.7%) 2	2 (0.7%) 8	4 (1.3%) 5	0.7420
Nervous system	2 (0.7%) 2	2 (0.7%) 2	2 (0.6%) 2	1.0000
Carotid artery stenosis	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Renal and urinary	2 (0.7%) 2	2 (0.7%) 2	0 (0.0%) 0	0.4056
Reproductive and breast	4 (1.3%) 4	2 (0.7%) 2	0 (0.0%) 0	0.0932
Endocrine disorders	3 (1.0%) 3	1 (0.3%) 1	1 (0.3%) 1	0.5453
Hyperparathyroidism	3 (1.0%) 3	0 (0.0%) 0	1 (0.3%) 1	0.2329
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	1 (0.3%) 1	4 (1.3%) 4	0.3803
Ear and labyrinth	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
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, 120 Day Safety Update, Table 7				

Adverse Events Leading to Withdrawal: Withdrawals due to AEs appear to show a slight trend towards more subjects in the DRFB group (IRBB 9%, DRFB 11%, DRBB 7%). A total of 82 subjects experienced an adverse event leading to withdrawal. Since the 52 week report 10 subjects experienced an adverse event leading to withdrawal (2 in the 5mg daily IRBB group, 5 in the 35mg weekly DRFB group, and 3 in the 35mg weekly DRBB group). As outlined in Table 45, gastrointestinal adverse events were the most common reason for withdrawal, and accounted for 45 of 82 (55%) study withdrawals.

Table 45, Trial 2007008 Adverse Events Leading to Withdrawal in ≥ 2 Subjects in any Treatment Group, ITT Population, 120 Day Safety Update

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	27 (8.8%) 40	33 (10.7%) 48	22 (7.1%) 36	0.3102
Gastrointestinal disorders	12 (3.9%) 18	19 (6.2%) 26	14 (4.5%) 21	0.4322
Abdominal pain	2 (0.7%) 2	4 (1.3%) 4	4 (1.3%) 4	0.7845
Diarrhea	2 (0.7%) 2	4 (1.3%) 4	0 (0.0%) 0	0.0932
Vomiting	1 (0.3%) 1	3 (1.0%) 3	0 (0.0%) 0	0.1346
Abdominal pain upper	0 (0.0%) 0	2 (0.7%) 2	5 (1.6%) 5	0.0769
Erosive esophagitis	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Abdominal pain lower	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Constipation	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Musculoskeletal and connective tissue disorders	2 (0.7%) 2	5 (1.6%) 7	2 (0.6%) 3	0.4885
Arthralgia	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
Myalgia	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Nervous system disorders	2 (0.7%) 2	3 (1.0%) 3	1 (0.3%) 1	0.5449
Headache	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Skin and subcutaneous tissue disorders	1 (0.3%) 1	4 (1.3%) 4	2 (0.6%) 2	0.4208
Eye disorders	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
General disorders and administration site conditions	2 (0.7%) 2	2 (0.7%) 2	2 (0.6%) 2	1.0000
Infections and infestations	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
Ear and labyrinth disorders	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Vertigo	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Endocrine disorders	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Hyperparathyroidism	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Injury, poisoning and procedural complications	2 (0.7%) 3	0 (0.0%) 0	1 (0.3%) 1	0.5541
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
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, 120 Day Safety Update, Table 8				

Upper Gastrointestinal AEs: Irritation of the upper gastrointestinal mucosa is a well described adverse effect of oral bisphosphonates. The EDTA in the DR formulation may enhance risedronate related GI toxicity, based on non-clinical data.

The incidence of UGI AEs in Trial 2007008 is given in Table 46. The preferred terms of abdominal pain, dyspepsia, and upper abdominal pain are the most common AEs in this grouping.

There were numerically more subjects in the 35 mg DRBB group that had AEs in this category (66, 21.4%) than in the 35 mg DRFB group (54, 17.6%) or 5 mg IRBB group (53, 17.3%). Since the 52 week data, 8 new subjects in the 5 mg IRBB group, 6 subjects in the 35 mg DRFB group, and 5 subjects in the 35 mg DRBB group developed AEs in this area. Preferred term categories with statistically significant differences in numbers of subjects were abdominal pain upper (5 mg IRBB group, 7 subjects; 35 mg DRFB group, 10 subjects, 35 mg DRBB group, 26 subjects; $p=0.0009$) and gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; $p=0.0366$). Other preferred terms which are associated with pain or discomfort (abdominal pain, dyspepsia, abdominal discomfort, abdominal tenderness, epigastric discomfort, and chest pain) either had higher numbers of subjects in the DR groups, especially the 35 mg DRBB group, without reaching statistical significance, or were neutral except chest pain with numerically more in the 5 mg IRBB group. In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat), 19 (6.2%) subjects in the 5 mg IRBB group, 31 (10.1%) subjects in the 35 mg DRFB group and 45 (14.6%) subjects in the 35 mg DRBB group reported AEs (Study 2007008, 120 Day Safety Update, EOT Table 16, EOT Table 23, Year 1 Final Report, Section 11, Table 61, Section 11 Table 69).

Reviewer comment: The HLT GI and abdominal pain numbers are obtained from the 120 Day Safety Update by adding numbers for subjects with and without upper GI history, then adding in the difference between HLT GI and abdominal pain HLT in the 1 year final report with and without PT abdominal pain lower. No additional subjects reported AEs of abdominal pain lower between the 52 week report and the 120 day safety update. It is possible, although unlikely, that number of subjects for the DR groups could be one or two less. No datasets or direct way of calculating these numbers are available with the 120 Day Safety Update.

The AE of esophagitis was equal across treatment groups with one per group. One subject in the 5 mg IRBB group and 2 subjects in the 35 mg DRFB group had erosive esophagitis. One subject in the 35 mg DRBB group was reported as having esophageal ulcer.

Table 46, Trial 2007008 Upper GI AEs, ITT Population, 120 Day Safety Update

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	53 (17.3%) 68	54 (17.6%) 75	66 (21.4%) 120	0.3476
Gastrointestinal disorders	48 (15.6%) 61	54 (17.6%) 73	65 (21.1%) 118	0.2106
Abdominal pain	9 (2.9%) 10	17 (5.5%) 19	18 (5.8%) 21	0.1694
Dyspepsia	15 (4.9%) 18	15 (4.9%) 20	12 (3.9%) 15	0.7845
Abdominal pain upper	7 (2.3%) 8	10 (3.3%) 14	26 (8.4%) 34	0.0009
Abdominal discomfort	1 (0.3%) 1	3 (1.0%) 3	5 (1.6%) 6	0.3160
Gastritis	6 (2.0%) 6	3 (1.0%) 3	4 (1.3%) 4	0.6150
Gastroesophageal reflux dis.	7 (2.3%) 7	3 (1.0%) 3	10 (3.2%) 13	0.1701
Erosive esophagitis	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Gastritis erosive	1 (0.3%) 1	2 (0.7%) 2	1 (0.3%) 1	0.8510
Hyperchlorhydria	5 (1.6%) 6	2 (0.7%) 2	5 (1.6%) 6	0.5132
Dysphagia	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Gastric ulcer	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastritis atrophic	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Melaena	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Esophagitis	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Abdominal tenderness	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Epigastric discomfort	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Gastrointestinal inflammation	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Gastrointestinal pain	0 (0.0%) 0	0 (0.0%) 0	4 (1.3%) 10	0.0366
Esophageal disorder	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Esophageal ulcer	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Reflux esophagitis	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
General disorders and administration site conditions	5 (1.6%) 5	1 (0.3%) 1	2 (0.6%) 2	0.2415
Chest pain	5 (1.6%) 5	1 (0.3%) 1	2 (0.6%) 2	0.2415
Infections and infestations	2 (0.7%) 2	1 (0.3%) 1	0 (0.0%) 0	0.3319
Helicobacter gastritis	2 (0.7%) 2	1 (0.3%) 1	0 (0.0%) 0	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, 120 Day Safety Update, Table 9

Sponsor analyzed upper GI AEs by maximum severity. Most events were graded mild and these were similar in number across treatment groups (42 in the 5 mg IRBB group, 37 in the 35 mg DRFB group, 42 in the 35 mg DRBB group). Each treatment group had one subject with an AE graded severe. More subjects numerically had AEs graded moderate in the DR groups and especially the DRBB group (10 in the 5 mg IRBB group, 16 in the 35 mg DRFB group, 23 in the 35 mg DRBB group).

The influence of NSAIDs and/or aspirin on the incidence of UGI AEs was evaluated. Subjects were classified as users or non-users based on concomitant medication usage reported with any use leading to classification as a user. The number of users was similar across treatment groups. More subjects who used NSAIDs/aspirin reported UGI AEs than non-users (users: 31/155 [20.0%], 5 mg IRBB; 34/164 [20.7%], 35 mg DRFB;

40/142 [28.2%], 35 mg DRBB; non-users: 22/152 [14.5%], 5 mg IRBB; 20/143 [14.0%], 35 mg DRFB; 26/166 [15.7%], 35 mg DRBB). Among users, the difference between the 35 mg DRBB group and the other 2 groups was mainly due to AEs of abdominal pain upper (3 subjects, 5 mg IRBB; 7 subjects, 35 mg DRFB; 16 subjects, 35 mg DRBB).

Subjects were identified using MedDRA preferred terms as having a medical history of UGI disorders. Not surprisingly, a higher percentage of subjects with a medical history of UGI disorders experienced UGI AEs during the study than subjects without a medical history of upper GI disorders. The percentage of subjects with a medical history of UGI disorders was 30.9% in the 5 mg IRBB group, 32.6% in the 35 mg DRFB group, and 29.2% in the 35 mg DRBB group. In subjects with a medical history of UGI disorders, the incidence of UGI AEs was similar between the 5 mg IRBB group (24.0%) and the 35 mg DRFB group (21.0%); the incidence of UGI AEs was higher in the 35 mg DRBB group (34.1%), mostly due to events of abdominal pain upper. In subjects without a medical history of upper GI disorders, the incidence of upper GI TEAEs were generally similar across treatment groups (14.2%, 5 mg IRBB; 15.9%, 35 mg DRFB, 16.1%, 35 mg DRBB).

Endoscopy or other appropriate GI diagnostic procedures were to be offered to all patients who developed a moderate or severe upper GI symptom. Only endoscopies were performed. Findings presented in Table 47 are for all patients who underwent endoscopy, including those who had it for reasons other than a moderate or severe GI symptom. A total of 41 patients (11 [3.6%], 5 mg IRBB; 15 [4.9%], 35 mg DRFB; 15 [4.9%], 35 mg DRBB) underwent an endoscopy procedure. Abnormal findings were similar across all 3 treatment groups. Eight (2.6%) in the 5 mg IRBB group, 8 (2.6%) in the 35 mg DRFB group, and 8 (2.6%) in the 35 mg DRBB had at least 1 abnormal mucosal finding. Two patients had ulcers (1 stomach, 35 mg DRFB; 1 esophageal, 35 mg DRBB), and no patients had perforations. One patient in the 5 mg IRBB group had bleeding in the stomach, but no ulcer.

Table 47, Trial 2007008 Abnormal Endoscopy Inflammatory Findings, 120 Day Safety Update

Treatment GI Site	Inflamm n (%) nAB	Erosion n (%) nAB	Bleeding n (%) nAB	Ulcerat. n (%) nAB	Perforat. n (%) nAB	Total n (%) nAB
5 mg IRBB (N = 307) Subjects with EGD = 11						
Esophagus	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	3 (1.0%) 3
Stomach	4 (1.3%) 4	3 (1.0%) 3	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	7 (2.3%) 8
Duodenum	2 (0.7%) 2	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	2 (0.7%) 3
Total	5 (1.6%) 9	3 (1.0%) 4	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	8 (2.6%) 14
35 mg DRFB (N = 307) Subjects with EGD = 15						
Esophagus	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	3 (1.0%) 3
Stomach	3 (1.0%) 3	2 (0.7%) 2	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	5 (1.6%) 6
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	4 (1.3%) 4	4 (1.3%) 4	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	8 (2.6%) 9
35 mg DRBB (N = 308) Subjects with EGD = 15						
Esophagus	2 (0.6%) 2	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	3 (1.0%) 3
Stomach	4 (1.3%) 4	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 5
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	6 (1.9%) 6	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	8 (2.6%) 8
n (%) = number (percent) of patients with abnormality: (%) = (n/Patients within specified treatment)x100%.						
nAB = number of abnormal findings.						
Source: Study 2007008, 120 Day Safety Update, Table 11						

Clinical Fractures Reported as Adverse Events: Clinical fractures reported as AEs included all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures and are shown in Table 48. A total of 43 subjects reported clinical fractures as AEs (13 [4.2%] subjects, 5 mg IRBB; 10 [3.3%] subjects, 35 mg DRFB; 20 [6.5%] subjects, 35 mg DRBB, p=0.1634). Since 52 week data 7 new subjects in the 5 mg IRBB group, 1 subject in the 35 mg DRFB group, and 8 subjects in the 35 mg DRFB group suffered a clinical fracture. Numerically more subjects in the DR regimens suffered radial fractures but this did not reach statistical significance (1 [0.3%] subject, 5 mg IRBB; 5 [1.6%] subjects, 35 mg DRFB; 5 [1.6%] subjects, 35 mg DRBB, p=0.2527). Overall, fracture types appear similar between groups.

Reviewer comment: Nearly as many fractures occurred between 52 weeks and the 120 Day Safety Update in the 5 mg IRBB group as the 35 mg DRBB group, and more than the 35 mg DRFB group. This is reassuring regarding disordered bone apposition with the DR formulation.

Table 48, Trial 2007008 All Clinical Fractures Reported as AEs, ITT Population, 120 Day Safety Update

All Fractures 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
All Fractures	13 (4.2%) 16	10 (3.3%) 12	20 (6.5%) 25	0.1634
Radius fracture	1 (0.3%) 1	5 (1.6%) 5	5 (1.6%) 6	0.2527
Rib fracture	1 (0.3%) 1	2 (0.7%) 2	2 (0.6%) 2	1.0000
Femoral neck fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Humerus fracture	0 (0.0%) 0	1 (0.3%) 1	2 (0.6%) 2	0.7771
Patella fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Pelvic fracture	1 (0.3%) 2	1 (0.3%) 1	0 (0.0%) 0	0.5546
Ulna fracture	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Ankle fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Clavicle fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Femur fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Fibula fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Foot fracture	1 (0.3%) 1	0 (0.0%) 0	4 (1.3%) 4	0.1345
Forearm fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Fractured sacrum	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Hand fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 2	1.0000
Spinal compression fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Stress fracture	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2	1.0000
Thoracic vertebral fracture	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Tibia fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Upper limb fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Wrist fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000

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 120 Day Safety Update, Table 15

If all fractures of the wrist, hip, leg, clavicle, humerus, and pelvis are considered (defined by Sponsor as osteoporosis-related non-vertebral fractures), numerically more subjects in the DRBB suffered an AE in this area (5 [1.6%] subjects, 5 mg IRBB; 7 [2.3%] subjects, 35 mg DRFB; 10 [3.2%] subjects, 35 mg DRBB, p=0.4520). This represents an increase of one subject each in the 5 mg IRBB and 35 mg DRFB groups and 4 subjects in the 35 mg DRBB group. Wrist area fractures showed the most difference of considered areas (2 [0.7%] subjects, 5 mg IRBB; 5 [1.6%] subjects, 35 mg DRFB; 7 [2.3%] subjects, 35 mg DRBB, p=0.2902).

Musculoskeletal AEs: Increased musculoskeletal pain has been reported with multiple bisphosphonates including risedronate. Selected musculoskeletal AEs were reviewed in Trial 2007008 for potential differences between treatment groups (arthralgia, back pain, musculoskeletal pain, myalgia, neck pain, and bone pain), as shown in Table 49. Arthralgias (9%) and back pain (8%) were the most common of these AEs. Similar

numbers and percents were again found for all treatment groups for these selected adverse events in the 120 Day Safety Update.

Table 49, Trial 2007008 Selected Musculoskeletal AEs, ITT Population, 120 Day Safety Update

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	58 (18.9%) 77	60 (19.5%) 92	69 (22.4%) 85	0.5179
Arthralgia	28 (9.1%) 33	28 (9.1%) 39	24 (7.8%) 29	0.7989
Back pain	21 (6.8%) 24	25 (8.1%) 29	26 (8.4%) 27	0.7716
Musculoskeletal pain	8 (2.6%) 8	11 (3.6%) 11	11 (3.6%) 12	0.7580
Myalgia	3 (1.0%) 3	4 (1.3%) 6	4 (1.3%) 4	1.0000
Neck pain	6 (2.0%) 7	4 (1.3%) 4	7 (2.3%) 7	0.7494
Bone pain	2 (0.7%) 2	3 (1.0%) 3	6 (1.9%) 6	0.4088

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 120 Day Safety Update, Table 17

Acute Phase Reactions: Not evaluated in the 120 Day Safety Update.

Ocular AEs: Inflammatory eye diseases, such as uveitis and scleritis, have been reported with bisphosphonate use. Ocular AEs in Trial 2007008 were uncommon and balanced across treatment groups (18 subjects (5.9%), 5 mg IRBB; 10 subjects (3.3%), 35 mg DRFB; 13 subjects (4.2%), 35 mg DRBB). The only preferred terms occurring in more than 1 subject per treatment group were cataract (6 subjects (2.0%), 5 mg IRBB; 2 subjects (0.7%), 35 mg DRFB; 3 subjects (1.0%), 35 mg DRBB) and conjunctivitis (4 subjects (1.3%), 5 mg IRBB; 1 subject (0.3%), 35 mg DRFB; 1 subject (0.3%), 35 mg DRBB). One case of iridocyclitis was reported in the 35 mg DRFB treatment group.

Common Adverse Events: Adverse events which occurred in 2% or more of any treatment group in the Phase 3 trial 2007008 are listed in Table 50. Since 52 week data was reported, 20 additional subjects in the 5 mg IRBB and 19 subjects each in the 35 mg DRFB and DRBB groups have reported an AE.

Overall, 75 to 83% of subjects suffered at least one AE. Of note is significantly more subjects with adverse events with the DRBB regimen (subjects with AE, 231 for 5 mg IRBB, 241 for 35 mg DRFB, and 257 for 35 mg DRBB regimens, p=0.0401). If subjects with AE are compared for 35 mg DRFB to 5 mg IRBB, the p-value is 0.3891. If subjects with AE are compared for 35 mg DRBB to 5 mg IRBB, the p-value is 0.0128.

System organ classes (SOC) with the most reported AEs across all treatment groups were infections and infestations (38%), gastrointestinal disorders (36%), and musculoskeletal and connective tissue disorders (30%). Preferred terms with the most AEs across treatment groups were arthralgia (9%), nasopharyngitis (8%), back pain

(8%), influenza (8%), diarrhea (7%), bronchitis (6%), urinary tract infection (5%), hypertension (5%), abdominal pain (5%), abdominal pain upper (5%), and constipation (5%).

No system organ classes had statistically significant differences between treatment groups for AEs. At the 0.1 significance level, hepatobiliary disorders, with 2 subjects (0.7%) each in the 5 mg IRBB and 35 mg DRFB groups and 8 subjects (2.6%) in the 35 mg DRBB group had difference between groups for subjects with AE (p= 0.0681). Five subjects in the DRBB group had cholecystitis or cholelithiasis compared to one each in the other 2 groups. Preferred terms with statistically significant differences between treatment groups for AEs were abdominal pain upper (5 mg IRBB with 7 subjects (2.3%), 35 mg DRFB with 10 subjects (3.3%), 35 mg DRBB with 26 subjects (8.4%), p=0.0009) and hiatal hernia (5 mg IRBB with 2 subjects (0.7%), 35 mg DRFB with 2 subjects (0.7%), 35 mg DRBB with 9 subjects (2.9%), p=0.0361). Osteoarthritis (5 mg IRBB with 9 subjects (2.9%), 35 mg DRFB with 6 subjects (2.0%), 35 mg DRBB with 2 subjects (0.6%), p=0.0929) was significantly different between groups at the 0.1 level.

SOCs cardiac disorders and blood and lymphatic disorders are no longer as extremely distributed as compared to 52 weeks. The preferred term vomiting is also no longer as extremely distributed.

The difference between the 35 mg DRBB group and the other 2 groups in the number of subjects reporting AEs was mostly due to higher incidences of AEs in the SOC gastrointestinal disorders and musculoskeletal and connective tissue disorders, with lesser increases in infections and infestations, general disorders and administrative site conditions, investigations, and cardiac disorders. The preferred term abdominal pain upper contributed most markedly to the excess of subjects with AE in the 35 mg DRBB group (16 more than 35 mg DRFB, 19 more than 5 mg IRBB).

Table 50, Trial 2007008 Most Common Adverse Events (≥2% in any Treatment Group), ITT Population, 120 Day Safety Update

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	231 (75.2%) 881	241 (78.5%) 967	257 (83.4%) 1037	0.0401
Gastrointestinal disorders	101 (32.9%) 175	114 (37.1%) 208	118 (38.3%) 246	0.3401
Diarrhea	19 (6.2%) 25	29 (9.4%) 31	20 (6.5%) 23	0.2562
Abdominal pain	9 (2.9%) 10	17 (5.5%) 19	18 (5.8%) 21	0.1694
Constipation	10 (3.3%) 12	16 (5.2%) 16	17 (5.5%) 20	0.3808
Dyspepsia	15 (4.9%) 18	15 (4.9%) 20	12 (3.9%) 15	0.7845
Vomiting	9 (2.9%) 9	15 (4.9%) 18	8 (2.6%) 11	0.2499
Nausea	14 (4.6%) 16	12 (3.9%) 15	13 (4.2%) 14	0.9378
Abdominal pain upper	7 (2.3%) 8	10 (3.3%) 14	26 (8.4%) 34	0.0009
Gastroesophageal reflux disease	7 (2.3%) 7	3 (1.0%) 3	10 (3.2%) 13	0.1701
Hiatus hernia	2 (0.7%) 2	2 (0.7%) 2	9 (2.9%) 9	0.0361

Clinical Review
Stephen R. Bienz, MD
NDA 22-560
Atelvia (Risedronate Sodium)

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
Infections and infestations	105 (34.2%) 167	125 (40.7%) 212	116 (37.7%) 200	0.2499
Nasopharyngitis	21 (6.8%) 24	28 (9.1%) 32	29 (9.4%) 36	0.4626
Influenza	23 (7.5%) 28	24 (7.8%) 30	25 (8.1%) 29	0.9877
Urinary tract infection	13 (4.2%) 14	19 (6.2%) 23	18 (5.8%) 22	0.5178
Bronchitis	17 (5.5%) 21	16 (5.2%) 21	18 (5.8%) 19	0.9831
Upper respiratory tract infection	9 (2.9%) 9	13 (4.2%) 13	10 (3.2%) 14	0.6923
Cystitis	10 (3.3%) 11	9 (2.9%) 10	6 (1.9%) 6	0.5893
Pharyngitis	6 (2.0%) 6	9 (2.9%) 9	12 (3.9%) 13	0.3799
Gastroenteritis	7 (2.3%) 7	8 (2.6%) 8	9 (2.9%) 9	0.9656
Herpes zoster	3 (1.0%) 3	7 (2.3%) 7	3 (1.0%) 3	0.3066
Sinusitis	7 (2.3%) 7	4 (1.3%) 5	3 (1.0%) 3	0.3928
Musculoskeletal and connective tissue disorders	85 (27.7%) 133	92 (30.0%) 150	100 (32.5%) 146	0.4359
Arthralgia	28 (9.1%) 33	28 (9.1%) 39	24 (7.8%) 29	0.7989
Back pain	21 (6.8%) 24	25 (8.1%) 29	26 (8.4%) 27	0.7716
Pain in extremity	11 (3.6%) 12	14 (4.6%) 14	10 (3.2%) 12	0.6799
Musculoskeletal pain	8 (2.6%) 8	11 (3.6%) 11	11 (3.6%) 12	0.7580
Osteoarthritis	9 (2.9%) 9	6 (2.0%) 6	2 (0.6%) 2	0.0929
Muscle spasms	8 (2.6%) 8	4 (1.3%) 4	11 (3.6%) 15	0.2141
Neck pain	6 (2.0%) 7	4 (1.3%) 4	7 (2.3%) 7	0.7494
Injury, poisoning and procedural complications	42 (13.7%) 67	40 (13.0%) 55	41 (13.3%) 60	0.9772
Fall	14 (4.6%) 15	14 (4.6%) 14	9 (2.9%) 9	0.5126
Contusion	11 (3.6%) 12	9 (2.9%) 10	7 (2.3%) 10	0.5906
Nervous system disorders	45 (14.7%) 64	38 (12.4%) 48	40 (13.0%) 43	0.6855
Dizziness	10 (3.3%) 10	9 (2.9%) 9	9 (2.9%) 10	0.9712
Headache	16 (5.2%) 16	9 (2.9%) 9	15 (4.9%) 15	0.3417
Sciatica	7 (2.3%) 7	4 (1.3%) 5	2 (0.6%) 2	0.1994
General disorders and administration site conditions	23 (7.5%) 26	27 (8.8%) 39	35 (11.4%) 46	0.2516
Skin and subcutaneous tissue disorders	18 (5.9%) 22	28 (9.1%) 34	26 (8.4%) 30	0.2719
Respiratory, thoracic and mediastinal disorders	25 (8.1%) 32	21 (6.8%) 27	22 (7.1%) 26	0.8336
Cough	10 (3.3%) 11	9 (2.9%) 9	6 (1.9%) 6	0.5893
Vascular disorders	21 (6.8%) 27	24 (7.8%) 24	26 (8.4%) 29	0.7690
Hypertension	18 (5.9%) 21	14 (4.6%) 14	16 (5.2%) 17	0.7646
Investigations	17 (5.5%) 23	20 (6.5%) 24	27 (8.8%) 30	0.2883
Blood parathyroid hormone increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7	0.2626
Metabolism and nutrition disorders	14 (4.6%) 15	19 (6.2%) 30	19 (6.2%) 20	0.6360
Hypercholesterolemia	4 (1.3%) 4	12 (3.9%) 12	7 (2.3%) 7	0.1239
Cardiac disorders	14 (4.6%) 16	17 (5.5%) 28	26 (8.4%) 35	0.1276
Blood and lymphatic system disorders	5 (1.6%) 5	12 (3.9%) 12	6 (1.9%) 6	0.1590

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
Psychiatric disorders	9 (2.9%) 11	11 (3.6%) 11	17 (5.5%) 22	0.2687
Depression	4 (1.3%) 4	4 (1.3%) 4	7 (2.3%) 7	0.6792
Eye disorders	18 (5.9%) 23	10 (3.3%) 13	13 (4.2%) 13	0.3083
Ear and labyrinth disorders	15 (4.9%) 18	9 (2.9%) 9	7 (2.3%) 8	0.1884
Vertigo	7 (2.3%) 10	7 (2.3%) 7	3 (1.0%) 3	0.3783
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (3.3%) 10	8 (2.6%) 8	11 (3.6%) 12	0.8410
Renal and urinary disorders	12 (3.9%) 13	11 (3.6%) 13	17 (5.5%) 22	0.4652
Endocrine disorders	9 (2.9%) 10	7 (2.3%) 7	11 (3.6%) 14	0.6704
Reproductive system and breast disorders	12 (3.9%) 14	6 (2.0%) 7	6 (1.9%) 10	0.2608
Immune system disorders	5 (1.6%) 6	3 (1.0%) 3	8 (2.6%) 9	0.3383
Hepatobiliary disorders	2 (0.7%) 2	2 (0.7%) 4	8 (2.6%) 8	0.0681
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 120 Day Safety Update, Table 5				

Marked Laboratory Abnormalities: Markedly abnormal laboratory values post baseline in Trial 2007008 were relatively uncommon and fairly equally spread across treatment groups except for PTH (≥ 98 ng/l), for which no protocol draws have been done in large numbers following 52 week data (next protocol draw is Week 104).

Table 51, Trial 2007008 Markedly Abnormal Lab Values Post Baseline, ITT Population, 120 Day Safety Update

Lab Test	5 mg IRBB Daily (N=307)		35 mg DRFB Weekly (N=307)		35 mg DRBB Weekly (N=308)	
	n (%)	N	n (%)	N	n (%)	N
Hematocrit < 28%	0	293	1 (0.3%)	300	1 (0.3%)	301
Hemoglobin < 9.3 g/dl	0	293	1 (0.3%)	300	1 (0.3%)	301
Platelets < $112 \times 10^3/\text{mm}^3$	2 (0.7%)	292	3 (1.0%)	299	2 (0.7%)	300
Leukocytes < $3.3 \times 10^3/\text{mm}^3$	3 (1.0%)	293	5 (1.7%)	300	8 (2.7%)	301
Neutrophils < $1.43 \times 10^3/\text{mm}^3$	3 (1.0%)	293	1 (0.3%)	299	1 (0.3%)	301
Lymphs < $0.72 \times 10^3/\text{mm}^3$	2 (0.7%)	293	4 (1.3%)	299	4 (1.3%)	301
Lymphs > $5.04 \times 10^3/\text{mm}^3$	0	293	1 (0.3%)	299	0	301
Eosinophils > $1.12 \times 10^3/\text{mm}^3$	6 (2.0%)	293	5 (1.7%)	299	2 (0.7%)	301
Basophils > $0.25 \times 10^3/\text{mm}^3$	0	293	1 (0.3%)	299	0	301
Calcium < 7.6 mg/dl	1 (0.3%)	303	1 (0.3%)	303	2 (0.7%)	305
Calcium > 11.3 mg/dl	2 (0.7%)	303	0	303	0	305
Phosphate < 1.9 mg/dl	1 (0.3%)	303	2 (0.7%)	303	0	305
Phosphate > 6.1 mg/dl	0	303	0	303	1 (0.3%)	305
Alk Phos > 150 U/l	7 (2.3%)	303	4 (1.3%)	303	6 (2.0%)	305
Bilirubin > 1.5 mg/dl	4 (1.3%)	303	1 (0.3%)	303	3 (1.0%)	305
ALT > 111 U/l	2 (0.7%)	303	1 (0.3%)	303	2 (0.7%)	305
AST > 108 U/l	0	303	0	303	1 (0.3%)	305

Lab Test	5 mg IRBB Daily (N=307)		35 mg DRFB Weekly (N=307)		35 mg DRBB Weekly (N=308)	
	n (%)	N	n (%)	N	n (%)	N
Potassium < 3.2 mEq/l	0	303	0	303	2 (0.7%)	305
Potassium > 6.0 mEq/l	0	303	2 (0.7%)	303	1 (0.3%)	305
iPTH > 97 pg/ml	16 (5.3%)	302	19 (6.3%)	302	38 (12.5%)	305

N=Number of subjects with post-baseline measurement within specified treatment.
 Subjects with multiple high/low values were counted only once.
 Source: Study 2007008 120 Day Safety Update, EOT Tables 31 and 38

Mean Change from Baseline: The mean values for all hematology parameters (hemoglobin, red blood cell count, hematocrit, platelet count, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were within the normal range for Week 78 for all treatment groups and were similar across treatment groups in Trial 2007008. The mean changes from baseline for Week 78 were reviewed and were very small for each hematology parameter.

The mean values for all chemistry parameters (glucose, creatinine, creatinine clearance, calcium, phosphate, albumin, alkaline phosphatase, bilirubin, ALT, AST, sodium, magnesium, potassium, chloride, and bicarbonate) were within the normal range at Week 78 for all treatment groups. iPTH was not measured at Week 78. The mean changes from baseline to Week 78 were generally small. An expected fall in alkaline phosphatase in all treatment groups continued at Week 78. There were no clinically important differences across groups for any chemistry parameter.

Prothrombin time, INR, and partial thromboplastin times were checked at Week 78 in Trial 2007008. For subjects not on anticoagulation with heparin or a vitamin K antagonist, mean values at Week 78 for all treatment groups were normal with no significant changes from baseline.

Shifts: Shift tables for all hematology parameters were reviewed for Trial 2007008. No significant shifts were noted at Week 78.

Shift tables for all chemistry parameters were reviewed. These were remarkable for the number of elevated alkaline phosphatase values at baseline which normalized during the trial, including Week 78. A number of subjects in all treatment groups showed shift from normal to high bicarbonate at Week 78 which was not as markedly present previously (42 (18.9%) 5 mg IRBB, 24 (11.4%) 35 mg DRFB, 49 (22.1%) 35 mg DRBB). The reason for this is unclear.

Vital Signs: Mean vital sign values in the Phase 3 trial 2007008 were normal at Week 78 for all vital signs tested (BP, HR, and T) in all treatment groups. No clinically significant changes from baseline were seen.

Shift tables for systolic blood pressure showed perhaps increased subjects who were normotensive at baseline and then high (>140) at Week 78, but these were relatively equal across treatment groups (22 subjects [10.1%], 5 mg IRBB; 25 subjects [11.1%], 35 mg DRFB; 31 subjects [14.7%], 35 mg DRBB). Markedly high blood pressures were uncommon. For systolic blood pressure at Week 78 one subject (in the 35 mg DRBB group) was markedly high (> 200 mmHg or \geq 180 mmHg and increase since baseline \geq 30 mmHg).

8 Postmarket Experience

Risedronate has been marketed since 1998. It is approved in more than 90 countries worldwide in immediate release formulations. The DR formulation is not approved for marketing in any country yet.

The most recent Periodic Safety Update Report for the IR formulation was submitted by the Sponsor on November 25, 2009 and covers the 6-month period 4/1/09 – 9/30/09, during which the estimate for worldwide dosing exposure was 1.6 million patient-years. Estimate for cumulative total exposure since 1998 was over 23 million patient-years. There were 1,356 subjects enrolled in 6 new or ongoing Phase 1 - 3 clinical trials during the period, with 409 patient-years exposure to study medication (risedronate or comparator).

There were no marketing authorization withdrawals or suspensions during the period for this report. There were no failures to obtain marketing authorization renewals. There were no clinical trial suspensions due to safety reasons. Previously a request was received, from the European reference member state for risedronate, for an EU formatted risk management plan (RMP) to be submitted. This document was pending final review comments from the European reference member state at the time of this report. The draft RMP submitted contains no newly identified or potential risks that have not previously been identified, discussed, reviewed, or monitored on an ongoing basis in the PSUR.

Health care professionals from 25 countries submitted 959 spontaneous AE reports, of which 65 were considered serious and unlisted and 31 were considered serious and listed during this period. From the medical literature, 26 reports were created, with 2 of them classified as serious and unlisted and 1 classified as serious and listed. Clinical and post-marketing studies resulted in 12 serious reports that were considered as suspected causally-related by investigators/reporters. Non-medically confirmed consumer reports totaled 749, of which 44 were classified as serious.

Spontaneous reports from health care professionals are higher than the 5 previous 6 month reporting periods. This appears driven by GI and musculoskeletal complaints which Sponsor attributes to increasing exposure and introduction of the newer doses of 17.5 mg once weekly (Japan only); 35 mg once weekly combined with calcium/vitamin

D; 75 mg 2 consecutive days/month, and 150 mg once monthly. New dosing options have, in the past, been associated with an increase in AE reporting. In examining increased reporting, a number of other SOCs have higher numbers of AEs reported compared to previously and as much of a percentage increase; GI and musculoskeletal complaints have a higher baseline. Perhaps the new dose forms, increased concern about long-term AEs with bisphosphonates, or other factors contribute to increased reporting. SAE rate of reporting does not appear to be increased.

Most common system organ classes of AEs reported by health care professionals were GI disorders, musculoskeletal and CT disorders, and general disorders and administration site. For unlisted AEs, most common system organ classes were GI disorders, general disorders and administration site, nervous system disorders, and musculoskeletal and CT disorders. For SAEs, most common system organ classes were musculoskeletal and CT disorders and GI disorders.

The new postmarketing events were reviewed with an in depth review of unlisted SAEs, as well as events over time by SOC. Osteonecrosis of the jaw and non-vertebral fracture were reviewed in some depth. New literature was reviewed.

The review of safety information received during this 6-month period does not indicate substantive changes to the cumulative safety data or change to the overall risk-benefit profile for risedronate. No new signal of concern for significant new AEs, drug interactions, or drug maladministration was identified from review of reports.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

As this is not a new molecular entity, no advisory committee meeting was held.

9.4 Selected Clinical Trial Reviews

Phase 2 Trial:

Study 2005107, Dose-finding: A Multicenter, Double Blind, Active-controlled, Parallel Design Study to Assess the Efficacy, Safety and Pharmacokinetics of Risedronate Upon Multiple Dose Oral Administration of a 35 mg Delayed-Release, a 50 mg Delayed-Release or a 35 mg Immediate-Release Formulation Administered Weekly for 13 Weeks to Postmenopausal Women

Objectives: The primary objective of this study was to compare the efficacy, based on serum C-telopeptide (CTX), of a 50 mg delayed-release risedronate tablet, administered immediately after a typical breakfast (DRFB), to that of the approved 35 mg immediate-release tablet, administered according to label at least 30 minutes prior to breakfast (IRBB) in postmenopausal women after 13 weeks of treatment. Urinary N-telopeptide (NTX) and bone specific alkaline phosphatase (BSAP) were also measured. Additional testing included:

- A 50 mg DR risedronate tablet, at least 30 minutes prior to breakfast (DRBB) to look for food effect
- A 35 mg DR risedronate tablet administered immediately after a typical breakfast (DRFB)
- Urinary pharmacokinetics were done on a subset of subjects.

Dates: First subject screening, July 14, 2006; last subject last visit, January 27, 2007.

Study Design: This was a 13-week, randomized, double-blind, triple-dummy, multiple-dose, active-controlled, multi-center (6 centers in the United States), parallel-group study in healthy post-menopausal women. Subjects were randomly assigned to risedronate using a 1:1:1:2 ratio, respectively to one of the following 4 treatment groups:

- 35 mg IR weekly, at least 30 minutes prior to breakfast (IRBB)
- 35 mg DR weekly, immediately following breakfast (DRFB)
- 50 mg DR weekly, at least 30 minutes prior to breakfast (DRBB)
- 50 mg DR weekly, immediately following breakfast (DRFB)

Following an 8-hour overnight fast, subjects were given 2 tablets at least 30 minutes prior to a typical breakfast (35 mg IR or placebo and 50 mg DR or placebo) and 2 tablets immediately following a typical breakfast (35 mg DR or placebo and 50 mg DR or placebo). Only one of the 4 weekly tablets was active; the other 3 were placebo.

Tablets taken before breakfast were to be taken with plain water (240 ml) and with the subject in an upright position. Subjects were to remain upright for at least 30 minutes following dosing. Tablets taken after breakfast were also to be taken with plain water (240 ml) but the subject was not restricted from lying down following dosing after breakfast.

All subjects received oral supplements of 1000 mg/day elemental calcium and 400 IU/day vitamin D throughout the treatment period. Calcium supplements were to be ingested at a different time of day than the study drug.

All subjects were admitted to the study site on Day -1 and remained at least until Day 1 procedures were completed. Those in the PK subset remained until Day 3, and had an additional confinement from Day 84 to Day 87 for an additional 48 hour urinary collection for PK.

During the periods of confinement and therefore for the PK measurements, a “typical breakfast” consisted of 1 bowl or cup of unsugared cereal, 200 ml of semi-skimmed milk, 2 slices of white bread with 2 pats of butter, and 200 ml of decaffeinated tea with 1 pack sugar (approximately 14 g of protein, 15 g of fat, 67 g of carbohydrate, and 457 calories). During non-confinement periods, breakfast consisted of the subjects’ normal breakfast.

Table 52, Trial 2005107 Schedule of Events

	Screen- ing	Pre- dose	Month 1					M 2	Month 3				
	Day												
Procedure	-45 to -1	-1	1	2*	3 ^{a*}	14	28	56	84*	85*	86*	87 ^{a*}	91
Informed Consent	x												
Medical History	x	x											
Height & Weight	x												
Physical Exam	x												x ^b

Clinical Review
Stephen R. Bienz, MD
NDA 22-560
Atelvia (Risedronate Sodium)

	Screen- ing	Pre- dose	Month 1					M 2	Month 3				
	Day												
Procedure	-45 to -1	-1	1	2*	3 ^{a*}	14	28	56	84*	85*	86*	87 ^{a*}	91
Vital signs	x		x				x	x					x
12-lead ECG	x												
Blood Sample ^c :													
Clinical Chemistry	x	x				x							x
Hematology	x	x											x
Coagulation		x											x
Hepatitis B, C, HIV	x												
Serum Pregnancy	x												
PTH	x												
FSH and Estradiol ^d	x												
25 OH Vitamin D	x												
TSH ^e	x												
Fasting Serum CTX and BAP		x	x ^f				x	x					x
Urine Sample:													
Urinalysis	x												
Urine Drug Screen	x	x											
Urine Pregnancy		x											
NTX Urine ^g		x	x [†]				x	x					x
24-hr Urine Calcium*		x*	x ^{f*}							x*	x*		
PK Urine Sample ^{h*}			x*	x*	x*					x*	x*	x*	
Confinement		x	x	x*					x*	x*	x*		
Study Drug:													
Administer			x							x*			
Dispense					x*		x	x					
Calcium & Vitamin D													
Administer			x	x*					x*	x*			
Dispense					x*								
Meal Diary (distribute/collect)					x*	x	x	x					x
Concomitant Medication		x	x	x*		x	x	x			x*		x
Adverse Event	x	x	x	x*	x*	x	x	x	x*	x*	x*	x*	x

* These events did not occur in the non-PK subset of subjects. Study drug and calcium and vitamin D supplements were dispensed and meal diary distributed at day 1 discharge

a Prior to discharge

b Brief physical exam done at final visit

c Fasting for the screening evaluation

d Only determined for subjects <65 years of age who had undergone hysterectomy without bilateral oophorectomy

e If TSH was outside of the normal range, a Free T4 was performed

f Pre-dose

g Urine samples were taken after an 8-hour fast, and at approximately the same time for each collection; that is, the 2nd urine that was voided between 6:00 am and 9:00 am

h A pre-dose urine sample for PK was obtained on Day 1 from the 24-hour calcium excretion urine sample. Urine PK samples were collected post-dose on Days 1 and 85 at 0-24 and 24-48 hours

	Screen- ing	Pre- dose	Month 1					M 2	Month 3				
	Day												
Procedure	-45 to -1	-1	1	2*	3 ^{a*}	14	28	56	84*	85*	86*	87 ^{a*}	91

Source: Study Number: 2005107, Final Report, Tables 1 and 2

Fasting serum CTX, BSAP, and urine NTX were measured at baseline and after 4, 8, and 13 weeks as noted in Table 52.

All laboratory samples collected for this study were analyzed by (b) (4). Analysis of bone turnover marker (BTM) samples was performed by (b) (4). Frozen specimens for the PK analysis were shipped to (b) (4).

Population: Women who were between 45 and 80 years of age, inclusive, ambulatory, in generally good health, and postmenopausal for at least 2 years were eligible to participate in this study. Two hundred subjects were planned for enrollment with 100 subjects to be included in the pharmacokinetic component of the trial.

Inclusion Criteria:

- Female, between the 45 and 80 years of age
- Willing and able to provide written informed consent
- Ambulatory
- In generally good health
- Postmenopausal (defined as 12 consecutive months without menses in a healthy woman) ≥2 years, naturally or surgically. A subject <65 years of age who had undergone hysterectomy without bilateral oophorectomy must have serum FSH ≥40 IU/L and estradiol ≤20 pg/ml (≤73 pmol/L).

Exclusion Criteria:

- Any previous or ongoing clinically significant illness that could prevent the subject from completing the study
- A history of alcohol or illicit drug abuse, or a reported habitual alcohol intake greater than 1.5 oz (ethanol equivalent) per day for the past 2 years
- Provided a blood donation of approximately 400 ml or more or a plasma donation of approximately 200 ml or more within 4 weeks prior to dosing
- A positive urine screen for drugs of abuse
- Currently active hyperthyroidism or osteomalacia
- Any allergic or abnormal reaction to bisphosphonates
- Currently using anticonvulsant medication
- Creatinine clearance of <30 ml/min, estimated based on Cockcroft and Gault formula
- Hypocalcemia or hypercalcemia, from any cause

- A serum thyroid stimulating hormone (TSH) value outside the normal laboratory range, which was confirmed by Free T4 levels outside the normal laboratory range
- A serum 25-hydroxy vitamin D level <12 ng/ml (30 nmol/L)
- Previously participated in this clinical trial
- A positive serum pregnancy test
- Positive serology results for hepatitis B, hepatitis C, or HIV
- A history of hyperparathyroidism, unless surgically corrected, as indicated by normal serum calcium levels for at least 12 months prior to dosing
- Any history of cancer within the previous 5 years, with the exceptions of dermal squamous and basal cell carcinoma with documented 6-month remission or history of successfully treated cervical carcinoma in situ with documented 12-month remission
- History of major surgical operation requiring in-patient hospitalization within 1 month prior to the screening visit or during the course of the study
- History of diabetes or uncontrolled hypertension, clinically significant uncontrolled cardiovascular, hepatic, renal, and gastrointestinal disease
- History of gastric ulcer, esophageal, gastric and intestinal bleeding or gastroesophageal reflux disease that required prescribed medication (H2 blocker or proton pump inhibitor) or frequent (>3 times/week) over-the-counter medications (antacids); history of Crohn's disease, ulcerative colitis, diverticular disease, polyps, or any surgery that could have changed gastrointestinal structure or motility
- History of frequent diarrhea, or constipation that required regular use of stool softener or laxative
- Depot injection >10,000 IU vitamin D in the previous 9 months
- Body mass index (BMI) >32 kg/m²
- Clinically significantly abnormal clinical laboratory parameters, as assessed by the Investigator
- Demonstrated a poor likelihood of completing the study and complying with protocol requirements
- Used any of the following medications within 3 months prior to dosing or used any of the following medications for more than 1 month at any time within 6 months prior to dosing:
 - oral or parenteral glucocorticoids (5 mg prednisone or equivalent/day)
 - anabolic steroids
 - estrogens (oral, skin patch, or gel), except for low dose vaginal products or insertable estrogen ring (0.2 mg/day 17- estradiol or 1.5 mg/day estropipate), selective estrogen receptor modulators, or estrogen-related drugs
 - progestins
 - calcitonin
 - vitamin D supplements (>1000 IU per day)
 - calcitriol, calcidiol, or alfacalcidol at any dose

- any bisphosphonate
- fluoride (≥ 10 mg/day)
- strontium (≥ 50 mg/day)
- parathyroid hormone, including teriparatide
- Participated in another clinical trial 30 days prior to the first dose
- An acute illness within 2 weeks prior to the first dose, unless approved by the Sponsor

Reviewer comment: Inclusion and exclusion criteria appear to be adequate.

Study Medication: The DR formulation consists of risedronate with (b) (4) edetate disodium dihydrate (EDTA) with an enteric coating designed to release the components at pH 5.5. The EDTA (b) (4)

All subjects received oral supplements of 1000 mg/day elemental calcium and 400 IU/day vitamin D throughout the treatment period. Calcium supplements were to be ingested at a different time of day than the study drug.

Efficacy Measures

Primary Efficacy Endpoint: Percent change from baseline in serum CTX at Week 13 (Day 91) comparing the 50 mg DRFB group and the 35 mg IRBB group

Secondary Efficacy Endpoints:

- Percent change from baseline in serum CTX at Week 13 (Day 91) comparing the 50 mg DRBB group and the 35 mg DRFB group to the 35 mg IRBB group
- Percent change from baseline in BSAP and urine NTX at Week 13 (Day 91) comparing the 50 mg DRFB group, 50 mg DRBB group, and 35 mg DRFB group to the 35 mg IRBB group
- Percent change from baseline in serum CTX, BSAP, and urine NTX at Week 13 (Day 91) comparing the 50 mg DRFB group to the 50 mg DRBB group and the 35 mg DRFB group

Pharmacokinetic Endpoints: (Done in the pharmacokinetic subset of subjects)

- The cumulative amount of risedronate excreted in urine
- The percentage of dose excreted in urine

Safety Measures:

- Physical examinations
- Vital signs
- Baseline ECG

- Laboratory evaluations including hematology, clinical chemistry (bicarbonate, bilirubin, calcium, chloride, cholesterol, creatinine, glucose, magnesium, alkaline phosphatase, potassium, protein, albumin, sodium, ALT, AST, BUN, triglycerides, phosphorus), coagulation (PT, aPTT), baseline hepatitis A and B and HIV, Pregnancy testing, baseline PTH, baseline 25 OH vitamin D, baseline TSH, baseline urinalysis, and urine drug screen
- Adverse event assessment

Study Methods: Electronic case report forms were used in this trial.

Withdrawal criteria:

- Subject withdrew consent at any time
- It was in the best interest of the subject, in the judgment of the Investigator in consultation with the Medical Monitor
- Subject developed an illness or required therapy that, in the judgment of the Investigator in consultation with the Medical Monitor, was likely to interfere with the evaluation of the study drug
- A protocol deviation that, in the opinion of the Investigator, in consultation with the Medical Monitor, may have compromised the study results.

If possible, any subject who was withdrawn from the study had all exit procedures performed at the time of withdrawal.

Statistical Analyses: The following populations were analyzed:

- The intent to treat (ITT) population subjects were randomized and received at least one dose of study medication. The number of subjects in the ITT population was 181.
- The primary-efficacy (PE) population consisted of subjects in the ITT population who had serum CTX values at both baseline and Week 13. The PE population consisted of 169 subjects.
- The per-protocol (PP) population excluded all subjects in the PE population who met additional criteria:
 - Could not evaluate the CTX percent change from baseline at Week 13 (Day 91)
 - Did not meet inclusion/exclusion criteria
 - Less than 80% compliant with study drug while on treatment
 - Received incorrect treatment at any time during the study
 - Un-blinded during the study
 - BTM values outside of the visit window

The PP population was used only to check the robustness of the primary efficacy analysis. One hundred fifty seven subjects are included in the PP population.

Demographic and baseline characteristics were summarized by treatment group. Summary statistics are provided for continuous variables and frequency distributions are provided for categorical variables. Continuous variables were analyzed using a one-way analysis of variance (ANOVA) model, with treatment group as factor. Discrete variables were compared using the Fisher's Exact Test.

The primary and secondary analyses were conducted by calculating the ratio of the mean percent change from baseline to Week 13 (Day 91) in BTMs in the various DR formulations and dose timings to that of the 35 mg IRBB group and the 50 mg DRFB to the other 2 DR doses. A 90% CI for the true ratio was computed. Analysis of variance was performed with treatment and centers as fixed effects and percent change from baseline in CTX at Week 13 (Day 91) as the response variable. Fieller's theorem was used to calculate the ratio and confidence interval. No multiple-comparison adjustments were made to p-values. Percent change from baseline in BTM measurements at the end of Week 4 (Day 28) and Week 8 (Day 56) were summarized by treatment group.

Pharmacokinetic parameters were summarized as ratios of parameters for the test treatments to parameters for the risedronate 35 mg IRBB group. Ratios of parameters for the risedronate 50 mg DRFB group to the risedronate 50 mg DRBB group were also summarized. Associated 95% CI levels are reported. Differences in PK parameters between Day 1 and Day 85 were calculated for each subject and summarized by treatment group. In addition, a signed rank test of the difference between Day 1 and Day 85 for the DR formulations was performed.

Protocol Amendments: This protocol was not amended except that a typographical error on the schedule of events was removed before the first subject enrolled.

Results

Patient Disposition: A total of 398 subjects were screened, 182 subjects were randomized, and 181 subjects received at least 1 dose of study drug and were included in the ITT population. One subject was withdrawn by the investigator before dosing for lymphocytosis. Overall, 168 subjects completed the study and 13 subjects were prematurely withdrawn. Table 53 summarizes screening, enrollment, and disposition by site. No marked disparities are noted except perhaps increased discontinuation and withdrawal for adverse event at site 103053, but enrollment at that site was relatively low.

Table 53, Trial 2005107 Screening, Enrollment, Disposition, and Adverse Events by Site

Site Number	Subjects Screened	Subjects Randomized n (%) ^a	Subjects Discontinued n (%) ^b	Discontinued Due to Protocol Violation n (%) ^b	Subjects Reporting Adverse Events n (%) ^b	Withdrawn Due to Adverse Events n (%) ^b

United States Overall	398	182 (45.7%)	14 (7.7%)	1 (0.5%)	121 (66.5%)	7 (3.8%)
103052	83	36 (43.4%)	3 (8.3%)	0 (0.0%)	25 (69.4%)	1 (2.8%)
103053	49	15 (30.6%)	5 (33.3%)	0 (0.0%)	8 (53.3%)	3 (20.0%)
103054	76	48 (63.2%)	1 (2.1%)	0 (0.0%)	27 (56.3%)	0 (0.0%)
103055	86	46 (53.5%)	2 (4.3%)	1 (2.2%)	31 (67.4%)	1 (2.2%)
103056	16	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
103069	88	36 (40.9%)	3 (8.3%)	0 (0.0%)	29 (80.6%)	2 (5.6%)

a Percentage was calculated as a proportion of subjects screened.
 b Percentage was calculated as a proportion of subjects randomized.
 Source: Study Number: 2005107, Final Report, EoT Table 1

No statistically significant differences between groups are noted in disposition Table 54 for proportion of subjects dropping out or for proportion of subjects dropping out for any major reason.

Table 54, Trial 2005107 Intent to Treat Population Disposition

	35 mg IRBB (N=37) n (%)	35 mg DRFB (N=36) n (%)	50 mg DRBB (N=36) n (%)	50 mg DRFB (N=72) n (%)	Fisher's Exact p-value
Completed Trial	33 (89.2%)	35 (97.2%)	35 (97.2%)	65 (90.3%)	0.3658
Did not Complete	4 (10.8%)	1 (2.8%)	1 (2.8%)	7 (9.7%)	0.3658
Adverse Events	2 (5.4%)	1 (2.8%)	0 (0.0%)	4 (5.6%)	0.6514
Lost to Follow-up	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0.3978
Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1.0000
Subject Decision	2 (5.4%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	0.4560

Source: Study Number: 2005107, Final Report, Table 4

Ninety-five subjects were in the PK subset. Of these 95 subjects, 89 subjects completed the study and 6 were prematurely withdrawn (see Table 55).

Table 55, Trial 2005107 PK Intent to Treat Population Disposition

	35 mg IRBB (N=20) n (%)	35 mg DRFB (N=19) n (%)	50 mg DRBB (N=18) n (%)	50 mg DRFB (N=38) n (%)	Fisher's Exact p-value
Completed Trial	17 (85.0%)	18 (94.7%)	18 (100.0%)	36 (94.7%)	0.3595
Did not Complete	3 (15.0%)	1 (5.3%)	0 (0.0%)	2 (5.3%)	0.3595
Adverse Events	1 (5.0%)	1 (5.3%)	0 (0.0%)	1 (2.6%)	1.0000
Subject Decision	2 (10.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0.3525

Source: Study Number: 2005107, Final Report, EoT Table 2

Protocol Violations: Of the 181 subjects in the ITT population, 96 subjects had at least 1 protocol “deviation”. Deviations and protocol violations were not defined by Sponsor in either the study report or the protocol. Deviations were reviewed by this reviewer in appendix 3.2 of the final study report. In general, these deviations appear to be minor protocol violations in record keeping and timing of dosing, food, visits, and samples, and are not expected to significantly affect study results. Study drug compliance, based on count of returned drug, was high, with only 1 subject (in the 50 mg DRBB group) < 80% compliant and with mean compliance in all groups exceeding 99%.

Demographics: The treatment groups were similar for demographic and baseline characteristics. Most subjects were Caucasian non-Hispanic or Hispanic. Mean age was 60 years with an age range of 45 to 79 years. Subjects in the PK subset and the per-protocol population were similar to those in the ITT population for demography and baseline characteristics. Table 56 shows demographic and baseline characteristics for the ITT population.

Table 56, Trial 2005107 Demographic and Baseline Characteristics, ITT Population

Parameter Statistic/Category	35 mg IRBB (N=37)	35 mg DRFB (N=36)	50 mg DRBB (N=36)	50 mg DRFB (N=72)	Overall (N=181)	p-value*
Age (years)						0.5993
Mean (SD)	61.1 (6.2)	58.9 (6.7)	60.0 (6.1)	59.7 (7.8)	59.9 (7.0)	
Min, Max	52, 78	45, 74	51, 74	45, 79	45, 79	
Race						0.5032
Asian (Oriental)	6 (16.2%)	6 (16.7%)	3 (8.3%)	10 (13.9%)	25 (13.8%)	
Black	0 (0.0%)	1 (2.8%)	3 (8.3%)	2 (2.8%)	6 (3.3%)	
Caucasian Non-Hispanic	17 (45.9%)	20 (55.6%)	12 (33.3%)	33 (45.8%)	82 (45.3%)	
Hispanic	13 (35.1%)	9 (25.0%)	14 (38.9%)	23 (31.9%)	59 (32.6%)	
Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.6%)	
Multi-Racial	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.6%)	
Other	1 (2.7%)	0 (0.0%)	4 (11.1%)	2 (2.8%)	7 (3.9%)	
Height (cm)						0.5422
Mean (SD)	159.2 (6.0)	159.7 (6.9)	161.4 (6.7)	160.5 (7.5)	160.2 (6.9)	
Min, Max	148, 172	144, 174	145, 173	142, 182	142, 182	
Weight (kg)						0.5320
Mean (SD)	67.9 (10.3)	66.2 (11.3)	69.8 (9.4)	68.5 (10.8)	68.2 (10.5)	
Min, Max	48.3, 91.1	41.6, 86.0	50.9, 90.3	44.3, 92.0	41.6, 92.0	
Tobacco Use						0.7360
Currently	4 (10.8%)	2 (5.6%)	1 (2.8%)	6 (8.3%)	13 (7.2%)	
Never	26 (70.3%)	23 (63.9%)	28 (77.8%)	49 (68.1%)	126 (69.6%)	
Previously	7 (18.9%)	11 (30.6%)	7 (19.4%)	17 (23.6%)	42 (23.2%)	

Alcohol Use						0.4050
Currently	20 (54.1%)	21 (58.3%)	13 (36.1%)	34 (47.2%)	88 (48.6%)	
Never	15 (40.5%)	15 (41.7%)	20 (55.6%)	34 (47.2%)	84 (46.4%)	
Previously	2 (5.4%)	0 (0.0%)	3 (8.3%)	4 (5.6%)	9 (5.0%)	

*Categorical p-values are Fisher's Exact and continuous p-values are one-way ANOVA
 Source: Study Number: 2005107, Final Report, Table 6

Concomitant Medications: Concomitant medication use was generally similar across treatment groups. Concomitant medications used by ≥15% of subjects were acetaminophen (all groups), acetylsalicylic acid (50 mg DRFB group), ibuprofen (35 mg IRBB group), and multivitamins (35 mg IRBB group). Few subjects took medications expected to have significant bone effects (e.g. HCTZ). Concomitant medication use is listed in Table 57. Protocol specified calcium and vitamin D are not included.

Table 57, Trial 2005107 Concomitant Medications Taken by >5% of Subjects, ITT Population

Therapeutic Class	35 mg IRBB (N=37) n (%)	35 mg DRFB (N=36) n (%)	50 mg DRBB (N=36) n (%)	50 mg DRFB (N=72) n (%)
Acetaminophen	10 (27.0%)	9 (25.0%)	8 (22.2%)	12 (16.7%)
Acetylsalicylic acid	4 (10.8%)	3 (8.3%)	1 (2.8%)	13 (18.1%)
Ascorbic acid	1 (2.7%)	4 (11.1%)	1 (2.8%)	5 (6.9%)
Calcium	0	2 (5.6%)	0	0
Diphenhydramine HCl	2 (5.4%)	1 (2.8%)	1 (2.8%)	1 (1.4%)
Folic acid	2 (5.4%)	0	0	1 (1.4%)
Glucosamine ± Chondroitin	2 (5.4%)	4 (11.1%)	0	1 (1.4%)
Herbal preparation	3 (8.1%)	2 (5.6%)	0	3 (4.2%)
Hydrochlorothiazide	0	1 (2.8%)	0	4 (5.6%)
Ibuprofen	7 (18.9%)	3 (8.3%)	2 (5.6%)	10 (13.9%)
Levothyroxine	4 (10.8%)	2 (5.6%)	3 (8.3%)	2 (2.8%)
Multivitamins	7 (18.9%)	2 (5.6%)	1 (2.8%)	8 (11.1%)
Naproxen	3 (8.1%)	1 (2.8%)	2 (5.6%)	1 (1.4%)
Pyridoxine HCl	2 (5.4%)	0	0	0
Rosuvastatin	2 (5.4%)	0	0	1 (1.4%)
Simvastatin	0	0	2 (5.6%)	1 (1.4%)
Tocopherol	0	3 (8.3%)	2 (5.6%)	4 (5.6%)

Source: Study Number: 2005107, Final Report, EoT Table 3

Efficacy

Change in Serum CTX: As noted in Table 58 below, the mean percent decrease in serum CTX was greater than 60% for all delayed release formulations, compared to a 43% decrease with the currently marketed immediate release formulation. The ratio of the mean percent change from baseline in CTX for the 50 mg DRFB regimen to the 35 mg IRBB regimen at Week 13 (the primary efficacy outcome, **bolded** in Table 58) was 1.54 with the 90% confidence interval not crossing 1.00 (90% CI = 1.18, 2.09) in the ITT population, indicating that this DR regimen suppressed CTX to a greater extent than the 35 mg IRBB regimen. The results of the analysis in the PP population were consistent with the primary analysis.

The 35 mg DRFB regimen and 50 mg DRBB regimen also suppressed CTX to a greater extent than the 35 mg IRBB regimen, with ratios of percent change from baseline at 13 weeks compared to the 35 mg IRBB regimen of 1.44 and 1.51 respectively, and the 90% confidence intervals not crossing 1.00 (see Table 58). Thus, all tested DR formulations suppress CTX to a greater extent than the approved 35 mg IR formulation.

The percent change from baseline in serum CTX at Week 13 comparing the 50 mg DRFB group to the 50 mg DRBB group and the 35 mg DRFB group gives ratios of 1.02 and 1.07 with the 90% confidence interval crossing 1.00 in both cases (90% CI = 0.82, 1.27 and 0.87, 1.32 respectively) (see Table 58). Within the limits of this trial, no difference in the effect of various DR formulations and dose times on CTX is found. The comparability of the 50 mg DRBB and 50 mg DRFB dosing in effect on CTX supports lack of food effect on the DR formulation.

Table 58, Trial 2005107 Mean Percent Change from Baseline to Week 13 of CTX, ITT Population

Treatment Group	N	LS Mean	95% Confidence Interval	Ratio vs. 35 mg IRBB (90% Confidence Interval)*	Ratio vs. 35 mg DRFB (90% Confidence Interval)*	Ratio vs. 50 mg DRBB (90% Confidence Interval)*
35 mg IRBB	34	-43.2	-55.8, -30.6			
35 mg DRFB	35	-62.1	-73.6, -50.6	1.44 (1.09, 1.96)		
50 mg DRBB	35	-65.1	-77.7, -52.5	1.51 (1.14, 2.07)		
50 mg DRFB	65	-66.3	-77.4, -55.2	1.54 (1.18, 2.09)	1.07 (0.87, 1.32)	1.02 (0.82, 1.27)

IRBB = Immediate Release Before Breakfast, DRFB = Delayed Release Following Breakfast, DRBB = Delayed Release Before Breakfast
 *90% confidence interval for ratios is protocol specified
 Source: Study Number: 2005107, Final Report, Table 8

Secondary Efficacy Outcomes: Other secondary endpoints included urine NTX, bone specific alkaline phosphatase, and pharmacokinetics.

Change in Urine NTX: As noted in Table 59 below, the mean percent decrease in urine type-1 collagen cross-linked N-telopeptide (NTX) corrected for creatinine clearance was greater than 43% for all delayed release formulations, compared to a 39% decrease with the currently marketed immediate release formulation. The ratios of the DR regimens to 35 mg IRBB reference treatment, as well as the ratios of the 50 mg DRFB group to the 50 mg DRBB group and the 35 mg DRFB group, at Week 13 for change in urine NTX from baseline are summarized in Table 59. All of the DR regimens suppress NTX to a similar degree as the immediate release formulation as the 90% confidence intervals for the ratios cross 1.00, but numerically all reduce NTX to a greater extent

than the immediate release formulation. The 50 mg DRFB regimen reduces NTX to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens based on the ratio 90% confidence intervals crossing 1.00.

Table 59, Trial 2005107 Mean Percent Change from Baseline to Week 13 of Urine NTX Corrected for Creatinine Clearance, ITT Population

Treatment Group	N	LS Mean	(95% Confidence Interval)	Ratio vs. 35 mg IRBB (90% Confidence Interval)	Ratio vs. 35 mg DRFB (90% Confidence Interval)	Ratio vs. 50 mg DRBB (90% Confidence Interval)
35 mg IRBB	34	-38.6	(-56.6, -20.5)			
35 mg DRFB	35	-46.6	(-63.0, -30.2)	1.21 (0.75, 2.10)		
50 mg DRBB	35	-43.7	(-61.6, -25.7)	1.13 (0.67, 2.00)		
50 mg DRFB	65	-54.3	(-70.1, -38.4)	1.41 (0.91, 2.40)	1.17 (0.80, 1.75)	1.24 (0.83, 1.99)

Source: Study Number: 2005107, Final Report, Table 9

Change in Bone Specific Alkaline Phosphatase: As noted in Table 60 below, the mean percent decrease in serum bone alkaline phosphatase (BSAP) at Week 13 was numerically greater for the 50 mg delayed release formulation compared to the 35 mg DR and IR formulations, but only the 50 mg DRBB treatment regimen was statistically greater using the 95% confidence interval. The ratios of the DR regimens to 35 mg IRBB reference treatment for change in serum BSAP from baseline all show suppression of BSAP to a similar degree as the immediate release formulation as the 90% confidence intervals (protocol specified) of the ratios cross 1.00. The 50 mg DRFB regimen reduces BSAP to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens based on the ratio 90% confidence intervals crossing 1.00.

Table 60, Trial 2005107 Mean Percent Change from Baseline to Week 13 of Serum Bone Alkaline Phosphatase, ITT Population

Treatment Group	N	LS Mean	(95% Confidence Interval)	Ratio vs. 35 mg IRBB (90% Confidence Interval)	Ratio vs. 35 mg DRFB (90% Confidence Interval)	Ratio vs. 50 mg DRBB (90% Confidence Interval)
35 mg IRBB	34	-11.0	(-19.6, -2.4)			
35 mg DRFB	35	-10.4	(-18.3, -2.5)	0.95 (0.32, 2.99)		
50 mg DRBB	35	-20.0	(-28.6, -11.4)	1.82 (0.93, 5.43)		
50 mg DRFB	65	-17.4	(-25.0, -9.8)	1.58 (0.80, 4.72)	1.67 (0.86, 4.67)	0.87 (0.50, 1.49)

Source: Study Number: 2005107, Final Report, Table 10

The mean percent changes from baseline for all the BTMs (CTX, NTX, and BSAP) seen in the 50 mg DRBB regimen were similar to those seen in the 50 mg DRFB regimen, suggesting no food effect.

Pharmacokinetics: The amount of risedronate recovered in urine within 48 hours of dosing on Day 1 and Day 85 was determined in the PK subset of subjects and is given in Table 61. The geometric least square mean of the Day 85 35 mg DRFB group is considerably higher than the Day 1 value (182.6 µg vs. 92.4 µg) with the Day 1 value falling outside the 95% confidence interval for the Day 85 value. This does not occur for any of the other dosing regimens. In addition, the Day 85 35 mg DRFB value is higher than either of the 50 mg DR regimens at either time point. None of the other regimens show a marked tendency for considerably higher values at Day 85 over Day 1. Sponsor reports no consistent change was noted over time for urinary excretion, as an equal number of subjects had increases and decreases in risedronate urinary excretion (Ae) at Day 85. This reviewer has doubts about the reproducibility of the Day 85 35 mg DRFB geometric mean data.

It would appear, from the means and ratio calculations in Table 61, that all of the DR formulations result in roughly twice the risedronate absorption as the approved IR formulation. Similar trends are seen both at Day 1 and Day 85. There is little difference between the 50 mg DR dose given 30 minutes before or immediately following breakfast. This supports lack of food effect. There also appears to be little difference in absorption between the 35 mg DR dose immediately following breakfast and the two 50 mg DR regimens. Sponsor reports this 2-fold increase in absorption for the DR formulations is similar to the increase observed when the 35 mg IR dose is given followed by a 4 hour instead of 30 minute fast. Sponsor contends the comparability of absorption for the 35 mg IR dose followed by a 4 hour fast and the 35 mg DRFB dose also argues for a lack of food effect.

Reviewer comment: This data argues for rather complete abolition of food effect with the delayed release [REDACTED] (b) (4) with the EDTA of the DR formulation.

Variability (coefficient of variation) for the geometric mean was 2- to 3-fold higher for the DR regimens compared to the 35 mg IRBB regimen.

Table 61, Trial 2005107 Risedronate Urinary Excretion over 48 Hours (Ae), Geometric Mean

Visit Treatment	N	Geometric LS Means (Ae, µg)	%CV	95% Confidence Interval	Ratio vs. 35 mg IRBB (95% Confidence Interval)	Ratio vs. 50 mg DRBB (95% Confidence Interval)
Day 1						
35 mg IRBB	20	60.5	118	30.8, 118.9		
35 mg DRFB	19	92.4	594	46.3, 184.6	1.53 (0.58, 4.01)	

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50 mg DRBB	18	154.7	349	75.8, 315.8	2.56 (0.96, 6.80)	
50 mg DRFB	38	140.2	288	85.6, 229.6	2.32 (1.01, 5.33)	0.91 (0.38, 2.14)
Day 85						
35 mg IRBB	17	60.0	99	33.9, 106.2		
35 mg DRFB	18	182.6	130	104.8, 318.0	3.04 (1.37, 6.75)	
50 mg DRBB	18	118.1	128	67.6, 206.1	1.97 (0.89, 4.36)	
50 mg DRFB	36	166.5	264	112.2, 247.0	2.77 (1.39, 5.55)	1.41 (0.72, 2.78)
Avg of Days 1 & 85						
35 mg IRBB	20	63.5		38.7, 104.2		
35 mg DRFB	19	134.1		80.7, 222.8	2.11 (1.04, 4.29)	
50 mg DRBB	18	135.3		80.2, 228.3	2.13 (1.04, 4.37)	
50 mg DRFB	38	143.7		100.1, 206.3	2.26 (1.23, 4.17)	1.06 (0.57, 2.00)
%CV=coefficient of variation for the geometric mean						
Source: Study Number: 2005107, Final Report, Table 16						

When arithmetic means are used as in Table 62, variability appears less and is similar between IR and DR regimens. The 35 mg DRFB regimen results in about 2.5 times and the 50 mg regimens both about 3 times the risedronate absorption of the 35 mg IRBB regimen.

Table 62, Trial 2005107 Risedronate Urinary Excretion over 48 Hours (Ae), Arithmetic Mean

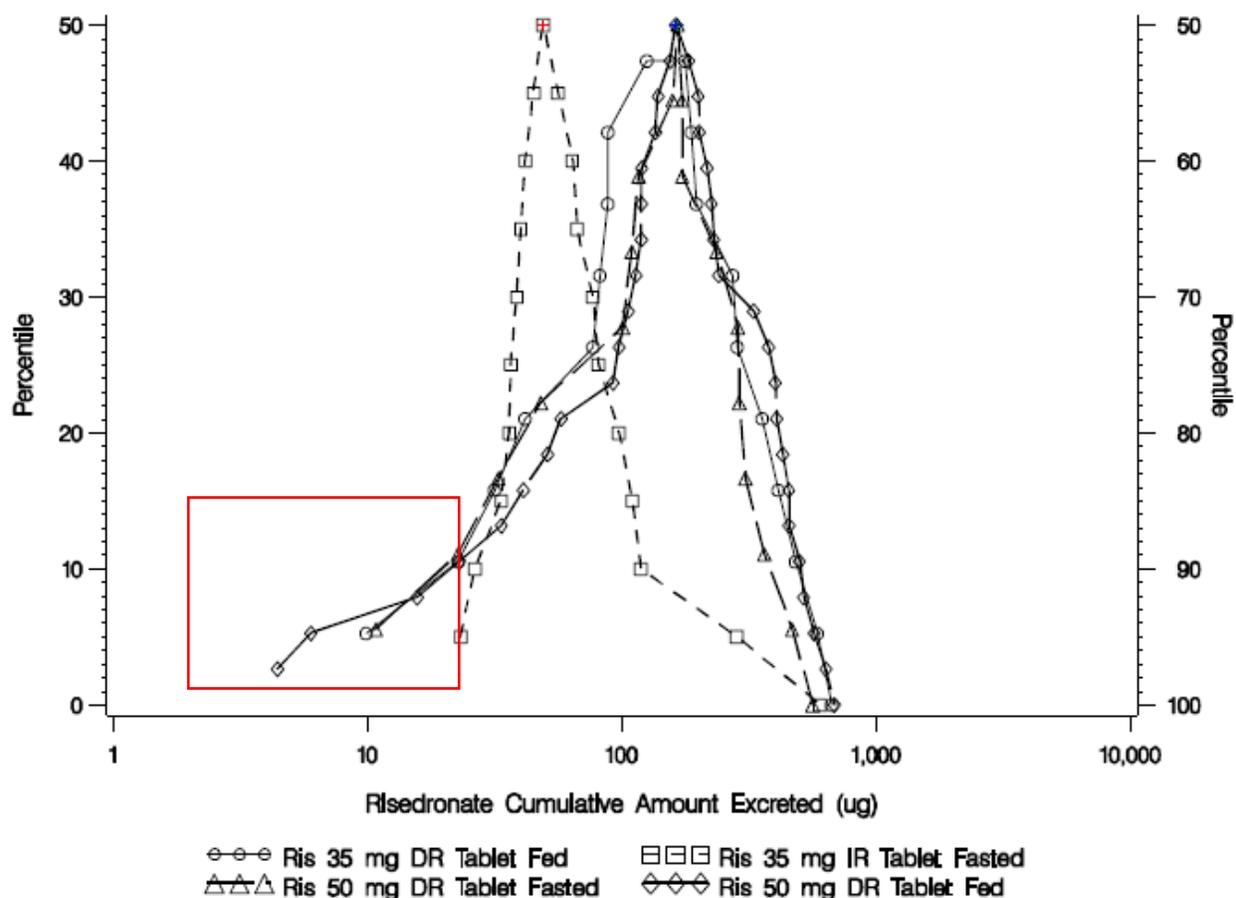
Visit Treatment	N	Arithmetic Mean (Ae, µg)	%CV	Ratio vs. 35 mg IRBB	Ratio vs. 50 mg DRBB
Day 1					
35 mg IRBB	20	100.8	141		
35 mg DRFB	19	233.4	96	2.41	
50 mg DRBB	18	405.9	155	4.19	
50 mg DRFB	38	283.1	97	2.92	0.98
Day 85					
35 mg IRBB	17	92.8	138		
35 mg DRFB	18	265.1	79	2.74	
50 mg DRBB	18	171.8	83	1.77	
50 mg DRFB	36	316.4	95	3.27	1.10
Avg of Days 1 & 85					
35 mg IRBB	20	96.8			
35 mg DRFB	19	249.3		2.58	
50 mg DRBB	18	288.9		2.98	
50 mg DRFB	38	299.8		3.10	1.04
%CV=coefficient of variation for the arithmetic mean					
Source: Study Number: 2005107, Final Report, EoT Tables 48 to 55					

Reviewer comment: This reviewer is more comfortable with arithmetic means due to lower variability but they do show increased risedronate absorption, which may be why Sponsor chose the geometric mean for the primary analysis. Another explanation for the Sponsor choosing the geometric mean may be that at least

some of the statistical packages used to analyze data primarily report the geometric mean.

Subjects with low urinary excretion of risedronate: A figure, provided by the Sponsor, raised concern about low absorption of risedronate in a subset of subjects on the DR formulation. About 10 percent of subjects in the DR groups appear to have a lower risedronate urinary excretion than any subject in the IR group as shown in the boxed area of Figure 1. This is not apparent in analysis of variability, perhaps because of an extended tail for the IR group at the upper end of the percentile curve while the extended tails for the DR groups are at the lower end, as indicated in the figure. Numbers are small (each point on the graph indicates the geometric mean of Day 1 and Day 85 values for a single subject), but consistent. This finding is especially surprising considering the overall higher absorption of the DR formulations.

Figure 1, Trial 2005107 Cumulative Urinary Risedronate Recovery by Treatment Group, Geometric Mean of Day 1 & 85



Source: Study Number: 2005107, Final Report, Figure 4

Reviewing the 48 hour risedronate excretion by subject (Study Number: 2005107, Final Report, EoT Tables 48 to 55) indicates the lowest risedronate excretion (Ae) in the 35 mg IRBB group at either time point (20 subjects measured on Day 1 and 17 on Day 85) was 12.95 µg. For the 35 mg DRFB group, 4 of 19 subjects on Day 1 were below that level, as were 0 of 18 on Day 85. For the 50 mg DRFB group, 3 of 38 subjects on Day 1 were below that level, as were 2 of 36 on Day 85. For the 50 mg DRBB group, 1 of 18 subjects on Day 1 was below that level, as were 0 of 18 on Day 85. Ten of 147 measures of urinary risedronate excretion (6.8%) with the DR formulation were lower than the lowest of 37 measures with the IR formulation.

The arithmetic mean of urinary excretion of risedronate on days 1 and 85 for the lowest excreters was compared to CTX change over the trial in Table 63. Using arithmetic mean rather than geometric mean resulted in somewhat fewer subjects in the DR groups with lower absorption than any in the IR group, but still 2 subjects in the 50 mg DRFB group and one in the 50 mg DRBB group were markedly below any subject in the IR group, and another subject in the 50mg DRBB group was somewhat below. There does appear to be attenuation of the reduction of CTX (less than 20% decrease) for most subjects in all groups with less than 30 to 35 µg risedronate excretion, including the IR group.

Table 63, Trial 2005107 CTX Change over 13 Weeks for the Lowest Risedronate Excreters

Age	Race/Eth	Sex	Mean Ae days 1&85 (µg)	Baseline CTX (ng/ml)	Day 91 CTX (ng/ml)	CTX % Change
35 mg IRBB (N=17)						
56	Hispanic	F	26.5	0.480	0.410	-14.6
69	Asian	F	27.3	0.080	0.100	25.0
54	Asian	F	33.6	0.750	0.600	-20.0
58	Caucasian	F	36.9	0.530	0.380	-28.3
52	Hispanic	F	44.9	1.015	0.620	-38.9
62	Caucasian	F	45.1	1.035	0.670	-35.3
35 mg DRFB (N=18)						
60	Caucasian	F	30.7	0.475	0.300	-36.8
74	Asian	F	46.3	0.265	0.005	-98.1
62	Hispanic	F	53.8	0.365	0.020	-94.5
58	Caucasian	F	88.1	0.505	0.280	-44.6
63	Caucasian	F	88.7	1.155	0.610	-47.2
50 mg DRFB (N=36)						
59	Hispanic	F	10.2	0.855	0.910	6.4
66	Caucasian	F	15.7	0.730	0.430	-41.1
53	Caucasian	F	28.0	0.305	0.250	-18.0
79	Asian	F	49.2	0.300	0.005	-98.3
58	Caucasian	F	107.0	0.505	0.130	-74.3
58	Hispanic	F	111.0	0.515	0.300	-41.7
60	Hispanic	F	111.7	0.970	0.420	-56.7
63	Caucasian	F	129.0	0.380	0.220	-42.1
50 mg DRBB (N=18)						

64	Hispanic	F	11.1	0.470	0.540	14.9
51	Black	F	23.2	0.660	0.680	3.0
67	Caucasian	F	41.8	0.525	0.150	-71.4
56	Asian	F	51.2	0.610	0.440	-27.9
59	Hispanic	F	114.7	0.815	0.600	-26.4

Source: Study Number 2005107, Final Report, EoT Tables 48-55 and data sets

Efficacy Conclusions: For the primary efficacy analysis, risedronate 50 mg DRFB suppressed CTX to a statistically significant greater extent than risedronate 35 mg IRBB. The 50 mg DRFB regimen of risedronate appears to have been more effective than an approved risedronate dose at suppressing this marker of bone resorption.

In addition, for the secondary endpoints, risedronate 50 mg DRBB and 35 mg DRFB also suppressed CTX to a statistically significant greater extent than risedronate 35 mg IRBB. Risedronate 50 mg DRFB suppressed CTX to a similar extent as the 50 mg DRBB and 35 mg DRFB regimens. The comparability of the 50 mg DRBB and 50 mg DRFB dosing in effect on CTX supports lack of food effect on the DR formulation.

For urine NTX, another marker of bone resorption, all of the DR regimens result in suppression to a similar statistical degree as the immediate release formulation, but numerically all reduce NTX to a greater extent than the immediate release formulation. The 50 mg DRFB regimen reduces NTX to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens.

All of the DR regimens result in suppression of BSAP, a marker of bone formation, to a similar degree as the immediate release formulation. The 50 mg DRFB regimen reduces BSAP to a similar degree as the 50 mg DRBB and 35 mg DRFB regimens.

If geometric means are considered, the 3 DR regimens (35 mg DRFB, 50 mg DRBB, and 50 mg DRFB) all result in absorption calculated on the basis of urinary excretion to be about 2 times that of the approved 35 mg IRBB regimen. If arithmetic means are considered, the 35 mg DRFB regimen has about 2.5 times and the 50 mg DR regimens about 3 times the absorption of the immediate release regimen.

Bone marker efficacy may translate into bone density (BMD) and fracture effectiveness. The Agency generally does not accept this for regulatory purposes, and the Phase 3 trial will need to show BMD efficacy with relation to a risedronate dose with proven fracture benefit. Higher risedronate absorption raises safety concerns including bone health (abnormal bone formation or mineralization) which will require bone histomorphometry data at equivalent high dose.

Safety

Events Rates: Similar percentages of subjects in the various treatment groups experienced adverse events (AE) as shown in Table 64. Serious adverse events were infrequent, with only 3 reported in 2 subjects (1.1%) (see Serious Adverse Events

below). Withdrawal for adverse events was also infrequent with 7 (3.9%) reported. The mean number of AEs per enrolled subject and mean number of AEs per subject with AEs were roughly comparable for the 35 mg IRBB, 35 mg DRFB, and 50 mg DRBB regimens, but both were about 70% higher in the 50 mg DRFB regimen, despite proportion of subjects suffering one or more AE being similar. The 50 mg DRFB group did have the highest risedronate absorption, but absorption in the 50 mg DRBB group was not much less.

Table 64, Trial 2005107 Adverse Event Rates, ITT Population

Category	35 mg IRBB (N=37) n (%) nAE	35 mg DRFB (N=36) n (%) nAE	50 mg DRBB (N=36) n (%) nAE	50 mg DRFB (N=72) n (%) nAE	Overall (N=181) n (%) nAE	p-value
AEs	27 (73.0%) 55	19 (52.8%) 44	24 (66.7%) 55	51 (70.8%) 170	121 (66.9%) 324	0.2397
Serious AEs	0 (0.0%) 0	1 (2.8%) 1	0 (0.0%) 0	1 (1.4%) 2	2 (1.1%) 3	0.8365
Withdrawn due to AEs	2 (5.4%) 4	1 (2.8%) 1	0 (0.0%) 0	4 (5.6%) 4	7 (3.9%) 9	0.6514
Deaths	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	
Mean Number of AEs per Enrolled Subject	1.5	1.2	1.5	2.4	1.8	
Mean Number of AEs per Subject with AEs	2.0	2.3	2.3	3.3	2.7	

n (%) = number (percent) of subjects within specified category and treatment
 nAE = number of adverse events within the specified category and treatment
 Source: Study Number: 2005107, Final Report, Table 12

Exposure: Duration of exposure to study drug is summarized in Table 65. More than 88% of subjects took study drug for the duration of the trial in all treatment groups.

Table 65, Trial 2005107 Extent of Exposure to Study Drug, ITT Population

Parameter Statistic	35 mg IRBB (N=37)	35 mg DRFB (N=36)	50 mg DRBB (N=36)	50 mg DRFB (N=72)
Subject-days of exposure				
Mean (SD)	82.2 (9.4)	84.6 (2.3)	82.7 (14.0)	78.6 (21.3)
Min	43	71	1	1
Max	85	85	85	86
Duration of Treatment				
> 0 Weeks	37 (100%)	36 (100%)	36 (100%)	72 (100%)
> 4 Weeks	37 (100%)	36 (100%)	35 (97%)	67 (93%)
> 8 Weeks	35 (95%)	36 (100%)	35 (97%)	66 (92%)
> 12 Weeks	33 (89%)	35 (97%)	35 (97%)	65 (90%)

Source: Study Number: 2005107, Final Report, Table 11

Deaths: No deaths were reported during this trial.

Serious Adverse Events: Two subjects in Study 2005107 had a total of 3 serious adverse events. A 60 year old Caucasian female in the 35 mg DRFB group was hospitalized for appendicitis on study day (b) (6). She recovered after a laparoscopic

appendectomy and continued in the trial. A 61 year old Caucasian female in the 50 mg DRFB group was hospitalized on study day (b) (6) with chest pain and cholelithiasis. She recovered following laparoscopic cholecystectomy. She withdrew from the trial.

Adverse Events Leading to Withdrawal: Seven subjects prematurely withdrew from the trial because of adverse events.

- 35 mg IRBB group, 2 subjects
 - A 55 year old Caucasian female withdrew from the trial on study day 91 for upper respiratory tract infection which developed on study day 69. The event outcome is unknown.
 - A 74 year old Caucasian female withdrew from the trial on study day 47 due to neck, shoulder, and back pain which developed on study day 13. The pain resolved on day 78, 35 days after study drug cessation..
- 35 mg DRFB group, 1 subject
 - A 52 year old Hispanic female withdrew from the trial on study day 84 for heartburn which developed on study day 73. This may have been occurring post-dose for a month. The event resolved.
- 50 mg DRBB group, no subjects
- 50 mg DRFB group, 4 subjects (note this group has about twice the subjects enrolled compared to the other groups)
 - A 61 year old Caucasian female withdrew from the trial on study day 16 for cholelithiasis. See SAEs above.
 - A 64 year old Caucasian female withdrew from the trial on study day 39 for bilateral leg pain which developed on study day 19. The pain resolved.
 - A 65 year old Caucasian female withdrew from the trial on study day 8 for loss of appetite which developed on study day 1. The event resolved.
 - A 73 year old Caucasian female withdrew from the trial on study day 18 for a second episode of gastroenteritis which developed on study day 16. Both episodes occurred about 1 day after study drug. EGD 14 days after the last dose demonstrated “lesions and inflammation in the antrum”. The event resolved.

Adverse Events Leading to Dose Alteration: No dose alterations due to adverse events were reported.

Adverse Events: The most common adverse events in Study 2005107 are listed in Table 66. Headache was the most frequently reported AE in all treatment groups. Other frequently reported AEs were gastrointestinal (nausea, abdominal pain, abdominal pain upper, diarrhea, dyspepsia) or musculoskeletal (back pain) in nature. There was a statistically significant increased incidence of diarrhea in the 50 mg groups (DRBB and DRFB regimens) compared to the 35 mg groups (IRBB and DRFB regimens), and a trend toward increased incidence of AEs in abdominal pain and abdominal pain upper in the DR regimens, especially the 50 mg DRFB regimen, compared to the 35 mg IRBB regimen.

The excess noted above under adverse event rates in the mean number of AEs per enrolled subject and mean number of AEs per subject with AEs for the 50 mg DRFB regimen appear to come primarily from the gastrointestinal disorders and nervous system disorders SOCs.

Table 66, Trial 2005107 Most Common Adverse Events, ITT Population (> 7% in any Treatment Group)

System Organ Class Preferred Term	35 mg IRBB (N=37) n (%) nAE	35 mg DRFB (N=36) n (%) nAE	50 mg DRBB (N=36) n (%) nAE	50 mg DRFB (N=72) n (%) nAE	p-value
Overall	27 (73.0%) 55	19 (52.8%) 44	24 (66.7%) 55	51 (70.8%) 170	0.2397
Musculoskeletal and connective tissue disorders	8 (21.6%) 12	9 (25.0%) 13	7 (19.4%) 8	18 (25.0%) 28	0.9325
Back pain	3 (8.1%) 3	4 (11.1%) 4	0 (0.0%) 0	3 (4.2%) 3	0.1313
Gastrointestinal disorders	12 (32.4%) 15	8 (22.2%) 11	13 (36.1%) 23	26 (36.1%) 69	0.5078
Abdominal pain upper	0 (0.0%) 0	3 (8.3%) 3	1 (2.8%) 1	8 (11.1%) 11	0.0972
Abdominal pain	1 (2.7%) 1	2 (5.6%) 2	2 (5.6%) 4	6 (8.3%) 9	0.7440
Dyspepsia	4 (10.8%) 4	2 (5.6%) 3	0 (0.0%) 0	4 (5.6%) 4	0.2726
Nausea	3 (8.1%) 3	2 (5.6%) 2	4 (11.1%) 4	9 (12.5%) 13	0.7503
Vomiting	2 (5.4%) 2	1 (2.8%) 1	3 (8.3%) 3	2 (2.8%) 2	0.6202
Diarrhea	1 (2.7%) 1	0 (0.0%) 0	6 (16.7%) 6	7 (9.7%) 14	0.0258*
Nervous system disorders	11 (29.7%) 13	8 (22.2%) 13	10 (27.8%) 11	19 (26.4%) 39	0.9116
Headache	7 (18.9%) 9	8 (22.2%) 11	10 (27.8%) 10	16 (22.2%) 26	0.8506
Infections and infestations	6 (16.2%) 6	3 (8.3%) 3	3 (8.3%) 3	7 (9.7%) 10	0.6910
Upper respiratory tract infection	3 (8.1%) 3	0 (0.0%) 0	1 (2.8%) 1	2 (2.8%) 3	0.3567
Respiratory, thoracic and mediastinal disorders	1 (2.7%) 2	3 (8.3%) 3	3 (8.3%) 3	5 (6.9%) 7	0.7376

*Significant at the p < 0.05 level (treatment difference using Fisher's Exact Test)
 Source: Study Number: 2005107, Final Report, EoT Table 32

Adverse Events of Special Interest:

Gastrointestinal: Gastrointestinal AEs are presented by MedDRA high level term and preferred term by treatment group in Table 67. The 50 mg DR regimens resulted in numerically slightly more subjects with adverse events and the 35 mg DR regimen slightly less than the reference 35 mg IR regimen, but this was not statistically significant. The mean number of GI SOC AEs per subject with AE increases markedly in the 50 mg DR regimens; in the 35 mg IRBB group it is 1.3, in the 35 mg DRFB group it is 1.4, in the 50 mg DRBB group it is 1.8, and in the 50 mg DRFB group it is 2.7. The various abdominal pain categories; nausea and vomiting; diarrhea; flatulence, bloating, and distention; and stomach discomfort are areas in which single subjects had multiple AEs.

Reviewer comment: This data is consistent with certain subjects having a sensitivity to risedronate. Higher doses appear to result in more and recurrent gastrointestinal AEs in those subjects.

The incidence of AEs associated with GI and abdominal pains was slightly higher in the 3 DR regimens, especially in the 2 FB groups, compared to the 35 mg IRBB regimen, but this was not statistically significant. As noted earlier, a statistically significant higher percentage of subjects in the 50 mg DR regimens reported diarrhea compared to the other groups.

Table 67, Trial 2005107 All Gastrointestinal SOC AEs, ITT Population

High Level Term Preferred Term	35 mg IRBB (N=37) n (%) nAE	35 mg DRFB (N=36) n (%) nAE	50 mg DRBB (N=36) n (%) nAE	50 mg DRFB (N=72) n (%) nAE	p-value
Overall	12 (32.4%) 15	8 (22.2%) 11	13 (36.1%) 23	26 (36.1%) 69	0.5078
GI and abdominal pains (excl oral and throat)	1 (2.7%) 1	5 (13.9%) 5	3 (8.3%) 6	12 (16.7%) 20	0.1317
Abdominal pain upper	0 (0.0%) 0	3 (8.3%) 3	1 (2.8%) 1	8 (11.1%) 11	0.0972
Abdominal pain	1 (2.7%) 1	2 (5.6%) 2	2 (5.6%) 4	6 (8.3%) 9	0.7440
Abdominal tenderness	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1	0 (0.0%) 0	0.3978
Dyspeptic signs and symptoms	5 (13.5%) 5	2 (5.6%) 3	0 (0.0%) 0	4 (5.6%) 4	0.1162
Dyspepsia	4 (10.8%) 4	2 (5.6%) 3	0 (0.0%) 0	4 (5.6%) 4	0.2726
Eructation	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0.6022
Nausea and vomiting symptoms	4 (10.8%) 5	2 (5.6%) 3	5 (13.9%) 7	9 (12.5%) 15	0.6994
Nausea	3 (8.1%) 3	2 (5.6%) 2	4 (11.1%) 4	9 (12.5%) 13	0.7503
Vomiting	2 (5.4%) 2	1 (2.8%) 1	3 (8.3%) 3	2 (2.8%) 2	0.6202
Dental pain and sensation disorders	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (2.8%) 2	0.8027
Toothache	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (2.8%) 2	0.8027
Diarrhea (excl infective)	1 (2.7%) 1	0 (0.0%) 0	6 (16.7%) 6	7 (9.7%) 14	0.0258*
Diarrhea	1 (2.7%) 1	0 (0.0%) 0	6 (16.7%) 6	7 (9.7%) 14	0.0258*
Flatulence, bloating and distension	1 (2.7%) 1	0 (0.0%) 0	1 (2.8%) 1	2 (2.8%) 5	0.9202
Abdominal distension	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1	0 (0.0%) 0	0.3978
Flatulence	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (2.8%) 5	0.8027
Gastrointestinal atonic and hypomotility disorders NEC	1 (2.7%) 1	0 (0.0%) 0	2 (5.6%) 2	3 (4.2%) 3	0.7280
Constipation	1 (2.7%) 1	0 (0.0%) 0	2 (5.6%) 2	2 (2.8%) 2	0.5661
Gastroesophageal reflux disease	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Gastrointestinal signs and symptoms NEC	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1	1 (1.4%) 4	0.8365
Stomach discomfort	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1	1 (1.4%) 4	0.8365
Intestinal hemorrhages	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Rectal hemorrhage	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Non-site specific gastrointestinal hemorrhages	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Hematochezia	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000

n (%) = number (percent) of subjects within specified category and treatment
nAE = number of adverse events within the specified category and treatment

*Significant at the p < 0.05 level (treatment difference using Fisher's Exact Test)
 Source: Study Number: 2005107, Final Report, Table 13

The same subject in the 50 mg DRFB group reported both recorded lower GI bleeds, rectal hemorrhage at study day ^(b)₍₆₎ and hematochezia at study day ^(b)₍₆₎, in conjunction with diarrhea and epigastric pain which also began at study day ^(b)₍₆₎. Both were recorded as mild. The subject recovered and continued the trial. Narrative and case report forms are not provided.

Musculoskeletal: The musculoskeletal SOC was reviewed for differences in incidence of adverse events between treatment groups as noted in Table 68. No significant differences were noted between groups for myalgia, arthralgia, bone pain, or other adverse events in this SOC. The most frequently reported adverse events were back pain and arthralgia.

Table 68, Trial 2005107 Musculoskeletal and Connective Tissue Disorders SOC AEs, ITT Population

High Level Term Preferred Term	35 mg IRBB (N=37) n (%) nAE	35 mg DRFB (N=36) n (%) nAE	50 mg DRBB (N=36) n (%) nAE	50 mg DRFB (N=72) n (%) nAE	p-value*
Musculoskeletal and connective tissue disorders (SOC)	8 (21.6%) 12	9 (25.0%) 13	7 (19.4%) 8	18 (25.0%) 28	0.9325
Musculoskeletal and connective tissue signs and symptoms NEC	4 (10.8%) 6	6 (16.7%) 9	3 (8.3%) 4	10 (13.9%) 13	0.7357
Back pain	3 (8.1%) 3	4 (11.1%) 4	0 (0.0%) 0	3 (4.2%) 3	0.1313
Musculoskeletal pain	2 (5.4%) 2	2 (5.6%) 2	1 (2.8%) 1	3 (4.2%) 3	1.0000
Pain in extremity	0 (0.0%) 0	2 (5.6%) 2	1 (2.8%) 1	5 (6.9%) 5	0.4433
Neck pain	1 (2.7%) 1	1 (2.8%) 1	1 (2.8%) 1	0 (0.0%) 0	0.3587
Musculoskeletal chest pain	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Musculoskeletal stiffness	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1	1 (1.4%) 1	0.8365
Joint related signs and symptoms	1 (2.7%) 1	2 (5.6%) 2	1 (2.8%) 1	5 (6.9%) 7	0.8423
Arthralgia	1 (2.7%) 1	2 (5.6%) 2	1 (2.8%) 1	5 (6.9%) 7	0.8423
Muscle related signs and symptoms NEC	1 (2.7%) 2	2 (5.6%) 2	1 (2.8%) 1	2 (2.8%) 2	0.8872
Muscle spasms	1 (2.7%) 2	2 (5.6%) 2	1 (2.8%) 1	2 (2.8%) 2	0.8872
Bone disorders NEC	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Exostosis	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.4%) 1	1.0000
Bone related signs and symptoms	2 (5.4%) 2	0 (0.0%) 0	0 (0.0%) 0	2 (2.8%) 2	0.4560
Bone pain	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (2.8%) 2	0.8027
Pain in jaw	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0.6022
Muscle pains	0 (0.0%) 0	0 (0.0%) 0	2 (5.6%) 2	3 (4.2%) 3	0.3618
Myalgia	0 (0.0%) 0	0 (0.0%) 0	2 (5.6%) 2	3 (4.2%) 3	0.3618
Soft tissue disorders NEC	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0.6022
Groin pain	1 (2.7%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0.6022

n (%) = number (percent) of subjects within specified category and treatment
nAE = number of adverse events within the specified category and treatment
*p-value is a test of treatment difference using Fisher's Exact Test)
Source: Study Number: 2005107, Final Report, EoT Table 31

Laboratory

Adverse Events: Few lab abnormalities were reported as adverse events. In the 35 mg IRBB group, one adverse event was reported for each of blood glucose increased, blood cholesterol increased, and blood triglyceride increased. These were all in the same subject. Another AE of hypercholesterolemia was reported. One subject in the 50 mg DRBB group had elevated ALT and AST reported as an AE. Another in the same group had hyponatremia. One subject in the 50 mg DRFB group had hypertriglyceridemia reported as an adverse event.

Marked Laboratory Abnormalities: Seven subjects reportedly had markedly abnormal laboratory which first occurred after study drug was administered for alkaline phosphatase (ALP), ALT, calcium, or potassium. The three for alkaline phosphatase all were in the 50 mg DRFB group. No narratives or CRFs are provided.

- A 52 year old Caucasian female had ALP values that were high at screening (133 U/L) and markedly high on Day 14 (151 U/L) but decreased to 102 U/L on Day 91, which was still above the normal range. ALT and AST values remained within the normal range throughout the study.
- A 60 year old Caucasian female had high ALP values at screening (123 U/L) and Day 14 (134 U/L) and a markedly high ALP on Day 91 (179 U/L). This subject also had elevated ALT values on Days 14 and 91, although AST values remained within the normal range.
- A 58 year old Asian female had high ALP values at screening (147 U/L) and admission (139 U/L) and a markedly high ALP on Day 14 (160 U/L). This subject's ALP value decreased to 104 U/L on Day 91, which was still above the normal range. ALT and AST values remained within the normal range throughout the study.

Reviewer comment: None of the above-mentioned subjects had relevant medical history or concomitant medications use.

Other extreme values following study medicine use are:

- A 57 year old Caucasian female in the 35 mg IRBB group with normal potassium at screening, admission, and Day 91 had a value of 6.3 mEq/l on Day 14.
- A 71 year old multiracial female in the 50 mg DRFB group with normal potassium at admission and Day 91 and 5.9 mEq/l at screening had a value of 6.5 mEq/l on Day 14.
- A 64 year old Caucasian female in the 50 mg DRBB group had normal transaminases at screening, admission, and Day 14. At Day 91 ALT was 160 U/l. AST was more mildly elevated at 59 U/l on Day 91.

- A 71 year old Caucasian female in the 50 mg DRBB group had a calcium level of 11.5 mg/dl on Day 14 with normal values at screening and Day 91.

Reviewer comment: Concomitant medications were reviewed and are unlikely to have caused any of these abnormal values. All abnormalities normalized by end of study except the ALT value found at end of study.

Mean Change from Baseline: Mean change from baseline for hematologic (hematocrit, hemoglobin, MCH, MCV, MCHC, platelet count, RBC count, and WBC count) and coagulation (PT, aPTT, INR) parameters by treatment groups were reviewed. All mean values were within normal range at all time points. No clinically important differences were noted from baseline to 13 weeks.

Mean change from baseline for serum chemistries were reviewed, including creatinine, BUN, calcium, phosphorus, magnesium, ALT, AST, ALP, bilirubin, albumin, protein, carbon dioxide, sodium, potassium, chloride, cholesterol, triglycerides, and glucose. All mean values were within normal range at all time points except cholesterol. Calcium decreased a mean of 0.29 mg/dl and phosphorus a mean of 0.34 mg/dl between baseline and week 13, but these changes were similar between treatment groups, including the approved 35 mg IRBB group. No clinically important differences were noted in any parameter from baseline to 13 weeks.

Twenty four hour urine calcium was performed for subjects in the PK subset only (N=95). An increase was noted in all treatment groups from baseline to Week 12, with the most marked increase of 31% in the approved 35 mg IRBB group, but mean values remained in the normal range.

Shifts: Shift tables were reviewed for hematology, coagulation, and chemistry parameters. No obvious clinically relevant patterns were observed. In the PK subset, 24 hour urinary calcium excretion was > 300 mg at 12 weeks after a normal value at baseline in 4 of 17 subjects in the 35 mg IRBB group, 1 of 18 subjects in the 35 mg DRFB group, 0 of 18 subjects in the 50 mg DRBB group, and 4 of 36 subjects in the 50 mg DRFB group. The DR formulation does not appear to be associated with increased urinary calcium beyond that experienced with the approved IR formulation (note calcium and vitamin D supplementation in all groups).

Vital Signs: Mean vital sign values were normal at all time points for all vital signs tested (BP, HR, and T) in all treatment groups. No clinically significant changes from baseline were seen.

Safety Conclusions: Similar percentages of subjects in the various treatment groups experienced adverse events (AEs), with 53 to 73% of subjects suffering at least 1 AE. Serious adverse events were infrequent, with only 3 reported in 2 subjects (1.1%). Withdrawal for adverse events was also infrequent with 7 (3.9%) reported. The mean

number of AEs per enrolled subject and mean number of AEs per subject with AEs were roughly comparable for the 35 mg IRBB, 35 mg DRFB, and 50 mg DRBB regimens, but both were about 70% higher in the 50 mg DRFB regimen, despite proportion of subjects suffering 1 or more AE being similar. The 50 mg DRFB group did have the highest risedronate absorption which could explain this, but absorption in the 50 mg DRBB group was not much less. The excess noted above under adverse event rates in the mean number of AEs per enrolled subject and mean number of AEs per subject with AEs for the 50 mg DRFB regimen appear to come primarily from the gastrointestinal disorders and nervous system disorders SOCs.

There was a statistically significant increased incidence of diarrhea in the 50 mg groups (DRBB and DRFB regimens) compared to the 35 mg groups (IRBB and DRFB regimens), and a trend toward increased incidence of AEs in abdominal pain and abdominal pain upper in the DR regimens, especially the 50 mg DRFB regimen, compared to the 35 mg IRBB regimen.

Discussion and Conclusions: All the DR regimens (35 mg DRFB, 50 mg DRBB, and 50 mg DRFB) are at least as effective as the approved 35 mg IRBB regimen at reducing the bone turnover markers (BTMs) CTX, NTX, and BSAP, and, in the case of CTX, are more effective. This corresponds with urinary PK data from the PK subset which showed, depending on the statistical analysis used, that absorption from the 35 mg DRFB regimen was 2.0 to 2.5 times higher and the 50 mg DR regimens 2.0 to 3.0 times higher than the 35 mg IRBB regimen.

The mean percent changes from baseline for all the BTMs (CTX, NTX, and BSAP) seen in the 50 mg DRBB regimen were similar to those seen in the 50 mg DRFB regimen, suggesting no food effect. Similar absorption of risedronate from the 50 mg DR regimens in the PK subset appears to confirm a lack of food effect. The absorption seen with the 35 mg DRFB regimen is similar to the predicted absorption of the 35 mg IR formulation given in the fasted state and followed by a 4-hour fast, which is approximately 2-fold higher than when dosed per label. This also supports a lack of food effect.

Data would indicate there may be a subset of subjects ($\leq 10\%$) with poor risedronate absorption from the DR formulation. This may be more common when the drug is taken postprandially and may compromise efficacy. Further analysis of other PK trials will be needed.

A statistically increased incidence of diarrhea in the 50 mg groups (DRBB and DRFB regimens) compared to the 35 mg groups (IRBB and DRFB regimens), a trend to increased incidence of AEs in the HLT Gastrointestinal and abdominal pain in the DRFB regimens (35 mg and 50 mg) compared to the 35 mg IRBB regimen, and a 70% increase in the adverse events per subject with adverse event in the 50 mg DRFB regimen indicate the possibility of increasing safety issues with increased absorption of

risedronate. These issues appear most marked for the 50 mg DRFB regimen, which appears to be the regimen with the highest absorption.

Sponsor concludes that, based on efficacy, pharmacokinetic, and safety results, the 35 mg DRFB regimen is similar to the 35 mg IRBB regimen. From a safety standpoint, in this relatively small trial, this reviewer concurs, but there is substantial evidence for greater absorption by 2.0 to 2.5 times of risedronate with the 35 mg DRFB regimen over the approved 35 mg IRBB regimen. Whether associated safety issues will emerge in a larger and longer trial will be seen. Diarrhea and the high level term gastrointestinal and abdominal pain should especially be reviewed. Bone histomorphometry at high dose will be needed to ensure no bone adverse events.

Bone marker efficacy may translate into bone density (BMD) and fracture effectiveness. The Agency generally does not accept this for regulatory purposes, and the Phase 3 trial will need to show BMD efficacy with relation to a risedronate dose with proven fracture benefit.

Phase 3 Trial:

Study 2007008: A Non-inferiority Comparison of 35 mg Delayed-release Risedronate, Administered Once-weekly Either Before or After Breakfast, and 5 mg Immediate-release Risedronate, Administered Once-daily Before Breakfast, in the Treatment of Postmenopausal Osteoporosis as Assessed Over 2 Years; a Phase III, Multicenter, Double-blind, Double-dummy, Randomized, Active-controlled, Parallel-group Study (Year 1 Final Report)

Objectives: The primary objectives of the study are:

- Assess the non-inferiority of risedronate, administered as a 35 mg delayed release once a week formulation administered immediately following breakfast (DRFB), compared to the 5 mg daily immediate release regimen administered at least 30 minutes before breakfast (IRBB), as determined by the percent change in lumbar spines BMD at Endpoint (last observation carried forward at week 52 [LOCF]).
- If, and only if, the delayed release immediately following breakfast regimen is non-inferior to the immediate release regimen: Assess the non-inferiority 35 mg delayed release once a week formulation administered at least 30 minutes before breakfast (DRBB), compared to the 5 mg daily immediate release regimen administered at least 30 minutes before breakfast (IRBB), as assessed by percent change from baseline in lumbar spine BMD at week 52.

Secondary objectives included:

- Change from baseline in lumbar spine BMD at Endpoint for all risedronate delayed release regimens: DRFB vs. IRBB and DRBB vs. IRBB

- Change and percent change from baseline in lumbar spine BMD at week 26, week 52, week 52-endpoint, week 104, and week 104-endpoint: DRFB vs. IRBB and DRBB vs. IRBB.
- If both DR once-a-week dosing regimens (BB and FB) are shown to be non-inferior to the 5 mg IR daily regimen based on lumbar spine BMD at Endpoint (Week 52), the DR results will be pooled and the superiority of the DR once-a-week regimen to the 5 mg IR daily regimen will be assessed based on percent change from baseline in lumbar spine BMD at Endpoint (Week 52).
- Change and percent change from baseline in bone turnover markers (CTX, NTX, BSAP) at week 13, week 26, week 52, week 52-endpoint, week 104, and week 104-endpoint: DRFB vs. IRBB and DRBB vs. IRBB.
- Change and percent change from baseline in total hip, femoral neck, and greater trochanter BMD at week 26, week 52, week 52-endpoint, week 104, and week 104-endpoint: DRFB vs. IRBB and DRBB vs. IRBB.
- Percentage of responders (subjects with a positive change in lumbar spine BMD) at week 52, week 52-endpoint, week 104, and week 104-endpoint
- Percentage of patients with at least 1 new vertebral body fracture at week 52, week 52-endpoint, week 104, and week 104-endpoint.

Reviewer comment: The Sponsor seeks approval for the delayed release formulation to be taken mornings (b) (4), with approval based on the interim 52 week study report.

Dates: Study initiation, November 12, 2007, study completion date for year 1, May 8, 2009

Study Design: This multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, non-inferiority trial is being conducted at 43 centers in 8 countries in North and South America and the European Union. The second year of the trial is ongoing and continues to be double-blinded.

Postmenopausal osteoporotic women \geq age 50 were randomized 1:1:1 to risedronate 5 mg IRBB daily, 35 mg DRFB weekly, or 35 mg DRBB weekly for 24 months. All subjects are supplemented with 1000 mg of elemental calcium and 800-1000 IU vitamin D throughout the trial. A schedule of trial procedures is given in Table 69. As previously noted only procedures through Visit 7 (Week 52) are included in this report.

Table 69, Trial 2007008 Schedule of Study Procedures

Procedure	Scrn	Baseline	Treatment Period									
	Day:			Week:								
	0	14 ^a	28 ^a	13 ^a	26 ^a	39 ^a	52 ^a	65 ^a	78 ^a	91 ^a	104 ^a	
	Visit			Visit								
	1	2	3	Phone	4	5	6	7	8	9	10	11 (Exit)

Clinical Review
Stephen R. Bienz, MD
NDA 22-560
Atelvia (Risedronate Sodium)

Procedure	Scrn	Baseline		Treatment Period									
		Day:			Week:								
		0	14 ^a	28 ^a	13 ^a	26 ^a	39 ^a	52 ^a	65 ^a	78 ^a	91 ^a	104 ^a	
		Visit			Visit								
	1	2	3	Phone	4	5	6	7	8	9	10	11 (Exit)	
Informed Consent	X												
Medical History	X												
Demographic Data	X												
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	
Physical Examination	X							X				X	
Height	X							X				X	
Weight	X	X			X	X		X				X	
Body Mass Index	X												
Vital Signs ^b	X	X	X		X	X	X	X	X	X	X	X	
ECG	X ^j	X				X ^j		X		X ^j		X	
DXA ^c	X					X		X				X	
X-ray													
Lateral Lumbar, Thoracic Spine	X							X				X	
AP Lumbar Spine	X												
Blood Collection													
Fasting Serum BAP & CTX		X			X	X		X				X	
Serum Chemistry	X	X	X		X	X		X		X		X	
Hematology	X	X			X	X		X		X		X	
Coagulation	X	X			X	X		X		X		X	
FSH & Estradiol ^d	X												
TSH	X												
25(OH) Vitamin D	X												
iPTH (1-84)	X ^j	X	X			X		X				X	
Urine Collection													
Urinalysis	X							X				X	
Urine NTX ^e		X			X	X		X				X	
24-hour Ca/Cr ^f		X						X					
Fecal Occult Blood ^g	X	X			X	X							
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Administer Study Drug		X											
Dispense Study Drug & Ca/Vit D		X			X	X	X	X	X	X	X		
Bone biopsy ^h												X	

a A visit window of ±3 days is allowed for each visit, calculated from baseline visit. If a study visit is scheduled for the day a subject is to take their weekly dose, the subject should not to take their weekly

Procedure	Scrn	Baseline		Treatment Period								
		Day:			Week:							
		0	14 ^a	28 ^a	13 ^a	26 ^a	39 ^a	52 ^a	65 ^a	78 ^a	91 ^a	104 ^a
		Visit			Visit							
	1	2	3	Phone	4	5	6	7	8	9	10	11 (Exit)
<p>dose until after fasting blood samples are obtained</p> <p>b Vital signs will be recorded after sitting 5 minutes and will include blood pressure, pulse rate, and body temperature</p> <p>c Single DXA measurements will be taken at screening and Week 26. DXA measurement in duplicate (patient getting off the DXA table between measurements) will be done at Week 52 and 104</p> <p>d FSH and estradiol to be done for subjects <65 years of age and who have undergone hysterectomy without bilateral oophorectomy to ensure subject is postmenopausal</p> <p>e Second morning void</p> <p>f Urinary calcium/creatinine will be done in a subset of patients</p> <p>g Fecal occult blood collection cards to be dispensed at the screening visit and must be negative prior to performing baseline procedures. Fecal occult blood collection cards to again be dispensed at the Week 13 visit and collected at the Week 26 visit. A colonoscopy should be performed in the event of a positive fecal occult blood test at this visit</p> <p>h Bone biopsies will be performed within 30 days of completion of the Week 104 visit at study centers that are able to perform bone biopsies, in patients who consent to the procedure</p> <p>i ECG and iPTH (1-84) at screening only apply to patients at Argentinean sites</p> <p>j ECGs at these visits apply only to patients at Argentinean sites who showed previously undiagnosed atrial fibrillation, atrial flutter, or tachyarrhythmias at screening</p> <p>Source: Study 2007008 Year 1 Final Report, Table 1</p>												

Population: Subjects are women aged 50 or older, ambulatory, and ≥ 5 years postmenopausal, who had at least 3 evaluable lumbar spine vertebral bodies between L1 and L4, and had osteoporosis.

Inclusion Criteria:

- female, ambulatory, and ≥ 50 years of age
- in generally good health
- postmenopausal (≥ 5 years since last menses, natural or surgical). FSH and estradiol levels for any patient < 65 years of age and who had undergone hysterectomy without bilateral oophorectomy must be respectively ≥ 40 IU/L and ≤ 20 pg/ml (≤ 73 pmol/L)
- at least 3 evaluable lumbar spine vertebral bodies of L1-L4
- met one of the following BMD criteria:
 - lumbar spine BMD (L1-L4) less than 0.772 g/cm² (Hologic) or 0.880 g/cm² (Lunar) or total hip BMD less than 0.637 g/cm² (Hologic) or 0.693 g/cm² (Lunar), corresponding to a T-score < -2.5 SD, or
 - lumbar spine BMD (L1-L4) less than 0.827 g/cm² (Hologic) or 0.940 g/cm² (Lunar) or total hip BMD less than 0.698 g/cm² (Hologic) or 0.756 g/cm² (Lunar), corresponding to a T-score < -2.0, and at least one prevalent vertebral fracture (T4-L4)
- willing and able to provide written informed consent

Exclusion Criteria:

- any previous or ongoing clinically significant illness that could prevent the subject from completing the study
- abuse of alcohol, prescription drugs, or illicit drugs

- any condition or disease that may interfere with the evaluation of lumbar spine BMD as determined in a screening radiograph by a radiologist at the central radiograph facility
- bilateral hip prostheses
- history of hyperparathyroidism, unless surgically corrected and with normal serum calcium levels for at least 12 months prior to enrollment (Exception: Subjects at Argentinean sites must have had an iPTH value at screening of ≤ 65 pg/ml, with an albumin-adjusted serum calcium value that was within the central laboratory reference range)
- uncontrolled hyperthyroidism or ongoing osteomalacia at the time of enrollment
- any history of cancer within the past 5 years, except for basal cell carcinoma or dermal squamous cell carcinoma with documented 6-month remission or successfully treated cervical carcinoma in situ with a documented 12-month remission
- body mass index (BMI) of >32 kg/m²
- a known allergy or intolerance to bisphosphonates or excipients in any of the formulations
- used intravenous bisphosphonates within the 12-month period prior to the first dose of study drug
- used (even 1 dose) of any the following medications within 3 months of the first dose of study drug or use of these medications for more than 1 month at any time between 3 and 6 months prior to the first dose of study drug:
 - Anabolic steroids
 - Estrogens (oral, skin patch, or gel), selective estrogen-receptor modulators (SERMs), or estrogen-related drugs, except for low dose vaginal creams, tablets, or an insertable estrogen ring (≤ 0.2 mg per day 17- β estradiol or ≤ 1.5 mg per day estropipate)
 - Progestins
 - Calcitonin
 - Vitamin D supplements (> 1200 IU per day)
 - Calcitriol, calcidiol, or alfacalcidol at any dose
 - Any bisphosphonate
 - Fluoride (≥ 10 mg per day)
 - PTH (1-84) and teriparatide (1-34)
 - Products in the phytoestrogen or isoflavone classes
 - Investigational bone active agents
- glucocorticoid use that met any of the following criteria:
 - continuous daily use of oral glucocorticoids at doses of ≥ 5 mg/day prednisone (or equivalent) for more than 1 month within the 3-month period prior to the first dose of study drug
 - used oral glucocorticoids in excess of a total of 150 mg prednisone (or equivalent) for 1 month within the 3-month period prior to the first dose of study drug
 - used intravenous or intramuscular glucocorticoids (at any dose) within the 3-month period prior to the first dose of study drug. Note: The use of intra-articular or epidural treatments were permissible, as were inhaled glucocorticoids taken at labeled doses for pulmonary conditions
- depot injection $> 12,000$ IU vitamin D in the past 9 months
- abnormal clinical laboratory results that were assessed as clinically significant by the Investigator
- creatinine clearance of < 30 ml/min, calculated using the Cockcroft & Gault formula at screening
- diagnosis of hypocalcemia or hypercalcemia from any cause, or a calcium value outside of the central laboratory reference range at screening. If the initial screening calcium value was outside of the reference range, patients may have undergone 1 additional retest; (Exception: Patients at Argentinean sites must have had an albumin-adjusted serum calcium value within the central laboratory reference range at screening. If the initial screening albumin-adjusted calcium value was outside of the reference range, patients may have undergone 1 additional retest)
- serum thyroid stimulating hormone (TSH) value outside the permissible range (less than the lower limit of normal or greater than twice the upper limit of normal). At screening, if a patient was

on thyroid hormone replacement therapy, the dose must have been stable for at least 6 weeks prior to randomization and the TSH value must have been within the normal range.

- serum 25-hydroxy vitamin D level < 12 ng/ml (30 nmol/L) at screening. Note: subjects who presented with a low (< 12 ng/ml [30 nmol/L]) serum 25-hydroxy vitamin D value at the initial screening may have received 4 to 6 weeks of vitamin D supplementation and undergone 1 additional re-test
- participation in another clinical trial 30 days prior to screening
- receipt, or planned receipt, of any other investigational drug or device, or participation in any other research study, during the course of this study
- lumbar spine BMD less than 0.497 g/cm² (Hologic) or 0.580 g/cm² (Lunar), corresponding to a T-score < -5.0
- used any anticonvulsant within 1 month prior to the first dose of study drug or used for more than 1 month within a 6-month period prior to the first dose of study drug
- a positive result from the screening fecal occult blood testing
- history of inflammatory bowel disease, malabsorption, or sprue
- used (even 1 dose) of strontium (≥ 50 mg/day) within 6 months prior to the first dose of study drug or for more than 3 months at any time in the past 10 years

Reviewer comment: Inclusion and exclusion criteria appear adequate.

Study Medication: Subjects took a 5mg IR risedronate tablet (active control, approved product) or placebo daily at least 30 minutes before breakfast. Once a week, in addition, a 35 mg DR risedronate or placebo was taken with the 5 mg IR risedronate/placebo before breakfast and a 35 mg DR risedronate or placebo was taken immediately after breakfast. Only one of the three regimens was an active tablet for each subject.

All tablets were taken with at least 4 oz/120 ml plain water per tablet with the subject in an upright position. The patient was instructed not to lie down for at least 30 minutes after dosing. At the baseline visit only, the first day's dose (2 tablets before breakfast and 1 immediately following breakfast) was taken in the presence of site personnel.

Reviewer comment: Currently approved risedronate IR formulations are to be taken with 6-8 oz. of plain water at least 30 minutes before the first food or drink of the day. Patients are not to lie down for 30 minutes after dosing. The amount of water used in this trial (4 oz.) is less than the labeled amount.

Missed doses were to be resumed with the skipped tablet(s) when remembered without taking more than one day's dose(s) on a single day. Day one of each week was to be the day the two weekly tablets were taken in addition to the daily tablet.

The DR formulation consists of risedronate with (b) (4) edetate disodium dihydrate (EDTA) with an enteric coating designed to release the components at pH 5.5. The EDTA (b) (4)

All subjects are being supplemented with 1000 mg of elemental calcium and 800-1000 IU vitamin D throughout the trial. These were not to be taken at the same time of day as study medications. They are procured and supplied locally by the study center and are not subjected to study drug accountability procedures.

Efficacy Measures

Primary Efficacy Endpoint: The change in lumbar spine BMD over 52 weeks comparing risedronate 35 mg DR weekly (following and then, if successful, before breakfast) to 5 mg IR daily (before breakfast) with last observation carried forward (LOCF) for non-inferiority.

Secondary Efficacy Endpoints: The efficacy of risedronate 35 mg DR weekly (following and before breakfast) compared to risedronate 5 mg IR daily (before breakfast) for:

- DXA measurements of lumbar spine and proximal femur (total hip, femoral neck, and trochanter) acquired at baseline to Weeks 26, 52, and week 52-endpoint
- If both DR weekly dosing regimens are shown to be non-inferior to the 5 mg IR daily regimen based on lumbar spine BMD at Week 52, the DR results will be pooled and the superiority of the DR once-a-week regimen to the 5 mg IR daily regimen will be assessed based on percent change from baseline in lumbar spine BMD at Week 52
- Percentage of responders (i.e., subjects who show a positive change in lumbar spine BMD from baseline) at Week 52
- Vertebral fractures assessed by semiquantitative analysis of lateral thoracic and lumbar spine radiographs (Genant Scoring Method) collected at screening to Week 52
- Urine NTX, serum CTX, and serum BAP assessed at baseline to Weeks 13, 26, and 52

Safety Measures:

- AEs
- Safety laboratory data
- ECG
- Vital signs
- Physical examination

Reviewer comment: In general, safety measures appear adequate. It is unclear if the anticipated calcium nadir is captured as calcium measurements near nadir are done at 2 and 13 weeks, with the nadir anticipated at several weeks.

Study Methods: This is an outpatient trial

Withdrawal criteria:

- Adverse event severe enough to warrant study drug withdrawal
- Subject voluntarily withdrew
- Subject was unblinded for any reason.

Subjects who were withdrawn from the study after administration of the first dose of study drug were not replaced.

Any subject who was withdrawn from the study was to have all Week 104 (exit) procedures performed if possible. If subjects withdrew within the first 3 months, DXA and spine x-ray were not performed unless a clinical vertebral fracture was suspected. Exit visit DXA, x-rays, and BTMs were also not performed for subjects who had these study assessments done within 3 months of termination.

All abnormal laboratory values that were considered clinically significant were repeated and followed until resolution or stabilization. A fecal occult blood sample was obtained from subjects who withdrew from the study before the fecal occult blood samples to be obtained at the Week 26 visit.

Subjects who experienced a serious AE or other AE that required follow-up remained under medical supervision until the AE resolved or stabilized. Any follow-up laboratory assessments were performed at a local laboratory.

Statistical Analyses: Three populations were defined for the 52 week statistical analysis:

- The intent-to-treat (ITT) population included all subjects who were randomized and took at least one dose of study medication. All safety assessments were analyzed based on the ITT population
- The primary efficacy (PE) population included all subjects who were randomized, received at least 1 dose of study drug, and had analyzable lumbar spine BMD data at both baseline and Week 52 or another post-baseline time (LOCF) (or other efficacy measure). This population was used for the primary efficacy analysis and for the superiority test of the DR regimens. It appears Sponsor used this population for secondary efficacy analysis if the appropriate post-baseline measure were available, rather than the entire ITT population as noted in the study report.
 - The per-protocol (PP) population included all subjects in the ITT population who had no major protocol deviations. The PP population was used to check the robustness of the non-inferiority analysis at Week 52.

For the primary analysis, in hierarchal order the percent change from baseline in lumbar spine BMD of the 35 mg DRFB regimen was compared to the 5 mg IRBB regimen. If non-inferiority was found, 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 was 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.

Reviewer comment: The non-inferiority margin of 1.0 to 1.5% has been used for bisphosphonate trials. For prior risedronate trials (35 mg once-a-week, 75 mg on 2 consecutive days per month, and 150 mg once-a-month), the non-inferiority margin has been 1.5%. A 95% *one-sided* CI, which is tighter than the current protocol 95% 2-sided CI, was used for the 35 mg weekly dose, but the 95% 2-sided CI was used for the monthly and twice monthly dosing trials. This non-inferiority margin and CI could be argued and the more stringent values insisted on but, given the known high absorption of the risedronate 35 mg DR regimens, this reviewer expects overall efficacy not to be an issue.

If both 35 mg DR regimens were found non-inferior to the 5 mg IR regimen, an assessment of the superiority of the 35 mg DR once-a-week regimens (pooled data) to the 5 mg IR daily regimen, based on the percent change in lumbar spine BMD at Endpoint, was performed.

All secondary efficacy variable analyses were based on the ITT population (all patients who were randomized and took at least one dose of study drug). For the continuous secondary efficacy variables, ANOVA was performed with treatment, anticoagulant use, and pooled center as fixed effects, except for lumbar spine BMD, where baseline lumbar spine BMD were added to the model to be consistent with the primary endpoint analysis. No adjustments for multiple comparisons were performed for the secondary efficacy analyses.

The focus of AE reporting and summarization was on treatment-emergent adverse events (TEAEs). Nominal p-values from Fisher's Exact Test for categorical results were provided in the summary tables to facilitate review.

Protocol Amendments: There were 3 amendments to this protocol.

Protocol Amendment 1, dated October 30, 2007, made the following changes:

- Corrected BMD values for total hip BMD in the inclusion criteria to correspond to desired T-scores.
- Modified the exclusion criteria to include investigational bone active agents.
- Increased the time period between strontium use and the first dose of study drug.
- Removed exclusion criterion for subjects who previously (within 4 months) used proton pump inhibitors (PPIs).

- Modified screening procedures to add BMD values for total hip.
- Added anticoagulant use as a fixed effect to the analysis of variance model for the primary and secondary efficacy analyses.

Protocol Amendment 2, dated February 14, 2008, was a country-specific amendment for study centers in Argentina as requested by the Argentinean Ministry of Health, and included the following:

- Modified the exclusion criteria to include a cut-off value for intact parathyroid hormone (iPTH) at ULN. This change necessitated adding an iPTH at the Screening visit.
- Modified the exclusion criteria to use albumin-adjusted serum calcium values to determine eligibility instead of serum calcium.
- Added an electrocardiogram (ECG) assessment to the Screening visit. In addition, for subjects who showed previously undiagnosed atrial fibrillation, atrial flutter, or tachyarrhythmias on the screening ECG, the site cardiologist must have approved the subject's participation in the study after the screening ECG, and the subject was to undergo ECGs at 6 month intervals during the study.

Protocol Amendment 3, dated May 19, 2009, made the following changes:

- Added an additional vendor (b) (4), to read and interpret spinal x-ray results, including re-evaluation of x-rays for all subjects who were randomized into the study, which were previously evaluated by the original vendor. Analysis of the secondary endpoint of new vertebral body fractures will be based solely on the (b) (4) evaluations. Sponsor submitted this protocol amendment to the Agency on May 20, 2009 (IND 74,086), documenting problems with readings and procedures at the original vendor.
- Added sample storage and archiving plans for bone biopsies. Also further clarified that biopsies will be performed only in patients who consent.
- Corrected spelling, formatting, and administrative errors.

Results

Patient Disposition: As outlined in Table 70, a total of 1859 subjects were screened and 923 subjects were randomized into Trial 2007008. 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%, 5 mg IRBB daily; 18%, 35 mg DRFB; 16%, 35 mg DRBB). The most common reasons for discontinuation were AE (8%, 5 mg IRBB daily; 9%, 35 mg DRFB; 5%, 35 mg DRBB) and voluntary withdrawal (7%, 5 mg IRBB daily; 8%, 35 mg DRFB; 8%, 35 mg DRBB). Reasons for voluntary withdrawal included personal reasons/problems, unwillingness to continue, unwillingness to take study medication as directed, and advice of family. The voluntary withdrawal category that included the highest number of patients was the "personal

reasons/problems” category (34 of 73 (47%)). Of the subjects who withdrew voluntarily, 10 in the 5 mg IRBB daily group (3%), 6 in the 35 mg DRFB group (2%), and 12 in the 35 mg DRBB group (4%) had an ongoing adverse event at the time of withdrawal.

Table 70, Trial 2007008 Subject Disposition, ITT Population

Parameter Category	5 mg IRBB Daily (N=307) n (%)	35 mg DRFB Weekly (N=307) n (%)	35 mg DRBB Weekly (N=308) n (%)	p-value*
Status				
Completed 52 weeks	257 (83.7%)	252 (82.1%)	258 (83.8%)	0.8361
Continued in Study, No Week 52 Visit	0 (0.0%)	0 (0.0%)	1 (0.3%)	1.0000
Discontinued on/prior to Week 52	50 (16.3%)	55 (17.9%)	49 (15.9%)	0.7735
Discontinuation Reason				
Adverse Events	25 (8.1%)	28 (9.1%)	16 (5.2%)	0.1450
Investigator Discretion	0 (0.0%)	0 (0.0%)	3 (1.0%)	0.1104
Lost to Follow-up	3 (1.0%)	2 (0.7%)	4 (1.3%)	0.9138
Voluntary Withdrawal	22 (7.2%)	25 (8.1%)	26 (8.4%)	0.8634
(Voluntary WD with ongoing AE)	10 (3.3%)	6 (2.0%)	12 (3.9%)	
Analysis Populations				
Intent-to-treat	307	307	308	
Primary Efficacy	270 (87.9%)	261 (85.0%)	271 (88.0%)	
Per-protocol	222 (72.3%)	217 (70.7%)	213 (69.2%)	
* Fisher's Exact Test				
Source: Study 2007008 Year 1 Final Report, Tables 2, 3, and datasets				

Protocol Violations: Major protocol violations are defined as:

- Subjects without evaluable lumbar spine BMD at baseline or at Week 52 due to any reason, including:
 - Missing data
 - Images not analyzable by the central DXA facility or x-ray not available for confirmation
 - Baseline lumbar spine BMD or x-ray measured more than 90 days prior to date of first dose
- Subjects who do not meet an inclusion or exclusion criterion
- Subjects who are unblinded up to and including the Week 52 visit
- Subjects who receive and take study drug not in accordance with randomization allocation any time through Week 52 visit
- Subjects who are less than 80% compliant with study drug for any of the dosing regimens (including any missing returns) during the first 52 weeks of treatment for Year 1
- Subjects who take pre-specified protocol-forbidden medications in significant bone-active quantities
- Subjects who had laboratory changes during the course of the study indicating hypercalcemia or possible metabolic bone disorder

The percent of subjects with protocol-defined major protocol violations was similar across the 3 groups (28%, 5 mg IRBB daily; 29%, 35 mg DRFB; 31%, 35 mg DRBB) as shown in Table 71. The most common major protocol violations were “no valid lumbar spine BMD percent change at Week 52” and “duration of exposure less than required”.

Table 71, Trial 2007008 Major Protocol Violations

Category	5 mg IRBB Daily n (%)	35 mg DRFB Weekly n (%)	35 mg DRBB Weekly n (%)
Subjects with Major Protocol Violation	85 (27.7%)	90 (29.3%)	95 (30.8%)
Violation*			
No Valid LS BMD % Change at Week 52	55 (17.9%)	60 (19.5%)	54 (17.5%)
Did Not meet Inclusion/Exclusion Criteria	17 (5.5%)	19 (6.2%)	21 (6.8%)
Took Excluded Medications	4 (1.3%)	6 (2.0%)	11 (3.6%)
Took Incorrect Study Medication	2 (0.7%)	1 (0.3%)	1 (0.3%)
< 80% Compliant with Daily Doses	16 (5.2%)	12 (3.9%)	25 (8.1%)
< 80% Compliant with Weekly BB Doses	16 (5.2%)	11 (3.6%)	21 (6.8%)
< 80% Compliant with Weekly FB Doses	16 (5.2%)	10 (3.3%)	22 (7.1%)
Lab Changes Indicate Metabolic Bone Disorder	7 (2.3%)	14 (4.6%)	11 (3.6%)
Duration of Exposure less than Required	50 (16.3%)	49 (16.0%)	45 (14.6%)
*Subjects could be excluded for more than one violation See text (Statistical Analysis) for population definitions Source: Study 2007008 Year 1 Final Report, Table 3			

Demographics: Demographic and baseline characteristics were balanced across treatment groups and are shown for the ITT population in Table 72. Fifteen percent of subjects were enrolled at US sites. Overall, 99.5% of patients were Caucasian, the mean age at screening was 66 years, and the mean number of years since menopause was 18. The mean baseline 25-hydroxy vitamin D level was 69.8 nmol/L (28 ng/mL). 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.

Table 72, Trial 2007008 Demographic and Baseline Characteristics, ITT Population

Parameter Statistic/Category	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)	Overall (N=922)	p- value
Age (years) at Screening Mean (SD) Min, Max	65.3 (7.4) 50.0, 84.0	65.8 (7.4) 50.0, 87.0	66.0 (7.5) 50.0, 83.0	65.7 (7.4) 50.0, 87.0	0.4818
Race Asian (Oriental) Caucasian	1 (0.3%) 306 (99.7%)	1 (0.3%) 305 (99.3%)	0 (0.0%) 306 (99.4%)	2 (0.2%) 917 (99.5%)	0.8512

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Hispanic Multi-Racial	97 (31.6%) 0 (0.0%)	96 (31.3%) 1 (0.3%)	96 (31.2%) 2 (0.6%)	289 (31.3%) 3 (0.3%)	
Years Since Menopause Mean (SD) Min, Max	17.5 (8.6) 5.0, 49.0	18.2 (8.0) 5.0, 52.0	18.8 (8.5) 5.0, 46.0	18.2 (8.4) 5.0, 52.0	0.1931
Body Mass Index (kg/m ²) Mean (SD)	25.5 (3.4)	25.0 (3.5)	25.3 (3.4)	25.3 (3.4)	0.2879
Creatinine Clearance Mean (SD) Min, Max	73.0 (18.7) 39.6, 142.0	71.2 (17.2) 34.0, 135.5	70.4 (16.3) 22.4, 142.4	71.6 (17.4) 22.4, 142.4	0.1600
Serum 25(OH) Vitamin D Mean (SD) (nmol/L) Min, Max	69.8 (24.0) 17.5, 162.2	70.4 (26.7) 15.0, 257.1	69.3 (24.4) 15.0, 172.2	69.8 (25.0) 15.0, 257.1	0.8568
Height (cm) Mean (SD)	157.3 (6.1)	156.6 (6.3)	156.8 (6.2)	156.9 (6.2)	0.3913
T-score for Lumbar Spine n Mean (SD) Min, Max	273 -3.12 (0.52) -4.9, -1.7	268 -3.11 (0.58) -4.7, 1.0	262 -3.11 (0.56) -4.8, -1.6	803 -3.11 (0.56) -4.9, 1.0	0.9723
T-score for Proximal Femur n Mean (SD) Min, Max	307 -2.96 (1.44) -5.7, 0.6	307 -2.95 (1.32) -6.2, 0.1	308 -2.94 (1.39) -6.0, 0.9	922 -2.95 (1.38) -6.2, 0.9	0.9873
Known Fracture Status n At Least 1 Prevalent Vertebral Fracture	291 70 (24.1%)	287 81 (28.2%)	299 87 (27.1%)	877 238 (27.1%)	0.3396
Source: Study 2007008 Year 1 Final Report, Tables 5, 6, and 7					

Reviewer comment: Sponsor does not explain the large number of subjects without available baseline lumbar spine T-scores (119), although only 6 subjects are missing lumbar spine DXA bone densities (available for 304 subjects in the 5 mg IRBB group, 304 subjects in the 35 mg DRFB group, and 308 subjects in the 35 mg DRBB group). The probable explanation is found in Appendix 13.2.6 listing 1, a BMD listing, where is stated “The calculation of lumbar spine T-score was only applied when all 4 lumbar spine vertebrae were intact.” Presumably, only T-scores for lumbar spines with all vertebrae 1 to 4 evaluable (e.g., without fracture, marked sclerosis) are listed in Table 72.

Similarly unexplained is the large number of subjects with baseline vertebral fracture status unknown (45). As records for baseline spine radiographs were found in the dataset for all subjects, subjects with unknown fracture status apparently are those who’s baseline spinal radiographs were read as indeterminate as to fracture status.

Concomitant Medications: The most common concomitant medications used by ≥ 10% of subjects in any treatment group, as well as other medications which may have

an effect on bone or risedronate DR absorption, are listed in Table 73. Statins were more used in the DR populations and NSAIDs in the IR and 35 mg DRFB groups but, generally, concomitant medication use was similar across treatment groups.

Table 73, Trial 2007008 Concomitant Medications (Therapeutic Class) used by ≥ 10% of Subjects in any Treatment Group and other Pertinant Medications

Therapeutic Class	5 mg IRBB Daily (N=307) n (%)	35 mg DRFB Weekly (N=307) n (%)	35 mg DRBB Weekly (N=308) n (%)
Overall	307 (100.0%)	307 (100.0%)	307 (99.7%)
Vitamin D and Analogues	307 (100.0%)	307 (100.0%)	307 (99.7%)
Calcium	307 (100.0%)	307 (100.0%)	307 (99.7%)
NSAIDs	125 (40.7%)	124 (40.4%)	99 (32.1%)
Salicylic Acid and Derivatives	57 (18.6%)	57 (18.6%)	57 (18.5%)
Beta Blocking Agents	60 (19.5%)	60 (19.5%)	77 (25.0%)
Ace-Inhibitors	50 (16.3%)	61 (19.9%)	70 (22.7%)
Hmg Coa Reductase Inhibitors	39 (12.7%)	56 (18.2%)	65 (21.1%)
Benzodiazepine Derivatives	54 (17.6%)	56 (18.2%)	63 (20.5%)
Antiinflammatory Products for Vaginal Administrat.	58 (18.9%)	53 (17.3%)	46 (14.9%)
Other Agents for Local Oral Treatment	52 (16.9%)	52 (16.9%)	54 (17.5%)
Acetaminophen, other Anilides	44 (14.3%)	44 (14.3%)	52 (16.9%)
Calcium Channel Blockers	46 (15.0%)	51 (16.6%)	46 (14.9%)
Proton Pump Inhibitors	31 (10.1%)	32 (10.4%)	36 (11.7%)
Thiazide Diuretics	24 (7.8%)	18 (5.9%)	28 (9.1%)
H2 Receptor Antagonists	27 (8.8%)	26 (8.5%)	22 (7.1%)
Corticosteroids, Systemic	15 (4.9%)	17 (5.5%)	21 (6.8%)
SSRIs	9 (2.9%)	8 (2.6%)	14 (4.5%)

Efficacy

Primary Efficacy Outcomes: The mean percent change from baseline in lumbar spine was the primary efficacy outcome. All three dosing regimens increased lumbar spine BMD significantly from baseline to Endpoint in the primary efficacy population, as shown in Table 74. The mean percent change from baseline in lumbar spine BMD was 3.1% for the 5 mg IRBB group and 3.4% for both the 35 mg DRFB group and 35 mg DRBB group.

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

Supportive analyses for percent change from baseline in lumbar spine BMD using a PP population and Week 52 time point were consistent with the primary analysis.

Table 74, 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	270	261	271
Least Squares Mean (g/cm ²)	0.757	0.758	0.758
Endpoint (52 weeks, LOCF)			
n	270	261	271
Arithmetic Mean (%) (SD)	3.112 (3.487)	3.369 (3.161)	3.404 (3.621)
LS Mean (%Δ from baseline)	3.118*	3.352*	3.414*
95% CI	2.710, 3.526	2.936, 3.767	3.007, 3.822
LS Mean Difference Compared to 5 mg IRBB		-0.233	-0.296
95% CI		-0.816, 0.349	-0.873, 0.281
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. P-values are not given by the Sponsor Source: Study 2007008 Year 1 Final Report, Table 11			

It should be noted that the lumbar spine BMD increase achieved in the 5 mg IRBB 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.

There were no treatment by pooled center (centers were pooled by country), or treatment by age interactions noted.

Secondary Efficacy Outcomes:

Bone Mineral Density:

Table 75 compares DXA measurements of lumbar spine and proximal femur (total hip, femoral neck, and trochanter) acquired at baseline with Weeks 26, 52, and Endpoint (Week 52 with LOCF) for the ITT population. Statistically significant BMD increases are noted at all post-baseline time-points for all sites. 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.

Table 75, Trial 2007008 BMD, % Change from Baseline, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
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Lumbar Spine			
Baseline n	304	304	308
LS Mean (g/cm ²)	0.757	0.759	0.758
Week 26 n	265	257	267
LS Mean (% change from baseline)	2.751*	2.854*	2.566*
95% CI	2.364, 3.139	2.460, 3.248	2.180, 2.952
LS Mean Difference from IR		-0.102	0.185
95% CI		-0.655, 0.451	-0.362, 0.733
Week 52 n	253	247	254
LS Mean (% change from baseline)	3.169*	3.359*	3.470*
95% CI	2.751, 3.586	2.937, 3.781	3.053, 3.887
LS Mean Difference from IR		-0.190	-0.301
95% CI		-0.784, 0.404	-0.891, 0.290
Endpoint n	270	261	271
LS Mean (% change from baseline)	3.118*	3.352*	3.414*
95% CI	2.710, 3.526	2.936, 3.767	3.007, 3.822
LS Mean Difference from IR		-0.233	-0.296
95% CI		-0.816, 0.349	-0.873, 0.281
Total Hip			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.760	0.761	0.762
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.613*	1.748*	1.685*
95% CI	1.354, 1.872	1.486, 2.010	1.426, 1.943
LS Mean Difference from IR		-0.135	-0.072
95% CI		-0.504, 0.234	-0.437, 0.294
Week 52 n	258	256	258
LS Mean (% change from baseline)	1.872*	2.201*	2.160*
95% CI	1.589, 2.154	1.917, 2.485	1.878, 2.443
LS Mean Difference from IR		-0.329	-0.289
95% CI		-0.730, 0.071	-0.688, 0.111
Endpoint n	279	274	280
LS Mean (% change from baseline)	1.785*	2.073*	2.075*
95% CI	1.508, 2.062	1.793, 2.352	1.799, 2.352
LS Mean Difference from IR		-0.288	-0.290
95% CI		-0.682, 0.106	-0.681, 0.101
Femoral Neck			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.687	0.687	0.689
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.120*	1.385*	1.246*
95% CI	0.792, 1.447	1.053, 1.716	0.920, 1.572
LS Mean Difference from IR		-0.265	-0.126
95% CI		-0.731, 0.201	-0.588, 0.336
Week 52 n	258	256	258
LS Mean (% change from baseline)	1.215*	1.554*	1.779*
95% CI	0.876, 1.554	1.214, 1.895	1.440, 2.118
LS Mean Difference from IR		-0.339	-0.563
95% CI		-0.820, 0.142	-1.043, -0.083
Endpoint n	279	274	280
LS Mean (% change from baseline)	1.180*	1.507*	1.717*
95% CI	0.853, 1.507	1.177, 1.838	1.390, 2.044

LS Mean Difference from IR 95% CI		-0.327 -0.793, 0.138	-0.537 -1.000, -0.074
Trochanter			
Baseline n	307	307	308
LS Mean (g/cm ²)	0.597	0.595	0.598
Week 26 n	273	267	275
LS Mean (% change from baseline)	1.900*	2.148*	2.164*
95% CI	1.470, 2.329	1.713, 2.583	1.736, 2.592
LS Mean Difference from IR		-0.249	-0.265
95% CI		-0.860, 0.363	-0.871, 0.342
Week 52 n	258	256	258
LS Mean (% change from baseline)	2.358*	2.925*	2.880*
95% CI	1.917, 2.800	2.482, 3.368	2.439, 3.322
LS Mean Difference from IR		-0.566	-0.522
95% CI		-1.192, 0.059	-1.147, 0.103
Endpoint n	279	274	280
LS Mean (% change from baseline)	2.186*	2.732*	2.764*
95% CI	1.746, 2.625	2.288, 3.175	2.326, 3.203
LS Mean Difference from IR		-0.546	-0.579
95% CI		-1.170, 0.078	-1.199, 0.042
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons			
Source: Study 2007008 Year 1 Final Report, Tables 13, 15, 16, and 17			

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. Results are shown in Table 76. 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. A p-value for the difference (0.2992) which is not significant confirms statistical equality given the limits of this trial.

Table 76, Trial 2007008 Lumbar Spine BMD, % Change from Baseline, Combined DR Treatment Groups, PE Population

	5 mg IRBB Daily (N=307)	35 mg DRFB+DRBB Weekly (N=615)
Baseline n	270	532
Least Squares Mean (g/cm ²)	0.757	0.758
Endpoint (52 weeks, LOCF) n	270	532
Least Squares Mean (%)	3.118*	3.383*
95% CI	2.710, 3.526	3.093, 3.674
LS Mean Difference		-0.265
95% CI		-0.766, 0.236
P-value		0.2992

* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons
 Source: Study 2007008 Year 1 Final Report, Table 12

Treatment Responders:

Approximately 82-87% of subjects were considered as treatment responders with a positive change from baseline in lumbar spine BMD at Week 52 and Endpoint, as shown in Table 77. Although slightly higher percentages responded in the DR treatment groups as compared to the IR group, the differences were not statistically significant.

Table 77 Trial 2007008 Response to Treatment (> 0% Change from Baseline in Lumbar Spine BMD), ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Week 52 n	253	247	254
Responder	208 (82.2%)	216 (87.4%)	218 (85.8%)
Non-responder	45 (17.8%)	31 (12.6%)	36 (14.2%)
Relative Risk (95%CI)		1.06 (0.99, 1.15)	1.04 (0.97, 1.13)
p-value		0.1072	0.2777
Endpoint n	270	261	271
Responder	221 (81.9%)	228 (87.4%)	231 (85.2%)
Non-responder	49 (18.1%)	33 (12.6%)	40 (14.8%)
Relative Risk (95%CI)		1.07 (0.99, 1.15)	1.04 (0.97, 1.12)
p-value		0.0926	0.2989

Source: Study 2007008 Year 1 Final Report, Table 14

Vertebral Fractures:

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 first 52 weeks of the trial was small and similar across all treatment groups, as indicated in Table 78. All 7 patients experienced only 1 new vertebral fracture. This trial was not powered for fracture endpoints.

Table 78, Trial 2007008 Incidence of New Morphometric Vertebral Fractures, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Week 52 n	254	253	257
≥ 1 New Fractured Vertebra	2 (0.8%)	2 (0.8%)	3 (1.2%)
No New Fractured Vertebra	252 (99.2%)	251 (99.2%)	254 (98.8%)
Relative Risk (95%CI)		1.00 (0.14, 7.07)	1.48 (0.25, 8.80)
p-value		1.0000	1.0000
Endpoint n	270	261	271
≥ 1 New Fractured Vertebra	2 (0.7%)	2 (0.8%)	3 (1.1%)
No New Fractured Vertebra	268 (99.3%)	259 (99.2%)	268 (98.9%)
Relative Risk (95%CI)		1.03 (0.15, 7.29)	1.49 (0.25, 8.87)

p-value		1.0000	1.0000
Source: Study 2007008 Year 1 Final Report, Table 21			

Clinical fractures were reported as adverse events.

Clinical Fractures Reported as Adverse Events: Clinical fractures reported as AEs included all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures and are shown in Table 79. A total of 27 subjects reported clinical fractures as AEs (6 [2.0%] subjects, 5 mg IRBB; 9 [2.9%] subjects, 35 mg DRFB; 12 [3.9%] subjects, 35 mg DRBB, p=0.3799). Although numerically more subjects in the DR regimens suffered clinical fractures, this difference did not reach statistical significance. Numerically more subjects in the DR regimens suffered radial fractures but again this did not reach statistical significance (1 [0.3%] subject, 5 mg IRBB; 5 [1.6%] subjects, 35 mg DRFB; 4 [1.3%] subjects, 35 mg DRBB, p=0.3024). Overall, fracture types appear similar between groups.

Reviewer comment: Even though not statistically significant, greater numbers of clinical fractures in the DR regimens concern this reviewer about disordered bone apposition with the higher risedronate exposure. Adequate bone biopsy information is needed.

Table 79, Trial 2007008 All Clinical Fractures Reported as AEs, ITT Population

All Fractures 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
All Fractures	6 (2.0%) 7	9 (2.9%) 11	12 (3.9%) 15	0.3799
Radius fracture	1 (0.3%) 1	5 (1.6%) 5	4 (1.3%) 5	0.3024
Hip fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Humerus fracture	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Patella fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Pelvic fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Rib fracture	0 (0.0%) 0	1 (0.3%) 1	2 (0.6%) 2	0.7771
Ulna fracture	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Ankle fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Clavicle fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Femur fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Fibula fracture	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hand fracture	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2	1.0000
Spinal compression fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Stress fracture	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2	1.0000
Thoracic vertebral fracture	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Tibia fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
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 33				

A listing of clinical fractures in the various treatment groups is given below.

- 5 mg IRBB Treatment Group
 - 75 year old Caucasian female with left tib-fib fracture in fall from ladder on study day (b) (6)
 - 66 year old Caucasian female with left distal radius fracture in fall on study day (b) (6)
 - 73 year old Caucasian female with left distal femur fracture in fall on study day (b) (6)
 - 79 year old Caucasian female with T12 compression fracture in fall on study day (b) (6)
 - 72 year old Caucasian female with left clavicle fracture in fall on study day (b) (6)
 - 72 year old Caucasian female with right ankle fracture in fall (different subject) on study day (b) (6)
- 35 mg DRFB Treatment Group
 - 62 year old Caucasian female with left distal radius fracture in fall from bus step on study day (b) (6)
 - 68 year old Caucasian female with right rib fracture (unconfirmed) from seat belt in MVA on study day (b) (6)
 - 67 year old Caucasian female with left radius and ulna fracture in fall on study day (b) (6)
 - 76 year old Caucasian female with left distal radius fracture in fall on study day (b) (6)
 - 78 year old Caucasian female with left femoral neck and left proximal humerus fractures in fall on study day (b) (6)
 - 71 year old Caucasian female with left radial fracture in fall on study day (b) (6)
 - 69 year old Caucasian female with right distal radius fracture in fall on study day (b) (6)
 - 58 year old Caucasian female with right patellar fracture in fall on study day (b) (6)
 - 71 year old Caucasian female with pelvic fracture (left os pubis) in fall on study day (b) (6)
- 35 mg DRBB Treatment Group
 - 67 year old Caucasian female with bilateral distal radial fractures in fall on study day (b) (6)
 - 68 year old Caucasian female with left distal radial fracture in fall on study day (b) (6)
 - 67 year old Caucasian female with left second and fourth finger fractures in fall on study day (b) (6)
 - 82 year old Caucasian female with right seventh rib fracture, no stated etiology, on study day (b) (6)
 - 70 year old Caucasian female with unconfirmed stress fractures of the right second metatarsal and third cuneiform, no stated etiology, on study day (b) (6)
 - 64 year old Caucasian female with left distal radius fracture in fall on study day (b) (6)

- 64 year old Caucasian female with left distal fibular fracture in fall (different subject) on study day (b) (6)
- 77 year old Caucasian female with proximal right humerus fracture in fall on study day (b) (6)
- 74 year old Caucasian female with distal right radial fracture in fall on study day (b) (6)
- 73 year old Caucasian female with right sixth rib fracture in fall on study day (b) (6)
- 2 clinical thoracic vertebral fractures in 2 subjects are not reported in Study 2007008 Year 1 Final Report, Appendix 13.2.7, Listing 5, Clinical Fracture. Listing 1 of the same appendix (Treatment Emergent Adverse Events) reports a 75 year old Caucasian female suffered worsening of a T8 fracture on study day (b) (6) and a 65 year old Caucasian female suffered a T11 fracture on study day (b) (6)

Markers of Bone Turnover:

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, as shown in Table 80. Statistically several of the DR regimens and time points were reduced to a greater extent than the corresponding IR regimen as indicated by the 95% CI of the difference not crossing zero. Numerically, however, every comparison between the DR regimens and the IR regimen at every post-baseline time point showed a greater drop for all BTMs in the DR treatment groups. These findings are consistent with the known higher absorption of risedronate from the DR formulation.

Table 80, Trial 2007008 Bone Turnover Markers, % Change from Baseline, ITT Population

	5 mg IRBB Daily (N=307)	35 mg DRFB Weekly (N=307)	35 mg DRBB Weekly (N=308)
Serum CTX			
Baseline n	307	306	307
Least Squares Mean (ng/mL)	0.64	0.64	0.67
Week 13 n	280	275	277
LS Mean	-42.3*	-46.8*	-46.1*
95% CI	-45.6, -39.0	-50.1, -43.4	-49.4, -42.7
LS Mean Difference from IR		4.5	3.7
95% CI		-0.3, 9.2	-1.0, 8.4
Week 26 n	274	265	273
LS Mean	-44.4*	-49.2*	-49.4*
95% CI	-47.9, -40.9	-52.7, -45.6	-52.9, -45.9
LS Mean Difference from IR		4.8	5.0
95% CI		-0.2, 9.8	0.0, 9.9
Week 52 n	258	256	258
LS Mean	-44.4*	-49.2*	-50.0*
95% CI	-48.1, -40.7	-52.9, -45.4	-53.8, -46.3

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LS Mean Difference from IR 95% CI		4.8 -0.5, 10.1	5.6 0.36, 10.9
Endpoint n	281	275	279
LS Mean	-42.2*	-48.7*	-47.7*
95% CI	-46.0, -38.4	-52.6, -44.9	-51.5, -43.9
LS Mean Difference from IR 95% CI		6.6 1.2, 11.9	5.5 0.2, 10.9
Urine NTX/Cr			
Baseline n	305	305	306
LS Mean (nmol BCE/mmol Creatinine)	76.0	74.6	73.0
Week 13 n	278	273	275
LS Mean	-42.6*	-46.4*	-45.4*
95% CI	-45.9, -39.3	-49.7, -43.1	-48.7, -42.1
LS Mean Difference from IR 95% CI		3.8 -0.9, 8.4	2.8 -1.8, 7.5
Week 26 n	271	265	272
LS Mean	-43.1*	-45.7*	-47.7*
95% CI	-46.4, -39.7	-49.1, -42.3	-51.1, -44.3
LS Mean Difference from IR 95% CI		2.6 -2.2, 7.4	4.6 -0.2, 9.4
Week 52 n	256	253	257
LS Mean	-42.2*	-47.3*	-46.9*
95% CI	-45.7, -38.7	-50.8, -43.8	-50.3, -43.4
LS Mean Difference from IR 95% CI		5.0 0.1, 10.0	4.6 -0.3, 9.6
Endpoint n	279	274	278
LS Mean	-40.2*	-46.6*	-44.6*
95% CI	-43.8, -36.7	-50.2, -43.0	-48.2, -41.1
LS Mean Difference from IR 95% CI		6.4 1.3, 11.4	4.4 -0.6, 9.4
Serum BSAP			
Baseline n	307	306	307
LS Mean (U/L)	28.6	27.3	27.5
Week 13 n	280	275	277
LS Mean	-23.4*	-25.1*	-25.2*
95% CI	-25.4, -21.3	-27.2, -23.1	-27.2, -23.1
LS Mean Difference from IR 95% CI		1.8 -1.1, 4.7	1.8 -1.1, 4.7
Week 26 n	274	265	273
LS Mean	-31.3*	-33.7*	-32.6*
95% CI	-33.3, -29.2	-35.8, -31.6	-34.6, -30.5
LS Mean Difference from IR 95% CI		2.4 -0.5, 5.3	1.3 -1.6, 4.2
Week 52 n	258	256	258
LS Mean	-31.9*	-33.5*	-33.5*
95% CI	-34.1, -29.7	-35.7, -31.2	-35.7, -31.3
LS Mean Difference from IR 95% CI		1.6 -1.6, 4.7	1.6 -1.6, 4.8
Endpoint n	281	275	279
LS Mean	-31.4*	-32.8*	-32.8*
95% CI	-33.5, -29.2	-35.0, -30.6	-35.0, -30.7

LS Mean Difference from IR 95% CI		1.4 -1.7, 4.5	1.5 -1.6, 4.5
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. Source: Study 2007008 Year 1 Final Report, Tables 18, 19, and 20			

Effect of Anti-acid Preparations:

As the DR formulation has a pH sensitive coat that releases drug above pH 5.5, a theoretical concern exists that proton pump inhibitors (PPIs) and, to a lesser extent, H2 blockers (H2) could induce early drug release and reduce absorption and efficacy. This is a concern especially when dosing of the DR formulation occurs following breakfast.

Percent change from baseline in lumbar spine BMD at Endpoint was analyzed using the covariance model to assess the effects of PPI use (see Table 81). PPI use was defined as any PPI use (≥ 1 day) during the trial. A statistically significant interaction was observed between treatment group and PPI use for lumbar spine BMD ($p=0.0047$, see notes following table), however, the number of subjects who used PPI during the study is small (31 subjects, 5 mg IRBB; 32 subjects, 35 mg DRFB; 36 subjects, 35 mg DRBB). When comparing the treatment groups individually, changes in lumbar spine BMD between PPI non-users and users were not statistically significant for the 5 mg IRBB and 35 mg DRFB groups, although both groups had less increase in BMD numerically in PPI users. A significant increase of lumbar spine BMD was seen in the 35 mg DRBB PPI users compared to non-users. This difference is not explained.

To the extent the small numbers here allow the conclusion, PPIs do not appear to negatively affect the efficacy of the risedronate DR formulation.

Additional analysis was performed to assess the effect of PPI or H2 Blocker use and the corresponding interaction with treatment on the percent change from baseline in lumbar spine BMD at Endpoint. PPI/H2 use was defined as use of a PPI and/or an H2 blocker for any duration (≥ 1 day) during the trial. Numbers of subjects were slightly larger; there were 50 subjects in the 5 mg IRBB group, 52 subjects in the 35 mg DRFB group, and 52 subjects in the 35 mg DRBB group that were PPI/H2 users. The effect PPI/H2 Blocker use on percent change from baseline in lumbar spine BMD was not statistically significant ($p=0.7651$). When individual treatment groups were considered, there were also no statistically significant differences between users and non-users ($p=0.5749$ for 5 mg IRBB, $p=0.9096$ for 35 mg DRFB and $p=0.2364$ for 35 mg DRBB). Furthermore, there was no significant interaction between treatment group and PPI/H2 blocker ($p=0.4318$).

Table 81, Trial 2007008 Lumbar Spine BMD, % Change from Baseline to Endpoint, PE PPI and H2 Non-users vs. Users

	5 mg IRBB Daily	35 mg DRFB Weekly	35 mg DRBB Weekly
PPI Use			
PPI Non-users			

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Endpoint n	242	236	239
Mean (%) (SD)	3.231 (3.462)	3.415 (3.171)	3.202 (3.422)
Min, Max	-5.54, 15.29	-6.60, 13.87	-8.97, 18.60
PPI Users			
Endpoint n	28	25	32
Mean (%) (SD)	2.080 (3.593)	2.938 (3.096)	4.917 (4.649)
Min, Max	-6.76, 9.08	-2.77, 9.80	-5.69, 17.43
Difference of Means* (Non-users – Users)	1.151	0.477	-1.715
P-value	0.0668	0.4661	0.0101
PPI/H2 Use			
PPI/H2 Non-users			
Endpoint n	225	220	228
Mean (%) (SD)	3.155 (3.478)	3.373 (3.229)	3.287 (3.337)
Min, Max	-5.54, 15.29	-6.60, 13.87	-8.40, 18.60
PPI/H2 Users			
Endpoint n	45	41	43
Mean (%) (SD)	2.895 (3.563)	3.348 (2.809)	4.023 (4.864)
Min, Max	-6.76, 12.23	-2.77, 9.80	-8.97, 17.43
Difference of Means** (Non-users – Users)	0.260	0.025	-0.736
P-value	0.5749	0.9096	0.2364
*Significant at p=0.0047 using analysis of covariance			
**Not significant (p=0.4318)			
Source: Study 2007008 Year 1 Final Report, Section 11 Tables 18-21 and Appendix 13.1.9.3, Listings 7 and 10			

Efficacy Conclusions: Both of the 35 mg weekly delayed release risedronate regimens (at least 30 minutes before breakfast [DRBB] and immediately following breakfast [DRFB]) were not inferior in efficacy to the approved 5 mg immediate release daily regimen (IRBB) in terms of the primary efficacy endpoint, lumbar spine bone mineral density (BMD) at 52 weeks. Lumbar spine BMD increased 3.4% for each of the DR regimens and 3.1% for the IR regimen with the upper limit of the 95% 2-sided CI for the difference 0.349% for the DRFB regimen and 0.281% for the DRBB regimen and a non-inferiority margin 1.5%. Statistical superiority for the DR regimens over the IR regimen was not shown, however, for lumbar spine BMD (p=0.299) as one of the secondary efficacy measures.

All treatment groups had statistically significant increases in mean percent change from baseline in lumbar spine, total proximal femur, femoral neck, and greater trochanter BMD at all time points (Weeks 26, 52, and Endpoint). At most BMD sites and time points the DR regimens tended to have higher increases in BMD, but these were not statistically significant when compared to the increases seen with the IR regimen.

Approximately 82-87% of subjects were considered as treatment responders with a positive change from baseline in lumbar spine BMD at Week 52 and Endpoint. Although slightly higher percentages responded in the DR treatment groups as compared to the IR group, the differences were not statistically significant.

Small numbers of new vertebral fractures (2 in the 5 mg IRBB group, 2 in the 35 mg DRFB group, and 3 in the 35 mg DRBB group) were reported in this trial. However, this trial is not powered for fracture endpoints.

All bone turnover markers (BTMs) (CTX, NTX, and bone specific alkaline phosphatase (BSAP)) were significantly reduced from baseline for all treatment groups at all post-baseline time points tested (13 Weeks, 26 Weeks, 52 Weeks, and Endpoint). The majority of the decrease in the levels of BTMs was observed by Week 13 in all treatment groups. Numerically every comparison between the DR regimens and the IR regimen at every post-baseline time point showed a greater drop for all BTMs in the DR treatment groups, although statistically only a few were significant.

Percent change from baseline in lumbar spine BMD at Endpoint was consistent between acid suppressor (ie, PPI/H2) users and non-users. Interpretation of that information is limited by small numbers (total of 85 subjects using PPIs, 129 subjects if PPIs and H2 antagonists are considered).

Safety

Events Rates: Adverse event rates are given in Table 82. Overall, 69 to 77 % of subjects suffered at least one AE. Of note is a trend toward more adverse events with the DR formulation, especially with the DRBB regimen (p=0.0572).

Only one death is reported in the trial which is in the 5 mg IRBB group (see Deaths below). Serious adverse events (SAEs) (about 7% of subjects) and withdrawals due to AEs (about 8% of subjects) appear balanced between groups.

Table 82, Trial 2007008 Adverse Event Rates, ITT Population

	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
AEs	211 (68.7%) 660	222 (72.3%) 734	238 (77.3%) 804	0.0572
Serious AEs	22 (7.2%) 24	20 (6.5%) 24	21 (6.8%) 25	0.9594
Deaths	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Withdrawn due to AEs*	25 (8.1%) 38	28 (9.1%) 43	19 (6.2%) 32	0.3567
Mean Number of AEs per Enrolled Subject	2.1	2.4	2.6	
Mean Number of AEs per Subject with AEs	3.1	3.3	3.4	
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) *Includes adverse events in 3 subjects with onset date in Year 1 that eventually led to withdrawal after Month 12. This causes a discrepancy between this table and the Subject Disposition Table 70. Source: Study 2007008 Year 1 Final Report, Table 23				

Exposure: The extent of exposure to study drug for the ITT population is shown in Table 83. About 80% of each treatment group received study drug for the 52 weeks. Mean subject-days of study drug exposure was similar across groups at approximately 320.

Table 83, 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	307	307	307
Mean (SD)	322.5 (101.6)	318.1 (110.3)	324.3 (102.6)
Min	1	2	1
Max	381	380	389
Duration of Treatment			
> 90 Days	282 (91.9%)	275 (89.6%)	281 (91.2%)
> 180 Days	270 (87.9%)	264 (86.0%)	271 (88.0%)
> 270 Days	258 (84.0%)	258 (84.0%)	264 (85.7%)
> 360 Days	245 (79.8%)	249 (81.1%)	250 (81.2%)

Source: Study 2007008 Year 1 Final Report, Table 22

Deaths: One death was reported in the trial. A 68 year old Caucasian non-Hispanic woman in the 5 mg IRBB group with a history of tobacco use, COPD, and hypertension suffered cardiac arrest on study day (b) (6). She was successfully resuscitated but remained in a coma and died (b) (6) days later.

Serious Adverse Events: 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 84. 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.

Table 84, 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				

Adverse Events Leading to Withdrawal: Adverse events leading to withdrawal were balanced between treatment groups. As outlined in Table 85, adverse events in the gastrointestinal disorders SOC were the most common reason for withdrawal, accounted for 41 of 72 withdrawals (57%).

Table 85, Trial 2007008 Adverse Events Leading to Withdrawal 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*	25 (8.1%) 38	28 (9.1%) 43	19 (6.2%) 32	0.3567
Gastrointestinal disorders	11 (3.6%) 17	17 (5.5%) 24	13 (4.2%) 20	0.5127
Abdominal pain	2 (0.7%) 2	4 (1.3%) 4	4 (1.3%) 4	0.7845
Diarrhea	2 (0.7%) 2	4 (1.3%) 4	0 (0.0%) 0	0.0932
Vomiting	1 (0.3%) 1	3 (1.0%) 3	0 (0.0%) 0	0.1346
Abdominal pain upper	0 (0.0%) 0	2 (0.7%) 2	4 (1.3%) 4	0.1752
Abdominal pain lower	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Constipation	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Musculoskeletal and connective tissue disorders	2 (0.7%) 2	4 (1.3%) 6	2 (0.6%) 3	0.6774
Myalgia	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Nervous system disorders	2 (0.7%) 2	3 (1.0%) 3	0 (0.0%) 0	0.2161
Headache	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Skin and subcutaneous tissue disorders	1 (0.3%) 1	3 (1.0%) 3	2 (0.6%) 2	0.7101
Eye disorders	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
General disorders and administration site conditions	2 (0.7%) 2	2 (0.7%) 2	2 (0.6%) 2	1.0000
Ear and labyrinth disorders	3 (1.0%) 3	0 (0.0%) 0	0 (0.0%) 0	0.0734
Vertigo	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Endocrine disorders	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Hyperparathyroidism	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Injury, poisoning and procedural complications	2 (0.7%) 3	0 (0.0%) 0	0 (0.0%) 0	0.2213
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) *Includes adverse events in 3 subjects with onset date in Year 1 that eventually led to withdrawal after Month 12. This causes a discrepancy between this table and the Subject Disposition Table 70. Source: Study 2007008 Year 1 Final Report, Table 27				

Adverse Events Leading to Dose Alteration: Dosage interruption was reported in 183 subjects; 57 in the 5 mg IRBB treatment group, 58 in the 35 mg DRFB group, and 68 in the 35 mg DRBB group.

Adverse Events: Adverse events which occurred in 2% or more of any treatment group are listed in Table 86. Overall, 69 to 77 % of subjects suffered at least one AE. Of note is a trend toward more adverse events with the DR formulation, especially with the DRBB regimen ($p=0.0572$). Biostatistics has reviewed this and reports the given p-value is based on subjects with AEs. If total AEs are analyzed (660 for 5 mg IRBB, 734 for 35 mg DRFB, and 804 for 35 mg DRBB regimens) the p-value by the Fisher's Exact Test is 0.0076, a moderately significant difference. Also noted are more AEs per enrolled subject and more AEs per subject with AEs in the DR regimens.

Biostatistics also did a comparison of the log transformed number of AEs among the three treatment groups. The transformation of number of AEs is $\ln(1+\text{number of AEs})$, which is monotone transformation and makes the distribution of number of AEs more like normal distribution. When comparing 35 mg DRFB to 5 mg IRBB, the p-value is 0.2277. When comparing 35 mg DRBB to 5 mg IRBB, the p-value is 0.0227.

Reviewer comment: A concern is raised by this data about more AEs with the 35 mg DR regimens, especially the prior to breakfast regimen, compared to the 5 mg IRBB regimen.

System organ classes (SOC) with the most reported AEs across all treatment groups were gastrointestinal disorders (32%), infections and infestations (31%), and musculoskeletal and connective tissue disorders (25%). Preferred terms with the most AEs across treatment groups were arthralgia (7%), nasopharyngitis (7%), diarrhea (7%), back pain (6%), and influenza (6%).

No system organ classes had statistically significant differences between treatment groups for AEs. Preferred terms with statistically significant differences between treatment groups for AEs were abdominal pain upper (5 mg IRBB with 7 subjects (2.3%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 23 subjects (7.5%), $p=0.0041$) and osteoarthritis (5 mg IRBB with 8 subjects (2.6%), 35 mg DRFB with 5 subjects (1.6%), 35 mg DRBB with 1 subject (0.3%), $p=0.0388$). If SOCs significant at < 0.1 are considered, more cardiac disorders in the DRBB group were reported (5 mg IRBB with 10 subjects (3.3%), 35 mg DRFB with 11 subjects (3.6%), 35 mg DRBB with 21 subjects (6.8%), $p=0.0807$), and more blood and lymphatic disorders in the DRFB group (5 mg IRBB with 2 subjects (0.7%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 4 subjects (1.3%), $p=0.0899$). Additional preferred terms with significance at the 0.1 level include vomiting (5 mg IRBB with 5 subjects (1.6%), 35 mg DRFB with 15 subjects (4.9%), 35 mg DRBB with 8 subjects (2.6%), $p=0.0589$) and hiatal hernia (5 mg IRBB with 1 subject (0.3%), 35 mg DRFB with 2 subjects (0.7%), 35 mg DRBB with 8 subjects (2.6%), $p=0.0516$).

No single preferred term seemed to contribute markedly to the excess of AEs over subjects with AEs (i.e., subjects appear to mostly have had multiple AEs with different preferred terms). It appears much more common that a subject would have several AEs within the same SOC and seems especially common with the gastrointestinal disorders SOC where, in the 35 mg DRBB group, AEs are more than double subjects with AE (AEs 214, subjects with AE 105).

The difference between the 35 mg DRBB group and the other 2 groups in the number of subjects reporting AEs was mostly due to higher incidences of AEs in the SOCs gastrointestinal disorders, general disorders and administration site conditions, investigations, and cardiac disorders. The gastrointestinal disorders SOC will be discussed in greater detail below in adverse events of special interest.

In the general disorders and administration site conditions SOC, 16 (5.2%) subjects in the 5 mg IRBB group, 25 (8.1%) subjects in the 35 mg DRFB group and 29 (9.4%) subjects in the 35 mg DRBB group reported AEs. The difference between the 35 mg DRBB group and the 5 mg IRBB group was mostly due to TEAEs of pain (0 subjects, 5 mg IRBB; 4 subjects, 35 mg DRBB), edema peripheral (2 subjects, 5 mg IRBB; 5 subjects, 35 mg DRBB), and drug intolerance (2 subjects, 5 mg IRBB; 5 subjects, 35 mg DRBB). Per the Sponsor, based on verbatim terms, the AEs of drug intolerance were related to calcium intolerance, and none were related to the use of risedronate.

In the investigations SOC, 12 (3.9%) subjects in the 5 mg IRBB group, 16 (5.2%) subjects in the 35 mg DRFB group and 24 (7.8%) subjects in the 35 mg DRBB group reported AEs. The most notable difference was observed in AEs of blood parathyroid hormone increased (3 subjects in 5 mg IRBB; 2 subjects, 35 mg DRFB; 7 subjects, 35 mg DRBB).

As mentioned above, in the cardiac disorders SOC, 10 (3.3%) subjects in the 5 mg IRBB group, 11 (3.6%) subjects in the 35 mg DRFB group and 21 (6.8%) subjects in the 35 mg DRBB group reported AEs. The difference between the 35 mg DRBB group and the 5 mg IRBB group was due to small differences in a variety of preferred terms, with no apparent pattern. A low number of serious cardiac events were reported in all treatment groups (1 subject, 5 mg IRBB; 1 subject, 35 mg DRFB; 3 subjects, 35 mg DRBB).

An excess of ocular AEs, especially conjunctivitis, although also uveitis and scleritis, with bisphosphonates has been reported. Ocular AEs were uncommon and balanced across treatment groups (12 subjects (3.9%), 5 mg IRBB; 8 subjects (2.6%), 35 mg DRFB; 9 subjects (2.9%), 35 mg DRBB). The only preferred terms occurring in more than 1 subject per treatment group were cataract (5 subjects (1.6%), 5 mg IRBB; 2 subjects (0.7%), 35 mg DRFB; 1 subject (0.3%), 35 mg DRBB) and conjunctivitis (3

subjects (1.0%), 5 mg IRBB; 1 subject (0.3%), 35 mg DRFB; 1 subject (0.3%), 35 mg DRBB). One case of iridocyclitis was reported in the 35 mg DRFB treatment group.

Table 86, Trial 2007008 Most Common Adverse Events (≥2% in any Treatment Group), ITT Population

System Organ Class Preferred Term	5 mg IRBB Daily (N=307) n (%) nAE	35 mg DRFB Weekly (N=307) n (%) nAE	35 mg DRBB Weekly (N=308) n (%) nAE	p-value
Overall	211 (68.7%) 660	222 (72.3%) 734	238 (77.3%) 804	0.0572
Gastrointestinal disorders	85 (27.7%) 142	101 (32.9%) 185	105 (34.1%) 214	0.1905
Diarrhea	15 (4.9%) 21	27 (8.8%) 29	18 (5.8%) 21	0.1366
Abdominal pain	9 (2.9%) 10	16 (5.2%) 18	15 (4.9%) 18	0.3417
Constipation	9 (2.9%) 10	15 (4.9%) 15	16 (5.2%) 16	0.3552
Vomiting	5 (1.6%) 5	15 (4.9%) 18	8 (2.6%) 11	0.0589
Dyspepsia	12 (3.9%) 14	12 (3.9%) 15	12 (3.9%) 14	1.0000
Nausea	12 (3.9%) 12	11 (3.6%) 14	10 (3.2%) 11	0.8813
Abdominal pain upper	7 (2.3%) 8	9 (2.9%) 13	23 (7.5%) 31	0.0041
Gastroesophageal reflux disease	5 (1.6%) 5	3 (1.0%) 3	8 (2.6%) 9	0.3383
Hiatus hernia	1 (0.3%) 1	2 (0.7%) 2	8 (2.6%) 8	0.0516
Infections and infestations	89 (29.0%) 125	100 (32.6%) 149	94 (30.5%) 145	0.6349
Influenza	19 (6.2%) 21	22 (7.2%) 24	18 (5.8%) 20	0.7892
Nasopharyngitis	16 (5.2%) 18	21 (6.8%) 23	26 (8.4%) 33	0.3022
Urinary tract infection	8 (2.6%) 9	15 (4.9%) 18	11 (3.6%) 12	0.3310
Bronchitis	13 (4.2%) 15	12 (3.9%) 15	13 (4.2%) 13	1.0000
Upper respiratory tract infection	8 (2.6%) 8	11 (3.6%) 11	9 (2.9%) 11	0.7895
Cystitis	7 (2.3%) 8	7 (2.3%) 8	5 (1.6%) 5	0.8075
Pharyngitis	3 (1.0%) 3	4 (1.3%) 4	9 (2.9%) 9	0.2097
Musculoskeletal and connective tissue disorders	73 (23.8%) 105	78 (25.4%) 115	78 (25.3%) 107	0.8786
Arthralgia	24 (7.8%) 29	21 (6.8%) 30	19 (6.2%) 23	0.7087
Back pain	18 (5.9%) 19	21 (6.8%) 24	19 (6.2%) 20	0.8870
Pain in extremity	7 (2.3%) 7	12 (3.9%) 12	8 (2.6%) 10	0.5213
Musculoskeletal pain	5 (1.6%) 5	6 (2.0%) 6	8 (2.6%) 8	0.7727
Osteoarthritis	8 (2.6%) 8	5 (1.6%) 5	1 (0.3%) 1	0.0388
Muscle spasms	7 (2.3%) 7	3 (1.0%) 3	9 (2.9%) 13	0.2089
Injury, poisoning and procedural complications	32 (10.4%) 46	29 (9.4%) 41	27 (8.8%) 40	0.7725
Fall	9 (2.9%) 10	12 (3.9%) 12	4 (1.3%) 4	0.1002
Contusion	10 (3.3%) 10	7 (2.3%) 8	6 (1.9%) 8	0.5620
Nervous system disorders	38 (12.4%) 49	26 (8.5%) 35	31 (10.1%) 34	0.2816
Dizziness	10 (3.3%) 10	8 (2.6%) 8	8 (2.6%) 9	0.8802
Headache	15 (4.9%) 15	8 (2.6%) 8	14 (4.5%) 14	0.3143
General disorders and administration site conditions	16 (5.2%) 18	25 (8.1%) 35	29 (9.4%) 39	0.1165
Skin and subcutaneous tissue disorders	16 (5.2%) 18	21 (6.8%) 23	21 (6.8%) 24	0.6646
Respiratory, thoracic and mediastinal disorders	17 (5.5%) 21	17 (5.5%) 21	20 (6.5%) 23	0.8929
Cough	7 (2.3%) 8	7 (2.3%) 7	5 (1.6%) 5	0.8075
Vascular disorders	14 (4.6%) 18	17 (5.5%) 17	19 (6.2%) 21	0.6956
Hypertension	11 (3.6%) 12	8 (2.6%) 8	10 (3.2%) 10	0.7956

Investigations	12 (3.9%) 17	16 (5.2%) 19	24 (7.8%) 27	0.1129
Blood parathyroid hormone increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7	0.2626
Metabolism and nutrition disorders	9 (2.9%) 9	12 (3.9%) 16	14 (4.5%) 14	0.6016
Hypercholesterolemia	2 (0.7%) 2	7 (2.3%) 7	6 (1.9%) 6	0.2261
Cardiac disorders	10 (3.3%) 10	11 (3.6%) 11	21 (6.8%) 28	0.0807
Blood and lymphatic system disorders	2 (0.7%) 2	9 (2.9%) 9	4 (1.3%) 4	0.0899
Psychiatric disorders	8 (2.6%) 9	9 (2.9%) 9	12 (3.9%) 17	0.7054
Eye disorders	12 (3.9%) 17	8 (2.6%) 11	9 (2.9%) 9	0.6677
Ear and labyrinth disorders	12 (3.9%) 14	7 (2.3%) 7	7 (2.3%) 7	0.4038
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.6%) 8	7 (2.3%) 7	6 (1.9%) 7	0.8246
Renal and urinary disorders	7 (2.3%) 7	7 (2.3%) 8	13 (4.2%) 16	0.3114
Endocrine disorders	7 (2.3%) 8	6 (2.0%) 6	10 (3.2%) 12	0.6466
Reproductive system and breast disorders	9 (2.9%) 10	5 (1.6%) 5	5 (1.6%) 6	0.4402
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 24				

Adverse Events of Special Interest:

Upper Gastrointestinal AEs: The incidence of UGI AEs is given in Table 87. The preferred terms of abdominal pain, dyspepsia, and upper abdominal pain are the most common AEs in this grouping.

Overall, statistically, the number of subjects with UGI AEs is balanced between treatment groups. However, there were numerically more subjects in the 35 mg DRBB group that had AEs in this category (61, 19.8%) than in the 35 mg DRFB group (48, 15.6%) or 5 mg IRBB group (45, 14.7%). The preferred term categories with statistically significant differences in numbers of subjects were abdominal pain upper (5 mg IRBB group, 7 subjects; 35 mg DRFB group, 9 subjects, 35 mg DRBB group, 23 subjects; p=0.0041) and gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; p=0.0366). Other preferred terms which are associated with pain or discomfort (abdominal pain, dyspepsia, abdominal discomfort, abdominal tenderness, epigastric discomfort, and chest pain) either had higher numbers of subjects in the DR groups, especially the 35 mg DRBB group, without reaching statistical significance, or were neutral. In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat) 19 (6.2%) subjects in the 5 mg IRBB group, 29 (9.4%) subjects in the 35 mg DRFB group and 40 (13.0%) subjects in the 35 mg DRBB group reported AEs (p=0.0164) (Study 2007008 Year 1 Final Report, Section 11 Table 49).

The AE of esophagitis was equal across treatment groups with one per group. Only one subject in the trial had erosive esophagitis (35 mg DRFB group).

Table 87, Trial 2007008 Upper GI AEs, 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	45 (14.7%) 54	48 (15.6%) 65	61 (19.8%) 106	0.2054
Gastrointestinal disorders	43 (14.0%) 52	48 (15.6%) 63	60 (19.5%) 104	0.1732
Abdominal pain	9 (2.9%) 10	16 (5.2%) 18	15 (4.9%) 18	0.3417
Dyspepsia	12 (3.9%) 14	12 (3.9%) 15	12 (3.9%) 14	1.0000
Abdominal pain upper	7 (2.3%) 8	9 (2.9%) 13	23 (7.5%) 31	0.0041
Gastritis	3 (1.0%) 3	3 (1.0%) 3	4 (1.3%) 4	1.0000
Gastroesophageal reflux disease	5 (1.6%) 5	3 (1.0%) 3	8 (2.6%) 9	0.3383
Abdominal discomfort	1 (0.3%) 1	2 (0.7%) 2	5 (1.6%) 6	0.2928
Hyperchlorhydria	6 (2.0%) 7	2 (0.7%) 2	5 (1.6%) 6	0.4183
Dysphagia	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Erosive esophagitis	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastric ulcer	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastritis atrophic	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Gastritis erosive	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Melaena	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Oesophagitis	1 (0.3%) 1	1 (0.3%) 1	1 (0.3%) 1	1.0000
Abdominal tenderness	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Epigastric discomfort	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Gastrointestinal inflammation	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Gastrointestinal pain	0 (0.0%) 0	0 (0.0%) 0	4 (1.3%) 8	0.0366
Esophageal disorder	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Esophageal ulcer	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
General disorders and administration site conditions	1 (0.3%) 1	1 (0.3%) 1	2 (0.6%) 2	1.0000
Chest pain	1 (0.3%) 1	1 (0.3%) 1	2 (0.6%) 2	1.0000
Infections and infestations	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Helicobacter gastritis	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
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 28				

The influence of NSAIDs and/or aspirin on the incidence of UGI AEs was evaluated. Subjects were classified as users or non-users based on concomitant medication usage reported with any use leading to classification as a user. The number of users was similar across treatment groups. More subjects who used NSAIDs/aspirin reported UGI AEs than non-users (users: 26/147 [17.7%], 5 mg IRBB; 28/152 [18.4%], 35 mg DRFB; 34/132 [25.8%], 35 mg DRBB; non-users: 19/160 [11.9%], 5 mg IRBB; 20/155 [12.9%], 35 mg DRFB; 27/176 [15.3%], 35 mg DRBB) (Study 2007008 Year 1 Final Report, Section 11 Table 60). Among users, the difference between the 35 mg DRBB group and the other 2 groups was mainly due to AEs of abdominal pain upper (3 patients, 5 mg IRBB; 6 patients, 35 mg DRFB; 14 patients, 35 mg DRBB) (Study 2007008 Year 1 Final Report, Text p. 90).

Subjects were identified using MedDRA preferred terms as having a medical history of UGI disorders. Not surprisingly, a higher percentage of subjects with a medical history of UGI disorders experienced UGI AEs during the study than subjects without a medical history of upper GI disorders. The percentage of subjects with a medical history of UGI disorders was 30.9% in the 5 mg IRBB group, 32.6% in the 35 mg DRFB group, and 29.2% in the 35 mg DRBB group. In subjects with a medical history of UGI disorders, the incidence of UGI AEs was similar between the 5 mg IRBB group (19/95, 20.0%) and the 35 mg DRFB group (19/100, 19.0%); the incidence of UGI AEs was higher in the 35 mg DRBB group (28/90, 31.1%), mostly due to events of abdominal pain upper. In subjects without a medical history of upper GI disorders, the incidence of upper GI TEAEs were generally similar across treatment groups (26/212 or 12.3%, 5 mg IRBB; 29/207 or 14.0%, 35 mg DRFB, 33/218 or 15.1%, 35 mg DRBB) (Study 2007008 Year 1 Final Report, Section 11 Table 61).

Endoscopy or other appropriate GI diagnostic procedures were to be offered to all patients who developed a moderate or severe upper GI symptom. Only endoscopies were performed. Findings presented in Table 88 are for all patients who underwent endoscopy, including those who had it for reasons other than a moderate or severe GI symptom. A total of 31 patients (8 [2.6%], 5 mg IRBB; 10 [3.3%], 35 mg DRFB; 13 [4.2%], 35 mg DRBB) underwent an endoscopy procedure. Abnormal findings were similar across all 3 treatment groups. Five (1.6%) in the 5 mg IRBB group, 5 (1.6%) in the 35 mg DRFB group, and 7 (2.3%) in the 35 mg DRBB had at least 1 abnormal mucosal finding. Two patients had ulcers (1 stomach, 35 mg DRFB; 1 esophageal, 35 mg DRBB), and no patients had perforations. One patient in the 5 mg IRBB group had bleeding in the stomach, but no ulcer.

Table 88, Trial 2007008 Abnormal Endoscopy Inflammatory Findings

Treatment GI Site	Inflamm n (%) nAB	Erosion n (%) nAB	Bleeding n (%) nAB	Ulcerat. n (%) nAB	Perforat. n (%) nAB	Total n (%) nAB
5 mg IRBB (N = 307) Subjects with EGD = 8						
Esophagus	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1
Stomach	3 (1.0%) 3	2 (0.7%) 2	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 6
Duodenum	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 2
Total	3 (1.0%) 5	2 (0.7%) 3	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 9
35 mg DRFB (N = 307) Subjects with EGD = 10						
Esophagus	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1
Stomach	3 (1.0%) 3	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	4 (1.3%) 5
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	3 (1.0%) 3	2 (0.7%) 2	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	5 (1.6%) 6
35 mg DRBB (N = 308) Subjects with EGD = 13						
Esophagus	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	2 (0.6%) 2
Stomach	4 (1.3%) 4	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	5 (1.6%) 5
Duodenum	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Total	5 (1.6%) 5	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	7 (2.3%) 7

n (%) = number (percent) of patients with abnormality: (%) = (n/Patients within specified treatment)x100%.

nAB = number of abnormal findings.

Source: Study 2007008 Year 1 Final Report, Table 30

Lower Gastrointestinal AEs: As the DR formulation delivers drug largely in the small intestine, lower GI AEs were evaluated. The incidence of lower GI AEs is shown in Table 89. There were no statistically different incidences among treatment groups for any SOC or PT except for gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; p=0.0366). Numerically more subjects in the DR regimens, especially the DRFB regimen, had AEs overall and in the GI disorders SOC which were mostly an increase of diarrhea and constipation reported in those groups.

Table 89, Trial 2007008 Lower GI AEs, 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	40 (13.0%) 57	55 (17.9%) 78	47 (15.3%) 65	0.2482
Gastrointestinal disorders	31 (10.1%) 46	49 (16.0%) 68	40 (13.0%) 56	0.0950
Diarrhea	15 (4.9%) 21	27 (8.8%) 29	18 (5.8%) 21	0.1366
Constipation	9 (2.9%) 10	15 (4.9%) 15	16 (5.2%) 16	0.3552
Abdominal pain lower	4 (1.3%) 4	6 (2.0%) 6	3 (1.0%) 3	0.5393
Hemorrhoids	2 (0.7%) 2	5 (1.6%) 5	1 (0.3%) 1	0.1906
Abdominal distension	4 (1.3%) 4	3 (1.0%) 3	2 (0.6%) 2	0.6557
Diverticulum	1 (0.3%) 1	2 (0.7%) 2	0 (0.0%) 0	0.3319
Hematochezia	0 (0.0%) 0	2 (0.7%) 2	0 (0.0%) 0	0.2213
Rectal polyp	0 (0.0%) 0	2 (0.7%) 2	1 (0.3%) 1	0.5541
Anal fissure	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Diverticulum intestinal	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Irritable bowel syndrome	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Melaena	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Colitis	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Colonic polyp	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Fecal incontinence	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Gastrointestinal inflammation	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Gastrointestinal pain	0 (0.0%) 0	0 (0.0%) 0	4 (1.3%) 8	0.0366
Hemorrhoidal hemorrhage	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Rectal hemorrhage	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Sigmoiditis	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Infections and infestations	10 (3.3%) 10	9 (2.9%) 10	8 (2.6%) 9	0.8586
Gastroenteritis	6 (2.0%) 6	6 (2.0%) 6	5 (1.6%) 5	0.9098
Diverticulitis	2 (0.7%) 2	2 (0.7%) 2	2 (0.6%) 3	1.0000
Appendicitis	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Gastroenteritis viral	2 (0.7%) 2	1 (0.3%) 1	1 (0.3%) 1	0.8510
Investigations	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Occult blood	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659

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 31

A colonoscopy was strongly recommended to all subjects who developed a moderate or severe lower GI symptom, but findings from all colonoscopies are recorded irrespective of indication. No subject underwent a lower GI procedure other than colonoscopy. A total of 17 subjects (3 [1.0%], 5 mg IRBB; 10 [3.3%], 35 mg DRFB; 4 [1.3%], 35 mg DRBB) underwent a colonoscopy. Two (0.7%) subjects in the 5 mg IRBB group had at least one abnormal finding (2 with diverticulae, 1 with polyp, and 1 with sigmoid inflammation). Eight (2.6%) subjects in the 35 mg DRFB group had at least one abnormal finding (5 with diverticulae, 3 with polyps, and 1 with sigmoid inflammation). Four (1.3%) subjects in the 35 mg DRBB group had at least one abnormal finding (2 with diverticulae, 3 with polyps, and 1 with rectal inflammation). Of the patients with abnormal findings, mucosal findings were similar across the 3 treatment groups, with one subject from each group with mucosal inflammation.

Fecal occult blood was assessed at Week 26. The number of subjects with positive fecal occult blood results was small and similar across groups (3 [1.1%] in 5 mg IRBB; 2 [0.8%] in 35 mg DRFB; and 3 [1.1%] in 35 mg DRBB).

Musculoskeletal AEs: Increased musculoskeletal pain has been reported with multiple bisphosphonates including risedronate. Selected musculoskeletal AEs were reviewed for potential differences between treatment groups (arthralgia, back pain, musculoskeletal pain, myalgia, neck pain, and bone pain), as shown in Table 90. Arthralgias (7%) and back pain (6%) were the most common of these AEs. Similar numbers and percents were found for all treatment groups for these selected adverse events.

Table 90, Trial 2007008 Selected Musculoskeletal AEs, ITT Population

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	46 (15.0%) 61	48 (15.6%) 71	53 (17.2%) 64	0.7561
Arthralgia	24 (7.8%) 29	21 (6.8%) 30	19 (6.2%) 23	0.7087
Back pain	18 (5.9%) 19	21 (6.8%) 24	19 (6.2%) 20	0.8870
Musculoskeletal pain	5 (1.6%) 5	6 (2.0%) 6	8 (2.6%) 8	0.7727
Myalgia	3 (1.0%) 3	4 (1.3%) 6	4 (1.3%) 4	1.0000
Neck pain	3 (1.0%) 3	3 (1.0%) 3	4 (1.3%) 4	1.0000
Bone pain	2 (0.7%) 2	2 (0.7%) 2	5 (1.6%) 5	0.5272

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 35

Acute Phase Reactions: Acute phase reactions have been reported with higher doses of risedronate used for intermittent dosing. Sponsor reports no cases of influenza-like

illness or pyrexia within 3 days after study drug administration and lasting 7 days or less.

Sponsor also evaluated MedDRA preferred terms which have been associated with acute phase reactions beginning within 3 days after study drug administration and lasting 7 days or less (Acute phase reaction, Arthralgia, Asthenia, Back pain, Burning sensation, Chest wall pain, Chills, Dizziness, Fatigue, Feeling hot, Fibromyalgia, Headache, Hot flush, Influenza like illness, Joint stiffness, Malaise, Muscle spasms, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myofascial pain syndrome, Nausea, Neck pain, Pain, Pain in extremity, Paraesthesia, Pyrexia, Vertigo, and Vomiting). No subject had more than 2 such AEs (For 5 mg IRBB, 4 subjects (1.3%) with at least 1 AE, 1 subject (0.3%) with 2 AEs, for 35 mg DRFB, 7 subjects (2.3%) with at least 1 AE, 2 subjects (0.7%) with 2 AEs, for 35 mg DRBB, 4 subjects (1.3%) with at least 1 AE, 0 subjects with 2 AEs). AEs associated with acute phase reactions in the expected time frame do not appear to be increased with the DR formulation.

Atrial Fibrillation: Increased atrial fibrillation with bisphosphonates has been reported in some trials and patient series. ECGs were performed on all subjects at baseline and Week 52. In addition, patients at sites in Argentina had an ECG at screening. If the screening ECG showed previously undiagnosed atrial fibrillation, atrial flutter, or tachyarrhythmias, the patient also had an ECG at Week 26.

Atrial fibrillation or flutter was present in 6 subjects at baseline (1 subject, 5 mg IRBB; 5 subjects, 35 mg DRFB). Of the subjects in normal sinus rhythm at baseline who had repeat ECGs at Week 52 or study exit, none had atrial fibrillation or atrial flutter. Treatment emergent adverse events of atrial fibrillation were reported for four subjects, one of whom had atrial fibrillation at baseline and one of whom had a history of paroxysmal atrial fibrillation.

- 77 year old female in the 35 mg DRFB group with hypertension had atrial fibrillation on the baseline ECG.
- 74 year old female in the 35 mg DRBB group with a history of paroxysmal atrial fibrillation, supraventricular tachycardia, and ischemic heart disease was hospitalized on study day (b) (6) with paroxysmal supraventricular tachycardia and treated with carvediol.
- 70 year old female in the 35 mg DRBB group with hypertension and hypercholesterolemia with an MI on study day (b) (6) followed by triple bypass and several adverse events, including atrial fibrillation. At the time of study withdrawal on day 295 she was in normal sinus rhythm.
- 73 year old female in the 35 mg DRBB group with hypertension, hypercholesterolemia, and a history of an unspecified arrhythmia developed atrial fibrillation on study day (b) (6) treated with cardioversion on day (b) (6).

Laboratory

Adverse Events: Table 91 lists all laboratory values reported as AEs. Most laboratory values as AEs occurred in only one or two cases. The only difference between treatment groups to reach statistical significance in this category was anemia, which was more common in the 35 mg DRFB group (6 subjects, compared to 1 in the 35 mg DRBB group and none in the 5 mg IRBB group). PTH increased and secondary hyperparathyroidism were more common in the 35 mg DRBB group, and hyperparathyroidism was more common in the 5 mg IRBB group, but these differences did not meet statistical significance. Sponsor reports 6 of 7 subjects diagnosed with secondary hyperparathyroidism are from a single site in Estonia, and 3 of the six had an onset date of Day 1 before they had taken study medication. Only one subject of these had sustained hypocalcemia.

Table 91, Trial 2007008 Laboratory Values as AEs, ITT Population

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
Blood cholesterol increased	1 (0.3%) 1	2 (0.7%) 2	1 (0.3%) 1	0.8510
Blood PTH increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 7	0.2626
Urinary sediment abnormal	0 (0.0%) 0	1 (0.3%) 1	0 (0.0%) 0	0.6659
Urine analysis abnormal	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Blood calcium decreased	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Blood glucose increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
aPTT prolonged	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
INR increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Prothrombin time prolonged	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Occult blood	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Occult blood positive	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
ALT increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
AST increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Transaminases increased	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Platelet count decreased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood creatinine increased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood urea increased	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Cr clearance decreased	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Blood alk. phos. increased	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Hypercholesterolemia	2 (0.7%) 2	7 (2.3%) 7	6 (1.9%) 6	0.2261
Hypercalcemia	0 (0.0%) 0	1 (0.3%) 1	2 (0.6%) 2	0.7771
Hypoglycemia	0 (0.0%) 0	1 (0.3%) 2	0 (0.0%) 0	0.6659
Hyponatremia	1 (0.3%) 1	1 (0.3%) 1	0 (0.0%) 0	0.5546
Vitamin D deficiency	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Hyperlipidemia	0 (0.0%) 0	0 (0.0%) 0	2 (0.6%) 2	0.3326
Dyslipidemia	2 (0.7%) 2	0 (0.0%) 0	0 (0.0%) 0	0.2213
Hypokalemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hyperuricemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Anemia	0 (0.0%) 0	6 (2.0%) 6	1 (0.3%) 1	0.0137
Leukopenia	2 (0.7%) 2	2 (0.7%) 2	1 (0.3%) 1	0.7517
Thrombocythemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hematuria	0 (0.0%) 0	1 (0.3%) 1	1 (0.3%) 1	1.0000
Leukocyturia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000

Renal failure acute	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
Renal failure chronic	1 (0.3%) 1	0 (0.0%) 0	1 (0.3%) 1	1.0000
Hyperparathyroidism, 2°	0 (0.0%) 0	2 (0.7%) 2	5 (1.6%) 6	0.0769
Hyperparathyroidism	3 (1.0%) 3	0 (0.0%) 0	1 (0.3%) 1	0.2329
Hypothyroidism	3 (1.0%) 3	2 (0.7%) 2	1 (0.3%) 1	0.5449
Hypoparathyroidism	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0.6659
Hyperbilirubinemia	0 (0.0%) 0	0 (0.0%) 0	1 (0.3%) 1	1.0000
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, Section 11 Table 49				

Marked Laboratory Abnormalities: Markedly abnormal laboratory values post baseline were relatively uncommon and fairly equally spread across treatment groups except for PTH (≥ 98 ng/l) (16 subjects [5.3%], 5 mg IRBB; 19 subjects [6.3%], 35 mg DRFB; 38 subjects [12.5%], 35 mg DRBB). This is evaluated further below.

Table 92, Trial 2007008 Markedly Abnormal Lab Values Post Baseline, ITT Population

Lab Test	5 mg IRBB Daily (N=307)		35 mg DRFB Weekly (N=307)		35 mg DRBB Weekly (N=308)	
	n (%)	N	n (%)	N	n (%)	N
Hematocrit < 0.8LLN	0	293	1 (0.3%)	300	1 (0.3%)	301
Hemoglobin < 0.8LLN	0	293	1 (0.3%)	300	1 (0.3%)	301
Platelets < 0.8LLN	2 (0.7%)	292	2 (0.7%)	299	1 (0.3%)	300
Leukocyte Count < 0.8LLN	2 (0.7%)	293	4 (1.3%)	300	5 (1.7%)	301
Neutrophils < 0.7LLN	2 (0.7%)	293	1 (0.3%)	299	1 (0.3%)	301
Lymphs < 0.7LLN	2 (0.7%)	293	4 (1.3%)	299	1 (0.3%)	301
Lymphs > 1.5ULN	0	293	1 (0.3%)	299	0	301
Eosinophils > 2ULN	5 (1.7%)	293	3 (1.0%)	299	2 (0.7%)	301
Basophils > 1.5ULN	0	293	1 (0.3%)	299	0	301
Calcium < 0.9LLN	1 (0.3%)	303	1 (0.3%)	303	1 (0.3%)	305
Calcium > 1.1ULN	2 (0.7%)	303	0	303	0	305
Phosphate < 0.8LLN	1 (0.3%)	303	2 (0.7%)	303	0	305
Phosphate > 1.2ULN	0	303	0	303	1 (0.3%)	305
Alk Phos > 1.5ULN	7 (2.3%)	303	4 (1.3%)	303	6 (2.0%)	305
Bilirubin > 1.3ULN	3 (1.0%)	303	1 (0.3%)	303	3 (1.0%)	305
ALT > 3ULN	2 (0.7%)	303	1 (0.3%)	303	1 (0.3%)	305
AST > 3ULN	0	303	0	303	1 (0.3%)	305
Potassium < 0.9LLN	0	303	0	303	2 (0.7%)	305
Potassium > 1.1ULN	0	303	2 (0.7%)	303	1 (0.3%)	305
iPTH > 1.5ULN	16 (5.3%)	302	19 (6.3%)	302	38 (12.5%)	305
N=Number of subjects with post-baseline measurement within specified treatment. Subjects with multiple high/low values were counted only once. Source: Study 2007008 Year 1 Final Report, Section 11 Tables 78 and 83						

Mean Change from Baseline: The mean values for all hematology parameters (hemoglobin, red blood cell count, hematocrit, platelet count, white blood cell (WBC))

count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) were within the normal range at all time points for all treatment groups and were similar across treatment groups. The mean changes from baseline at all time points were reviewed and were very small for each hematology parameter.

The mean values for all chemistry parameters (glucose, creatinine, creatinine clearance, calcium, phosphate, albumin, alkaline phosphatase, bilirubin, ALT, AST, sodium, magnesium, potassium, chloride, bicarbonate, and iPTH) were within the normal range at all time points for all treatment groups except iPTH was high for the 35 mg DRBB group at week 13 (67 pg/ml, not a protocol time for measurement, only 14 subjects measured). The mean changes from baseline to each post-baseline time point were generally small. An expected fall in alkaline phosphatase in all treatment groups was noted by week 13 which persisted through the rest of the reported period. There were no clinically important differences across groups for any chemistry parameter.

Urinalysis (pH, ketones, protein, glucose, blood, and bilirubin) was performed by dipstick at baseline, Week 52, and/or exit. Microscopy was performed only in subjects with abnormal urinalysis. A review of the urinalysis data showed no clinically relevant signals.

Prothrombin time, INR, and partial thromboplastin times were checked at baseline and weeks 13, 26, and 52. For subjects not on anticoagulation with heparin or a vitamin K antagonist, mean values at all time points for all treatment groups were normal with no significant changes between time points. Individual values for the 18 subjects on anticoagulation therapy were reviewed, with no pattern of change noted.

Shifts: Shift tables for all hematology parameters were reviewed. A very slight predilection towards baseline leukocytopenia normalizing was noted in all treatment groups. No significant shifts were noted.

Shift tables for all chemistry parameters were reviewed. These were remarkable for the number of elevated alkaline phosphatase values at baseline which normalized during the trial. Hypocalcemia in subjects normocalcemic at baseline was slightly more prevalent at day 14, especially in the DRBB group, than later in the trial, when shift to hypocalcemia was about equal between groups. This is further discussed below (see next section). High iPTH values in subjects with normal values at baseline tended to be present in large numbers at day 14 for all treatment groups, but this tendency lessened later in the trial. The 35 mg DRBB group may have shown a greater tendency for iPTH increase (see next section).

Intact PTH and mineral metabolism: As elevated PTH was frequently seen, further evaluation from datasets was performed and results for protocol time points are shown in Table 93. As noted, 115 subjects (37.3%) in the DRBB treatment group had an elevated PTH at some point during the trial, compared to 101 subjects (32.9%) in the

DRFB group and 94 subjects (30.6%) in the IR group. High iPTH values in subjects with normal values at baseline tended to be present in large numbers at day 14 for all treatment groups (32 subjects [12.7%], 5 mg IRBB; 44 subjects [17.7%], 35 mg DRFB; 50 subjects [19.1%], 35 mg DRBB, from shift tables), but this tendency lessened later in the trial (at Week 52, 18 subjects [8.0%], 5 mg IRBB; 19 subjects [8.6%], 35 mg DRFB; 25 subjects [10.9%], 35 mg DRBB, from shift tables). The time point with the most subjects with elevated levels was 2 weeks for all treatment groups. Prolonged elevation was present in a number of subjects, especially in the DRBB group. In that group, 48 subjects (15.6%) had a high PTH at week 26 or 52 after a normal baseline measurement compared to 26 (8.5%) in the IR group.

Markedly high iPTH (>98 pg/ml) and shifts of iPTH from normal to markedly high were also assessed. At Day 14, 3 subjects (1.2%) in the 5 mg IRBB group, 7 subjects (2.8%) in the 35 mg DRFB group, and 13 subjects (5.0%) in the 35 mg DRBB group had developed markedly high iPTH values (from shift tables). Markedly elevated PTH was noted at some point during the trial in 37 subjects (12.0%) in the DRBB treatment group compared to 19 subjects (6.2%) in the DRFB group and 20 subjects (6.5%) in the IR group. The time point with the most subjects with markedly elevated levels was again 2 weeks for all treatment groups. Prolonged elevation was present in a greater number of subjects in the DRBB group with 8 subjects (2.6%) having a high PTH at week 26 or 52 after a normal baseline measurement compared to 5 subjects (1.6%) in the DRFB group and 2 subjects (0.7%) in the IR group.

Table 93, Trial 2007008 Serum PTH from Datasets

	5 mg IR Daily	35 mg DRFB Wkly	35 mg DRBB Wkly
N	307	307	308
High PTH at screening ¹ or baseline	43 (14.0%)	38 (12.4%)	36 (11.7%)
High PTH at 2 weeks	58 (18.9%)	68 (22.1%)	70 (22.7%)
High PTH at 26 weeks	29 (9.4%)	30 (9.8%)	47 (15.3%)
High PTH at 52 weeks	35 (11.4%)	30 (9.8%)	42 (13.6%)
High PTH at any protocol time	94 (30.6%)	101 (32.9%)	115 (37.3%)
High PTH at 26 or 52 weeks with normal at baseline and screening ¹	26 (8.5%)	33 (10.7%)	48 (15.6%)
Very high PTH at screening ¹ or baseline	9 (2.9%)	4 (1.3%)	9 (2.9%)
Very high PTH at 2 weeks	14 (4.6%)	13 (4.2%)	23 (7.5%)
Very high PTH at 26 weeks	6 (2.0%)	3 (1.0%)	13 (4.2%)
Very high PTH at 52 weeks	5 (1.6%)	7 (2.3%)	11 (3.6%)
Very high PTH at any protocol time	20 (6.5%)	19 (6.2%)	37 (12.0%)
Very high PTH at 26 or 52 weeks with normal at baseline and screening ¹	2 (0.7%)	5 (1.6%)	8 (2.6%)
DRFB = delayed release formulation immediately following breakfast weekly DRBB = delayed release formulation at least 30 minutes before breakfast weekly High PTH ≥ 66 pg/ml Very high PTH ≥ 98 pg/ml 1 Screening PTH only done in Argentine subjects Source: Trial 2007008 datasets			

The mean values for serum calcium, phosphorus, and magnesium were within the normal range at all time points and similar across treatment groups, with no large or clinically important mean changes at any time point. Shifts in phosphorus and magnesium were small and not clinically meaningful. Shift to hypocalcemia was slightly more prevalent at day 14, especially in the DRBB group (8 subjects [2.8%], 5 mg IRBB; 9 subjects [3.2%], 35 mg DRFB; 15 subjects [5.1%], 35 mg DRBB) than later in the trial, when shift to hypocalcemia was about equal between groups (at Week 52, 7 subjects [2.8%], 5 mg IRBB; 5 subjects [2.0%], 35 mg DRFB; 7 subjects [2.8%], 35 mg DRBB). Few markedly abnormal calcium or phosphorus levels were noted on treatment, with no more than 2 subjects a category from any treatment group.

A subset of 356 subjects underwent 24 hour urine collection for calcium excretion and creatinine clearance at baseline and Week 52. Mean urinary calcium excretions were normal and similar between treatment groups at baseline and 52 weeks. No pattern of change from baseline to Week 52 was observed.

Reviewer comment: There appears to be more PTH elevation in the DRBB treatment group which, in some subjects, is prolonged, but this appears not to be associated with major effects on mineral levels or urinary calcium excretion with only the slight shift to hypocalcemia at Day 14 noted. As there is probably similar or perhaps slightly less risedronate absorption with DRBB dosing compared to DRFB if absorption is proportional to the 50 mg DR formulation in Trial 2005107, perhaps the EDTA plays a role. How EDTA dosed at least 30 minutes before breakfast could interfere with calcium absorption or otherwise raise PTH is unclear. Perhaps increased absorption of EDTA occurs with an empty stomach but absorption is reported as < 5% of an oral dose. The EDTA used in the DR formulation is edetate disodium, which will cause hypocalcemic tetany with rapid IV infusion, rather than edetate calcium disodium, which would likely cause problems with risedronate absorption.

Various risedronate IR strengths have not shown PTH elevation relative to risedronate 5 mg. There appears to have been some mean PTH elevation with risedronate for a prolonged period of time, as much as 36 months, in the initial Phase 3 risedronate vs. placebo trials, but limited information on those trials is available.

Vital Signs: Mean vital sign values were normal at all time points for all vital signs tested (BP, HR, and T) in all treatment groups. No clinically significant changes from baseline were seen. BMI for all treatment groups was at or slightly above 25.0 kg/m² and stable.

Shift tables for systolic blood pressure showed perhaps increased subjects in the DR regimens who were normotensive at baseline and then high (>140) especially at 52

weeks or endpoint (at Week 52, 23 subjects [10.4%], 5 mg IRBB; 31 subjects [14.0%], 35 mg DRFB; 40 subjects [17.8%], 35 mg DRBB). For diastolic blood pressure the increase (considered high at >89) was more equal across treatment groups (at Week 52, 31 subjects [13.7%], 5 mg IRBB; 29 subjects [13.3%], 35 mg DRFB; 28 subjects [12.1%], 35 mg DRBB). How much of this increase is from the common increase of blood pressure with age is unknown. A similar trend was not found in other risedronate trials for which shift tables were available. Markedly high blood pressures were uncommon. For systolic blood pressure 5 subjects (1.8%) in the 5 mg IRBB group at week 26 and 6 (2.3%) in the 35 mg DRFB group at week 39 were markedly high (> 200 mmHg or \geq 180 mmHg and increase since baseline \geq 30 mmHg). No other treatment group and time point had more than 2 subjects in this category. For diastolic blood pressure, at no time point did more than 2 subjects in a treatment group have a markedly high measurement (> 115 mmHg or \geq 105 mmHg and increase since baseline \geq 20 mmHg).

Safety Conclusions: Pharmacokinetic trials have shown an increased systemic absorption of 2 to 4 time of the 35 mg risedronate DR formulation, whether taken at least 30 minutes before breakfast or immediately after breakfast, over approved IR doses. Safety is thus a primary concern for the DR formulation.

A trend toward more subjects with adverse events with the DR formulation, especially the DRBB regimen, is noted (68.7% for 5 mg IRBB, 72.3% for 35 mg DRFB, and 77.3% for 35 mg DRBB, $p=0.0572$). More adverse events per subject with adverse event are reported with the DR regimens (3.1 for 5 mg IRBB, 3.3 for 35 mg DRFB, and 3.4 for 35 mg DRBB). When log transformed number of AEs among the three treatment groups is compared, there are statistically increased AEs in the DRBB group (number of AEs 660 for 5 mg IRBB, 734 for 35 mg DRFB, and 804 for 35 mg DRBB, DRFB to IR $p=0.2277$, DRBB to IR $p=0.0227$).

The Phase 2 dose finding trial 2005107, a shorter 13 week trial, had one group (50 mg DRFB) with about 65% more AEs per subject with AE, while the number of AEs per subject with AE was similar in the other three groups (35 mg IRBB, 35 mg DRFB, and 50 mg DRBB). This tends to corroborate the increased AEs per subject with AEs in the DR regimens.

Only one death was reported and serious adverse events and adverse events resulting in withdrawal are equivalent between groups and without concerning signals. Adverse events in the gastrointestinal disorder SOC were the most common reason for withdrawal for all treatment groups.

System organ classes (SOC) with the most reported AEs across all treatment groups were gastrointestinal disorders (32%), infections and infestations (31%), and musculoskeletal and connective tissue disorders (25%). Preferred terms with the most AEs across treatment groups were arthralgia (7%) nasopharyngitis (7%), diarrhea (7%),

back pain (6%), and influenza (6%). No system organ classes had statistically significant differences between treatment groups for AEs. Preferred terms with statistically significant differences between treatment groups for AEs were abdominal pain upper (5 mg IRBB with 7 subjects (2.3%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 23 subjects (7.5%), $p=0.0041$), osteoarthritis (5 mg IRBB with 8 subjects (2.6%), 35 mg DRFB with 5 subjects (1.6%), 35 mg DRBB with 1 subject (0.3%), $p=0.0388$), and gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; $p=0.0366$). In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat) 19 (6.2%) subjects in the 5 mg IRBB group, 29 (9.4%) subjects in the 35 mg DRFB group and 40 (13.0%) subjects in the 35 mg DRBB group reported AEs ($p=0.0164$).

A total of 27 subjects reported clinical fractures as AEs (6 [2.0%] subjects, 5 mg IRBB; 9 [2.9%] subjects, 35 mg DRFB; 12 [3.9%] subjects, 35 mg DRBB, $p=0.3799$). Although numerically more subjects in the DR regimens suffered clinical fractures, this difference did not reach statistical significance. Overall, fracture types appear similar between groups. Greater numbers of clinical fractures in the DR regimens concern this reviewer about disordered bone apposition with the higher risedronate exposure. Adequate bone biopsy information is needed.

Markedly elevated PTH (>98 pg/ml) occurred in 20 subjects (6.5%) in the 5 mg IRBB group, 19 subjects (6.2%) in the 35 mg DRFB group, and 37 subjects (12.0%) in the 35 mg DRBB group. This peaked at Day 14, when 14 subjects (4.6%) in the 5 mg IRBB group, 13 subjects (4.2%) in the 35 mg DRFB group, and 23 subjects (7.5%) in the 35 mg DRBB group had markedly high iPTH values. By Week 52, 5 subjects (1.6%) in the 5 mg IRBB group, 7 subjects (2.3%) in the 35 mg DRFB group, and 11 subjects (3.6%) in the 35 mg DRBB group had markedly high iPTH values. Prolonged elevation was present in a greater number of subjects in the DRBB group with 8 subjects (2.6%) having a high PTH at week 26 or 52 after a normal baseline measurement compared to 5 subjects (1.6%) in the DRFB group and 2 subjects (0.7%) in the IR group. Subjects with markedly high PTH levels may remain more common in the DRBB group. Shift tables confirm elevated PTH most marked at Day 14, but with perhaps continuation at Week 52, especially in the DRBB group. A slight tendency to hypocalcemia was noted in the shift tables, especially at Day 14 in the DRBB group, but mean values for calcium, magnesium, and phosphorus were normal at all time points with similar values for all treatment groups and with no large or clinically important mean changes at any time point. Only 2 subjects, both in the 5 mg IRBB group, were withdrawn for hyperparathyroidism.

Shift tables for systolic blood pressure showed perhaps increased subjects in the DR regimens who were normotensive at baseline and then high (>140) especially at 52 weeks or endpoint (at Week 52, 23 subjects [10.4%], 5 mg IRBB; 31 subjects [14.0%], 35 mg DRFB; 40 subjects [17.8%], 35 mg DRBB). For diastolic blood pressure the increase (considered high at >89) was more equal across treatment groups (at Week

52, 31 subjects [13.7%], 5 mg IRBB; 29 subjects [13.3%], 35 mg DRFB; 28 subjects [12.1%], 35 mg DRBB). How much of this increase is from the common increase of blood pressure with age is unknown. Markedly high blood pressures were uncommon.

Discussion and Conclusions: By all measures, both of the 35 mg weekly delayed release risedronate regimens (at least 30 minutes before breakfast [DRBB] and immediately following breakfast [DRFB]) are superior to placebo and, in the case of lumbar spine bone mineral density (BMD), are not inferior in efficacy to the approved 5 mg immediate release daily regimen (IRBB) (3.4% increased lumbar spine BMD for each of the DR regimens, 3.1% for the IR regimen, upper limit of the 95% 2-sided CI for the difference 0.349% for the DRFB regimen and 0.281% for the DRBB regimen, non-inferiority margin 1.5%). Lumbar spine BMD non-inferiority was the primary efficacy measure.

Almost always numerically, and in some cases statistically, the DR regimens are superior to the IR regimen in this BMD trial which also measured bone turnover markers (BTMs). This is not surprising given the known high absorption of the DR formulation. Statistical superiority for the DR regimens over the IR regimen was not shown, however, for lumbar spine BMD ($p=0.299$) as one of the secondary efficacy measures. This trial is not powered for fracture endpoints.

A trend toward more subjects with adverse events with the DR formulation, especially the DRBB regimen is noted, which almost reaches statistical significance (68.7% for 5 mg IRBB, 72.3% for 35 mg DRFB, and 77.3% for 35 mg DRBB, $p=0.0572$). When log transformed number of AEs among the three treatment groups is compared, there are statistically increased AEs in the DRBB group (number of AEs 660 for 5 mg IRBB, 734 for 35 mg DRFB, and 804 for 35 mg DRBB, DRFB to IR $p=0.2277$, DRBB to IR $p=0.0227$).

No system organ classes had statistically significant differences between treatment groups for AEs. Preferred terms with statistically significant differences between treatment groups for AEs were abdominal pain upper (5 mg IRBB with 7 subjects (2.3%), 35 mg DRFB with 9 subjects (2.9%), 35 mg DRBB with 23 subjects (7.5%), $p=0.0041$), osteoarthritis (5 mg IRBB with 8 subjects (2.6%), 35 mg DRFB with 5 subjects (1.6%), 35 mg DRBB with 1 subject (0.3%), $p=0.0388$), and gastrointestinal pain (5 mg IRBB group, 0 subjects; 35 mg DRFB group, 0 subjects, 35 mg DRBB group, 4 subjects; $p=0.0366$). In the MedDRA high level term (HLT) gastrointestinal and abdominal pains (excluding oral and throat) 19 (6.2%) subjects in the 5 mg IRBB group, 29 (9.4%) subjects in the 35 mg DRFB group and 40 (13.0%) subjects in the 35 mg DRBB group reported AEs ($p=0.0164$).

A total of 27 subjects reported clinical fractures as AEs (6 [2.0%] subjects, 5 mg IRBB; 9 [2.9%] subjects, 35 mg DRFB; 12 [3.9%] subjects, 35 mg DRBB, $p=0.3799$). Although numerically more subjects in the DR regimens suffered clinical fractures, this difference

did not reach statistical significance. Greater numbers of clinical fractures in the DR regimens concern this reviewer about disordered bone apposition with the higher risedronate exposure. Adequate bone biopsy information at appropriate risedronate dose is needed.

Markedly elevated PTH (>98 ng/l) occurred in 16 subjects (5.3%) in the 5 mg IRBB group, 19 subjects (6.3%) in the 35 mg DRFB group, and 38 subjects (12.5%) in the 35 mg DRBB group. This peaked at Day 14, when 14 subjects (4.8%) in the 5 mg IRBB group, 13 subjects (4.5%) in the 35 mg DRFB group, and 22 subjects (7.4%) in the 35 mg DRBB group had markedly high iPTH values. By Week 52, 5 subjects (1.9%) in the 5 mg IRBB group, 7 subjects (2.7%) in the 35 mg DRFB group, and 11 subjects (4.2%) in the 35 mg DRBB group had markedly high iPTH values. Subjects with markedly high PTH levels may remain more common in the DRBB group. This reviewer feels longer follow up is needed.

Shift tables for systolic blood pressure showed perhaps increased subjects in the DR regimens who were normotensive at baseline and then high (>140) especially at 52 weeks or endpoint (at Week 52, 23 subjects [10.4%], 5 mg IRBB; 31 subjects [14.0%], 35 mg DRFB; 40 subjects [17.8%], 35 mg DRBB). For diastolic blood pressure the increase (considered high at >89) was more equal across treatment groups. Markedly high blood pressures were uncommon. This reviewer feels longer follow up is needed.

Phase 1 PK Trials with DR Comparison to IR:

Study 2003066: An Open-label, Single-center, Single-dose, Randomized, Parallel-group Study to Compare Absorption of Risedronate 50 mg in Healthy Volunteers Following Oral Administration of an Immediate Release Tablet or (b) (4) Capsule with Delivery to the Ascending Colon

(b) (4) This brief review is primarily focused on overall safety.

Study type and objective: This is a single dose bioavailability study comparing absorption of risedronate with and without EDTA in a capsule to release drug in the ascending colon to an immediate release risedronate.

Study design: Nine subjects in each of three treatment groups received a single dose of study drug:

- Treatment A: Risedronate 50 mg in an (b) (4) capsule to release drug in the ascending colon
- Treatment B: Risedronate 50 mg and EDTA (b) (4) in an (b) (4) capsule
- Treatment C: Risedronate 50 mg immediate release (IR) tablet.

Study drug was given with 240 ml of water. (b) (4) capsules were electronically opened when radioactive tracers confirmed the desired location in the ascending colon had been reached. Subjects were fasted overnight before dosing and for an additional 4 hours for the IR tablet or 2 hours after capsule activation for the (b) (4) capsule.

Population: Healthy males and females age 18 to 45 were eligible to enroll. All 27 subjects were male.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: Two subjects in the (b) (4) capsule Risedronate EDTA group were excluded from analysis due to failure of the capsule to activate before elimination.

Brief summary of pharmacokinetics: Urinary excretion was reduced by 70% for risedronate released from the capsule in the ascending colon compared to the immediate release risedronate taken fasting with a further 4 hours of fasting after dosing. Adding EDTA to the capsule increased excretion to 60% above the IR risedronate (see Table 94).

Table 94, Trial 2003066 Risedronate Urinary Excretion

	Risedronate IR	Risedronate in Capsule	Ris + EDTA in Capsule
A'e (%)	0.410	0.123	0.655
Excretion compared to IR dose in percent		30	160
A'e = % of dose excreted over 72 hours Source: Study report 2003066 EoT Table 4			

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: None

Adverse events: One AE was reported by 1 subject with the IR tablet, 4 AEs were reported by three subjects with the (b) (4) capsule, and 8 AEs were reported by 4 subjects with the capsule with EDTA (N = 9 for each treatment group).

IR tablet:

- 1 subject with arthralgia

(b) (4) capsule:

- 1 subject with arthralgia and monocytes increased
- 1 subject with monocytes increase
- 1 subject with injury

(b) (4) capsule with EDTA:

- 1 subject with headache, myalgia, and epigastric pain
- 1 subject with arthralgia and asthenia
- 1 subject with back pain and contusion
- 1 subject with monocytes increased

Reviewer comment: This is a small single dose trial which makes interpretation difficult, but more AEs are noted with risedronate delivered to the ascending colon, especially with EDTA added, than with the IR risedronate. A number of these AEs are known to be associated with risedronate (arthralgia, myalgia, epigastric pain, asthenia, back pain). If indeed AEs are increased, it may be site of delivery, increased absorption (with the EDTA), the EDTA, or another factor.

Study 2004035: An Open-label, Single-dose, Randomized, Parallel-group Study to Compare Relative Absorption of 35 mg Risedronate Delivered to Various Segments of the Gastrointestinal Tract, With and Without Food, versus Oral Administration in Healthy Volunteers

(b) (4) This brief review is primarily focused on overall safety.

Study type and objective: This is a single dose bioavailability study comparing absorption of risedronate with EDTA in a capsule to release drug at various intestinal sites under fed and fasted conditions to an immediate release (IR) risedronate.

Study design: Nine to eleven subjects in each of 8 treatment groups received a single dose of study drug:

- Treatment A: Risedronate 35 mg IR followed by a 4 hour fast
- Treatment B: Risedronate 35 mg and EDTA (b) (4) in an (b) (4) capsule (study capsule)/jejunal release fasted
- Treatment C: Study capsule/jejunal release fed
- Treatment D: Study capsule /terminal ileal release fasted
- Treatment E: Study capsule /terminal ileal release fed
- Treatment F: Study capsule /ascending colon release fasted
- Treatment G: Study capsule /ascending colon release fed
- Treatment H: Study capsule /distal colon release fasted

Study drug was given with 240 ml of water. (b) (4) capsules were electronically opened when radioactive tracers confirmed the desired location in the intestine had been reached. Subjects were fasted overnight before dosing and for an additional 4 hours for the IR tablet or 2 hours after capsule activation for the (b) (4) capsule fasted groups. (b) (4) capsule fed groups had a light breakfast and took the capsule 3 hours later with another breakfast immediately on passing of the capsule from the stomach.

Sponsor reports this odd dosing in relation to food was to quicken capsule clearance from the stomach.

Population: Healthy males and females age 18 to 45 were eligible to enroll. Seventy five subjects were male, and 4 were female.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: Two subjects withdrew, one for personal reasons and the other as the (b) (4) capsule could not be activated.

Brief summary of pharmacokinetics: Better absorption was observed generally from small intestinal sites when both fasting and fed administration are considered. Jejunal release offers the best combination of absorption, absorption consistency fasting and fed, and low coefficient of variation (see Table 95, CV not shown).

Reviewer comment: Why ascending colon absorption is so much poorer here than in Trial 2003066 is not clear. The Sponsor also comments on this and attributes it to an “anomaly”.

Table 95, Trial 2004035 Risedronate Urinary Excretion

Treatment Group	N	Geo. Mean A'e	Ratio Trt vs. IR	Fed/Fasted at Site
35 mg IR	10	0.377	--	--
Jejunum fasted	9	0.271	0.720	--
Jejunum fed	9	0.260	0.690	0.96
Terminal ileum fasted	9	0.272	0.722	--
Terminal ileum fed	10	0.308	0.816	1.13
Ascending colon fasted	10	0.036	0.096	--
Ascending colon fed	10	0.056	0.150	1.56
Descending colon fasted	9	0.277	0.736	--

A'e = % of dose excreted over 72 hours
Source: Study report 2004035 EoT Table 5

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: None

Adverse events: As Trial 2004035 is small and single dose, interpretation of adverse event data is difficult. More subjects with small intestinal release of risedronate and EDTA may have AEs, and subjects with terminal ileal release seem to have had more total AEs (see Table 96). These sites tended to have higher absorption than other

intestinal sites. MedDRA classification of AEs was reviewed and many in all groups appear to be typical of those expected with risedronate.

Table 96, Trial 2004035 Adverse Events

Treatment Group	N	Subjects with AE (%)	Total AEs	Aes per Subject
35 mg IR	10	3 (30%)	7	0.70
Jejunum fasted	9	6 (67%)	9	1.00
Jejunum fed	11	4 (36%)	5	0.45
Terminal ileum fasted	9	5 (56%)	12	1.33
Terminal ileum fed	10	6 (60%)	17	1.70
Ascending colon fasted	10	4 (40%)	10	1.00
Ascending colon fed	10	0	0	0
Descending colon fasted	10	3 (30%)	8	0.80

Source: Trial 2004035 EoT Table 6

Reviewer comment: It is difficult to make much of AEs in this single dose trial, although there may be a tendency toward more subjects with AEs and more AEs in the higher absorbing small intestinal sites with the combination of risedronate and EDTA, especially the terminal ileum.

Study 2004132: An Open-label, Multi-center, Single-dose, Randomized, Parallel-group Study to Assess the Relative Absorption of Four Orally Administered 35 mg Delayed-release Prototype Risedronate Formulations Following an Overnight Fast or a High-fat Meal Compared to a 35 mg Immediate-release Risedronate Tablet Following an Overnight Fast in Healthy Adult Volunteers

This trial is reviewed in greater depth by ClinPharm. This brief review is primarily focused on overall safety.

Study type and objective: This is a single dose bioavailability study comparing absorption of risedronate with EDTA with four delayed release coatings under fed and fasted conditions to an immediate release (IR) risedronate.

Study design: Sixteen to 20 subjects in each of 9 treatment groups received a single dose of study drug:

- Risedronate 35 mg IR followed by a 4 hour fast
- Risedronate 35 mg and EDTA (b) (4) (test drug) with pH 5.5 delayed release (designed to release above pH 5.5) low coating fasted and fed
- Test drug with pH 5.5 delayed release high coating fasted and fed
- Test drug with pH 5.5 delayed release/sustained release high coating fasted and fed
- Test drug with pH 7.0 delayed release high coating fasted and fed

Subjects were fasted overnight before dosing. Study drug was given with 240 ml of water. Fasted subjects continued to fast an additional 4 hours post dose. Fed subjects received a high fat breakfast before the study drug.

Population: Healthy males and females age 40 to 70 were eligible to enroll. One hundred twenty subjects were male and 40 were female.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: Two subjects were withdrawn for incomplete urine collections, one from the IR group and one from the delayed release/sustained release fed group. The cause for exclusion from analysis of another 4 subjects is not given (1 subject in the IR group, 2 subjects from the pH 5.5 high coating fasted group, and 1 subject from the pH 5.5 high coating fed group).

Brief summary of pharmacokinetics: Urinary excretion of the various DR formulations ranged from 6 to 57% that of the IR formulation. The DR pH 5.5 low coating formulation had the best combination of absorption, absorption consistency fasting and fed, and low coefficient of variation (see Table 97).

Table 97, Trial 2004132 Risedronate Urinary Excretion

Treatment	N	Geometric Mean A'e (CV%)	Ratio vs. IR	Ratio of Fed to Fasted
IR, Fasted	18	0.520 (51%)		
DR, pH 5.5, Low Coating, Fasted	18	0.220 (110%)	0.423	
DR, pH 5.5, Low Coating, Fed	18	0.161 (97%)	0.309	0.730
DR, pH 5.5, High Coating, Fasted	16	0.298 (95%)	0.573	
DR, pH 5.5, High Coating, Fed	16	0.082 (183%)	0.158	0.275
DR/SR, pH 5.5, High Coating, Fasted	16	0.154 (113%)	0.296	
DR/SR, pH 5.5, High Coating, Fed	18	0.032 (138%)	0.061	0.206
DR, pH 7.0, High Coating, Fasted	18	0.108 (169%)	0.208	
DR, pH 7.0, High Coating, Fed	16	0.038 (172%)	0.072	0.347

A'e = % of dose excreted over 72 hours
 Source: Study Report 2004132 Table 5

A subset of subjects had scintigraphic evaluation of study drug disintegration with radioactive tracers. The cumulative amount of risedronate recovered in urine appeared to be independent of site of release prior to the ascending colon, after which it appeared to decrease. An inverse relationship appeared to exist between the cumulative amount recovered in urine and the total time for disintegration (increasing time leading to a decrease in urinary excretion).

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: None

Adverse events: As Trial 2004132 is small and single dose, interpretation of adverse event data is difficult. More subjects with delayed release risedronate and EDTA may have AEs compared to the IR risedronate, but that is not the case for all groups (see Table 98). MedDRA classification of AEs was reviewed and many in all groups appear to be typical of those expected with risedronate.

Table 98, Trial 2004132 Adverse Events

Treatment	N	Subjects with AE (%)	Total AEs	AEs per Subject
IR, Fasted	20	5 (25%)	8	0.40
DR, pH 5.5, Low Coating, Fasted	18	2 (11%)	6	0.33
DR, pH 5.5, Low Coating, Fed	18	6 (33%)	13	0.72
DR, pH 5.5, High Coating, Fasted	18	8 (44%)	12	0.67
DR, pH 5.5, High Coating, Fed	17	3 (18%)	5	0.29
DR/SR, pH 5.5, High Coating, Fasted	16	6 (38%)	9	0.56
DR/SR, pH 5.5, High Coating, Fed	19	8 (42%)	13	0.68
DR, pH 7.0, High Coating, Fasted	18	8 (44%)	10	0.56
DR, pH 7.0, High Coating, Fed	16	5 (31%)	8	0.50

Source: Study Report 2004132 Table 7

A large number GI SOC AEs were noted in the DR formulation to be carried forward (pH 5.5, low coating) compared to the IR formulation (1 for IR, 4 and 10 respectively for the DR pH 5.5 low coating fasted and fed).

Reviewer comment: Although more subjects in the DR risedronate + EDTA groups may have had AEs compared to the IR risedronate, numbers are small in this single dose study. There may be more GI SOC AEs in the DR formulation carried forward (pH 5.5 low coating) than the IR formulation.

Study 2007120: A Randomized, Open-label, Single-dose, Four-period Crossover Study to Assess the Influence of a High-fat Meal on the Relative Bioavailability of a 35 mg Delayed-release Formulation of Risedronate Compared to the Same 35 mg Delayed-release Formulation under Fasted Conditions and a 35 mg Immediate-release Formulation Administered Fasted or 30 Minutes Prior to a High-fat Meal in Postmenopausal Women

This trial is reviewed in greater depth by ClinPharm. This brief review is primarily focused on overall safety.

Study type and objective: This is a randomized, 4 period, single dose per period crossover bioavailability study comparing absorption of a delayed release (DR)

risedronate 35 mg with EDTA (b) (4) to an immediate release (IR) risedronate 35 mg under different dosing conditions.

Study design: Four 4 day treatment periods were separated by washout periods of 14 to 21 days. Subjects were randomly assigned to 1 of 12 treatment sequences of:

- 35 mg DR administered orally after an overnight (10 hour) fast, followed by a 4-hour fast (35 mg DR Fasted)
- 35 mg DR administered orally after an overnight fast, within 5 minutes after ingesting a high-fat meal (35 mg DR Fed)
- 35 mg IR administered orally after an overnight fast, followed by a 4-hour fast (35 mg IR Fasted)
- 35 mg IR administered orally after an overnight fast, 30 minutes before ingesting a high-fat meal (35 mg IR Per-label)

The study drug was administered with at least 120 ml of water.

Population: Surgically sterile or postmenopausal females age 40 to 70 were eligible to participate.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: Of 76 subjects entering, 74 completed the trial. One subject was withdrawn for participating in another study at the same time and another for using false ID at study entry.

Brief summary of pharmacokinetics: Systemic exposure following taking the 35 mg DR formulation after a high fat breakfast is over twice that of the 35 mg IR formulation per label (see Table 99).

Table 99, Trial 2007120 Risedronate Urinary Excretion

	Ae (µg)	A'e (%)	Ae ratio to 35 mg IR per label
35 mg IR fasted	124.7	0.356	2.16
35 mg IR per label	57.7	0.165	
35 mg DR fasted	180.0	0.514	3.12
35 mg DR fed	126.4	0.361	2.19

Ae = risedronate excreted over 72 hours, A'e = % of dose excreted over 72 hours
Source: Study Report 2007120, Tables 3 and 4

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: None

Adverse events: Subjects with adverse events are equal after IR and DR formulations (see Table 100). MedDRA classification of AEs was reviewed and many in all groups appear to be typical of those expected with risedronate.

Table 100, Trial 2007120 Adverse Events

	35 mg IR Per-label (N=75)	35 mg IR Fasted (N=75)	35 mg DR Fed (N=75)	35 mg DR Fasted (N=76)
	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE
AEs	15 (20%) 27	21 (28%) 34	20 (27%) 40	16 (21%) 35
n = number of subjects, nAE = number of adverse events Source: Study Report 2007120, Table 5				

More musculoskeletal and CTD SOC AEs were seen with the DR formulation (5 after 35 mg IR per label, 2 after 35 mg IR fasted, 6 after 35 mg DR fed, and 8 after 35 mg DR fasted groups) and more headaches with the 35 mg IR fasted dose (5 after 35 mg IR per label, 15 after 35 mg IR fasted, 7 after 35 mg DR fed, and 6 after 35 mg DR fasted groups).

Reviewer comment: In this single dose per treatment period, 4 period crossover trial, there is little difference between the DR and IR arms in AEs. More musculoskeletal and CTD SOC AEs are seen after the DR formulation.

Study 2008052: A Randomized Open-label, Single-dose, Four-period Crossover Study to Assess the Influence of Food on the Relative Bioavailability of a Risedronate 20 mg Delayed-release (DR) Tablet and to Compare the 20 mg DR Tablet to 35 mg DR and 35 mg Immediate-release Tablets in Postmenopausal Women

This trial is reviewed in greater depth by ClinPharm. This brief review is primarily focused on overall safety.

Study type and objective: This is a randomized, 4 period, single dose per period crossover bioavailability study comparing absorption of a delayed release (DR) risedronate 20 mg with EDTA (b) (4) taken fed and fasted to an immediate release (IR) risedronate 35 mg taken per label. A 35 mg DR tablet taken fed was also included.

Study design: Four 4 day treatment periods were separated by washout periods of 14 to 17 days. Subjects were randomly assigned to 1 of 12 treatment sequences of:

- 20 mg DR administered orally after an overnight (10 hour) fast, within 5 minutes after ingesting a high-fat meal (20 mg DR Fed)
- 20 mg DR administered orally after an overnight fast, followed by a 4-hour fast (20 mg DR Fasted)
- 35 mg DR Fed

- 35 mg IR administered orally after an overnight fast, 30 minutes before ingesting a high-fat meal (35 mg IR per label)

The study drug was administered with at least 120 ml of water.

Population: Surgically sterile or postmenopausal females age 40 to 70 were eligible to participate.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: Of 94 subjects entering, 92 completed the trial. One subject “voluntarily withdrew” and another withdrew for an AE.

Brief summary of pharmacokinetics: Systemic exposure following taking the 35 mg DR formulation after a high fat breakfast was over four times that of the 35 mg IR formulation per label in this trial (see Table 101). Systemic exposure following taking the 20 mg DR formulation after a high fat breakfast is still twice that of the 35 mg IR formulation per label.

Table 101, Trial 2008052 Risedronate Urinary Excretion

	N	Ae (µg)	A'e (%)	Ae ratio to 35 mg IR per label
35 mg IR per label	93	47.2	0.13	
35 mg DR fed	90	197.1	0.56	4.2
20 mg DR fed	94	93.1	0.46	2.0
20 mg DR fasted	93	75.4	0.37	1.6

Ae = risedronate excreted over 72 hours, A'e = % of dose excreted over 72 hours
 Source: Study Report 2008052, Tables 3 and 4

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: A 60 year old Caucasian female withdrew with pyrexia and cough 18 days after risedronate 20 mg DR fasted between treatment period 3 and 4. The event was reported as ongoing.

Adverse events: In this trial, more subjects had AEs after the 35 mg DR formulation following a high fat breakfast than after the 35 mg IR per label. Many more total AEs were reported after the 35 mg DR formulation (see Table 102).

Table 102, Trial 2008052 Adverse Events

	35 mg IR Per-label (N=94)	35 mg DR Fed (N=93)	20 mg DR Fed (N=94)	20 mg DR Fasted (N=93)

	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE
AEs	21 (22%) 32	26 (28%) 77	24 (26%) 46	14 (15%) 24
n = number of subjects, nAE = number of adverse events Source: Study Report 2008052, Table 5				

A review of adverse event differences after the 35 mg IR and 35 mg DR treatments showed substantially more after the DR formulation in the following SOC:

- GI SOC (8 subjects with 9 AEs after IR, 14 subjects with 30 AEs after DR and especially more diarrhea, abdominal pain, and nausea after DR)
- General disorders SOC (3 subjects with 4 AEs after IR, 7 subjects with 8 AEs after DR and especially more chills after DR)
- Musculoskeletal and CTD SOC (5 subjects with 6 AEs after IR, 10 subjects with 13 AEs after DR and especially more in HLT MS and CTD signs and symptoms after DR)
- Nervous system SOC (6 subjects with 6 AEs after IR, 13 subjects with 18 AEs after DR and especially more headaches after DR)
- Skin and subcutaneous tissue SOC (1 subject with 1 AE after IR, 4 subjects with 5 AEs after DR)

Reviewer comment: More subjects had AEs and especially more AEs were present after dosing with risedronate DR 35 mg after breakfast than the 35 mg IR per label in this single dose per treatment period crossover trial. Many of these AEs are typically associated with risedronate. The AE difference may have to do with the exceptionally high systemic exposure difference noted in this trial.

Given that this is a crossover trial, more credibility may be given to the increased number of adverse events, as that increase is greater than the increase in subjects with adverse events.

Study 2008076: A Randomized, Partially-blinded, Single-rising-Dose, Multicenter, Parallel-design, Phase I, Tolerability, and Pharmacokinetic Study of 3 Delayed-release Risedronate Formulations Compared to a 150 mg Immediate-release Risedronate Formulation in Normal Healthy Women Between the Ages of 40-70

This trial is reviewed in greater depth by ClinPharm. This brief review is primarily focused on overall safety.

Study type and objective: The objectives of this single dose parallel group study were to explore the tolerability and bioavailability of the risedronate 75, 100, and 150 mg delayed-release (DR) formulation tablets (presumably with (b) (4) EDTA, this is not stated) relative to the risedronate 150 mg immediate-release (IR) formulation tablet after a single oral dose. Potential of a monthly DR dose was being explored. The Sponsor

reports, as absorption and tolerability criteria were met with the first cohort with the 75 mg DR and 100 mg DR doses, the cohort with the 150 mg DR dose was not studied.

Study design: Sixteen or 32 subjects in each of 5 treatment groups received a single dose of study drug:

- 75 mg DR risedronate administered orally after an overnight (10-hour) fast, followed by a 4-hour fast (75 mg DR fasted)
- 75 mg DR risedronate administered orally after an overnight fast, within 5 minutes after ingesting a high-fat meal (75 mg DR fed)
- 100 mg DR fasted
- 100 mg DR fed
- 150 mg IR risedronate administered orally after an overnight fast, 30 minutes before ingesting a high-fat meal (150 mg IR per-label)

Study drug was given with 120 ml of bottled water. Only bottled water with low calcium carbonate content was allowed from 10 hours before dosing to 4 hours post dose.

Population: Surgically sterile or postmenopausal females age 40 to 70 were eligible to participate.

Efficacy measures: Urine was collected for risedronate analysis for 72 hours after dosing.

Subject disposition: All 112 subjects entering the trial completed it.

Brief summary of pharmacokinetics: The 75 mg DR formulation fed had about the same urinary excretion as the 150 mg IR per label. The 100 mg DR formulation fed had 1.5 times the urinary excretion of the 150 mg IR per label. At both DR doses, urinary excretion of the fasted was about 15% higher than the fed regimen (see Table 103).

Table 103, Trial 2008076 Risedronate Urinary Excretion

	N	Ae (µg)	A'e (%)	Ae ratio to 150 mg IR per label
150 mg IR per label	16	339.0	0.226	
75 mg DR fasted	16	408.6	0.545	1.2
75 mg DR fed	32	348.1	0.464	1.0
100 mg DR fasted	16	583.2	0.583	1.7
100 mg DR fed	32	507.9	0.508	1.5

Ae = risedronate excreted over 72 hours, A'e = % of dose excreted over 72 hours
Source: Study Report 2008076, Tables 5 and 6

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events: None

Adverse events: More subjects in the DR treatment groups had AEs, and that trend was greater with the higher dose. The DR groups all had at least twice the AEs per subject as the IR group (see Table 104).

Table 104, Trial 2008076 Adverse Events

	150 mg IR Per-label (N=16)	75 mg DR Fasted (N=16)	75 mg DR Fed (N=32)	100 mg DR Fasted (N=16)	100 mg DR Fed (N=32)
	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE
AEs	6 (38%) 13	8 (50%) 37	18 (56%) 69	12 (75%) 45	21 (66%) 52
AEs per subject	0.8	2.3	2.2	2.8	1.6
n = number of subjects, nAE = number of adverse events Source: Study Report 2008076, Table 7					

A review of adverse event differences showed the following SOCs with substantially more AEs in the DR treatment groups:

- GI SOC, especially diarrhea in the 100 mg DR fasted group and GI pain HLT all DR groups
- General disorders SOC, especially chills and pain
- Musculoskeletal and CTD SOC, especially HLT MS and CTD signs and symptoms
- Nervous system SOC, especially headache

Subjects with at least 1 AE potentially associated with acute phase reactions by type and time were more frequent in the DR treatment groups (38-56% compared to 25% in the IR group).

Reviewer comment: Clearly a trend is present toward more subjects with AEs and more AEs with increasing DR risedronate dose compared to the 150 mg IR dose in this single dose trial. This reviewer wonders if the adverse event trend contributed to Sponsor not proceeding with the 150 mg DR cohort.

The DR doses in this trial are of course higher than that of the current NDA application.

Phase 1 DR Time of Day and Concomitant Calcium Trial:

Study 2008138: A Randomized Open-label, Multi-center, Single-dose, 3-period Crossover Study to Assess the Influence of a Standard Dinner or a 600 mg Calcium/400 IU Vitamin D Tablet with a Standard Breakfast on the Relative Bioavailability of 35 mg Delayed-release Risedronate Compared to

35 mg Delayed-release Risedronate Administered with a Standard Breakfast in Healthy Women Age 40 to 70 Years

This trial is reviewed in greater depth by ClinPharm. This is a brief review of efficacy and safety findings.

Study type and objective: This single dose, 3 period, crossover study was to assess the relative bioavailability of risedronate 35 mg DR immediately after a standard breakfast and a 600 mg calcium/400 IU vitamin D tablet and immediately after a standard evening meal (dinner), compared to risedronate 35 mg DR administered immediately after a standard breakfast.

Study design: During each of three treatment periods, subjects were admitted the day before study drug administration and remained at the study center for 3 days following administration. Treatment periods were separated by washout periods lasting 14 to 17 days.

Subjects received in random order in the three treatment periods:

- Risedronate 35 mg DR after an overnight (10 hour) fast within 5 minutes after a standard breakfast and taking 1 tablet of 600 mg elemental calcium as calcium carbonate plus 400 IU vitamin D. No additional food was allowed for at least 4 hours post-dose
- Risedronate 35 mg DR oral tablet after a 6 hour fast within 5 minutes after completing a standard dinner. No additional food was allowed for at least 4 hours post-dose
- Risedronate 35 mg DR oral tablet after an overnight (10 hour) fast within 5 minutes after a standard breakfast. No additional food was allowed for at least 4 hours post-dose

Study drug was administered with at least 4 oz/120 ml of plain water. The subject was not to lie down for at least 30 minutes after dosing.

Population: Surgically sterile or postmenopausal females age 40 to 70 were eligible to participate.

Efficacy measures: Urine samples for risedronate PK analysis were collected for 72 hours after dosing.

Subject disposition: Of 106 subjects randomized, 101 received study drug and 94 completed the trial. Voluntary withdrawals accounted for 4 subjects not completing, and 3 subjects withdrew due to an AE. Two subjects had non-detectable levels of risedronate for all collections in 1 period. These subjects had measurable levels of risedronate in the other 2 periods. Subjects who did not have data from 2 treatment periods were not included in the PK analysis.

Brief summary of pharmacokinetics: As shown in Table 105, taking calcium carbonate and vitamin D in the dosage given reduced risedronate urinary excretion for the DRFB dosing by 38%. Taking the DR risedronate following dinner increased risedronate urinary excretion by 86% over the following breakfast regimen.

Numbers of subjects are lower than those listed in Table 106 for having taken the various regimens. In tables in the study report these are listed as “could not calculate” but are not explained.

Table 105, Trial 2008138 Risedronate Urinary Excretion

	N	Ae (µg)	A'e (%)	Ae ratio to 35 mg DRFB
35 mg DRFB	96	120.2	0.344	
35 mg DRFB & Ca/D	87	74.2	0.212	0.62
35 mg DR after dinner	95	222.9	0.637	1.86

Ae = risedronate excreted over 72 hours, A'e = % of dose excreted over 72 hours
 Source: Study Report 2008138, Tables 3 and 4

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events:

- 42 year old Caucasian female withdrew due to strep pharyngitis during the DRFB+Ca/vitD period. The event resolved in 4 days.
- 68 year old Caucasian female withdrew due to a tooth abscess during the DRFB+Ca/vitD period. The event resolved in 8 days.
- 64 year old Caucasian female withdrew due to intestinal flu during the DR dinner period. The event resolved in 3 days.

Adverse events: Total AEs and subjects with AEs were similar between treatment groups (see Table 106).

Table 106, Trial 2008138 Adverse Events

	35 mg DRFB (N=100)	35 mg DRFB & Ca/D (N=97)	35 mg DR after dinner (N=96)	Overall (N=101)
	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE
AEs	24 (24%) 69	24 (25%) 51	30 (31%) 51	59 (58%) 171
AEs per subject	0.7	0.5	0.5	1.7

n = number of subjects, nAE = number of adverse events
 Source: Study Report 2008138, Table 5

Overall, the most frequently reported AE across all treatment regimens was headache (ranging from 4–6% after each treatment). The remaining AEs were generally GI, comprised largely of nausea, diarrhea, constipation, and abdominal pain upper, or

musculoskeletal in nature. Musculoskeletal and connective tissue disorders SOC AEs occurred more frequently in the 35 mg DR after dinner and 35 mg DRFB regimens compared to the 35 mg DRFB & Ca/D regimen (10 subjects [10%] each, 35 mg DR after dinner and 35 mg DRFB regimens, 3 subjects [3%], 35 mg DRFB & Ca/D regimen).

Phase 1 DR Esomeprazole Effect Trial:

Study 2007027: A Randomized, Open-label, Crossover Study to Assess the Influence of Esomeprazole Magnesium on the Relative Bioavailability of a 35 mg Delayed-release Formulation of Risedronate in Postmenopausal Women

This trial is reviewed in greater depth by ClinPharm. This is a brief review of efficacy and safety findings.

Study type and objective: The objective of this 3 period crossover trial was to assess the effect of esomeprazole (eso), administered 1 hour prior to breakfast or dinner, on the bioavailability of risedronate 35 mg DR administered within 15 minutes following breakfast.

Study design: Subjects were admitted to a study center for three 9 day treatment periods with a washout period of at least 7 days between confinements. On days 1 – 8 subjects were in random order assigned to one of the following treatments:

- Placebo 1 hour prior to breakfast and 1 hour prior to the evening meal
- Placebo 1 hour prior to breakfast and esomeprazole 40 mg 1 hour prior to the evening meal
- Esomeprazole 40 mg 1 hour prior to breakfast and placebo 1 hour prior to the evening meal

On the sixth day of each treatment period, all subjects received risedronate 35 mg DR within 15 minutes following breakfast.

Risedronate DR was taken with at least 4 oz/120 ml of plain water. The subject was not to lie down for at least 30 minutes after dosing.

Population: Surgically sterile or postmenopausal females age 40 to 70 were eligible to participate.

Efficacy measures: Urine samples for risedronate PK analysis were collected for 72 hours after risedronate dosing.

Subject disposition: Of 87 subjects randomized to this trial, 2 withdrew for AEs and one for personal reasons. One subject was not compliant with protocol, missing the final esomeprazole on study day 8 before dinner in treatment period 3.

Brief summary of pharmacokinetics: When esomeprazole was taken prior to supper, risedronate absorption from the DR formulation taken following breakfast was reduced by 32%. When esomeprazole was taken prior to breakfast, risedronate absorption from the DR formulation taken following breakfast was reduced by 48% (see Table 107).

Table 107, Trial 2007027 Risedronate Urinary Excretion

	N	Ae (µg)	A'e (%)	Ae ratio to 35 mg DRFB
35 mg DRFB	85	155.7	0.445	
35 mg DRFB, eso before breakfast	84	80.6	0.230	0.52
35 mg DRFB, eso before dinner	83	105.7	0.302	0.68
Ae = risedronate excreted over 72 hours, A'e = % of dose excreted over 72 hours Source: Study Report 2004027, Tables 3 and 10				

Sponsor comments that with the reduced absorption/excretion of risedronate DR with esomeprazole, excretion is still in the range of that seen with the 35 mg IR formulation, so no loss of efficacy would be expected.

Safety:

Deaths: None

Serious adverse events: None

Withdrawal for adverse events:

- 44 year old Caucasian female with upper abdominal pain a day after her first risedronate DR dose. The event resolved in 1 day.
- 46 year old Caucasian female with nausea, vomiting, diarrhea, and flu-like symptoms 3 days after her second risedronate DR dose. The event resolved in 2 days

Adverse events: The percentages of subjects with AEs were similar across the 3 treatment regimens. More total AEs were reported during esomeprazole before breakfast than placebo or esomeprazole before dinner (see Table 108).

Table 108, Trial 2007027 Adverse Events

	35 mg DRFB/placebo (N=85)	35 mg DRFB/eso before breakfast (N=85)	35 mg DRFB/eso before dinner (N=85)	Overall (N=86)
	n (%) nAE	n (%) nAE	n (%) nAE	n (%) nAE
AEs	27 (32%) 58	32 (38%) 85	30 (35%) 60	54 (63%) 203
AEs per subject	0.7	1.0	0.7	2.4
n = number of subjects, nAE = number of adverse events Source: Study Report 2007027, Table 5				

Adverse events were generally similarly distributed, regardless of treatment. The most frequently reported AEs were diarrhea, headache, abdominal pain, and nausea.

Phase 1 DR Bioequivalence (Commercial to Phase 3 Product) Trial:

Study 2008119: A Multi-center, Randomized, Double-blind, Two-treatment, Two-period, Two-sequence, Crossover Study to Assess the Bioequivalence of the Phase III and commercial Risedronate 35 mg Delayed-release Formulations in Healthy Male and Female Subjects

This trial is reviewed in greater depth by ClinPharm. This is a brief review of efficacy and safety findings.

Study type and objective: This 2 period crossover trial was to assess the bioequivalence (BE) between the commercial and the Phase 3 risedronate 35 mg DR formulations, based on C_{max} and AUC, following single dose oral administration.

Study design: During each of two treatment periods, subjects were admitted the day before study drug administration and remained at the study center for 3 days following administration. Treatment periods were separated by washout periods lasting 14 to 17 days.

Subjects received in random order:

- One risedronate 35 mg DR Phase 3 tablet administered orally after an overnight (10-hour) fast, followed by a 4-hour fast
- One 35 mg DR commercial tablet administered orally after an overnight (10-hour) fast, followed by a 4-hour fast

Risedronate DR was taken with at least 4 oz/120 ml of plain water. The subject was not to lie down for at least 30 minutes after dosing.

Population: Healthy males and surgically sterile or postmenopausal females age 18 to 65 were eligible to participate. Mean age of the subjects was 40 years with 62% males and 38% females. Mean age of female subjects (47) was older than male subjects (36). The majority of subjects were Hispanic (65%).

Efficacy measures: Urine for 72 hours and blood samples for 30 hours were collected for risedronate PK analysis.

Subject disposition: There were 579 subjects randomized and 538 dosed. Thirty seven subjects were not dosed as exclusionary criteria were met prior to dosing. The additional 4 subjects were alternates that were not needed.

A site with 53 subjects closed after period 1 dosing. These data could not be verified via the standard query process therefore, these PK data were not included in the PK analyses.

Of the 538 subjects dosed, 85 withdrew and 453 completed the trial. The majority of the withdrawals were from the closed site. Other reasons given for withdrawal are similar for the two treatment groups and include 16 voluntary withdrawals, 9 for AEs (2 of these from the closed site), 3 for protocol violations, 3 lost to follow up, 2 investigator discretion, and 1 “unable to meet protocol criteria”.

Brief summary of pharmacokinetics: For the primary PK parameters of C_{max} and AUC, the commercial risedronate 35 mg DR tablet was bioequivalent to the Phase III risedronate 35 mg DR tablet as demonstrated by the 90% CIs of the ratios that were within the 0.80 – 1.25 range (see Table 109).

Table 109, Trial 2008119 Pharmacokinetic Parameters

	Phase 3 Risedronate 35 mg DR (N=467) (95% CI)	Commercial Risedronate 35 mg DR (N=471) (95% CI)	Commercial/Phase 3 Ratio (90% CI)
C _{max} (ng/ml)	14.1 (12.5, 15.8)	13.8 (12.3, 15.5)	0.98 (0.88, 1.08)
AUC (ng*h/ml)	34.2 (30.3, 38.6)	34.2 (30.3, 38.7)	1.00 (0.90, 1.11)
t _{max} (h)	3.0 (2.9, 3.1)	3.0 (2.9, 3.1)	1.01 (0.98, 1.05)
A _e (µg)	158 (140, 178)	163 (145, 183)	1.03 (0.93, 1.14)
A'e (%)	0.451 (0.401, 0.507)	0.465 (0.414, 0.522)	1.03 (0.93, 1.14)

Source: Study Report 2008119, Table 3

PK data for the Phase 3 and commercial tablets were combined and evaluated by gender (Table 110). For C_{max} and AUC, the ratio of each parameter for males to females was approximately 0.8 and the ratio of t_{max} for males to females was approximately 1.0. For A_e and A'e, the ratio of each parameter for males to females was approximately 0.9. When the PK parameters of the 2 formulations were separately analyzed by gender, similar results were observed.

Table 110, Trial 2008119 Combined PK Parameters by Gender

	Males (N=298) (95% CI)	Females (N=184) (95% CI)	Male/Female Ratio (90% CI)
C _{max} (ng/ml)	12.7 (11.3, 14.2)	15.3 (13.1, 18.0)	0.82 (0.70, 0.97)
AUC (ng*h/ml)	30.9 (27.4, 34.8)	37.9 (32.2, 44.7)	0.81 (0.69, 0.96)
t _{max} (h)	3.0 (2.9, 3.1)	3.0 (2.8, 3.1)	1.02 (0.98, 1.07)
A _e (µg)	153 (136, 172)	168 (143, 196)	0.91 (0.78, 1.07)
A'e (%)	0.437 (0.389, 0.492)	0.479 (0.410, 0.561)	0.91 (0.78, 1.07)

Source: Study Report 2008119, Table 4

Safety:
 Deaths: None

Serious adverse events: A 45 year old Hispanic male 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.

Withdrawal for adverse events: Five (1%) subjects in the Phase 3 35 mg DR treatment and 4 (1%) subjects in the commercial 35 mg DR treatment withdrew from the study due to an AE.

Withdrew during or after the Phase III 35 mg DR treatment period:

- 50 year old Hispanic female withdrew due to gastritis the day after dosing. The event resolved in 4 days.
- 20 year old Caucasian male withdrew due to gastro esophageal reflux disease the day after dosing. The event was reported as ongoing.
- 25 year old multiracial male withdrew due to elevated blood pressure the day after dosing. The event resolved in 7 days.
- 59 year old Hispanic female withdrew due to worsening of cephalgia the day of dosing. The event resolved in 1 day.
- 45 year old Hispanic male withdrew due to a right ankle fracture (b) (4) days after dosing. The event was reported as ongoing.

Withdrew during or after the Commercial 35 mg DR treatment period:

- 28 year old Caucasian male withdrew due to emesis the day of dosing. The event resolved the same day.
- 40 year old Black male withdrew due to myalgia the day after dosing. The event resolved in 3 days.
- 32 year old Hispanic male withdrew due to influenza 20 days after dosing. The event was reported as ongoing.
- 25 year old Hispanic male withdrew due to nausea and loose stool 16 days after dosing. The event resolved in 2 days.

Adverse events: Subjects with adverse events and total adverse events were comparable between treatment groups.

Table 111, Trial 2008119 Adverse Events

	Phase 3 Risedronate 35 mg DR (N=496)	Commercial Risedronate 35 mg DR (N=498)
	n (%) nAE	n (%) nAE
AEs	131 (26%) 286	133 (27%) 273
n = number of subjects, nAE = number of adverse events Source: Study Report 2008119, Table 5		

A smaller percentage of men (35%) experienced an AE than women (50%). The most frequently reported AEs were those associated with the GI disorders SOC (13%, Phase 3, 11%, commercial), MS and CT disorders SOC (7%, Phase 3, 10%, commercial), and nervous system disorders SOC (9%, Phase 3, 9%, commercial). The most frequently reported AEs by PT were diarrhea (8%, Phase 3, 6%, commercial) and headache (7%,

Phase 3, 8%, commercial). There was little difference in the number of subjects reporting AEs by treatment except for the PT abdominal distension (7 [1%], Phase 3, 1 [< 1%], commercial) and abdominal pain lower (0 [0%], Phase 3, 4 [1%], commercial).

9.5 High Risedronate Dose Bone Histomorphometry with the Immediate Release Formulation

Risedronate absorption with the 35 mg DR formulation may be 2.1 times that of the approved 35 mg IR formulation as assessed by pharmacokinetic parameters in the Phase 2 dose finding trial 2005107. Other trials with direct comparison show as much as 4.2 times the absorption (see Table 112). BMD changes in the Phase 3 trial 2007008 and bone turnover markers in both Trials 2005107 and 2007008 tend to be numerically, and in some cases statistically, more changed for the 35 mg DR formulation than for the approved IR formulations (35 mg in Trial 2005107 and 5 mg in Trial 2007008). These findings are consistent with what would be expected with higher risedronate absorption. In addition, there is evidence in the Phase 3 trial for prolonged PTH elevation in some subjects on the 35 mg DR formulation. Clinical fractures after 52 weeks in the Phase 3 trial are numerically, although not statistically, more frequent with the DR regimens. All of these increase concern for bone safety, particularly with regard to bone formation and apposition.

Given these concerns, bone histomorphometry at the anticipated risedronate absorption is essential to approval of the Risedronate 35 mg DR formulation. In the Phase 3 trial 2007008 bone biopsy is to be done at the 2 year time point. However, only 52 week data is submitted with this NDA. Note that late in the review cycle the 2 year bone biopsy data from Trial 2007008 was submitted and is reviewed in Section 7.4.5.1.

The Sponsor believes that historical bone biopsy data is adequate to support the safety of the proposed 35 mg delayed release dose. The Sponsor specifically cites bone histomorphometry data from four studies:

Trial HMR4003E/ 3001: A 2-year randomized, double-blind, active controlled study of risedronate immediate release 35 mg and 50 mg once weekly, compared to risedronate immediate release 5 mg daily in women with postmenopausal osteoporosis. A total of 86 subjects underwent biopsy of the iliac crest after tetracycline labeling. Paired bone biopsy data was collected at baseline and year 2. The mean age of the population was 67 with a range of 52-87 years.

Trial 2005032: A 2-year randomized, double-blind, active controlled study of risedronate immediate release 150 mg once monthly compared to risedronate immediate release 5 mg daily in women with postmenopausal osteoporosis. A total of 62 subjects underwent biopsy of the iliac crest after tetracycline labeling. Bone biopsy data was collected at year 2. The mean age of the population was 66 with a range of 52-81 years.

Trial 2004012: A 2-year randomized, double-blind, active controlled study of risedronate immediate release 75 mg two consecutive days once monthly compared to risedronate immediate release 5 mg daily in women with postmenopausal osteoporosis. A total of 14 subjects underwent biopsy of the iliac crest after tetracycline labeling. Bone biopsy data was collected at year 2. The mean age of the population was 62 with a range of 53-76 years.

Trial 1998033: A 2-year randomized, double-blind, placebo controlled study of risedronate immediate release 5 mg daily, 15 mg daily and 50 mg once weekly, compared to placebo in men and women with knee osteoarthritis. A total of 60 subjects underwent biopsy of the iliac crest after tetracycline labeling. Bone biopsy data was collected at year 2. Overall, 24 (40%) men and 36 (60%) women underwent biopsy. The mean age of bone biopsy participants was 58. Twenty six women (72% of women) were postmenopausal and 20 women (56% of women) were at least 5 years postmenopausal, matching the menopausal requirement for the Phase 3 trial of Risedronate DR.

A major concern regarding the adequacy of these bone biopsy specimens relates to the increased risedronate exposure seen with the risedronate DR formulation and whether the risedronate exposure seen in patents participating any of the bone histomorphometry studies to date approximate that exposure. The Sponsor argues that C_{max}, AUC, or A_e (urinary excretion) may be used to compare expected risedronate exposure.

None of the trials to date with bone histomorphometry listed above had PK measurements, so other trials with that data had to be relied on for expected PK for the various IR doses. In the DR development program, trials with direct comparison to IR risedronate only used the 35 mg IR dose and only measured A_e (urinary excretion). Sponsor uses a 35 mg DR bioequivalence trial (2008119) to bridge to C_{max} and AUC comparisons, as those levels were measured in that trial (Table 112).

The Sponsor argues that, based on C_{max} levels equivalent to or greater than that of risedronate 35 mg DR in Trial 2008119 (C_{max} = 14.1 ng/ml), the 50 mg IR group in Trials HMR4003E/3001 and 1998033, the 75 mg IR group in Trial 2004012, and the 150 mg group in Trial 2005032 provide bone histomorphometry applicable to the current application (C_{max} of 50 mg IR 22.0 ng/ml in Trial HMR4003E/1001, C_{max} of 75 mg IR 19.2 ng/ml in Trial 2004051, and C_{max} of 150 mg IR 55.5ng/ml in Trial 2003080. Note in Trial 2003080 C_{max} for 50 mg IR (7.9 ng/ml) did not exceed that for 35 mg DR).

The Sponsor further argues, based on normalized AUC (over one month) or normalized A_e equivalent to or greater than that of risedronate 35 mg DR in Trials 2008119 and 2007120 (AUC 148 ng*hr/ml for Trial 2008119, A_e 683 µg (fasted) and 547 µg (fed) respectively), the 15 mg IR daily group in Trial 1998033, the 50 mg IR weekly group in Trial HMR4003E/3001, and the 150 mg monthly group in Trial 2005032 provide bone

histomorphometry applicable to the current application. In reviewing Table 112, if AUC is used, 5 mg IR daily, 35 mg IR weekly, and 75 mg 2 consecutive days per month are also appropriate doses to provide bone histomorphometry. Ae values indicate 5 mg daily and 75 mg 2 consecutive days per month are appropriate doses to provide bone histomorphometry.

Reviewer comment: That all approved and listed tested IR doses provide appropriate bone histomorphometry is inappropriate given the known higher absorption of the risedronate DR formulation.

That higher doses of the IR formulation of risedronate produce a higher Cmax than the 35 mg DR formulation is not surprising. Certainly a higher Cmax could lead to bone abnormalities, but the absence of bone abnormalities in these groups, as has been shown, does not show safety.

Risedronate IR absorption has generally been shown to be linear with dose and dose proportional. Weekly and monthly approved doses of risedronate IR are direct multiples of the daily dose by the number of days between doses. All approved IR doses should therefore give reasonably similar AUC and Ae values normalized over time in the same population under the same conditions. Of course, different populations and conditions may yield different values, making ratios the best comparator. AUC ratio and Ae ratio comparisons are critical to determining the appropriateness of bone histomorphometry data. Only Ae ratios are available in the DR development program. A review of Table 112 shows only the 15 mg IR daily group in Trial 1998033 provides bone histomorphometry at an appropriate absorption, i.e., an Ae ratio to an approved IR dose \geq the Ae ratio of the 35 mg DR to 35 mg IR. If the highest DR Ae ratio found is considered (4.2), none of the IR doses for which bone histomorphometry is available are appropriate for comparison.

Table 112, Risedronate PK Comparisons

Study/type Dose (dosing condition)	Population/ Regimen	Cmax (ng/ml)	AUC ¹ (ng*h/ml)	Ae ^{1,3} (µg)	Ae Ratio ²
Risedronate DR Studies					
2007120/Ph 1 X-over 35 mg DR (fasted) (N=75)	PM fem/	ND	ND	779	3.1
35 mg DR (fed) (N=72)		ND	ND	547	
35 mg IR (30-min) (N=73)		ND	ND	250	
2008119/Ph 1 BE X-over 35 mg DR (fasted) (N=467)	M&PMF/	14.1	148	683	
2005107/Ph 2 13 week 35 mg DR (FB) (N=19)	PM fem/ OAW	ND	ND	581	2.1
35 mg IR (label) (N=20)		ND	ND	275	
2008052/Ph 1 X-over 35 mg DR (fed) (N=90)	PM fem/	ND	ND	853	4.2
35 mg IR (30-min) (N=93)		ND	ND	204	

Risedronate IR Studies					
2000009/Ph 1 4 mo PK 15 mg (label) (N=28) 5 mg (label) (N=24)	M & F/ daily daily	4.9 1.7	732 277	1816 715	2.5
HMR4003E/1001/13 wk 35 mg (label) (N=19) 50 mg (label) (N=20) 5 mg (label) (N=18)	PM fem/ OAW OAW daily	10.6 22.0 1.9	231 441 284	525 1131 830	0.6 1.4
2004051/Ph 1 4 mo PK 75 mg (60' BB)(N=28) 5 mg (60' BB) (N=26)	PM fem/ 2CDM daily	19.2 1.7	169 169	845 796	1.1
2003080/Ph 1 single dose 150 mg (*) (N=56) 50 mg (fasted) (N=12)	PM fem/	55.5 7.9	265 154	820 531	1.5
<p>OAW = once a week; 2CDM = 2 consecutive days a month; ND = parameter not measured; label = at least 30 minutes before breakfast; fasted = after an overnight fast that was continued for additional 4 hours; fed = immediately after a high-fat meal; 30-min = 30 minutes before a high-fat meal; BB = before breakfast; Ae = urinary excretion</p> <p>* The 150 mg group includes subjects given drug with hard water. Most subjects in this group were dosed per label but some may have been dosed fasted</p> <p>1 AUC and Ae normalized to over a month</p> <p>2 Ae ratios are relative to reference dose (earliest approved dose or lower dose) within each study</p> <p>3 For IR studies, the Ae was obtained by modeling, for DR studies, Ae was collected over 72 hours</p> <p>Source: Efficacy Information Amendment 1.11.3, C-Table 1, individual study reports</p>					

Another method of arguing this is as follows:

- The current risedronate label lists oral bioavailability of IR risedronate as 0.63%. This is under standard fasting conditions (fasting for 10 hours before and 4 hours after dosing, confirmed by reviewing old submissions).
- The current label reports risedronate IR absorption is reduced by 55% when taken per label (food effect).
- Risedronate IR absorption is generally considered to be linear and dose proportional over the ranges considered here (5 to 150 mg). Systemic clearance is also considered to be not concentration dependent.
- Labeled condition risedronate IR bioavailability is about 0.63% X 0.45 = 0.28%.
- When taken per label, expected risedronate IR yearly absorptions are as follows:
 - For 5 mg daily: 5 X 365 X 0.0028 = 5.1 mg
 - For 35 mg weekly: 35 X 52 X 0.0028 = 5.1 mg
 - For 150 mg monthly (or 75 mg two consecutive days per month): 150 X 12 X 0.0028 = 5.0 mg
 - For 50 mg weekly: 50 X 52 X 0.0028 = 7.3 mg
 - For 15 mg daily: 15 X 365 X 0.0028 = 15.3 mg
- Using ClinPharm's calculation for risedronate 35 mg DR absorption under fed conditions of 0.64%, expected yearly absorption is: 35 X 52 X 0.0064 = 11.6 mg.

The only IR dose with expected yearly absorption which meets or exceeds that of the 35 mg weekly DR dose is 15 mg daily.

Bone Histomorphometry Available at Applicable Doses: As argued, the 15 mg IR daily risedronate group in Trial 1998033 is the only group with bone biopsy data with sufficiently high risedronate exposure to match that expected with the currently considered 35 mg DR weekly formulation. Trial 1998033 was a two year trial of risedronate 5 and 15 mg daily, 50 mg weekly, and placebo for the treatment of knee osteoarthritis with 1232 subjects randomized. Males and females age 40 to 80 were entered into the trial.

Unpaired bone biopsies were obtained from a subset of subjects at Month 24. Based on consenting subjects, 14 on 5 mg, 17 on 15 mg, 18 on 50 mg, and 11 on placebo underwent iliac crest bone biopsy using tetracycline double-labeling. Quantitative and qualitative histopathological analyses were performed.

Of the 17 subjects in the 15 mg group, ten were female (see Table 113). Two of the 10 were premenopausal and four others less than 5 years postmenopausal. Only four of the biopsy subjects from this treatment group match the PMO trial populations in being at least 5 years postmenopausal, but of course differ by indication for being in a trial.

- 69 year old Caucasian female with double label and no pathological findings.
- 64 year old Caucasian female with a fragmented biopsy, only one cortex, and much artifact with limited tissue area. Single label but no double label present. No pathological findings.
- 57 year old Caucasian female with double label and no pathological findings.
- 54 year old Black female with insufficient bone tissue for histomorphometric measurements except for cortical measurements on the single cortex. Double labeling observed. No pathological findings.

Normal lamellar bone, normal osteoid, and normal mineralization were found in the three subjects in whom these were evaluable, and there was no evidence of woven bone or osteomalacia in those subjects. None of these subjects had cortical trabecularization.

Full histomorphometric indices were obtained on only 2 subjects of this group with indices not dependent on double labeling in a third. In general these were consistent with the reduced bone turnover expected with risedronate when compared to placebo. The 69 year old subject had a mineralization lag time prolonged to 130 days and formation period of 849 days but high bone volume and trabecular thickness. The meaning of those findings in a single subject is unclear.

In Table 113 mean values of several histomorphometric parameters are compared for risedronate 15 mg daily subjects, 5 mg daily subjects, and placebo subjects. The values of those parameters for the 15 mg daily female subjects, grouped by menopausal status, are then given.

Osteoid thickness: Osteoid thickness can be used a marker of bone formation. Increases in osteoid thickness would be expected in the setting of a mineralization defect. Osteoid thickness in risedronate treated subjects was not statistically different from placebo (placebo 5.09 μm vs. 5 mg 4.44 μm , $p=0.444$, and 15 mg 4.30 μm , $p=0.348$). Individual female subjects in the 15 mg treatment group were not clearly different from mean values.

Osteoid volume (OV/BV): Osteoid volume represents the percentage of bone volume that is non-mineralized osteoid. A clear increase in OV/BV would support the hypothesis of impaired mineralization. The mean osteoid volume in the risedronate groups was below placebo and this difference reached statistical significance for the 15 mg group (placebo 0.91% vs. 5 mg 0.43%, $p=0.057$, and 15 mg 0.30%, $p=0.039$). Individual female subjects in the 15 mg treatment group were all lower than the placebo mean value. In this group, values for subjects ≥ 5 years postmenopausal and subjects premenopausal trended less than subjects < 5 years postmenopausal, but subject numbers are small enough to make generalizations difficult.

Osteoid surface (OS/BS): The osteoid surface/bone surface ratio reflects bone remodeling. The mean osteoid surface in the risedronate groups was below placebo and this difference reached statistical significance for the 15 mg group (placebo 9.51% vs. 5 mg 5.28%, $p=0.056$, and 15 mg 3.77%, $p=0.032$). This is an expected finding given the anti-resorptive nature of risedronate. In the 15 mg group, values for subjects ≥ 5 years postmenopausal and subjects premenopausal trended less than subjects < 5 years postmenopausal, but subject numbers are small enough to make generalizations difficult.

Adjusted apposition rate (Aj.AR): The adjusted apposition rate represents the mineral apposition rate or the bone formation rate averaged over the entire osteoid surface. A decrease could indicate impairment of mineralization and the potential of the drug to induce osteomalacia. Adjusted apposition rate in risedronate treated subjects was not statistically different from placebo (placebo 0.31 $\mu\text{m}/\text{d}$ vs. 5 mg 0.21 $\mu\text{m}/\text{d}$, $p=0.524$, and 15 mg 0.20 $\mu\text{m}/\text{d}$, $p=0.977$). In the 15 mg group, values for subjects ≥ 5 years postmenopausal, subjects < 5 years postmenopausal, and subjects premenopausal are not clearly different.

Mineralization lag time (Mlt): Mineralization lag time (Mlt) is the interval between osteoid formation and mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. Mineralization lag time in risedronate treated subjects was not statistically different from placebo (placebo 20.5 days vs. 5 mg 35.3 days, $p=0.618$ and 15 mg 65.7 days, $p=0.128$), although certainly there is a trend to longer times with increasing risedronate. In the 15 mg group, values for subjects ≥ 5 years postmenopausal, subjects < 5 years postmenopausal, and subjects premenopausal are not clearly different, but numbers of subjects are small.

Activation frequency (Ac.f): The activation frequency represents the probability that a new cycle of remodeling will be initiated at any point of the bone surface. The activation frequency in the risedronate groups was below placebo and this difference reached statistical significance (placebo 0.33/yr vs. 5 mg 0.12/yr, p=0.006, and 15 mg 0.07/yr, p=0.002).

Bone formation rate/surface referent (BFR/BS): Mean bone formation rate/bone surface in the risedronate groups was below placebo and this difference reached statistical significance (placebo 0.029 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$ vs. 5 mg 0.011 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$, p=0.012, and 15 mg 0.005 $\mu\text{m}^3/\mu\text{m}^2/\text{d}$, p=0.003).

Reviewer comment: In these histomorphometric values the anti-resorptive effect of risedronate is seen, which is more marked with the 15 mg daily risedronate compared to the 5 mg risedronate daily doses. Although not reaching statistical significance, the longer mineralization lag time with risedronate 15 mg daily is concerning.

Table 113, Bone Histomorphometry in OA Trial 1998033

Treatment Group	N	Osteoid Thickness (μm)	Osteoid Volume (%)	Osteoid Surface (%)	Adjusted Apposition Rate($\mu\text{m}/\text{d}$)	Mineral. Lag Time (days)	Activ. Freq.	Bone Form. Rate/BS ($\mu\text{m}^3/\mu\text{m}^2/\text{d}$)
15 mg daily, Mean(SEM)	15	4.30(0.17)	0.30(0.09)	3.77(0.96)	0.20(0.06)	65.7(21.9)	0.07(0.02)	0.005(0.001)
Placebo, Mean(SEM)	7	5.09(0.55)	0.91(0.25)	9.51(2.52)	0.31(0.07)	20.5(4.2)	0.33(0.09)	0.029(0.009)
p-value*		0.348	0.039	0.032	0.977	0.128	0.002	0.003
5 mg daily, Mean(SEM)	14	4.44(0.22)	0.43(0.09)	5.28(1.04)	0.21(0.05)	35.3(8.0)	0.12(0.02)	0.011(0.002)
p-value*		0.444	0.057	0.056	0.524	0.618	0.006	0.012
15 mg Daily Female Subjects								
Subject	Yrs PM							
≥ 5 years postmenopausal								
69 YOWF	19	5.2	0.15	3.1	0.04	130	0.01	0.0012
Double label , no pathological findings								
64 YOWF	18	4.1	0.02	0.43	NE	NE	NE	NE
Fragmented, one cortex, much artifact, limited tissue area. Single label, no double label. No pathological findings.								
57 YOWF	8	5.6	0.23	2.08	0.53	10.5	0.11	0.0111
Double label, no pathological findings								
54 YOFB	5	NE	NE	NE	NE	NE	NE	NE
Insufficient bone tissue for histomorphometry except on single cortex. Double label present. No pathological findings								
< 5 years postmenopausal								
58 YOWF	4	3.4	0.83	10.22	0.02	209.5	0.02	0.0017
Double label, no pathological findings								
58 YOWF	3	3.4	0.78	9.18	0.16	21.9	0.2	0.0144
Double label, no pathological findings								
52 YOWF	3	4.3	0.25	4.58	0.09	48.2	0.05	0.0041

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Double label, no pathological findings								
53 YOWF	2	3.9	0.21	2.53	0.22	18	0.06	0.0054
Fragmented, two pieces with 1 cortex each. Double label, no pathological findings								
Premenopausal								
56 YOWF		3.6	0.03	0.62	0.61	5.9	0.05	0.0038
Only 1 cortex readable. Double label, no pathological findings								
47 YOWF		4.3	0.03	0.91	NE	NE	NE	NE
No label, no pathological findings								
PM = postmenopausal								
* Mean value in each treatment group compared to placebo using an ANOVA after adjusting for investigative site								
Source: Final Report Trial 1998033 Appendix 5.18 Table 1 and Appendix 3.16 Tables 1, 2, and 3								

Conclusions: Adequate bone histomorphometric data is required for approval of this NDA due to increased risedronate absorption by greater than two times over that of approved formulations. There is inadequate bone histomorphometry at comparable doses available in historical trials. What data is available at comparable doses is in an osteoarthritis population rather than a postmenopausal osteoporosis population. This NDA was submitted with 52 week data from a 2 year Phase 3 trial, however, bone biopsies done in a subset of subjects at the end of year 2 were submitted late in the review cycle and are reviewed in Section 7.4.5.1.

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

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/s/

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07/08/2010

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07/09/2010