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ORIGINAL ARTICLE

Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years

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Abstract
Summary Bone mineral density response to once weekly delayed-release formulation of risedronate, given before or following breakfast, was non-inferior to that seen with traditional immediate-release risedronate given daily before breakfast. Delayed-release risedronate is a convenient dosing regimen for oral bisphosphonate therapy that might avoid poor compliance.
Introduction This 2-year, randomized, controlled, non-inferiority study assessed the efficacy and safety of a delayed-release (DR) 35-mg weekly oral formulation of risedronate that allows subjects to take their weekly risedronate dose before or immediately after breakfast. Results from the first year of the study were published previously (McClung et al. Osteoporos Int 23(1):267-276, 2012); we now report the final results after 2 years.
Methods Women with postmenopausal osteoporosis were randomly assigned to receive risedronate 5 mg immediate-release (IR) daily (n=307) at least 30 min before breakfast, or risedronate 35 mg DR weekly, either immediately following breakfast (FB, n=307) or at least 30 min before breakfast (BB, n=308). Bone mineral density (BMD), bone turnover markers (BTMs), fractures, adverse events, and bone histomorphometry were evaluated.
Results A total of 248 subjects (80.8 %) in the IR daily group, 234 subjects (76.2 %) in the DR FB weekly group, and 240 subjects (77.9 %) in the DR BB weekly group completed the 2-year study. After 2 years of treatment, BMD increases at the lumbar spine and total hip with the weekly DR doses similar to or greater than that with the IR daily dose. Decreases in BTMs were similar or significantly lower in the DR groups. Bone histomorphometry results did not differ among the DR weekly and the IR daily formulations. The three regimens were similarly well tolerated.
Conclusions Risedronate 35 mg DR weekly is as effective and as well tolerated as risedronate 5 mg IR daily, and will allow subjects to take their weekly risedronate dose immediately after breakfast.

Keywords Bone mineral density · Delayed-release · Enteric-coated · Histomorphometry · Osteoporosis · Risedronate · Weekly

Trial registration Clinicaltrials.gov Identifier: NCT00541658

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Introduction

Oral bisphosphonates are the most commonly prescribed medications for the treatment of osteoporosis. The gastrointestinal absorption of oral bisphosphonates is very limited

and, when given with food or beverages other than plain water, the bioavailability is severely compromised or negligible resulting in loss of skeletal benefit [2]. Because of this, these drugs must be taken on an empty stomach with a wait of 30–60 min before other food, drinks, or mineral supplements can be consumed. The effect of food on diminishing the bioavailability of oral bisphosphonates is mediated by calcium and perhaps other divalent cations that limit the transit of bisphosphonates across gastrointestinal surfaces [2, 3]. When subjects are queried about how they take oral bisphosphonates, more than half are found to be taking them with food or other beverages or not waiting the appropriate time before eating [4]. Additionally, some subjects perceive the standard oral bisphosphonate dosing regimens as awkward or inconvenient, and this may contribute to the observation that many subjects discontinue their oral bisphosphonate drugs within the first few months of treatment [4, 5]. The combination of limited persistence and poor compliance might explain the results of studies in the clinic that demonstrate less effectiveness of oral bisphosphonate therapy than have been observed in clinical trials [6, 7].

We previously described the initial results of a phase III study comparing a delayed-release (DR) formulation of risedronate that can be taken following meals [1]. The DR tablets contain 35 mg of risedronate and EDTA (a chelating agent that binds calcium and other divalent cations with higher affinity than does risedronate) and have a pH-sensitive enteric coating that disintegrates in the relatively alkaline environment of the proximal small intestine where absorption of bisphosphonates is most efficient. These changes in the formulation of the weekly 35 mg tablet were made to minimize the food effect on risedronate absorption, allowing the drug to be taken before or after meals.

After 12 months of therapy, increases in bone mineral density (BMD) and reduction in markers of bone turnover were not inferior with the risedronate 35 mg DR formulation given before or immediately following breakfast compared to daily dosing with 5 mg of the original immediate-release (IR) formulation taken at least 30 min before breakfast. The efficacy and safety results after 24 months of treatment are reported here.

Materials and methods

Study design

This randomized, double-blind, active-controlled, parallel-group study was conducted at 43 study centers in North America, South America, and the European Union. The first subject was screened in November 2007, and the last subject observation took place in April 2010. The study was performed in accordance with good clinical practice and the ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the appropriate institutional review boards or ethics committees and the subjects gave written, informed consent to participate. The Identifier number for this study at Clinicaltrials.gov was NCT00541658.

Subjects

This has been described in detail previously [1]. Postmenopausal women were eligible to participate in the study if they were at least 50 years of age, ambulatory, had osteoporosis defined as a BMD T-score in the lumbar spine or total hip of −2.5 or lower or a T-score of −2.0 or lower with at least one prevalent vertebral fracture (T4 to L4), and were in generally good health without contraindications to risedronate therapy or other reasons to not be in the clinical study. Those subjects with baseline serum 25-hydroxyvitamin D levels <12 ng/ml were not eligible to participate in the study.

Treatments

Subjects were randomly assigned to one of three treatment groups: risedronate 5 mg IR daily or risedronate 35 mg DR once weekly before or immediately following breakfast. The minimization method of Pocock and Simon was used for randomization [8]. Eligible subjects who gave consent were stratified across study centers by anticoagulant use (since fecal occult blood testing was performed during the first 12 months of the study) and then randomly assigned within each study center in a 1:1:1 ratio to the three treatment groups. All subjects took nine study tablets each week: an IR tablet or placebo before breakfast daily; a 35-mg DR tablet or placebo before breakfast once weekly (DR BB); and another 35-mg DR tablet or placebo following breakfast once weekly (DR FB). All placebo tablets were identical in appearance to their corresponding active tablets (i.e., 5 mg IR or 35 mg DR) and supplied in identical blister cards. The 5-mg IR tablets and the 35-mg DR tablets assigned for before-breakfast intake were taken on an empty stomach in the morning at least 30 min before the first food or drink of the day; the 35-mg DR tablets assigned for following-breakfast intake were taken immediately after breakfast. All tablets were taken with at least 4 ounces of plain water, and subjects were instructed to remain in an upright position for at least 30 min after dosing. Compliance was assessed by tablet counts. Calcium (1,000 mg/day) and vitamin D (800–1,000 IU/day) were supplied to all subjects with instructions to take these supplements with a meal other than breakfast and not with the study medication. Most subjects took the calcium supplements in divided doses.

Efficacy assessments

Dual energy X-ray absorptiometry (DXA) measurements of the lumbar spine and proximal femur were obtained at baseline and after 26, 52, and 104 weeks using instruments manufactured by Lunar Corporation (GE Healthcare, Madison, WI, USA) or Hologic (Waltham, MA, USA). DXA scans collected at the clinical sites were sent to a central facility for quality control and analysis (Synarc, San Francisco, CA, USA).

New incident vertebral fractures were assessed by semi-quantitative morphometric analysis of lateral thoracic and lumbar spine radiographs collected at screening and after 52 and 104 weeks [9]. Radiographs were reviewed for quality and analyzed for fracture at a central site (Synarc, San Francisco, CA, USA).

Biochemical markers of bone turnover [serum bone-specific alkaline phosphatase (BAP), urinary type-1 collagen cross-linked N-telopeptide corrected by urinary creatinine (NTX), serum type-1 collagen cross-linked C-telopeptide (CTX)] were performed at a central laboratory (Pacific Biometrics, Seattle, WA, USA) in fasting samples collected at baseline and after 13, 26, 52, and 104 weeks. Details and performance characteristics of the assays have been described previously [1]. Assays of samples collected at week 104 were performed at different times than assays of samples collected at earlier time points.

Safety assessments

Physical examinations were performed at baseline and after 52 and 104 weeks. Vital signs, concomitant medications, and adverse event reports were recorded at regular clinic visits throughout the study. Blood samples for standard laboratory measurements were collected at baseline and after 13, 26, 52, 78, and 104 weeks of treatment. Serum chemistry measurements were also obtained after 14 days. Urinalysis was performed at baseline and week 104. Specimens were analyzed by Quintiles Central Laboratory (Marietta, GA, USA).

Electrocardiograms were assessed at baseline and after 52 and 104 weeks. Transiliac crest bone biopsies for bone histomorphometric assessment were performed in nine study sites at week 104 from a total of 45 subjects. Prior to the bone biopsy procedure, subjects took tetracycline (1,000 mg daily) or demeclocycline (600 mg daily) for two 3-day periods, separated by a 14-day drug-free interval. The bone biopsy samples were collected 5–14 days after the last dose of tetracycline or demeclocycline. Biopsies were processed and analyzed at a single center (Creighton University, Omaha, NE, USA), and results were derived by previously reported methods [10].

Statistical analysis

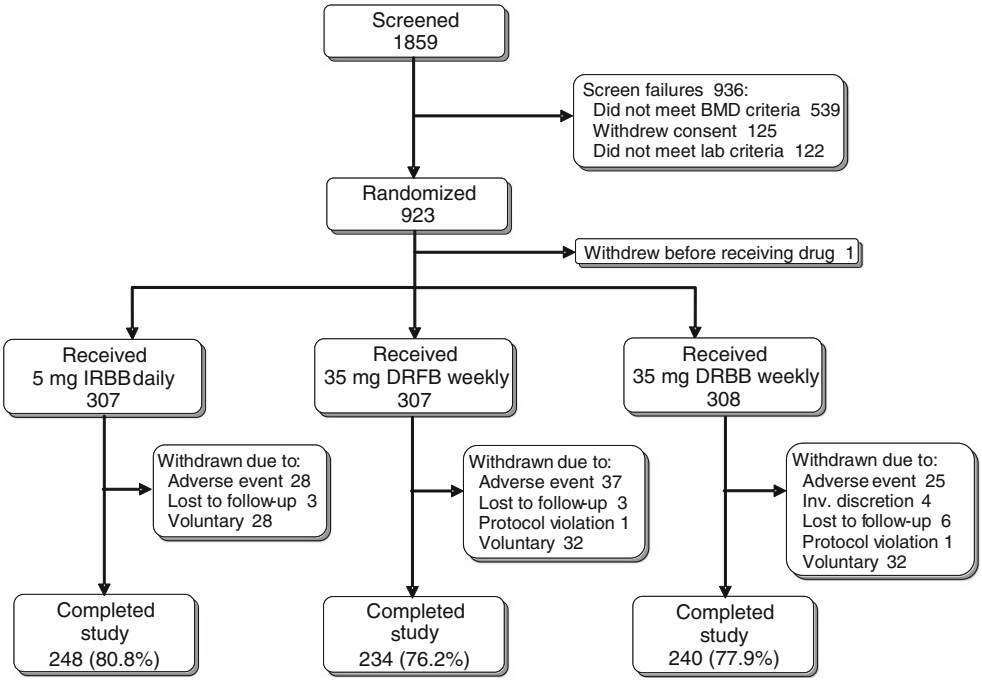
A complete description of the statistical methodology has been reported previously [1]. The primary endpoint analysis was a non-inferiority test comparing the least squares mean percent change from baseline in lumbar spine BMD in the DR weekly and the IR daily groups after 52 weeks, employing a predefined non-inferiority margin of 1.5 % and a one-sided type I error of 2.5 %. The primary efficacy variable was the percent change from baseline in lumbar spine BMD at week 52-Endpoint; the last valid post-baseline measurement was used when the week 52 value was missing (LOCF). Predefined secondary outcomes included changes in BMD at the lumbar spine and regions of the proximal femur, changes in biochemical markers of bone turnover, and incidence of morphometric vertebral fractures at week 104. No changes in secondary outcomes were made during the course of the study. Efficacy analyses were performed in the intent-to-treat (ITT) population consisting of all subjects who were randomized, received at least one dose of study drug, and had analyzable BMD or bone marker data at baseline and at least one posttreatment time point. Ninety-five percent, two-sided confidence intervals (CIs) for the treatment difference were constructed and used to determine differences between IR daily and each of the DR weekly treatment groups. Nonparametric methods were used to perform the statistical analysis of all bone biopsy parameters. The nonparametric Wilcoxon rank sum test was used for between-group comparisons. The nonparametric Hodges–Lehmann CIs (95 %) were constructed for the median differences between groups.

Results

Subjects

A total of 1,859 women were screened; of these, 923 subjects were randomized, and 922 subjects received at least one dose of study drug (Fig. 1). Baseline characteristics were previously described and were similar across treatment groups [1]. The median daily dose of calcium was 1,000 mg for all three treatment groups, and the median daily dose of vitamin D was 800 IU for all three treatment groups. A similar percentage of subjects in each treatment group completed the 104-week study (IR daily group, 80.8 %; DR FB weekly group, 76.2 %; DR BB weekly group, 77.9 %). The most common reasons given for withdrawal, which occurred at similar incidences across all three treatment groups, were adverse event and voluntary withdrawal. A high percentage of ITT subjects in all groups (96.7 % of subjects in the IR daily group, 96.7 % of subjects in the DR FB weekly group, and 95.1 % of subjects in the DR BB weekly group) took at least 80 % of the study tablets.

Fig. 1 Disposition of subjects



Efficacy assessments

As reported previously, all three treatment groups experienced significant improvements from baseline in lumbar spine BMD after 1 year of treatment. The response to both the 35-mg DR groups at week 52 was shown to be non-inferior and not superior to that observed with the 5-mg IR tablet. All three treatment groups continued to show significant improvements from baseline in lumbar spine BMD during the second year of the study with both 35-mg DR groups showing significantly greater increases than the 5-mg IR group (Fig. 2). The least squares mean percent change from baseline in lumbar spine BMD at week 104 was 5.5 % (95 % CI, 5.0 to 6.0 %) in the DR FB weekly group, 5.4 % (95 % CI, 4.9 to 5.9 %) in the DR BB weekly group, and 4.4 % (95 % CI, 3.8 to 4.9 %) in the IR daily group. The least squares mean difference between the DR FB group and the IR group was −1.15 (95 % CI=−1.9, −0.4), and the least squares mean difference between the DR BB group and the IR group was −1.04 (95 % CI=−1.8, −0.3).

Progressive increases in BMD at proximal femur sites (total hip, femoral neck, and femoral trochanter) were observed during the second year of the study (Fig. 2). Significant increases from baseline were observed at all time points in all treatment groups. Both DR groups showed greater increases than the IR daily group at the femoral trochanter at week 104 and endpoint and at the total hip at week 104 (least squares mean difference of DR FB group vs. IR group at week 104=-0.64 [95 % CI −1.18, −0.11]). The response in the total hip was also greater at endpoint with the 35-mg DR FB dose and at the femoral neck at week 104 and endpoint with the 35-mg DR BB dose compared to the 5-mg IR dose. Significant decreases from baseline in NTX/creatinine, CTX, and BAP were observed at all time points in all treatment groups (Fig. 3). The decreases in CTX in both DR groups were statistically greater than with the 5-mg IR dose at week 104 and endpoint. The changes in NTX/creatinine or BAP were not significantly different among treatment groups at the end of year 2. No differences were observed in any BMD or bone turnover marker (BTM) response between both of the DR regimens at any time point. New incident morphometric vertebral fractures occurred in five subjects in the IR daily group, two subjects in the DR FB weekly group, and six subjects in the DR BB weekly group (not statistically significant between DR and IR groups).

Safety assessments

Overall, the adverse event profile was similar across the three treatment groups (Table 1). The incidence of upper and lower gastrointestinal adverse events was similar across groups. However, the incidence of events related to upper abdominal pain was higher in the DR BB group than in the other two groups; most of these events were judged to be mild or moderate.

Adverse events of special interest for bisphosphonates include clinical fractures, musculoskeletal adverse events, acute phase reactions, and osteonecrosis of the jaw (ONJ). Clinical fractures are defined as all non-vertebral fractures and symptomatic, radiographically confirmed vertebral fractures that occurred after randomization and were reported as adverse events. Acute phase reactions are defined as influenza-like illness and/or pyrexia starting within 3 days

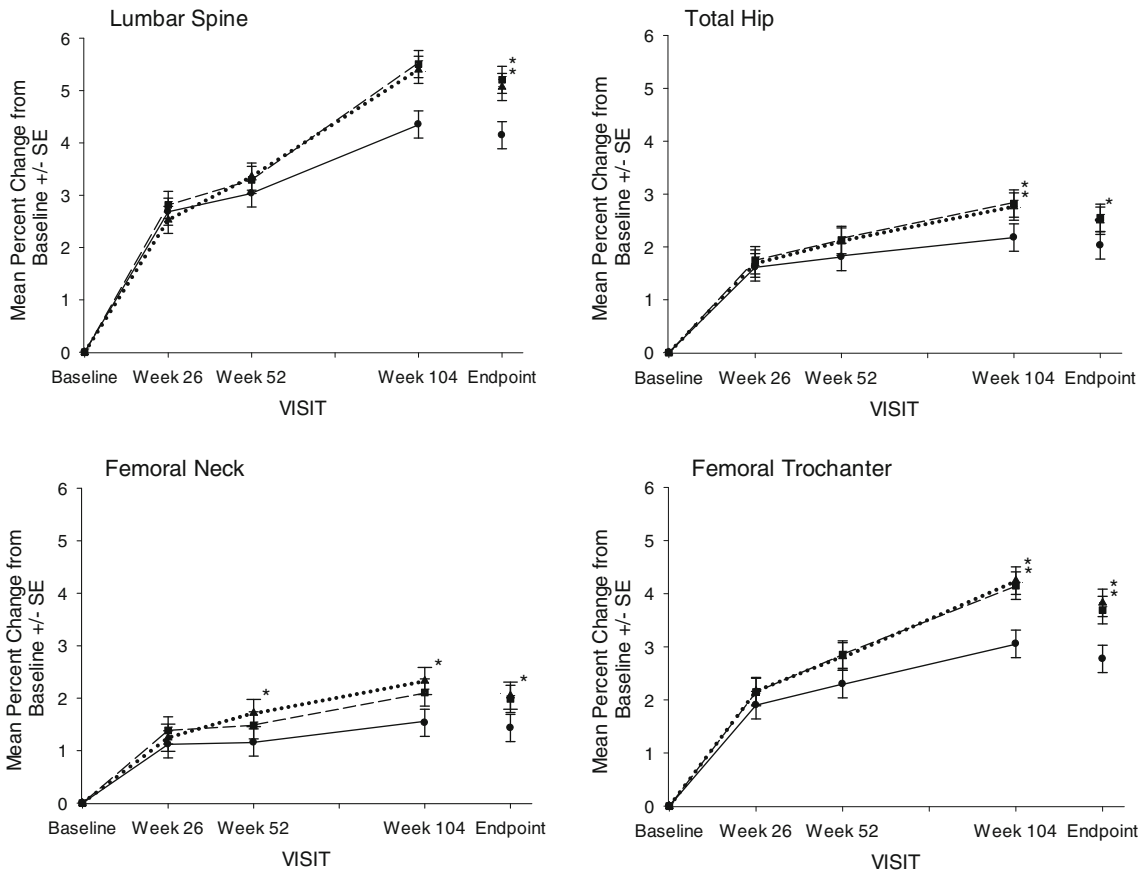


Fig. 2 Mean percent change from baseline ± SE in bone mineral density over 2 years in women receiving risedronate 5 mg IR daily (*solid lines with black circles*), 35 mg DR FB weekly (*dashed lines with black squares*), or 35 mg DR BB weekly(*circle dashed lines with black triangles*). *Asterisk* represents statistically significant difference between IR daily and DR weekly treatment group

following the first dose of study drug and having duration of 7 days or less. Clinical fracture and musculoskeletal adverse events were reported by similar proportions of subjects across treatment groups (Table 1). No cases of acute phase reaction or ONJ were reported. Other than the expected small, transient, and asymptomatic decreases in serum calcium seen within the first few weeks of treatment, no clinically important differences or trends were seen across groups for any laboratory parameter measured, including measures of hepatic and renal function, and electrocardiograms during the 2-year study.

No histological abnormalities were observed in any of the biopsy specimens, and double tetracycline label was detected in all 45 biopsies. Static and dynamic histomorphometric measurements and bone mineralization parameters were similar across treatment groups (Table 2).

Discussion

Risedronate 5 mg IR daily significantly reduces the incidence of major fragility fractures in women with postmenopausal osteoporosis and of vertebral fractures in subjects receiving glucocorticoids [11–14]. Fracture risk reduction occurs within months of beginning therapy and appears to persist with treatment for at least 7 years [15–17]. Weekly and monthly IR dosing forms of risedronate were developed to make dosing more convenient and acceptable and in the hope of improving persistence with treatment [18, 19]. However, all of these regimens, like other oral bisphosphonate dosing schedules, require dosing at least 30 min before food or drink. Even taking oral bisphosphonates with tap water or bottled water can decrease bioavailability [20]. None of the current oral bisphosphonate dosing schemes solves the possible detrimental effect of poor compliance with dosing instructions on bisphosphonate absorption and clinical effectiveness. That the impact of poor compliance can be important was demonstrated by the significant blunting of the BMD response to risedronate IR given between meals compared to being taken before breakfast [21]. The unique risedronate weekly DR formulation, consisting of both the addition of a chelating agent and the enteric coating, promotes disintegration of the tablet in the small intestine. This formulation obviates the food effect and minimizes the concern about poor compliance.

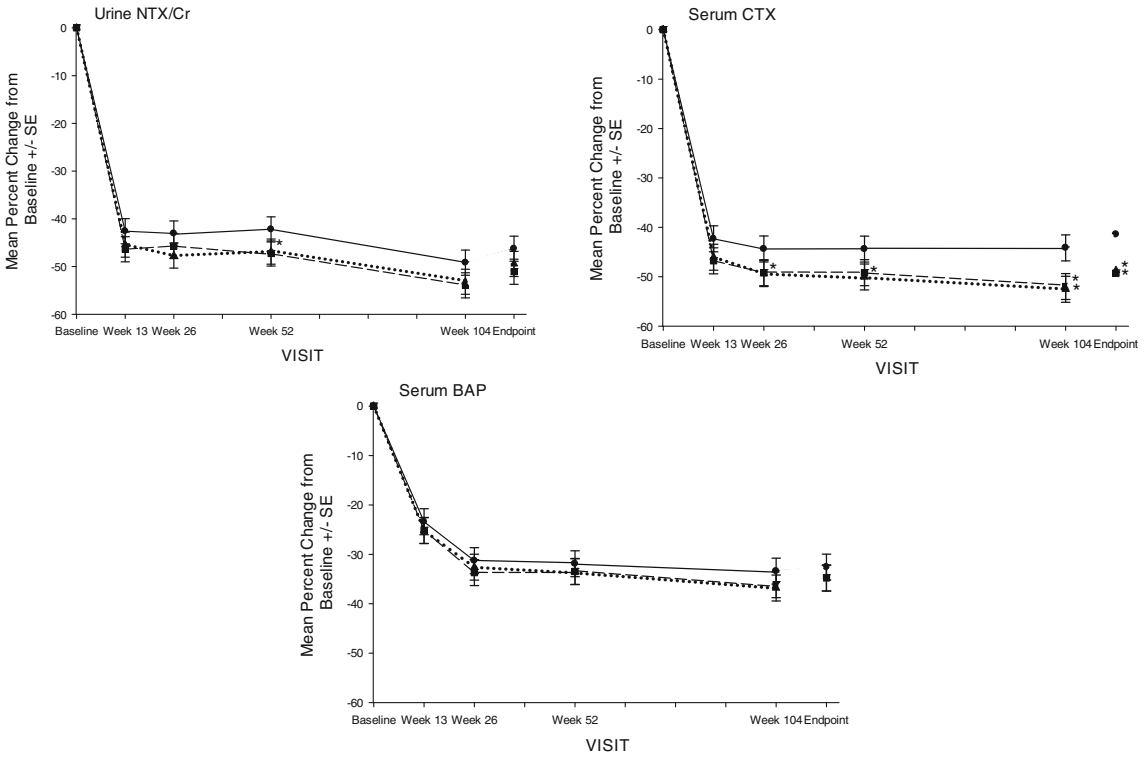


Fig. 3 Mean percent change from baseline ± SE in bone turnover markers over 2 years in women receiving risedronate 5 mg IR daily (*solid lines with black circles*), 35 mg DR FB weekly (*dashed lines with black squares*), or 35 mg DR BB weekly (*circle dashed lines with black triangles*). *Asterisk* represents statistically significant difference between IR daily and DR weekly treatment group

Extending the observations from the 12-month analysis of this study, the results presented here demonstrate that the increases in bone mineral density and the decreases in biochemical markers of bone turnover at 2 years were at least as great with both DR dosing regimens compared to the risedronate IR daily dose. The greater responses in lumbar spine and femoral trochanter BMD and serum CTX to the DR doses are unexpected. It is unlikely that this is explained simply by a difference in the 5-mg daily dose and the 35-mg weekly dose since the BMD and marker responses to risedronate 5 mg daily IR and 35 mg weekly IR were not different over a 2-year treatment interval [18]. The greater response could be due to increased bioavailability of the DR formulation compared to the IR daily dose. Enteric coating did not affect bioavailability of alendronate 70 mg [22]. Since a formal dose-ranging study with risedronate was never performed, it is uncertain that the 5 mg daily IR or 35 mg weekly IR dose is at the top of the dose–response curve. Supporting this possibility is the observation that the changes in lumbar spine and proximal femur BMD and in BTMs were somewhat greater with a weekly IR dose of risedronate at 50 mg compared to those observed with the 5 mg daily or 35 mg weekly doses [18]. Thus, it is possible that a modest increased bioavailability could result in greater responses in bone turnover and bone mineral density. However, the increased response observed with risedronate 50 mg weekly IR dose was observed within the first 6 months of treatment and did not separate further from the lower doses with continued therapy out to 2 years. Furthermore, in the limited testing of risedronate DR bioavailability, no clear difference was noted compared to IR dosing [23].

Another possible explanation is that compliance with the IR daily dosing instructions was suboptimal, even in the setting of a clinical trial where subjects were seen and reminded of proper dosing instructions more often than occurs in clinical practice. The protection from the food effect afforded by the DR formulation would, in theory, obviate the effect of poor compliance. Subjects were seen less frequently during the second year of our study than during the first year, and it is possible that compliance with dosing diminished with continued use. This effect would not be captured by the standard strategy of assessing treatment compliance by simply counting tablets taken by the study participants. If suboptimal compliance is the explanation for the observed difference in our clinical study, it is probable that an even greater difference would occur between the DR and IR preparations in daily practice.

Table 1 Summary of adverse events

	Risedronate		
	5 mg IR daily (*N*=307) *n* (%)	35 mg DR FB weekly (*N*=307) *n* (%)	35 mg DR BB weekly (*N*=308) *n* (%)
Adverse events	243 (79.2)	250 (81.4)	264 (85.7)
Serious adverse events	31 (10.1)	32 (10.4)	32 (10.4)
Deaths	1 (0.3)	1 (0.3)	0 (0.0)
Withdrawn due to an adverse event	28 (9.1)	37 (12.1)	25 (8.1)
Most common adverse events associated with withdrawal			
Gastrointestinal disorder	13 (4.2)	21 (6.8)	14 (4.5)
Most common adverse events			
Arthralgia	33 (10.7)	29 (9.4)	27 (8.8)
Back pain	27 (8.8)	29 (9.4)	29 (9.4)
Nasopharyngitis	24 (7.8)	32 (10.4)	38 (12.3)
Influenza	23 (7.5)	27 (8.8)	25 (8.1)
Urinary tract infection	20 (6.5)	21 (6.8)	22 (7.1)
Diarrhea	19 (6.2)	30 (9.8)	21 (6.8)
Upper abdominal pain	8 (2.6)	11 (3.6)	26 (8.4)
Adverse events of special interest			
Clinical vertebral fracture	1 (0.3)	0 (0.0)	3 (1.0)
Clinical nonvertebral fracture	15 (4.9)	13 (4.2)	20 (6.5)
Upper gastrointestinal tract adverse events	56 (18.2)	59 (19.2)	69 (22.4)
Selected musculoskeletal adverse events[a]	66 (22.1)	67 (21.8)	77 (25.0)
Adverse events potentially associated with acute phase reaction[b]	4 (1.3)	7 (2.3)	4 (1.3)

[a]Includes arthralgia, back pain, bone pain, musculoskeletal pain, musculoskeletal discomfort, myalgia, and neck pain

[b]Includes symptoms of influenza-like illness or pyrexia with a start date within the first 3 days after the first dose of study drug and duration of 7 days or less

The histomorphometric results seen in this study were consistent with those seen after 1, 3, and 5 years in previous 5 mg risedronate IR studies in women with postmenopausal osteoporosis [24–28]. In those studies, no histological abnormalities or defects in matrix mineralization were noted, and long-term treatment with risedronate preserved bone material properties. Bone turnover was reduced by 1 year to levels observed in healthy premenopausal women, and turnover was not reduced further with longer term treatment. In our study, after 2 years of treatment, no histological or mineralization abnormalities were observed in any of the risedronate-treated groups. Importantly, persistent bone turnover was evident as noted by the presence of tetracycline label in all 45 biopsy samples. This contrasts with the histomorphometric results with alendronate and denosumab that demonstrated absent tetracycline labels in many subjects [29, 30]. This apparent difference in the level of turnover observed on treatment is consistent with the study by Rosen and colleagues in which the approved dose of alendronate (70 mg weekly) reduced markers of bone turnover significantly more than did the approved dose of risedronate IR (35 mg weekly) [31]. The clinical implications of the reported differences among different drugs on indices of bone turnover are not known, but knowing that bone remodeling is not "over suppressed" with risedronate is reassuring.

Overall, the tolerability of the weekly DR regimens was similar to that observed with the daily IR treatment. These data are consistent with previous studies in which the tolerability was similar in subjects receiving placebo or daily IR risedronate and in subjects receiving weekly or monthly IR risedronate compared to daily IR therapy. Upper abdominal pain occurred somewhat more frequently in the DR BB groups while slightly more subjects experienced diarrhea with the DR FB regimen, but these differences did not result in more subjects discontinuing from study medication. As expected, no cases of osteonecrosis of the jaw or atypical femoral fractures were observed in these subjects who received treatment for only 2 years. These data support the results of previous large studies that demonstrated good tolerability and short-term safety of risedronate therapy.

The number of subjects experiencing clinical fractures was very low, precluding the chance of observing differences among dosing regimens. Thus, it is unclear whether the greater effects of the DR regimen on bone mineral density and bone turnover, compared to IR daily dosing, would result in better fracture protection.

Table 2 Summary of bone histomorphometry

	Risedronate						Hodges–Lehmann estimation of location shift (95 % CI) *P* value[a]	
	5 mg IR daily		35 mg DR FB weekly		35 mg DR BB weekly			
	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*N*	35 mg DR FB vs 5 mg IR	35 mg DR BB vs 5 mg IR
Bone turnover parameters								
Mineral surface/bone surface (double + half single tetracycline label), %	1.35±1.09	17	1.34±1.55	15	1.33±1.03	12	−0.27 (−0.84, 0.62) 0.3079	−0.07 (−0.72, 0.96) 0.8075
Osteoid surface/bone surface, %	6.38±3.54	17	8.69±8.62	15	9.21±7.60	12	0.24 (−3.37, 5.94) 0.8651	0.59 (−1.60, 5.21) 0.6902
Bone formation rate/bone surface (double + half single tetracycline label), $\mu m^3/\mu m^2$/day	0.0072±0.0055	16	0.0059±0.0076	13	0.0070±0.0043	11	−0.0017 (−0.0058, 0.0013) 0.1476	−0.0001 (−0.0038, 0.0046) 0.9214
Eroded (resorption) surface/bone surface, %	1.57±0.94	17	1.21±0.49	15	1.81±0.80	12	−0.21 (−0.93, 0.25) 0.4168	0.30 (−0.54, 0.92) 0.3190
Activation frequency (double + half single tetracycline label), per year	0.09±0.07	16	0.08±0.11	13	0.09±0.06	11	−0.02 (−0.07, 0.02) 0.2010	0.01 (−0.04, 0.06) 0.7854
Bone mineralization parameters								
Osteoid thickness, μm	5.8±0.9	17	5.2±0.8	15	5.3±0.6	12	−0.6 (−1.1, 0.0) 0.0337	−0.3 (−1.0, 0.2) 0.2221
Osteoid volume/bone volume, %	0.81±0.63	17	0.99±1.22	15	0.97±0.96	12	−0.08 (−0.43, 0.49) 0.6101	0.00 (−0.31, 0.56) 1.000
Mineral apposition rate, μm/day	0.47±0.11	16	0.45±0.16	13	0.50±0.15	11	−0.04 (−0.14, 0.08) 0.3913	0.03 (−0.10, 0.14) 0.5870
Mineralization lag time (double + half single tetracycline label), days	91.8±85.0	16	108.0±91.3	13	131.7±172.7	11	16.3 (−24.1, 68.0) 0.4560	7.9 (−39.0, 53.7) 0.6930

[a] *P* value from Wilcoxon rank sum test

These 2-year results confirm that weekly administration of the 35-mg DR formulation results in changes in BMD and bone turnover that are at least as effective in increasing BMD and reducing bone turnover as the daily IR dosing regimen that is known to significantly reduce the incidence of fragility fractures in postmenopausal women with osteoporosis. A weekly dosing regimen that can be taken following breakfast is more convenient for many subjects with busy schedules or in older subjects who must take many other medications each morning. More importantly, the DR formulation of risedronate provides confidence to clinicians that poor compliance with dosing recommendations will be less likely to blunt the therapeutic effectiveness of risedronate.

Many factors influence the choice of a treatment for subjects with osteoporosis including confidence in antifracture efficacy, tolerability, individual subject circumstances affecting compliance, and persistence as well as subject preferences. Having an oral bisphosphonate that can be given following breakfast is a useful addition to our menu of treatment options.

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