Drug Class Review
Oral Bisphosphonates in the Treatment of Osteoporosis

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel
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The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Objectives

To review the efficacy, safety, and administration of the bisphosphonates alendronate and risedronate in the treatment and prevention of osteoporosis.

Table 1. Currently available products

Generic	Brand	Manufacturer
Alendronate	Fosamax	Merck
Risedronate	Actonel	Aventis and Procter & Gamble

I. Introduction[1,2,3,4,5]

Osteoporosis is characterized by abnormalities in bone remodeling resulting in a reduction in bone mass per unit volume and changes in the microarchitecture of primarily cortical bone. The imbalance in bone remodeling is due to the net rate of absorption exceeding the net rate of formation. Histologic changes in bone include a decrease in cortical thickness and a decrease in number and size of trabeculae in cancellous bone. Mineralization is not affected, and the osteoporotic bone is brittle but not soft.

Measurement and screening of osteoporosis is most accurately accomplished using Dual-energy x-ray absorptiometry (DXA) to assess bone density. DXA measurements of the lumbar spine and proximal femur provide reproducible values and are used to assess the risk for fractures, detect osteoporosis, and determine response to treatment. The World Health Organization defines osteoporosis based on Bone Mineral Density (BMD). They commonly express the BMD as a T score, which is the number of standard deviations (SD) below the mean BMD value for normal young adults. T scores between –1 and –2.5 SD are defined as osteopenia and values at least –2.5 SD below the young adult mean are termed osteoporosis.

Osteoporosis affects an estimated 10 million Americans of which 80% are women and 20% are men. It can occur as a primary disorder due to aging or estrogen loss in postmenopausal women, a secondary disorder associated with endocrine disorders, systemic inflammatory disease, or other chronic illnesses, or it may be drug induced through the administration of glucocorticoids, LHRH agonists, or antiestrogens. Bone loss associated with estrogen deficiency and aging manifests at predominantly cancellous skeletal sites such as the lumbar spine, proximal femur, hip, and forearm. Fracture is the most clinically significant manifestation of the disease. One in 2 women and 1 in eight men over 50 will sustain a fracture due to osteoporosis in their lifetime. Vertebral fractures are most prevalent, but hip fractures are the most serious because of the high rates of disability and mortality associated with these fractures. Risk factors for developing osteoporosis include female sex, thin and/or small frame, advanced age, family history of osteoporosis, postmenopause, low-calcium diet, inactive lifestyle, smoking, low testosterone levels in men. The risk factors for osteoporosis-related fractures include prior low-trauma fractures in adults and a low BMD with or without fractures. The estimated expenditures for osteoporosis and related fractures were $17 billion in 2001according to the National Osteoporosis Foundation.

Osteoporosis in men is not uncommon, however little attention has been given to the disease thought to be primarily a female disease. By using fracture as an outcome, it is estimated that the lifetime risk in males is 13-25%. It is unclear if using the same WHO criteria for men, i.e. 2.5SD below the reference standard for young men, is appropriate due to the differences in peak bone mass for men versus women. Men also tend to develop osteoporosis a decade late in life than women. Thus, hip fractures in men occur at a more

advanced age and carry a higher mortality. The major causes of osteoporosis in men include alcohol abuse, excess glucocorticoids, and hypogonadism while 40-50% will not have a clear-cut etiology. There is some evidence that estrogen is involved in establishing peak bone mass in males, and that estrogen resistance or deficiency may predispose to osteoporosis in these rare cases.

The goals of pharmacotherapy of osteoporosis include prevention of bone loss for patients with osteopenia or at risk secondary to iatrogenic causes, or increase in bone mass in patients with osteoporosis to prevent fractures. Bisphosphonates are analogues of pyrophosphate that inhibit osteoclast activity, which inhibits bone resorption. They bind to hydroxyapatite crystals and are released during the process of bone remodeling. This binding to hydroxyapatite crystals may also affect the pharmacokinetics of the drugs and allow for long dosing intervals. Alendronate and risedronate are bisphosphonates currently approved for the prevention and treatment of osteoporosis.

II. Pharmacology/Pharmacokinetics[6,7,8,9,10]

Bisphosphonates are analogues of pyrophosphate in which oxygen is replaced by carbon yielding P-C-P. This structure is resistant to hydrolysis by acids or enzymes. The R_2 position on the carbon atom is responsible for potency characteristics. Alendronate contains a primary nitrogen atom in an alkyl chain at R_2 and has intermediate potency. Risedronate has a nitrogen atom within a heterocyclic ring and is one of the most potent bisphosphonates.

The exact mechanism of action of the bisphosphonates has not been fully realized. All of the compounds bind onto the calcium of hydroxyapatite, which inhibits calcification. This does not explain the antiresorptive effects. At the tissue level, bisphosphonates reduce bone turnover, which slows down total bone loss. At the cellular level, the target is inhibition of osteoclast recruitment, adhesion, shortening of lifespan of the osteoclasts, and inhibition of osteoclast activity either through a direct action or by action on cells that modulate osteoclast activity. At the molecular level, the primary mechanism involves the indirect inhibition of prenylation (post-translational lipid modification) of small proteins involved in bone resorption. The result is inhibition of osteoclast activity and apoptosis.

Table 2 Pharmacokinetic Profiles

	Alendronate	Risedronate
Absorption	<1% bioavailability 2 hours before food	0.65% bioavailability
Volume of distribution	28L (excluding bone) 640,000 L including bone	6.3L/kg
Plasma protein binding	78% primarily to albumin	24%
Metabolism	Little or none	Little or none
Excretion	Renal	Renal
T1/2	10.5 years (terminal half-life)	480 hours

Bisphosphonates have a low bioavailability due to their low lipophilicity and negative charge. In addition, they chelate calcium in the gut making them partially insoluble. Oral administration with food or calcium containing supplements reduces the bioavailability, and the manufacturers recommend administration with water after an over night fast and at least 30 minutes prior to the first meal of the day. Concomitant therapy with calcium products, antacids, or other oral medications with divalent cations should be avoided because of the interference with absorption. In a study of 127 healthy volunteers, risedronate was administered on various dose schedules before and after meals. The extent of absorption was similar when administered 0.5 and 1 hour before breakfast and 2 hours after dinner.[11] The bisphosphonates are sequestered in bone and then slowly released. This may explain why bone resorption remains below baseline rates for years after discontinuation of alendronate.

III. FDA Approved Indications

Table 3. FDA-approved indications

	Alendronate	Risedronate
Primary Osteoporosis	1. Treatment of osteoporosis in postmenopausal women 2. Treatment of osteoporosis in men	Treatment of osteoporosis in postmenopausal women
Osteoporosis prevention	Prevention of osteoporosis in postmenopausal women at high risk	Prevention of osteoporosis in postmenopausal women at high risk
Secondary Osteoporosis	Treatment of glucocorticoid induced osteoporosis in men and women receiving the daily equivalent of ≥ 7.5mg of prednisone who have a low bone mass density	Prevention and treatment of glucocorticoid induced osteoporosis in men and women initiating or continuing systemic therapy with a daily equivalent of ≥ 7.5mg of prednisone
Paget's	Treatment of Paget's bone disease in men and women	Treatment of Paget's bone disease in men and women

IV. Dose

Table 4. Dose

Indication	Alendronate	Risedronate
Primary Osteoporosis	Women: 70mg/once a week or 10mg/day Men: 10mg/day Alternatively 70mg/once a week	Postmenopausal women: 5mg/day or 35mg/once a week
Osteoporosis prevention	35mg/once a week or 5mg/day	5mg/day or 35mg/once a week
Secondary Osteoporosis	5mg/day except in postmenopausal women no on estrogen 10mg/day	Prevention or Treatment: 5mg/day
Paget's	40mg/day for 6 months	30mg/day for 2 months

V. Efficacy[12,13]

There are several options for defining efficacy in clinical trials in osteoporosis. Prevention trials evaluate antiresorptive therapy for the ability to prevent further bone loss. Treatment trials evaluate antiresorptive therapy for prevention of new fractures. In fact, the reduction in fracture risk is often considered the most important endpoint in treatment trials. Although vertebral fractures are the earliest and most common fractures seen in osteoporosis, few trials use the incidence of vertebral fractures as the endpoint, in part due to the need for large numbers of patients and the underreporting of fracture symptoms by patients. Hip fractures cause more morbidity and mortality, but have a low incidence requiring too many patients to detect a difference in therapy from placebo.

Many studies use surrogate markers to measure the efficacy of antiresorptive therapy. BMD has been well established in the diagnosis of osteoporosis. Because of the relationship of low BMD and increased fracture risk, many have extrapolated this data to show reductions in fracture risk secondary to increases in BMD due to antiresorptive therapy even though this relationship is not well defined. Biochemical markers of bone turnover may indicate antiresorptive drug activity but their ability to predict fracture risk has not been verified and they are only used in clinical trials.

It is thus difficult to compare anti fracture efficacy in trials because few have used fracture incidence as the primary outcome. There have not been any head-to-head trials of bisphosphonates. This review is limited to randomized, double blind studies of at least one year's duration which measured fracture incidence or changes in BMD as the primary outcome in postmenopausal women or in men. In addition, clinical trials in steroid-induced osteoporosis are included. A more complete table of clinical trial events is attached in the Appendix.

Table 5. Alendronate in Primary Osteoporosis

Fracture Prevention	
Liberman et al. 1995[14] Alendronate Phase III Osteoporosis Group	5, 10, or 20mg x 2 years then continued for 1 year (20mg dose changed to 5mg)
Black et al. 1996[15] Fracture Intervention Trial (FIT)	5mg/day; at month 24 dose changed to 10mg/day
Ensrud et al. 1997[16] FIT subgroup analysis	5mg/day for 24 months then changed to 10mg/day
Cummings et al. 1998[17] FIT (arm with no prevalent vertebral fractures)	5mg/day for 24 months than changed to 10mg/day
Prevention of Bone Loss	
Chestnut et al. 1995[18]	5 or 10mg/day for 2 years 20mg/day for 1 year, then placebo for 1 year 40mg/day for 1 year then placebo for 1 year 40mg/day for 3 months, then 2.5mg/day for 21 months
Devogelaer et al. 1996[19]	5, 10, or 20mg/day for 2 years Optional year 3: Remain on blinded treatment (20mg/day blindly changed to 5mg/d) or If patient did not consent to blinded treatment, open label 5mg/d or Discontinue therapy
Tucci et al. 1996[20] U.S. Alendronate Phase III Osteoporosis Treatment Study Group	5, 10, or 20mg/day for 2 years Year 3: Continue DB therapy for all consenting patients (20mg/day blindly switched to 5mg/day)
Bone et al. 1997[21]	1, 2.5, or 5mg/day for 2 years
Pols 1999 [22] Fosamax International Trial Study Group (FOSIT)	10mg/day for 12 months
Tonino et al. 2000[23] Phase III Osteoporosis Treatment Study Group	Years 1-3 as in Liberman et al. above Years 4-5 If randomized to Alendronate continue therapy All placebo patients + 61 others received open-label 10mg/day Years 6-7 Original placebo patients discontinued therapy Original 20mg/day →5mg/day received placebo All others continued same Alendronate therapy
Greenspan et al. 2002[24]	10mg/day

Table 6. Risedronate in Primary Osteoporosis

Fracture Prevention	
Harris, et al. 1999[25] Vertebral Efficacy with Risedronate Therapy (VERT) Study Group N.A.	2.5 or 5mg versus placebo
Reginster, et al. 2000[26] Vertebral Efficacy with Risedronate Therapy (VERT) Study Group Europe	2.5mg (2.5 d/c'd after 2 years), 5mg versus placebo
McClung, et al. 2001[27] Hip Intervention Program Study Group	2.5mg or 5mg versus placebo
Prevention of Bone Loss	
Clemmesen, et al. 1997[28]	2.5mg continuous therapy or 2.5mg cyclic therapy versus placebo
Fogelman, et al. 2000[29]	2.5mg (d/c at 9/13 centers) or 5mg versus placebo

All patients in the alendronate studies also received calcium supplements, vitamin D supplements, or both. Alendronate has been shown to significantly increase bone density versus placebo in postmenopausal women with osteoporosis in six trials (n=188 to 1908). The optimal dose appears to be 10mg/day although many different daily doses have been utilized. The majority of the increase occurs over the first 6-12 months and has been maintained during 7 years of treatment.

Fracture prevention was the primary outcome of the comprehensive Fracture Intervention Trial (FIT). A review of fracture risk indicates that vertebral fracture risk is increased in patients with prevalent vertebral

fractures, and the risk of a new vertebral fracture is increased within the first year of an initial incident fracture.[30] This trial assessed the ability of alendronate to reduce the risk of vertebral fractures and other clinical fractures in postmenopausal women with existing vertebral fractures (n=2027) and in those without existing vertebral fractures (n=4272). The study results show that alendronate 5 or 10mg/day significantly reduced the risk of radiographic and clinical vertebral fractures and hip fractures in both populations. An additional analysis of the effects of alendronate on bed-disability days and limited activity days due to back pain in women with existing vertebral fractures found that alendronate therapy significantly reduced the days of bed-disability and limited activity days versus placebo.[31]

Risedronate was evaluated against placebo in 9129 women in the VERT and Hip intervention studies for the prevention of fractures in postmenopausal women with osteoporosis. All women received calcium or calcium plus vitamin D. Risedronate 5mg/day was found to significantly reduce the risk of new vertebral and nonvertebral fractures when compared to placebo. It also decreased the risk for hip fractures in women with confirmed osteoporosis. In the 2 studies evaluating the effects on BMD as an endpoint, risedronate 5mg/day significantly increased BMD compared to placebo. A meta-analysis of trials reporting fracture incidence confirms that risedronate reduces the incidence of vertebral and non-vertebral fractures when compared to placebo.[32]

Table 7. Alendronate in Primary Osteoporosis-Comparative Trials and Combination Therapy

Adami, et al. 1993[33]	ALN 10 or 20mg/ day or placebo Open label intranasal calcitonin 100IU/day
Lindsay, et al. 1999[34]	ALN 10mg/day or placebo in addition to ongoing HRT
Rittmaster, et al. 2000[35]	ALN 10mg/d in women previously on 1 year of PTH or placebo therapy
Bone, et al. 2000[36]. Alendronate 10mg vs conjugated equine estrogen (CEE)	1. placebo ALN and placebo CEE 2. CEE and placebo ALN 3. ALN and placebo CEE 4. ALN and CEE
Downs, et al. 2000[37]	ALN 10mg /day or Intranasal calcitonin 100IU/day or Placebo
Johnell, et al. 2002[38]	1. Raloxifene 60mg/d 2. ALN 10mg/day 3. Raloxifene 60mg + ALN 10mg/day

Table 8. Risedronate in Primary Osteoporosis-Combination Therapy

Harris 2001[39]	5mg + 0.625mg CEE Placebo + 0.625mg CEE

A series of trials examining the effects of combination bisphosphonate therapy or comparative trials with other agents used to treat osteoporosis have been conducted. Alendronate increases BMD significantly greater than placebo or inhaled calcitonin. When combined with hormone replacement therapy, alendronate has an additive effect on BMD, increasing bone mass greater than HRT alone or alendronate alone, especially at the lumbar spine. When given after PTH, alendronate reverses cortical bone loss and increases BMD. The combination of raloxifene and alendronate increased BMD greater than the use of raloxifene alone. When compared to alendronate alone, except for BMD at the femoral neck, the combination did not significantly increase BMD at other sites.

Risedronate and hormone replacement therapy produced slight, but significant increases in BMD at the femoral neck and midshaft radius compared to HRT alone. The effects at other sites were similar between the two treatment groups and significantly better than placebo.

Table 9. Alendronate- Prevention of Osteoporosis in Postmenopausal Women

Hosking, et al. 1998[40] Early Postmenopausal Intervention Cohort Study Group	1. 2.5mg, 5mg, or placebo or open label estrogen/progestin 2. 2.5mg, 5mg, or placebo
Ravn, et al. 1999[41] Early Postmenopausal Intervention Cohort Study Group	Years 3-4: continue same therapy as above or replace with placebo
McClung, et al. 1998[42] Alendronate Osteoporosis Prevention Study Group	1. 1, 5, or 10mg/day 2. Placebo 3. 20mg/day for 2 years, then placebo for 1 year
Ravn, et al. 2000[43] Alendronate Osteoporosis Prevention Study Group	Years 4-5 1. Open label alendronate 5mg/day for patients previously receiving placebo or 5mg/day for 3 years 2. Observation for those previously on 20mg/day for 2 years and placebo for 1 year

Table 10. Risedronate – Prevention of Osteoporosis in Postmenopausal Women

Mortensen, et al. 1998[44]	5mg/day or 5mg/day for 14 days then placebo for 14 days vs placebo

Two studies (n=263 and n=1609) examined the ability of alendronate to prevent osteoporosis in early menopause. Although the studies differed in design, they both showed that 5mg alendronate maintained BMD at the lumbar spine hip, and total body and was most pronounced during the first 1-2 years of therapy, even if placebo was given for 2 years which allowed for decreases in baseline BMD. Withdrawal of alendronate after 2 years caused bone loss at the same rate as placebo. Similarly, 5mg per day of risedronate increased BMD during 24 months of therapy. Cyclical therapy did not totally prevent bone loss, but the resulting BMD was statistically greater than placebo.

Table 11. Alendronate in Steroid-induced Osteoporosis

Saag, et al. 1998[45]	5 or 10mg vs placebo
Adachi et al. 2001[46]	5 or 10mg vs placebo
Lau, et al. 2001[47] (inhaled steroids)	10mg vs placebo

Table 12. Risedronate in Steroid-induced Osteoporosis

Cohen, at al. 1999[48]	2.5 or 5mg vs placebo
Wallach, et al. 2000[49]	2.5 or 5mg vs placebo
Reid, et al 2000[50]	2.5 or 5mg vs placebo

Prolonged use of corticosteroids is known to induce osteoporosis. The mechanism is uncertain but involves decreased osteoblast activity, increased bone resorption, decreased intestinal absorption of calcium, decreased renal tubular reabsorption of calcium, and changes in the formation of osteoid. The majority of the bone loss occurs within the first 6-12 months of therapy.

Alendronate was studied in 560 patients (28-33% males in each group) receiving the equivalent of ≥ 7.5mg of prednisone per day. The first study duration was 48 weeks, which was extended another year in the second study. Alendronate 5 or 10mg/day significantly increased BMD at the lumbar spine, trochanter, and femoral neck relative to placebo and baseline. Alendronate 10mg was more effective than 5 mg in postmenopausal women not receiving estrogen therapy. Similar results were seen in women on inhaled steroids receiving ≥800mcg of beclomethasone, budesonide, or fluticasone per day.

Risedronate was studied in the prevention of osteoporosis in patients starting corticosteroid treatment, and the treatment of osteoporosis in patients on long-term steroid therapy with low BMD. In the prevention study, risedronate 5mg per day (32.5-35.5% males in each group) maintained the BMD at the lumbar spine and femoral neck, and increased the BMD at the trochanter. Risedronate 2.5mg maintained the BMD but differences versus placebo were less and only significant at the lumbar spine and trochanter. In the treatment study, 5mg per day (36-39% males in each group) significantly increased the BMD at the lumbar

spine, trochanter, and femoral neck compared to placebo. Combining the data from both studies yields a 70% reduction in the incidence of vertebral fractures on risedronate 5mg per day.

In the VA, adherence to guidelines for the prevention and management of glucocorticoid-induced osteoporosis published by the American College of Rheumatology was recently evaluated. The key points from the guideline include: baseline BMD at the lumbar spine and femoral neck, adequate dietary calcium intake, intake of vitamin D 800IU/day, assessment and treatment of hypogonadism, and antiresorptive therapy for patients with T-scores below –1SD. The results in 72 patients who met entry criteria found that 43 patients had BMD measured sometime after starting prednisone and 32 had documented low BMD. Of those 32, 19 had contraindications to testosterone therapy, and 7/13 remaining patients were hypogonadal and were treated with testosterone. Six patients received adequate calcium and multivitamin therapy. Twenty of 32 men with low bone mass (63%) did not receive antiresorptive therapy, and guidelines were more closely adhered to in the rheumatology clinic.[51] The updated guidelines include recommendations for prevention of osteoporosis with calcium, vitamin D, and a bisphosphonate at the start of therapy with ≥5mg per day of prednisone equivalent and duration of therapy of ≥3 months.[52]

Table 13. Alendronate in Primary Osteoporosis - Men

Orwall, et al. 2000[53]	10mg/day vs placebo
Ringe, et al. 2001[54]	10mg/day vs 1-alfacalcidol 1mcg/day

Table 14. Risedronate in Steroid-induced Osteoporosis-Men

Reid, et al. 2001[55]	2.5mg, 5mg vs placebo

The majority of the data on osteoporosis research has been directed at women. As previously stated, a clear definition of osteoporosis in men (greater than 2.5 standard deviations below the young adult mean) has never been validated and the use of bone mineral density as a basis for treatment options has not been studied. Although men have a gradual loss of bone density after age 30, primary osteoporosis is relatively rare secondary to increased peak bone mass, shorter life expectancy, and lack of a menopause equivalent. Secondary causes of osteoporosis in men include hypogonadism, glucocorticoid excess, alcoholism, thyroid or parathyroid disease, osteomalacia, or neoplasm.[56]

Long-term testosterone deficiency is an important secondary risk factor, accounting for up to 30% of cases of men with osteoporosis. The role of testosterone in bone resorption is not well known. Androgens may modulate osteoblast proliferation and differentiation, may affect various growth factors important in osteoblast proliferation, or may affect calcitonin. It is also postulated that testosterone deficiency affects bone resorption because of the lack of conversion by aromatase to estradiol. Several reports document the effects of therapy-induced testosterone deficiency on bone resorption in men. Testosterone deficiency, either secondary to orchiectomy or gonadotropin releasing hormone agonists, has produced bone loss in men with prostate cancer. Suppression of testosterone with gonadotropin releasing hormone agonist also sensitizes the skeleton to PTH, promoting bone loss. Finally, androgen suppression for prostate cancer increases the risk of skeletal fracture, with the risk increasing with duration of suppression.[57,58,59,60]

Hip fractures in males carry a higher one-year mortality rate than in females. Outcomes of secondary prevention measures in men with hip fractures are unclear. Recently, the records of 43 veterans who sustained hip fractures not due to high impact trauma were examined to determine outcomes and if any secondary prevention strategies were employed. Two patients died in the hospital from complications, nine patients died within 1 year of fracture (26% mortality). None of the original 41 patients discharged from the hospital had osteoporosis documented in their medical records, and only 3/25 patients who had DXA scans available to them had BMD measurements before or within 6 months after the fracture. In addition, none were prescribed a bisphosphonate before the fracture or at discharge.[61] An earlier study comparing practice patterns of expert physicians in treating men with osteoporotic hip fracture with current practices at

a VA center found that VA patients were seldom evaluated for osteoporosis following a hip fracture and did not receive antiresorptive therapy even on follow-up.[62]

Alendronate 10mg/day effectively increased BMD in all measured skeletal sites compared to placebo. All patients had primary osteoporosis or secondary osteoporosis due to hypogonadism. The 241 patients were between the ages of 31 and 87 with BMD at the femoral neck at least 2 SD below the mean value in normal young men. Men receiving alendronate experienced statistically significantly less height loss and quantitatively less vertebral fractures than those on placebo. There was no difference in the incidence of nonvertebral fractures between the groups. There were more withdrawals due to adverse effects in the placebo group (11%) versus the alendronate group (3%).[49] In a smaller comparative trial, 134 men with osteoporosis received either alendronate or 1-alfacalcidol (a vitamin D analogue) for 2 years. Alendronate increased BMD at the lumbar spine and femoral neck significantly more than 1-alfacalcidol. The number of new vertebral fractures was significantly less in the alendronate group, although it did not significantly reduce the number of patients with new fractures or the incidence of nonvertebral fractures. Loss of height was significantly less in the alendronate group.

Risedronate has not been studied in primary osteoporosis in men. A subgroup analysis was performed on men enrolled in two double blind clinical trials of risedronate in patients on corticosteroid therapy. The analysis found that risedronate significantly increased BMD at the lumbar spine, femoral neck, and femoral trochanter compared to baseline and placebo. The men on risedronate also experienced a significant reduction in vertebral fractures.[51]

Other: Both alendronate and risedronate are indicated in the treatment of Paget's disease in men and women.

Once weekly dosing: Due to sequestration in the bone, bisphosphonates may be given on a once a week schedule with results similar to daily dosing. Alendronate 70mg once weekly was compared with 35mg twice a week and 10mg daily in the treatment of osteoporosis. Mean increases in BMD in the lumbar spine, total hip, femoral neck, trochanter and total body were similar for all doses. All doses reduced biochemical markers of bone turnover. A similar incidence of GI adverse events was seen in all groups. The once-weekly group had less serious upper GI adverse events and a trend towards less esophageal events.[63] A 10-week study comparing alendronate 70mg once a week to placebo or placebo followed by aspirin found similar results for safety and tolerability.[64]

Postmenopausal women with osteoporosis were randomly assigned to receive risedronate 5mg daily, 35mg once weekly, or 50mg once weekly in a blinded fashion. Assessment of BMD at 12 months of therapy showed significant changes from baseline in BMD within each group at the lumbar spine, total hip, femoral neck, and trochanter. There were no statistically significant differences between the groups with regard to mean percent change from baseline in BMD at any site. All doses reduced biochemical markers of bone turnover. A similar incidence in adverse events, including upper gastrointestinal adverse events, was seen in all groups.[65]

VI. Safety[1-2,]

Contraindications

All bisphosphonates carry contraindications of hypersensitivity to any component, hypocalcemia, and inability to stand or sit upright for at least 30 minutes, which increases the risk for upper gastrointestinal irritation. Alendronate also carries a contraindication of abnormalities of the esophagus (e.g. stricture, achalasia), which may delay gastric emptying.

Precautions

Hypocalcemia should be corrected before initiation of therapy. Because of the effects of the bisphosphonates on bone mineral metabolism, it is important to ensure adequate calcium intake (1500mg/day) and vitamin D (800IU/day) especially in patients taking glucocorticoids and in patients with Paget's disease.

Gastrointestinal toxicity has been reported with both bisphosphonates. Esophagitis, esophageal ulcers and erosions, dyspepsia, nausea, and vomiting have all been reported. Occasionally, esophageal symptoms have been accompanied by bleeding and have required hospitalization. The possible mechanism of GI tract damage has not been fully investigated. It is likely due to topical irritation directly damaging GI mucosa. Tablets lodged in the esophagus or dissolved in the stomach but contacting the esophagus as part of reflux disease are probable causes of esophageal irritation. Risk factors for upper GI adverse events include upper GI tract disease and concomitant NSAIDs or aspirin. In order to minimize GI adverse events, manufacturers of both drugs recommend swallowing the tablet upon arising for the day with a full glass of water (6-8 ounces) and not to lie down for at least 30 minutes and, for alendronate, until after the first food of the day.

Table 15. Alendronate GI Toxicity

<table>
<tr><th>Study</th><th>Patients</th><th>Outcomes</th></tr>
<tr><td colspan="3">Short-term studies in healthy volunteers</td></tr>
<tr><td>Lanza 1998[66]</td><td>N=79
100% women</td><td>% of patients with gastric/duodenal mucosal erosion on Day 8 or 15 (Lanza score ≥2)
PL = 18.2 ALN 5mg = 18.2 ALN 10mg = 23.8 ASA 650mg = 100 (p<0.001 vs PL & ALN)
Gastric Ulcers
ALN 5mg = 1 ALN 10mg = 1 ASA 650mg = 3
Esophageal Erosion in 5 patients (3 in the PL group)</td></tr>
<tr><td>Graham 1999[67]</td><td>N=24
35% men</td><td>Visible gastric mucosal damage
PL = 12.5% ALN = 37.5% P=0.09
Ulcer or erosion PL = 0 ALN = 6 (p<0.005)</td></tr>
<tr><td>Marshall 2000[68]</td><td>N=87
49% men</td><td>% of patients with visible upper gastrointestinal damage:
ASA = 92.3% ALN = 68% PL = 48%
Gastric ulcers: ASA = 5 ALN = 2 PL = 0
% of patients with esophageal erosion:
ASA = 34.6 ALN = 24 PL = 20</td></tr>
<tr><td>Lowe 2000[69]</td><td>N=32
100% women</td><td>Number of patients and Lanza score after endoscopy
<table>
<tr><th></th><th>1 month</th></tr>
<tr><td>Esophageal lesions
ALN
PL</td><td>
0
3 (1 each grade 1,2,3)</td></tr>
<tr><td>Gastric lesions
ALN
PL</td><td>
1 (grade 2)
2 (1 each grade 2,3)</td></tr>
</table>
Symptom scores increased after treatment in both groups but were not significant.</td></tr>
<tr><td>Graham 2001[70]</td><td>N=26
31% men
ALN vs NAP vs Combination</td><td>
<table>
<tr><td colspan="5">Number of patients with gastric mucosal damage</td></tr>
<tr><td></td><td>Mucosal hemorrhage</td><td>1 or 2 erosions</td><td>≥3 areas of erosion</td><td>Large areas of erosion or ulcer</td></tr>
<tr><td>ALN</td><td>1</td><td>2</td><td>3</td><td>2</td></tr>
<tr><td>NAP</td><td>0</td><td>4</td><td>10</td><td>3</td></tr>
<tr><td>ALN +NAP</td><td>0</td><td>1</td><td>9</td><td>14</td></tr>
<tr><td colspan="5">Number of patients with duodenal mucosal damage</td></tr>
<tr><td>ALN</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>NAP</td><td>1</td><td>1</td><td>2</td><td>0</td></tr>
<tr><td>ALN + NAP</td><td>0</td><td>6</td><td>1</td><td>1</td></tr>
</table>
No esophageal lesions in any treatment group</td></tr>
<tr><td>Lanza 2002[71]
Once-a-week dose</td><td>N=277
32.5% men</td><td>Mean Lanza scores
Gastric erosion: PL = 0.35 ALN = 0.32 ASA = 3.09
Duodenal erosion: PL = 0.14 ALN = 0.12 ASA = 1.22
Esophageal erosion: PL = 0.12 ALN = 0.16 ASA = 0.15</td></tr>
</table>

<table>
<tr><td colspan="3">Studies in patients receiving long-term treatment</td></tr>
<tr><td>Ettinger 1998[72] (Telephone survey Kaiser)</td><td>N=812
100% women</td><td>32.7% reported new upper-gastrointestinal symptoms
Those with rx's for acid-related disorders more likely to report symptoms
A higher % of those who complied with absorption instructions had symptoms
34.9% discontinued therapy- 51.9% due to GI symptoms</td></tr>
<tr><td>Bauer 2000[73]</td><td>N=6459
FIT trial</td><td>Upper GI Events (%)
<table>
<tr><td></td><td>ALN</td><td>PL</td></tr>
<tr><td>Any UGI AE</td><td>47.5</td><td>46.2</td></tr>
<tr><td>Any gastric or duodenal AE</td><td>4</td><td>4</td></tr>
<tr><td>Any esophageal AE</td><td>10</td><td>9.4</td></tr>
<tr><td>Any GI or duodenal perforation, ulceration, bleeding</td><td>1.6</td><td>1.9</td></tr>
</table>
The proportion of patients reporting any UGI event was similar between the 5 and 10mg groups.</td></tr>
<tr><td>Miller 2000[74]</td><td>N=172
100% women
(Rechallenge after discontinuation of alendronate b/o GI AE)</td><td>UGI AE's causing discontinuation of study therapy
<table>
<tr><td></td><td>ALN</td><td>PL</td></tr>
<tr><td>Abd pain</td><td>3</td><td>5</td></tr>
<tr><td>Abd regurgitation</td><td>4</td><td>3</td></tr>
<tr><td>Nausea</td><td>3</td><td>2</td></tr>
<tr><td>GE reflux</td><td>0</td><td>3</td></tr>
<tr><td>Dyspepsia</td><td>1</td><td>0</td></tr>
<tr><td>Vomiting</td><td>1</td><td>0</td></tr>
<tr><td>Dysphagia</td><td>1</td><td>0</td></tr>
<tr><td>Esophagalgia</td><td>0</td><td>1</td></tr>
</table>
Overall clinical adverse effects (%)
ALN = 52.3 PL = 63.1</td></tr>
</table>

ALN=alendronate RIS=risedronate PL=placebo NAP=Naprosyn Lanza Scores: 0=normal mucosa 1=mucosal hemorrhages only 2=one or two erosions 3=numerous (3-10) erosions 4=>10erosions or an ulcer

Short-term endoscopic studies in small numbers of volunteers give conflicting results and their relevance to clinical practice is questionable. Some show no relationship between endoscopic findings and GI adverse event reporting, while others suggest that daily and weekly dosing do not increase the risk for upper GI damage over placebo. While there was no increased incidence of upper GI tract irritation in the large osteoporosis trials, it is argued that patients in those trials received extra counseling on drug administration, were excluded from the study if they had pre-existing GI tract diseases, and had fewer coexisting conditions, putting them at decreased risk for GI adverse events. Patients who had previously discontinued alendronate due to a GI tract adverse effect were rechallenged with alendronate or placebo and no difference was found in the incidence of discontinuation attributed to GI tract adverse events. Post-marketing surveillance of 470,000 patients receiving alendronate found 199 adverse event reports related to the esophagus, of which 26% were classified as serious or severe. Sixteen percent required hospitalization. Nine patients had a history of upper GI tract disease. Sixteen patients took the tablet with inadequate amounts of water and 18 patients did not remain upright for 30 minutes following the dose. Timing of symptoms was available for 43 patients. Nineteen had symptoms within 7 days of starting alendronate, and 39 within one month.[75] A telephone survey of 812 women receiving alendronate 10mg/day revealed that 13.5% did not comply with the instructions that helped improve GI tolerability (6-8 ounces of water and remain upright for at least 30 minutes) and 51.7% did not comply with instructions which enhance absorption (eat no food 2 hours before and 30 minutes after the drug, use no other liquid except water, take no other medications/supplements with alendronate). Interestingly, the study found a higher percentage of new GI symptoms in patients who were compliant with the instructions.[71]

Table 16. Risedronate GI toxicity

Study	Patients	Outcomes
Lanza 2000[76]	N=80 100% women	Esophageal lesions: RIS = 1 PL = 2 ASA = 1 Esophageal ulcer: RIS = 0 PL = 0 ASA = 1 Gastric lesions: RIS = 16% PL = 4% ASA = 96% Gastric ulcers: RIS = 0% PL = 4% ASA = 32% ASA vs PL (p=0.01) ASA vs RIS (p=0.002) PL vs RIS (p=1.00) Dyspepsia and abdominal pain (no.): RIS = 5 PL = 6 ASA = 14

Adachi 2001[77] (Tolerability in patients intolerant of alendronate)	N=67 100% women	

Outcome	PL	RIS	Odds Ratio	95% CI
Discontinuation %	16.1	11.4	0.66	0.11 to 3.52
Completion %	67.7	80	1.87	0.54 to 6.8
Any gastrointestinal AE %	19.4	20.0		
Mod to severe gastrointestinal AE %	16.1	11.4		

Taggart 2002[78] (Pooled analysis from Phase III trials)	N=10,068 1.2-1.3% men			

	PL	RIS	RR	P
Endoscopy				
Esoph inflammation	14.2%	17.1%	1.2	0.55
Esoph erosion	11.1	10.6	0.95	>0.99
Esoph ulcer	14.2	9.4	0.66	0.23
Stom inflammation	15.4	20.6	1.33	0.26
Stom erosion	8	12.6	1.57	0.21
Stom ulcer	24.1	28	1.16	0.46
Duod inflammation	6.3	6.3	1.01	>0.99
Duod erosion	1.9	4	2.13	0.34
Duod ulcer	12.6	8	0.64	0.21
GI tract adverse events				
Any UGI AE	29.6	29.8	1.01	0.77
Abd pain	9.3	9.6	1.03	0.61
Gastritis	2	2.3	1.13	0.37
GI tract bleeding	0.7	0.9	1.22	0.30

% of pts with an UGI AE was 3X higher in users of H_sRA and/or PPIs
% of pts with and UGI AE slightly higher in ASA/NSAID users

In large clinical trials, the incidence of GI adverse events is similar between risedronate and placebo. This was confirmed by a meta-analysis of 9 phase III trials. In a small sample of postmenopausal women, endoscopic changes following therapy with risedronate, placebo and aspirin were compared for erosions and ulcer formation. Differences in the percentage of patients with gastric ulcers were significant for the aspirin and risedronate groups and the aspirin and placebo groups but not between the placebo and risedronate groups. Women intolerant of alendronate were able to tolerate both placebo and risedronate for a 3-month period, with similar discontinuation rates due to upper GI adverse events.

Table 17. GI Toxicity-Comparison trials

Study	Patients	Outcomes
Lanza 2000[79]	N=515 100% women RIS 5mg/day vs ALN 10mg/day	Gastric Ulcers: (Day 14) Overall % RIS = 4.1 ALN = 13.2 p=<0.001 Odds ratio (ALN vs RIS) = 3.78 Incidence also significantly lower on days 8 and 15 in the risedronate group Mean EGD Scores (Range 0 to 4) on Day 15

	RIS	ALN
Esophagus	0.15	0.13
Stomach	0.91*	1.56
Duodenum	0.11	0.20

* p ≤0.001
Esophageal erosions similar between groups; esophageal ulcers in 3 subjects on alendronate, none in risedronate subjects

Lanza 2000[80] ALN 40mg RIS 30mg PL PL → ASA	N=235 (35-37.1% men) RIS 30mg/d vs ALN 40mg/d	Mean Gastric Erosion Scores Day 29 (Range 0-4) PL = 0.31 RIS = 0.73 ALN = 0.89 ASA = 3.07 NSS between ALN and RIS Mean Esophageal Erosion Scores Day 29 (Range 0-4) PL = 0.25 RIS = 0.11 ALN = 0.06 ASA = 0.22 NSS between all groups

The incidence of gastric ulcers was significantly higher in the alendronate group versus the risedronate group following 14 days of therapy. Mean gastric erosion scores were also significantly higher in the alendronate group versus the risedronate group, while esophageal and duodenal erosion scores were similar

between the groups. A smaller study evaluating erosion scores as the primary outcome after 28 days of therapy with either alendronate, risedronate, or aspirin found no difference between alendronate and risedronate in gastric erosion scores and no difference in any group in esophageal erosion scores.

The following tables were adapted from the product package inserts.

Table 18. Adverse Events in Osteoporosis Trials

	Alendronate		Risedronate
GI			
Abdominal pain	1.5 – 6.6%		11.6
Nausea	1.1 - 3.6		10.9
Dyspepsia	1.1 – 3.6		
Constipation	3.1		
Diarrhea	0.6 – 3.1		10.6
Flatulence	0.2 – 2.6		4.6
Acid regurgitation	1.1 – 2.0		
Esophageal ulcer	0.1 – 1.5		
Vomiting	0.2 – 1.0		
Dysphagia	0.1 – 1.0		
Gastritis	0.6		2.5
Musculoskeletal			
Pain	0.4 – 4.1		4.6
Muscle cramp	0.2		3.5
Arthralgia			23.7
Joint disorder			6.8
Myalgia			6.6
Bone disorder			4.0
Bursitis			3.0
Tendon disorder			3.0
Nervous System			
Headache	0.2 – 2.6		
Dizziness			6.4
Depression			6.8
Insomnia			4.7
Anxiety			4.3
Neuralgia			3.8
Vertigo			3.3
Hypertonia			2.2
Paresthesia			2.1
Special senses			
Taste perversion	0.1 – 0.5		
Cataract			5.9
Conjunctivitis			3.1
Otitis Media			2.5
Body as a Whole			
Infection			29.9
Back pain			26.1
Pain			13.6
Neck pain			5.3
Asthenia			5.1
Chest pain			5.0
Neoplasm			3.3
Hernia			2.9
Cardiovascular			
Hypertension			10.0
Cardiovascular Disorder			2.5
Angina			2.5
Respiratory			
Pharyngitis			5.8
Rhinitis			5.7
Dyspnea			3.8
Pneumonia			3.1
Skin and appendages			
Rash			7.7
Pruritus			3.0

Skin Carcinoma			2.0
Urogenital UTI Cystitis			 10.9 4.1

Similar adverse events have been reported in once a week dosing studies, and in studies for all other indications.

Drug Interactions

Calcium supplements/antacids: It is likely that calcium supplements and other divalent cations will interfere with absorption of either drug. Patients should wait at least 30 minutes after taking either bisphosphonate before taking other medications.

Hormone replacement therapy: Estrogen ± progestin has been studied with both alendronate and risedronate. The combination generally decreases bone turnover to a greater extent than either therapy separately. Long-term use of the combinations has not been studied

NSAIDS/ASA: Although many of the clinical trials included patients who were receiving NSAIDS or aspirin and the reported gastrointestinal adverse events were similar to placebo, caution is advised when using NSAIDS with bisphosphonates because of the potential for gastric irritation. The incidence of upper GI adverse events was increased in patients taking alendronate (>10mg/day) and aspirin.

H_2RA/PPIs: In clinical studies with risedronate, about 21% of patients used H_2RAs or PPIs without changes in the incidence of upper GI adverse events.

Geriatric Use:
In clinical trials with both drugs, a significant number of patients were between 65 and 75 years old, and 17% were greater than 75 years old.

Renal Insufficiency:
Alendronate is not recommended in patients with a creatinine clearance < 35ml/minute. Risedronate is not recommended in patients with a creatinine clearance < 30ml/minute.

Pregnancy:
Category C

VII. Utilization and Cost

	FY2002 (10/01 thru 05/02)	FY2002 (10/01 thru 05/02)	FY2002 (10/01 thru 05/02)
	Patients	Day30rxs	TLQty
Alendronate 10MG TAB	14,131	75,218	2,231,583
Alendronate 35MG TAB	1,175	5,270	22,792
Alendronate 5MG TAB	1,400	6,757	203,908
Alendronate 70MG TAB	25,135	133,602	536,020
Risedronate 30MG TAB	587	2,629	25,032
Risedronate 5MG TAB	639	3,003	89,943

	Cost per tablet	Cost per 4 weeks Therapy
Alendronate 10mg	1.195	33.46
Alendronate 70mg	8.36	33.44
Alendronate 5mg	1.20	33.60
Alendronate 35mg	8.36	33.44
Risedronate 5mg	1.11	31.08
Risedronate 35mg	7.75	31.00

VIII. Conclusion and Recommendations

Alendronate and risedronate have been shown in large clinical trials to prevent new fractures or increase BMD in postmenopausal women diagnosed with osteoporosis, as well as prevention of further bone loss in postmenopausal women who do not have osteoporosis. Both have been shown to increase BMD and lower the risk of vertebral fractures in men and women on corticosteroid therapy who are diagnosed with steroid-induced osteoporosis. In addition, risedronate has been shown to prevent osteoporosis in men and women in the early part of steroid therapy. Only alendronate has been specifically studied in primary osteoporosis in men, yielding similar results as in postmenopausal women. A subgroup analysis of men in the risedronate corticosteroid studies showed statistically significant results compared to placebo. GI toxicity is a potential problem, however, information from the large clinical trials and information from GI endoscopy trials fails to fully characterize the risk. Most clinical and endoscopy trials show the incidence is similar to placebo, but post-marketing surveillance has shown some alendronate esophagitis which may be related to improper dosing. Head to head endoscopic trials of GI toxicity were short term. One compared alendronate 10mg/day and risedronate 5mg/day and revealed a 9.1% absolute risk reduction in the overall incidence of gastric ulcers at 14 days in those taking risedronate.[78] The relationship between endoscopy findings and clinical symptoms is unclear. Weekly dosing has been shown to yield equivalent results and may have a lower incidence of GI toxicity than daily dosing.

Alendronate and risedronate produce similar results with regard to treatment and prevention of osteoporosis, and treatment of steroid-induced osteoporosis. Although prevention of steroid induced osteoporosis and treatment of men with primary osteoporosis have only been shown with one of the drugs (risedronate and alendronate, respectively), these are class effects and equivalent outcomes would be expected. The VHA should consider these two drugs equivalent clinically, and choose one for use based on best value.

Appendix

Alendronate Trials-Prevention of Bone Loss in Women with Osteoporosis

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Chestnut 1995
N=188
Primarily Caucasian
R, DB, PC, MC

Grant from Merck Research Laboratories</td>
<td>PL daily for 2 yrs
ALN
5mg/d for 2 yrs
10mg/d for 2 yrs
20mg/d for 1 yr, PL x1yr
40mg/d x1 yr, PL x1yr
40mg/d x3 mos, then 2.5mg/d x 21 mos</td>
<td>1.Dose-response effect on BMD
2. Effect on biochemical markers, calcium metabolism, safety, tolerability</td>
<td>
<table>
<tr><th></th><th>PL mean (n=31)</th><th>ALN mean (n=157)</th></tr>
<tr><td>Age
1° Caucasian</td><td>63.6</td><td>62.9</td></tr>
<tr><td>Yrs since Menopause</td><td>16.9</td><td>15</td></tr>
<tr><td>Ca intake (mg)</td><td>1019</td><td>819.9</td></tr>
<tr><td>L spine BMD (g/cm^2)</td><td>0.75</td><td>0.75</td></tr>
<tr><td>Hip BMD</td><td>0.69</td><td>0.73</td></tr>
<tr><td>Forearm BMD</td><td>0.54</td><td>0.56</td></tr>
<tr><td>Alk phos (U/L)</td><td>58.2</td><td>55.2</td></tr>
<tr><td>Osteocalcin (ng/ml)</td><td>4.00</td><td>3.48</td></tr>
<tr><td>Deoxypyridinoline</td><td>82.5</td><td>80.3</td></tr>
</table>
</td>
<td>Mean % change in BMD at 24 months
<table>
<tr><th></th><th>PL</th><th>5mg</th><th>10mg</th><th>20/P</th><th>40/P</th><th>40/2.5</th></tr>
<tr><td>L spine</td><td>-1.35</td><td>7.27</td><td>7.21</td><td>6.24</td><td>6.16</td><td>4.48</td></tr>
<tr><td>Hip</td><td>-1.2</td><td>3.57</td><td>5.27</td><td>5.83</td><td>3.34</td><td>2.45</td></tr>
<tr><td>T body</td><td></td><td>1.58</td><td>2.53</td><td></td><td></td><td></td></tr>
<tr><td>Femoral Neck</td><td></td><td>3.02</td><td>5.03</td><td></td><td></td><td></td></tr>
</table>
P <0.001 for comparisons between PL and all ALN groups

Mean % change in Biochemical Markers
<table>
<tr><th></th><th>PL</th><th>5mg</th><th>10mg</th><th>20/P</th><th>40/P</th><th>40/2.5</th></tr>
<tr><td>DPyr
6-9mos
24 mos</td><td>
-1.9
-1.9</td><td>
-4.8
-4.8</td><td>
-47.3
-47.3</td><td>
-53.2
-14</td><td>
-62.5
-21</td><td>
-62.5
-21</td></tr>
<tr><td>OC
6-9mos
24mos</td><td>
1
20</td><td>
-38
-48</td><td>
-53.4
-53.4</td><td>
-54.8
-39</td><td>
-57.5
-39</td><td>
-57.4
-38</td></tr>
</table>
</td>
</tr>
<tr>
<td>Devogelaer 1996
N=516
R, DB, PC, MC x2 years
+
optional open label in
year 3

Grant from Merck Research Laboratories</td>
<td>PL daily for 2 years
ALN
5,10, or 20mg for 2 yrs

Optional year 3:
1. Continued on blinded therapy
2. Patients on 20mg/d blindly switched to 5mg/day
3. Pts not agreeing to continued blind treatment receive open label 5mg/d</td>
<td>1. BMD in L spine, proximal femur, distal forearm, and total body
2. Stature, urinary deoxypryidinoline, serum alk phosphatase</td>
<td>
<table>
<tr><th>Mean</th><th>PL (n=192)</th><th>5mg (n=98)</th><th>10mg (n=96)</th><th>20/5mg (n=99)</th></tr>
<tr><td>Age</td><td>62.7</td><td>61.2</td><td>63.2</td><td>63</td></tr>
<tr><td>Yrs since menopause</td><td>15.2</td><td>13.3</td><td>16</td><td>16.6</td></tr>
<tr><td>Ca intake (mg)</td><td>660</td><td>642</td><td>764</td><td>666</td></tr>
<tr><td>Spine BMD (g/cm^2)</td><td>0.7</td><td>0.72</td><td>0.7</td><td>0.72</td></tr>
</table>
</td>
<td>Mean % change in BMD at 36 months
<table>
<tr><th></th><th>PL</th><th>5mg</th><th>10mg</th><th>20mg/5mg</th></tr>
<tr><td>L spine</td><td>-0.6</td><td>4.9</td><td>6.8</td><td>7.8</td></tr>
<tr><td>Fem neck</td><td>-0.7</td><td>2.9</td><td>4.8</td><td>3.5</td></tr>
<tr><td>T Body</td><td>-1.0</td><td>1.0</td><td>1.6</td><td>1.6</td></tr>
<tr><td>Distal Forearm</td><td>-2.0</td><td>-0.6</td><td>0.6</td><td>0.7</td></tr>
</table>
P < 0.001 for comparisons between PL and all ALN groups except in 5mg group at the distal forearm

Percent change from placebo of biochemical markers
<table>
<tr><th></th><th>5mg</th><th>10mg</th><th>20mg/5mg</th></tr>
<tr><td>D Pyr</td><td>36</td><td>40-50</td><td>40-50</td></tr>
<tr><td>Alk Phos</td><td colspan="3">Maximum decrease after 3-6 months which was maintained through 36 months</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Tucci 1996
N=478
R, DB, PC,MC
U.S. Alendronate Phase III Osteoporosis Treatment Study Group

Grant from Merck Research Laboratories

Grant from Merck Research Laboratories</td>
<td>PL x2 years
ALN
5, 10, or 20mg/d for 2 years

Year 3- option to:
1. Continue DB treatment
2. 20mg group blindly changed to 5mg/d</td>
<td>1. BMD in L spine, Ca regulating hormones, biochemical indices of bone turnover
2. BMD at proximal femur & other sites, incidence of vertebral fractures, progression of vertebral deformities, height loss</td>
<td>
<table>
<tr><th></th><th>PL (n=192)</th><th>5mg (n=98)</th><th>10mg (n=94)</th><th>20mg/5 (n=94)</th></tr>
<tr><td>Age 1°Caucasian</td><td>64</td><td>66.5</td><td>63.9</td><td>63.8</td></tr>
<tr><td>Yrs since menopause</td><td>17.8</td><td>18.9</td><td>17.1</td><td>17.1</td></tr>
<tr><td>Ca intake (mg)</td><td>810</td><td>848</td><td>764</td><td>766</td></tr>
<tr><td>L spine BMD (g/cm^2)</td><td>0.72</td><td>0.7</td><td>0.7</td><td>0.73</td></tr>
<tr><td>Fem neck BMD</td><td>0.61</td><td>0.59</td><td>0.58</td><td>0.62</td></tr>
<tr><td>T Hip BMD</td><td>0.7</td><td>0.67</td><td>0.67</td><td>0.69</td></tr>
<tr><td>D forearm BMD</td><td>0.55</td><td>0.53</td><td>0.54</td><td>0.53</td></tr>
<tr><td>T Body BMD</td><td>0.94</td><td>0.93</td><td>0.94</td><td>0.93</td></tr>
</table>
</td>
<td>Mean % change in BMD at 36 months
<table>
<tr><th></th><th>PL</th><th>5mg</th><th>10mg</th><th>20mg/5</th></tr>
<tr><td>L spine</td><td>-0.76</td><td>5.55</td><td>9.59</td><td>7.84</td></tr>
<tr><td>Fem neck</td><td>-1.6</td><td>2.88</td><td>4.66</td><td>3.22</td></tr>
<tr><td>T hip</td><td>-0.86</td><td>3.65</td><td>4.97</td><td>4.86</td></tr>
<tr><td>D forearm</td><td>-1.73</td><td>-0.37</td><td>0.32</td><td>0.92</td></tr>
<tr><td>T Body</td><td>-0.88</td><td>0.33</td><td>1.58</td><td>1.86</td></tr>
</table>
P < 0.001 for comparisons between PL and all ALN groups

Mean % decrease from baseline biochemical markers
<table>
<tr><th></th><th>PL</th><th>5mg</th><th>10mg</th><th>20mg/5</th></tr>
<tr><td>D Pyr</td><td>18</td><td>46</td><td>53</td><td>58</td></tr>
<tr><td>Alk phos</td><td colspan="4">Decreased over 1st six months to plateau at 25% below baseline; at year 3, 10mg dose→27.5% and 5mg →22.1% (p≤0.02)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Bone 1997
N=359
R, DB, PC,MC</td>
<td>PL for 2 years
ALN
1, 2.5, or 5mg/d x2 yrs</td>
<td>1. BMD
2. Biochemical measures, BSAP, OC, UNTx, UDPyr</td>
<td>
<table>
<tr><th></th><th>PL (n=91)</th><th>1mg (n=86)</th><th>2.5mg (n=89)</th><th>5mg (n=93)</th></tr>
<tr><td>Age</td><td>71.1</td><td>71.1</td><td>70.0</td><td>70.8</td></tr>
<tr><td>Yrs since menopause</td><td>22.8</td><td>24.2</td><td>22.2</td><td>24.8</td></tr>
<tr><td>Race (%) Caucasian</td><td>96.7</td><td>98.8</td><td>96.6</td><td>97.8</td></tr>
<tr><td>L spine BMD</td><td>0.71</td><td>0.70</td><td>0.72</td><td>0.73</td></tr>
<tr><td>Ca intake</td><td>900</td><td>813</td><td>880</td><td>831</td></tr>
<tr><td>Prevalent vertebral fx (%)</td><td>34.1</td><td>41.9</td><td>36</td><td>37</td></tr>
</table>
</td>
<td>Mean % change in BMD vs baseline
<table>
<tr><th></th><th>PL</th><th>1mg</th><th>2.5mg</th><th>5mg</th></tr>
<tr><td>L spine</td><td>0.56</td><td>1.21</td><td>4.1</td><td>6.23</td></tr>
<tr><td>Fem neck</td><td>-1.51</td><td>-0.30</td><td>0.01</td><td>1.8</td></tr>
<tr><td>T Body</td><td>0.20</td><td>0.26</td><td>0.70</td><td>1.35</td></tr>
<tr><td>Forearm</td><td>-0.50</td><td>-0.94</td><td>0.11</td><td>0.66</td></tr>
</table>
P < 0.001 for comparisons between PL and ALN 5mg except at distal forearm

Mean % change in biochemical markers from baseline
<table>
<tr><th></th><th>PL</th><th>1mg</th><th>2.5mg</th><th>5mg</th></tr>
<tr><td>D Pyr/Cr</td><td></td><td>-17.82</td><td>-27.97</td><td>-29.40</td></tr>
<tr><td>NTx/Cr</td><td>-15</td><td>-13.66</td><td>-57.41</td><td>-66.46</td></tr>
<tr><td>Alk phos</td><td>-5.75</td><td>-11.66</td><td>-16</td><td>-28.86</td></tr>
<tr><td>OC</td><td>-2.87</td><td>-10.75</td><td>-38.74</td><td>-45.02</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr><td>Grant from Merck Research Laboratories</td><td></td><td></td><td></td><td>New skeletal fractures(N)<table><tr><th></th><th>PL</th><th>1mg</th><th>2.5mg</th><th>5mg</th></tr><tr><td>New vertebral</td><td>6</td><td>4</td><td>3</td><td>4</td></tr><tr><td>New nonvertebral</td><td>16</td><td>15</td><td>9</td><td>9</td></tr></table></td></tr>
<tr><td>Pols 1999
N=1908
R,DB,PC,MC
Fosamax International Trial Study Group
FOSIT

Support by Merck & Co., Inc.</td><td>PL for 12 months
ALN 10mg/d x12mos</td><td>1. BMD
2. BSAP, urinary telopeptide crosslinks</td><td><table><tr><th></th><th>PL (n=958)</th><th>ALN (n=950)</th></tr><tr><td>Age</td><td>62.8</td><td>62.8</td></tr><tr><td>Yrs since menopause</td><td>15.9</td><td>15.8</td></tr><tr><td>BMD
L spine
Fem neck
Trochanter</td><td>
0.72
0.62
0.55</td><td>
0.72
0.63
0.55</td></tr><tr><td>BSAP (mg/ml)</td><td>13.1</td><td>13.0</td></tr><tr><td>NTx/Cr (pmol)</td><td>63.1</td><td>60.7</td></tr></table></td><td>Mean % change in BMD from baseline<table><tr><th></th><th>PL</th><th>ALN</th></tr><tr><td>L spine</td><td>0.1</td><td>5</td></tr><tr><td>Fem neck</td><td>-0.2</td><td>2.3</td></tr><tr><td>Trochanter</td><td>0.4</td><td>4.1</td></tr></table>P < 0.001 for comparisons between PL and ALN

Mean % change in biochemical markers from baseline<table><tr><th></th><th>PL</th><th>ALN</th></tr><tr><td>BSAP</td><td>11</td><td>52</td></tr><tr><td>U NTx</td><td>21</td><td>74</td></tr></table></td></tr>
<tr><td>Tonino 2000
N=350
R, DB, PC,MC
+ open label
Phase III Osteoporosis Treatment Study Group
(second 2 year extension)

Support by Merck Research Laboratories</td><td>ALN 5mg or 10mg in years 6-7
PL years 6-7
(20mg yrs 1-2, 5mg yrs 3-5)

Years 1-3
PL
ALN 5, 10 or 20mg
(20mg changed to 5mg in year 3)

Years 4-5
All on ALN remained on same dose
Those on PL + 61 who chose open label drug received ALN 10mg</td><td>Efficacy, safety, and tolerability of and additional 2 years of therapy monitored by BMD, U NTx, and BSAP</td><td>Mean characteristics<table><tr><td>Age</td><td>63</td></tr><tr><td>Yrs since menopause</td><td>16</td></tr><tr><td>L spine BMD</td><td>0.71</td></tr><tr><td>Prevalent vertebral fxs (%)</td><td>21</td></tr><tr><td>NTx/Cr mmol</td><td>87.5</td></tr><tr><td>BSAP ng/ml</td><td>18.1</td></tr><tr><td>Ca intake</td><td>734</td></tr></table></td><td>Mean % change in BMD from 60 months and baseline<table><tr><th></th><th>5mg (n=113)</th><th>10mg (n=122)</th><th>20mg/5/PL (n=115)</th></tr><tr><td>L spine
Month 60
Baseline</td><td>
1.45
8.2</td><td>
1.6
11.44</td><td>
0.2
8.94</td></tr><tr><td>Fem neck
Month 60
Baseline</td><td>
0.32
2.64</td><td>
0.49
4.87</td><td>
-0.46
3.15</td></tr><tr><td>T Body
Month 60
Baseline</td><td>
-0.29
1.65</td><td>
0.35
3.13</td><td>
-0.5
2.46</td></tr><tr><td>Forearm
Month 60
Baseline</td><td>
0.06
-0.24</td><td>
0.31
1.04</td><td>
-0.84
0.38</td></tr></table></td></tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Mean % change from month 6 & baseline of biochemical markers
<table><tr><td></td><td>5mg</td><td>10mg</td></tr><tr><td>NTx/Cr
Month 6
Baseline</td><td>
-65
-71.3</td><td>
-75
-71.9</td></tr><tr><td>BSAP
Month 6
Baseline</td><td>
-40
-44.6</td><td>
-55
-52.3</td></tr></table></td></tr>
<tr><td>Greenspan 2002
N=327
R, DB, PC, MC
Ambulatory females in LTC

Grant support from Merck & Co., Inc.</td><td>PL
ALN 10mg/d x 24 months</td><td>BMD, biochemical markers, incidence of fractures</td><td><table><tr><td>Mean Age</td><td>78.5</td></tr><tr><td>Caucasian</td><td>97%</td></tr><tr><td>Mean T scores (hip & spine)</td><td>-3.5 to –2.4</td></tr><tr><td>Prevalent fractures</td><td>55%</td></tr></table></td><td>Mean % change in BMD from baseline
<table><tr><td></td><td>PL
(n=</td><td>ALN</td></tr><tr><td>L spine</td><td></td><td>7.4</td></tr><tr><td>Fem neck</td><td></td><td>3.4</td></tr><tr><td>Trochanter</td><td></td><td>4.7</td></tr></table>P < 0.001 for comparison between PL and ALN

Mean % change in biochemical markers from baseline
<table><tr><td></td><td>PL</td><td>ALN</td></tr><tr><td>BSAP</td><td>-7</td><td>-78</td></tr><tr><td>NTx/Cr</td><td>0</td><td>-57</td></tr></table>
New fractures: Placebo 11% Alendronate 8% NSS</td></tr>
</table>

Alendronate Trials- Prevention of Fractures

Liberman 1995

Trial: Liberman 1995; N=909; R, DB, PC, MC; Alendronate Phase II Osteoporosis Treatment Study Group

Dose: PL X 3 years; ALN 5,10, or 20mg/d for 2 years, then continued x1 year but 20mg blindly changed to 5mg

Measured Outcome: 1. BMD of L spine, femoral neck, trochanter, forearm, total body; 2. Vertebral fractures

Baseline Characteristics

Means	PL (n=355)	ALN (n=526)
Age	64	64
Yrs since menopause	17	16
Vertebral fx (%)	52.6	57
L spine BMD	0.71	0.71
Fem neck BMD	0.6	0.6
Trochanter BMD	0.53	0.52
T Body BMD	0.93	0.92

Results

Mean % Vertebral Fractures

	PL	ALN
All	6.2	3.2*
Age <65	4.7	3.7
Age ≥65	7.9	2.6
With previous fx	19.1	13.4
Without previous fx	2.0	1.0
USA	4.5	1.6
International	7.9	4.9

* P=0.03

Mean nonvertebral fractures PL 9.6% ALN 7.5%

BMD increased significantly in all patients on alendronate and decreased in all patients on placebo. The 10mg dose was more effective than the 5mg dose and as effective as the 20mg/5mg.

Grant support from Merck Research Laboratories

Black 1996, Ensrud 1997

Trial: Black 1996; Ensrud 1997; N=2027 (with prevalent vertebral fractures); R, DB, PC, MC; Fracture Intervention Trial Subgroup Analysis (FIT)

Dose: PL for 3 years; ALN 5mg/d x 2 years, then 10mg/d x 1 year

Measured Outcome: 1. New vertebral fractures; 2. Clinical fractures, non-spine fractures, symptomatic vertebral fractures

Baseline Characteristics

	PL (n=1005)	ALN (n=1022)
Age		
<65	159	171
65-74	571	587
75-80	275	264
Mean	71	70.7
Caucasian %	98.8	99.7
Fem Neck BMD g/cm^2	0.564	0.567
Vertebral fractures at baseline		
1	681	719
≥2	324	303

Results

New Vertebral Fractures by Risk Subgroup (%)

	PL	ALN
All	15	8*
Age		
<75	13.4	6.6
≥75	19.4	12
Baseline fem neck BMD		
<0.59	18.5	9.9
≥0.59	9.7	5.2
Baseline Vertebral fxs		
1	8.9	5.2
≥2	28.3	14.6

*p < 0.001

New Clinical Fractures %
PL 18.2 ALN 13.6

Support by Merck Research Laboratories

Trial	Dose	Measured Outcome	Baseline Characteristics	Results
Cummings 1998 N=4272 without vertebral fractures R, DB, PC, MC Fracture Intervention Trial (FIT) Support by Merck Research Laboratories	PL for 4 years ALN 5mg/d for 2 years, then 10mg/d for 2 years	1. Clinical fractures , excluding pathologic fractures 2. Vertebral fractures 3. BMD 4. Stature	See table below	See tables below

	PL (n=2218)	ALN (n=2214)
Age %		
<65	33.3	34.5
65-74	53.7	52.6
75-80	13	12.9
Mean years	67.7	67.6
Fem neck % BMD SDs below peak		
>2.5	36.6	37
2-2.5	32	32.8
1.5-2	31.1	30.2
Mean g/cm^2	0.593	0.592
Mean L spine BMD	0.842	0.841

Mean % with ≥ 1 Fracture

	PL	ALN	RH	p
Any clinical fracture	14.1	12.3	0.86	0.07
Any non-vertebral fracture	13.3	11.8	0.88	0.13
Hip fracture	1.1	0.9	0.79	0.44
Wrist fracture	3.2	3.7	1.19	0.28
Other clinical	10.2	8.2	0.79	0.02
Vertebral fracture				
≥ 1	3.8	2.1	0.56	0.002
≥ 2	0.5	0.02	0.4	0.11

Fracture % as a function of femoral neck T scores

	PL	ALN	RH
Clinical Fractures T score			
< -2.5	19.6	13.1	0.64
-2.5 to –2.0	12.3	12.7	1.03
-2.0 to –1.6	9.5	10.9	1.14
Vertebral Fractures T score			
< -2.5	5.8	2.9	0.5
-2.5 to –2.0	3.6	1.9	0.54
-2.0 to –1.6	1.5	1.3	0.82

Alendronate- Prevention of Osteoporosis

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>McClung 1998
N=447
R, DB, PC,MC
Alendronate Osteoporosis Prevention Study Group

Grant Support by Merck Research Laboratories</td>
<td>PL for 3 years
ALN 1, 5, or10mg/d x3 years
ALN 20mg/d x2 yrs then PL x1 year</td>
<td>1. BMD of L spine
2. BMD of proximal femur, total body, forearm, biochemical markers of resorption</td>
<td>
<table>
<tr><th></th><th>PL (n=90)</th><th>1 (n=92)</th><th>5 (n=88)</th><th>10 (n=88)</th><th>20/P (n=89)</th></tr>
<tr><td>Age</td><td>51.3</td><td>51.7</td><td>52</td><td>52.1</td><td>52.1</td></tr>
<tr><td>Months since menopause</td><td>28.4</td><td>22.1</td><td>22.5</td><td>19.2</td><td>20.2</td></tr>
<tr><td>BMD spine</td><td>0.93</td><td>0.92</td><td>0.92</td><td>0.93</td><td>0.94</td></tr>
<tr><td>Ca intake mg</td><td>482</td><td>471</td><td>590</td><td>458</td><td>479</td></tr>
</table>
</td>
<td>Mean % change in BMD at 36 months
<table>
<tr><th></th><th>PL</th><th>1</th><th>5</th><th>10</th><th>20/PL</th></tr>
<tr><td>L spine</td><td>-3.5</td><td>-1.16</td><td>2.89</td><td>3.95</td><td>4.97</td></tr>
<tr><td>Fem neck</td><td>-3.95</td><td>-1.65</td><td>1.10</td><td>2.27</td><td>1.87</td></tr>
<tr><td>Trochanter</td><td>-2.58</td><td>0.03</td><td>2.71</td><td>4.39</td><td>3.51</td></tr>
<tr><td>T Body</td><td>-2.26</td><td>-1.0</td><td>0.32</td><td>1.03</td><td>.052</td></tr>
<tr><td>Forearm</td><td>-3.85</td><td>-3.43</td><td>-2.27</td><td>-0.92</td><td>-1.25</td></tr>
</table>
P < 0.001 in comparison between PL and ALN except at forearm in 1mg group (p > 0.05) and T Body in 1mg group (p < 0.05)

Percent Decrease in biochemical markers (all on alendronate)
<table>
<tr><td>Dpyr</td><td>35-45</td></tr>
<tr><td>NTx/Cr</td><td>65-70</td></tr>
<tr><td>BSAP</td><td>40-60</td></tr>
<tr><td>Osteocalcin</td><td>40-60</td></tr>
</table>
</td>
</tr>
<tr>
<td>Hosking 1998
N=1609
R, DB, PC, MC
Early Postmenopausal Intervention Cohort Study Group

Grant Support from Merck Research Laboratories</td>
<td>1. PL for 2 years
ALN 2.5 or 5mg
Or
estrogen/progestin (open label) CEE/ medroxyprogesterone in USA, cyclic estradiol/ norethindrone in Europe

2. PL for 2 years
ALN 2.5 or 5 mg
(estrogen/progestin was contraindicated)</td>
<td>BMD</td>
<td>
<table>
<tr><th></th><th>PL (n=502)</th><th>2.5 (n=499)</th><th>5 (n=498)</th><th>E/P (n=110)</th></tr>
<tr><td>Age yrs</td><td>53</td><td>53</td><td>54</td><td>53</td></tr>
<tr><td>Caucasian %</td><td>85</td><td>87</td><td>81</td><td>89</td></tr>
<tr><td>BMD</td><td></td><td></td><td></td><td></td></tr>
<tr><td>L spine</td><td>0.94</td><td>0.93</td><td>0.95</td><td>0.93</td></tr>
<tr><td>Hip</td><td>0.85</td><td>0.84</td><td>0.85</td><td>0.84</td></tr>
<tr><td>Forearm</td><td>0.52</td><td>0.52</td><td>0.52</td><td>0.52</td></tr>
<tr><td>T Body</td><td>1.04</td><td>1.03</td><td>1.04</td><td>1.03</td></tr>
</table>
</td>
<td>Mean % change in BMD at 24 months
<table>
<tr><th></th><th>PL</th><th>2.5</th><th>5</th><th>E/P</th></tr>
<tr><td>L spine</td><td>-1.8</td><td>2.3</td><td>3.5</td><td>4.0</td></tr>
<tr><td>Hip</td><td>-1.4</td><td></td><td>1.9</td><td>1.8</td></tr>
<tr><td>Fem neck</td><td>-1.6</td><td></td><td>1.3</td><td></td></tr>
<tr><td>Trochanter</td><td>-0.9</td><td></td><td>3</td><td></td></tr>
<tr><td>Forearm</td><td>-2.5</td><td></td><td>-1.4</td><td>-0.3</td></tr>
<tr><td>T Body</td><td>-1.8</td><td></td><td>0.7</td><td>1.2-2.6</td></tr>
</table>
P < 0.001 for comparisons between PL and ALN and E/P</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Ravn 1999
N=1609
R, DB, PC, MC
Early Postmenopausal Intervention Cohort Study Group
4 year results</td>
<td>See above
For years 3-4, Alendronate was either continued or replaced by a placebo</td>
<td>1. BMD
2. NTx, osteocalcin, BSAP</td>
<td>See above</td>
<td>Mean % Change in BMD at 4 years
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td><td>CEE/M</td><td>Es/Nor</td></tr>
<tr><td>Lspine</td><td>-2.9</td><td>2.2</td><td>4</td><td>7.5</td><td>4.7</td></tr>
<tr><td>Hip</td><td>-1.6</td><td>1.7</td><td>3.0</td><td>4.7</td><td>3</td></tr>
<tr><td>T Body</td><td>-2.9</td><td>0.3</td><td>1.0</td><td>4.4</td><td>1.0</td></tr>
<tr><td>Forearm</td><td>-3.9</td><td>-2.1</td><td>-1.7</td><td>1.3</td><td>0.3</td></tr>
<tr><td colspan="6">NTx/Cr, C-telopeptides, osteocalcin: all decreased to premenopausal range except in placebo group58</td></tr>
</table>
</td>
</tr>
<tr>
<td>Ravn 2000
N=160
R, DB, PC, MC
Alendronate Osteoporosis Prevention Study Group
5 year Follow up

Grant support by Merck Research Laboratories</td>
<td>Years 1-3
PL or ALN 1,5,10mg Or ALN 20mg for 2 years then PL for 1 year

Years 4-5
ALN 5mg open label ALN 20mg x2yrs, then PL x 1 year received no treatment</td>
<td>BMD, NTx, C-telopeptide</td>
<td>
<table>
<tr><td></td><td>5mg (n=52)</td><td>PL/5mg (n=56)</td><td>20/PL/NT (n=</td></tr>
<tr><td>Age</td><td>51.9</td><td>51.7</td><td>52.2</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>Mean % Change in BMD at 60 months
<table>
<tr><td></td><td>5mg</td><td>PL/5mg</td><td>20mg/PL/NT</td></tr>
<tr><td>L spine</td><td>2.5</td><td>-0.1</td><td>2.5-2.8</td></tr>
<tr><td>Trochanter</td><td>3.2</td><td>Stable</td><td>2.5-2.8</td></tr>
<tr><td>Fem Neck</td><td>Stable</td><td>-2.5</td><td>Stable</td></tr>
<tr><td>T Body</td><td>Stable</td><td>-0.15</td><td>Stable</td></tr>
<tr><td>Forearm</td><td>-3.4</td><td>-4.8</td><td>-5.0</td></tr>
</table>
P < 0.001 compared to baseline for ALN only at spine, trochanter, & forearm
P< 0.001 for PL/5mg at femoral neck

NTx & C-telopeptide: Decreased to 70-80% below baseline by 12 months on either 5mg or 20mg; withdrawal caused markers to increase to 40-60% below baseline</td>
</tr>
</table>

Alendronate- Combination Therapy in Osteoporosis

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Adami 1993
N=286
R, DB, PC, MC
1 year interim analysis</td>
<td>PL x 1 year
ALN 10 or 20mg
Intranasal calcitonin 100 IU/d</td>
<td>1. BMD of L spine
2. BMD of femoral neck and trochanter

Support by Merck Research Laboratories</td>
<td>
<table>
<tr><td></td><td>PL (n=71)</td><td>ALN10 (n=68)</td><td>ALN20 (n=72)</td><td>Calc (n=75)</td></tr>
<tr><td>AGE</td><td>59</td><td>59</td><td>59</td><td>60</td></tr>
<tr><td>L spine BMD</td><td>0.73</td><td>0.74</td><td>0.74</td><td>0.73</td></tr>
<tr><td>Fem neck BMD</td><td>0.62</td><td>0.63</td><td>0.64</td><td>0.62</td></tr>
<tr><td>Trochanter BMD</td><td>0.53</td><td>0.53</td><td>0.51</td><td>0.51</td></tr>
</table>
</td>
<td>Mean % Change in BMD from Baseline at 12 months
<table>
<tr><td></td><td>PL</td><td>ALN 10</td><td>ALN 20</td><td>Calc</td></tr>
<tr><td>L spine</td><td>-0.3</td><td>4.4</td><td>5.8</td><td>0.3</td></tr>
<tr><td>Fem neck</td><td>-0.2</td><td>2.9</td><td>2.9</td><td>0.3</td></tr>
<tr><td>Trochanter</td><td>0.2</td><td>3.5</td><td>4.0</td><td>0.7</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Lindsey 1999
N=428
R, SB, PC, MC

Grant support by Merck & Co, Inc.</td>
<td>PL + HRT x12 months
ALN 10mg + HRT</td>
<td>1. BMD of L spine
2, BSAP, NTx</td>
<td>
<table>
<tr><td></td><td>HRT + ALN (n=214)</td><td>HRT + PL (n=214)</td></tr>
<tr><td>Age</td><td>61.9</td><td>61.5</td></tr>
<tr><td>Caucasian %</td><td>98.1</td><td>95.3</td></tr>
<tr><td>Duration of HRT yrs</td><td>9.7</td><td>9.5</td></tr>
<tr><td>BMD L spine</td><td>0.799</td><td>0.795</td></tr>
<tr><td>BMD Fem neck</td><td>0.614</td><td>0.613</td></tr>
</table>
</td>
<td>Mean % increase in BMD
<table>
<tr><td></td><td>HRT + ALN</td><td>HRT + PL</td></tr>
<tr><td>L spine</td><td>3.7</td><td>1.1</td></tr>
</table>
Mean values
<table>
<tr><td></td><td>HRT + ALN</td><td>HRT + PL</td></tr>
<tr><td>NTx</td><td>18</td><td>36</td></tr>
<tr><td>BSAP</td><td>6.1</td><td>8.5</td></tr>
</table>
</td>
</tr>
<tr>
<td>Rittmaster 2000
N=75
R, DB, PC + open label

Support by Allelix Biopharmaceuticals, Astra USA, Inc, and Merck & Co, Inc</td>
<td>Year 1
PL or PTH 50.75, or 100mcg SC daily

Year 2
ALN 10mg/dau</td>
<td>1. BMD
2. T Body BMD in a subset
osteocalcin, BSAP, NTx</td>
<td>
<table>
<tr><td>Age yrs</td><td>64</td></tr>
<tr><td>T score L spine</td><td>-3.2</td></tr>
<tr><td>T score fem neck</td><td>-2.4</td></tr>
</table>
</td>
<td>Mean % change in BMD
<table>
<tr><td></td><td>PL</td><td>50mcg</td><td>75mcg</td><td>100mcg</td></tr>
<tr><td>L spine</td><td>8</td><td>12</td><td>14</td><td>15</td></tr>
<tr><td>T Body</td><td>3.4</td><td>3.1</td><td>1.9</td><td>3.5</td></tr>
</table>
Mean values
<table>
<tr><td></td><td>12 months</td><td>24 months</td></tr>
<tr><td>Osteocalcin
PTH→ALN
PTH→PL</td><td>
28
13</td><td>
6
4</td></tr>
<tr><td>BSAP
PTH→ALN
PTH→P:</td><td>
29
15</td><td>
11
8</td></tr>
<tr><td>NTx
PTH→ALN
PTH→PL</td><td>
101
57</td><td>
24
18</td></tr>
</table>
</td>
</tr>
<tr>
<td>Bone 2000
N=425
R, DB, PC, MC
Alendronate/Estrogen Study Group

Grant support from Merck Research Laboratories</td>
<td>1. PL ALN + PL CEE
2. PL ALN + CEE
3. ALN + PL CEE
4. ALN + CEE</td>
<td>BMD, BSAP, NTx</td>
<td>
<table>
<tr><td></td><td>PL (n=50)</td><td>ALN (n=92)</td><td>CEE (n=143)</td><td>ALN/CEE (n=140)</td></tr>
<tr><td>Age</td><td>62</td><td>61</td><td>61</td><td>62</td></tr>
<tr><td>Yrs since menopause</td><td>23</td><td>22</td><td>21</td><td>22</td></tr>
<tr><td>Caucasian %</td><td>88</td><td>92</td><td>87</td><td>92</td></tr>
<tr><td>Lspine BMD t score</td><td>-2.5</td><td>-2.5</td><td>-2.6</td><td>-2.5</td></tr>
<tr><td>BSAP ng/ml</td><td>14</td><td>14</td><td>15</td><td>14</td></tr>
<tr><td>NTx pmol/mcmol Cr</td><td>46</td><td>52</td><td>51</td><td>47</td></tr>
</table>
</td>
<td>Mean % Change in BMD at 2 years
<table>
<tr><td></td><td>PL</td><td>ALN</td><td>CEE</td><td>ALN/CEE</td></tr>
<tr><td>L spine</td><td>-0.6</td><td>6.0</td><td>6.0</td><td>8.3</td></tr>
<tr><td>T Hip</td><td>0.3</td><td>4.0</td><td>3.4</td><td>4.7</td></tr>
<tr><td>Fem neck</td><td>-0.6</td><td>2.9</td><td>2.6</td><td>4.2</td></tr>
<tr><td>Trochanter</td><td>0.5</td><td>5.9</td><td>4.3</td><td>6.5</td></tr>
<tr><td>T Body</td><td>0.1</td><td>1.3</td><td>1.7</td><td>2.0</td></tr>
</table>
Mean % Change Biomarkers
<table>
<tr><td></td><td>ALN</td><td>CEE</td><td>ALN/CEE</td></tr>
<tr><td>NTx</td><td>-61</td><td>-52</td><td>-70</td></tr>
<tr><td>BXAP</td><td>-50</td><td>-49</td><td>-60</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Downs 2000
N=299
R, DB, PC, MC + open label

Funded and supported by Merck & Co., Inc.</td>
<td>1. PL or
2. ALN 10mg or
3. or intranasal calcitonin</td>
<td>BMD, BXAP, NTx</td>
<td>
<table>
<tr><th></th><th>ALN</th><th>Calc</th><th>PL</th></tr>
<tr><td>Age</td><td>64.6</td><td>64.1</td><td>64.6</td></tr>
<tr><td>Yrs since menopause</td><td>16.5</td><td>16.1</td><td>16.5</td></tr>
<tr><td>Caucasian %</td><td>97.5</td><td>95.9</td><td>98.3</td></tr>
<tr><td>L spine T score</td><td>-2.54</td><td>-2.54</td><td>-2.36</td></tr>
<tr><td>Fem neck T</td><td>-2.63</td><td>-2.71</td><td>-2.59</td></tr>
</table>
</td>
<td>
Mean % Change BMD
<table>
<tr><th></th><th>PL</th><th>ALN</th><th>Calc</th></tr>
<tr><td>L spine</td><td>0</td><td>5</td><td>1.3</td></tr>
<tr><td>Trochanter</td><td>-0.2</td><td>2.9</td><td>0.5</td></tr>
<tr><td>Fem Neck</td><td>-1.2</td><td>2.9</td><td>0.5</td></tr>
</table>
Mean % Change Biomarkers
<table>
<tr><th></th><th>PL</th><th>ALN</th><th>Calc</th></tr>
<tr><td>BSAP</td><td>0</td><td>-40</td><td>-7</td></tr>
<tr><td>NTx</td><td>5</td><td>-60</td><td>-10</td></tr>
</table>
</td>
</tr>
<tr>
<td>Johnell 2002
N=331
R, DB, PC, MC

Support by Eli Lilly & Co.</td>
<td>1. Raloxifene 60mg/d
2. ALN 10mg/d
3. Raloxifene 60mg + ALN 10mg
4. PL</td>
<td>1. BMD
2. Biochemical markers</td>
<td>
<table>
<tr><th></th><th>PL (n=82)</th><th>RLX (n=82)</th><th>ALN (n=84)</th><th>RLX/ALN (n=84)</th></tr>
<tr><td>Age</td><td>63.8</td><td>63.4</td><td>63.7</td><td>63.8</td></tr>
<tr><td>Yrs since menopause</td><td>17.6</td><td>15.6</td><td>16.5</td><td>17.1</td></tr>
<tr><td>L spine BMD</td><td>0.76</td><td>0.77</td><td>0.78</td><td>0.76</td></tr>
<tr><td>Fem neck BMD</td><td>0.62</td><td>0.62</td><td>0.62</td><td>0.61</td></tr>
<tr><td>OC mcg/L</td><td>23.6</td><td>25.9</td><td>25.9</td><td>24.7</td></tr>
<tr><td>BSAP mcg/L</td><td>14.6</td><td>14.6</td><td>14.5</td><td>14.5</td></tr>
<tr><td>CTx/Cr</td><td>277.6</td><td>299.8</td><td>288.9</td><td>258.6</td></tr>
<tr><td>NTx/Cr</td><td>50.6</td><td>53.2</td><td>54.3</td><td>52.8</td></tr>
</table>
</td>
<td>
Mean % Change in BMD at 1 year
<table>
<tr><th></th><th>PL</th><th>RLX</th><th>ALN</th><th>RLX/ALN</th></tr>
<tr><td>L spine</td><td>-0.04</td><td>2.1</td><td>4.3</td><td>5.3</td></tr>
<tr><td>Fem neck</td><td>-0.2</td><td>1.7</td><td>2.7</td><td>3.7</td></tr>
</table>
Mean % Change in Biomarkers
<table>
<tr><th></th><th>PL</th><th>RLX</th><th>ALN</th><th>RLX/ALN</th></tr>
<tr><td>OC</td><td>-1.2</td><td>-25.7</td><td>-42.3</td><td>-54.3</td></tr>
<tr><td>BSAP</td><td>-11.8</td><td>-32.2</td><td>-52.1</td><td>-54.1</td></tr>
<tr><td>CTx/Cr</td><td>-16</td><td>-46.5</td><td>-74.2</td><td>-81.0</td></tr>
<tr><td>NTx/Cr</td><td>7.1</td><td>-23.8</td><td>-58.4</td><td>-63.3</td></tr>
</table>
</td>
</tr>
</table>

Alendronate-Steroid-Induced Osteoporosis

Trial

Saag 1998
N=477
R, DB, PC, MC
Glucocorticoid-Induced Osteoporosis Intervention Study Group
All patients taking at least 7.5mg of prednisone or equivalent daily

Grant support by Merck & Company and the General Clinical Research Centers Programs, National Center for Research Resources, NIH

Dose

ALN 5 or 10mg
PL for 48 weeks

Measured Outcome

1. BMD L spine
2. BMD Hip, T Body
   Biochemical markers of bone turnover
3. Vertebral fractures

Baseline Characteristics

	PL (n=159)	ALN5 (n=161)	ALN10 (n=157)
Age	54	56	55
Men	52	45	44
Premenopausal	40	34	30
Postmenopausal	67	82	83
Caucasian %	89	89	88
Duration of steroid therapy %			
<4mo	33	34	34
4-12mo	21	21	20
>12mo	46	45.6	46
Median daily dose in prednisone equivalents	11	10	10
Mean NTX/Cr	41	42	41
Mean BSAP mcg/ml	10	10	10
L spine BMD	0.95	0.92	0.93

Results

Mean % Change in BMD at week 48

	PL	ALN 5	ALN 10
L spine			
All	-0.4	2.1	2.9
Men	-0.7	3.4	2.9
Premenopausal	-0.3	2.0	2.0
Postmenopause & estrogens	-0.6	1.6	1.6
Postmenopause no estrogens	-0.1	1.5	4.0
Duration of steroid therapy			
<4mo	-1.0	1.4	0.2
4-12mo	-0.6	2.4	2.5
>12mo	0.2	2.5	2.8
Fem neck BMD	-1.2	1.2	1.0
T Body BMD	-0.03	0.4	0.7

P < 0.001 for comparison between PL and ALN at L spine (5 &10), femoral neck (5 & 10), and trochanter (10mg ALN)
P < 0.01 for comparison between PL and ALN at trochanter (5mg) and total body (10mg)

New Vertebral Fracture Incidence %

	PL	ALN
All	3.7	2.3
Men	2.1	1.4
Premenopausal	0	0
Postmenopausal	7.6	3.7

Non-vertebral fractures 4.4% in both placebo and alendronate

Biochemical Markers:
Excretion of NTx decreased 60% in alendronate groups
BSAP decreased by 27% in alendronate groups

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Adachi 2001
N=208
R, DB, PC, MC
12 month extension of Glucocorticoid-Induced Osteoporosis Intervention Study Group

Grant support by Merck & Co., Inc., and the General Clinical Research Centers Programs, the National Center for Research Resources, NIH</td>
<td>ALN 5 or 10mg
PL
(29 patients in Europe received ALN 2.5mg for 48 weeks and were blindly switched to ALN 10mg- data not included)</td>
<td>1. BMD L spine
2. BMD hip, T Body
Biochemical markers
Vertebral fractures</td>
<td>
<table>
<tr><th></th><th>PL (n=61)</th><th>ALN 5 (n=63)</th><th>ALN 10 (n=55)</th></tr>
<tr><td>Age</td><td>54</td><td>53</td><td>53</td></tr>
<tr><td>Males %</td><td>31</td><td>29</td><td>27</td></tr>
<tr><td>Menopause status %
Pre
Post + E
Post no E</td><td>
28
11
30</td><td>
25
16
30</td><td>
25
15
33</td></tr>
<tr><td>Duration of steroid therapy %
<4mo
4-12mo
>12mo</td><td>
30
21
49</td><td>
29
21
51</td><td>
35
24
42</td></tr>
<tr><td>Median daily dose in prednisone equivalents</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>L spine BMD</td><td>0.93</td><td>0.92</td><td>0.93</td></tr>
<tr><td>NTx/Cr</td><td>42.5</td><td>41.9</td><td>45.2</td></tr>
<tr><td>BSAP</td><td>9.5</td><td>9.7</td><td>10.1</td></tr>
</table>
</td>
<td>
Mean % Change in BMD
<table>
<tr><th></th><th>PL</th><th>ALN 5</th><th>ALN 10</th></tr>
<tr><td>L spine</td><td>-0.77</td><td>2.84</td><td>3.85</td></tr>
<tr><td>Fem neck</td><td>-2.93</td><td>0.4</td><td>0.61</td></tr>
<tr><td>T Body</td><td>-0.36</td><td>0.77</td><td>1.09</td></tr>
</table>
P ≤ 0.05 for comparison between PL and ALN at all sites

Mean % Change in L spine by Subgroup
<table>
<tr><th></th><th>PL</th><th>ALN 5</th><th>ALN 10</th></tr>
<tr><td>Men</td><td>0.65</td><td>4.29</td><td>6.29</td></tr>
<tr><td>Women
Premenopausal
Postmenopausal on E
Postmenopausal Not on E</td><td>-1.43
-3.98
-0.73
-0.96</td><td>2.25
5.36
1.95
0.75</td><td>2.92
1.4
3.91
2.31</td></tr>
<tr><td>Duration of steroid therapy
<4mo
4-12mo
>12mo</td><td>
-2.92
-1.39
0.92</td><td>
2.01
4.01
2.91</td><td>
3.9
7.97
5.02</td></tr>
</table>
Incidence (%) of Vertebral Fractures at 24 months
<table>
<tr><th></th><th>PL</th><th>ALN</th></tr>
<tr><td>ALL</td><td>6.8</td><td>0.7*</td></tr>
<tr><td>Time
Year 1
Year 2</td><td>
1.7
5.1</td><td>
0.7
0</td></tr>
<tr><td>Men
Women
Premenopausal
Postmenopausal</td><td>0
10
5.9
13</td><td>0
1
0
1.6</td></tr>
</table>
*p = 0.026

Biochemical markers:
BSAP decreased 25% and NTx decreased 60% on all doses of ALN during first 48 weeks to within the lower normal range of premenopausal women.
</td>
</tr>
</table>

Trial	Dose	Measured Outcome	Baseline Characteristics			Results
Lau 2001 n-78 R, DB, PC	PL for 12 mo ALN 10mg (patients were on inhaled beclomethasone, budesonide, or fluticasone)	BMD of L spine, T hip, trochanter, femoral neck		PL (n=40)	ALN (n=38)	Mean % Change BMD from Baseline
			Age	47.2	50.2	
			Menopause status			
			Pre	21	20	
			Post	19	18	
			Steroid use			
			PO w/i 12mo	5	7	
			Wks of po	17	20	
			Wks of inhaled	262	283	
			Diagnosis			
			Asthma	38	32	
			COPD	2	6	
			BMD			
			L spine	0.83	0.87	
			Fem neck	0.68	0.71	
			Trochanter	0.91	0.93	
			T hip	0.79	0.79	
			% w/ T score			
			-2 to –2.49	15	7.9	
			-2.5 to –3	10	7.9	

	PL	ALN
Premenopausal		
L spine	-0.11	1.84
Fem neck	-0.81	0.84
Trochanter	-1.35	0.95
T Hip	-0.71	1.82
Postmenopausal		
L spine	-0.93	4.27
Fem neck	-0.16	1.11
Trochanter	-0.56	1.23
T Hip	-0.0001	1.91

P < 0.05 for femoral neck
P < 0.01 for trochanter
P < 0.001 for L spine and hip

Support from Merck Sharp and Dohme Pharmaceuticals

Alendronate-Osteoporosis in Men

Trial

Orwall 2000
N=241
R, DB, PC, MC

Grant from Merck

Dose

PL for 2 years
ALN 10mg

Measured Outcome

1. BMD of L spine, hip, T body
2. Serum testosterone, estradiol, vertebral fractures

Baseline Characteristics

	PL (n=95)	ALN (n=146)
Age	63	63
Caucasian %	99	97
Free testosterone %		
Normal	64	64
Low	36	36
BMD T score		
L spine	2.1	2.0
Fem neck	2.3	2.2
Hip	2.1	2.1
% vertebral fractures	52	49
NTx/Cr	40	35
BSAP	13	13

Results

Mean % Change in BMD at 24 months

	PL	ALN
L spine	1.8	7.1
Fem neck	-0.1	2.5
Trochanter	1.3	4.3
Hip	0.6	3.1
T body	0.4	2.0

Effect on L spine similar with normal and low testosterone.
Effect of ALN independent of estradiol concentration
P < 0.001 for all sites

Mean % decrease of biomarkers at 24 months

	PL	ALN
NTx/Cr	-9	-59
BSAP	-5	-38
Height	-2.4mm	-0.6mm

% Occurrence of Fractures

	PL	ALN
Vertebral	7.1	0.8
Other	5.3	4.1

Withdrawal from study (%)

	PL	ALN
B/O AE's	11	3
Personal reasons	5.3	6.1
Lost to f/u (#)	1	4

Drug related Adverse Events (%)

	PL	ALN
Serious	14	17
UGI tract		
Any	22	25
Abd pain	4	8
Acid reflux	5	5
Esophagitis	1	1
Dyspepsia	1	6
Musculoskeletal	53	47
Nervous system	20	25
Respiratory	49	45
Skin	22	23
Urogenital	17	17

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Ringe 2001
N=134
R, open label

Support form Merck & Co.</td>
<td>ALN 10mg
1-alfacalcidiol for 24 months</td>
<td>BMD</td>
<td>
<table>
<tr><td></td><td>AC</td><td>ALN</td></tr>
<tr><td>Age</td><td>66</td><td>68</td></tr>
<tr><td>L spine T score
Fem neck T score</td><td>-3.35
-2.56</td><td>-3.42
-2.53</td></tr>
<tr><td>Prevalent vertebral fracture %</td><td>53</td><td>54</td></tr>
</table>
</td>
<td>
Mean % Change from baseline at 24 months
<table>
<tr><td></td><td>AC</td><td>ALN</td></tr>
<tr><td>L spine BMD</td><td>2.8</td><td>10.1</td></tr>
<tr><td>Fem neck</td><td>2.2</td><td>5.2</td></tr>
</table>
P < 0.001 for comparison at lumbar spine

% fractures
<table>
<tr><td></td><td>AC</td><td>ALN</td></tr>
<tr><td>Vertebral</td><td>18.2</td><td>7.3</td></tr>
<tr><td>Nonvertebral</td><td>12.1</td><td>8.7</td></tr>
<tr><td>Stature</td><td>-8.3mm</td><td>-1.4mm</td></tr>
</table>
Safety: No treatment related withdrawals
Adverse Events: AC 31% ALN 26%
</td>
</tr>
</table>

Risedronate- Fracture Prevention in Osteoporosis

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Clemmesen 1997
N=132
R, DB, PC, MC</td>
<td>1. 2.5mg/day continuous
2. 2.5mg/day for 14 days then placebo for 10 weeks
3. Placebo</td>
<td>1. BMD
2. Fractures</td>
<td>
<table>
<tr><td></td><td>PL</td><td>Continuos</td><td>Cyclic</td></tr>
<tr><td>Age</td><td>70</td><td>67</td><td>68</td></tr>
<tr><td>Time since menopause</td><td>23</td><td>18</td><td>20</td></tr>
<tr><td>BMD spine</td><td>0.747</td><td>0.801</td><td>0.786</td></tr>
<tr><td>OC</td><td>11.5</td><td>10.3</td><td>11.2</td></tr>
<tr><td>Serum alk phos</td><td>138</td><td>132</td><td>131</td></tr>
</table>
</td>
<td>
Incidence of Fractures
<table>
<tr><td></td><td>PL</td><td>Continuos</td><td>Cyclic</td></tr>
<tr><td>N. nonvertebral fxs</td><td>4</td><td>4</td><td>9</td></tr>
<tr><td>N. new vertebral fxs</td><td>20</td><td>13</td><td>15</td></tr>
</table>
BMD spine No statistically significant changes from baseline
OC decreased to a level 25-30% below baseline
AP decreased to a level 15% below baseline
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Harris 1999
N=2458
R, DB, PC, MC
Vertebral Efficacy with Risedronate Therapy (VERT) Study Group North America

Supported by Procter & Gamble Pharmaceuticals and Hoechst Marion Roussel</td>
<td>PL for 3 years
RIS 2.5 or 5mg
(2.5mg group was discontinued after 1 year)</td>
<td>1. Incidence of new vertebral fractures, BMD
2. Nonvertebral fractures, biochemical markers</td>
<td>
<table>
<tr><td></td><td>PL (n=820)</td><td>2.5mg (n=817)</td><td>5mg (n=821)</td></tr>
<tr><td>Age</td><td>68</td><td>69</td><td>68</td></tr>
<tr><td>Time since menopause</td><td>24</td><td>24</td><td>24</td></tr>
<tr><td>Mean # vertebral fxs</td><td>2.3</td><td>2.7</td><td>2.5</td></tr>
<tr><td>L spine T score</td><td>-2.4</td><td>-2.4</td><td>-2.4</td></tr>
<tr><td>Fem neck BMD</td><td>0.602</td><td>0.597</td><td>0.58</td></tr>
<tr><td>L spine BMD</td><td>0.829</td><td>0.839</td><td>0.832</td></tr>
</table>
</td>
<td>
Incidence of Fractures
<table>
<tr><td></td><td>PL</td><td>2.5mg</td><td>5mg</td></tr>
<tr><td>Vertebral fxs
Year 0-1
Year 0-3</td><td>
6.4%
16.3</td><td>
3.8</td><td>
2.4
11.3*</td></tr>
<tr><td>Nonvertebral fxs
Year 0-3</td><td>
8.4</td><td></td><td>
5.2**</td></tr>
</table>
*p = 0.003 ** p = 0.02

Mean % Change in BMD
<table>
<tr><td></td><td>PL</td><td>5mg</td></tr>
<tr><td>L spine</td><td>1.1</td><td>5.4</td></tr>
<tr><td>Fem neck</td><td>-1.2</td><td>1.6</td></tr>
<tr><td>Trochanter</td><td>-0.7</td><td>3.3</td></tr>
</table>
P < 0.05 for comparison between PL and AL

% Change in biochemical markers
<table>
<tr><td></td><td>PL</td><td>RIS</td></tr>
<tr><td>BSAP
6mo
3years</td><td>
-12
-7</td><td>
-35
-33</td></tr>
<tr><td>Dpyr
6mo
3years</td><td>
-8
-1</td><td>
-38
-26</td></tr>
</table>

Adverse Events (%)
<table>
<tr><td></td><td>PL</td><td>RIS</td></tr>
<tr><td>Any event
Drug-related
Serious event</td><td>95
29
27</td><td>97
34
29</td></tr>
<tr><td>Withdrawal due to AE</td><td>17</td><td>17</td></tr>
<tr><td>Any UGI AE
Mod-Severe
Dyspepsia
Abd pain
Gastritis
Esophagitis
Doudenitis</td><td>27
13
11
12
3
2
0.2</td><td>30
13
13
13
4
1
1</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Reginster 2000
N=1226
R, DB, PC, MC
Vertebral Efficacy with Risedronate Therapy (VERT) Study Group Europe and Australia</td>
<td>PL for 3 years
RIS 2.5 or 5mg
(2.5mg discontinued after 2 years b/o superiority of 5mg dose)</td>
<td>1. Incidence of new vertebral fractures
2. BMD, nonvertebral fractures, biochemical markers</td>
<td>
<table>
<tr><th></th><th>PL (n=407)</th><th>2.5 (n=408)</th><th>5 (n=407)</th></tr>
<tr><td>Age</td><td>71</td><td>71</td><td>71</td></tr>
<tr><td>Time since menopause</td><td>25</td><td>24</td><td>25</td></tr>
<tr><td>Med # of vertebral fxs</td><td>3</td><td>3</td><td>4</td></tr>
<tr><td>L spine BMD</td><td>0.787</td><td>0.792</td><td>0.776</td></tr>
<tr><td>Fem neck BMD</td><td>0.5</td><td>-0.583</td><td>0.573</td></tr>
<tr><td>L spine T score</td><td>-2.77</td><td>-2.69</td><td>-2.84</td></tr>
</table>
</td>
<td>
Incidence of Fractures
<table>
<tr><th></th><th>PL</th><th>5mg</th></tr>
<tr><td>Vertebral
Year 0-1
Year 0-3</td><td>
13
29</td><td>
5.6
18.1*</td></tr>
<tr><td>Nonvertebral
Year 0-3</td><td>
16</td><td>
10.9</td></tr>
</table>
*p < 0.001
Mean % Change in BMD
<table>
<tr><th></th><th>PL</th><th>RIS</th></tr>
<tr><td>L spine</td><td>↑</td><td>5.9</td></tr>
<tr><td>Fem neck</td><td>↔</td><td>3.1</td></tr>
<tr><td>Trochanter</td><td>↓</td><td>6.4</td></tr>
<tr><td>Midshaft radius</td><td>↓</td><td>2.1</td></tr>
</table>
P < 0.001 for comparison between PL and RIS

Mean Decrease in biochemical markers
<table>
<tr><th></th><th>5mg</th></tr>
<tr><td>Dpyr</td><td>-33%</td></tr>
<tr><td>BSAP</td><td>-37%</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Fogelman 2000
N=541
R, DB, PC, MC
Bmd-mn Study Group</td>
<td>PL for 24 months
RIS 2.5 or 5mg
(2.5mg dose was dropped at 9/13 study centers)</td>
<td>1. BMD
2. Biochemical markers, fractures</td>
<td>
<table>
<tr><td></td><td>PL (n=180)</td><td>2.5mg (n=184)</td><td>5mg (n=177)</td></tr>
<tr><td>Age</td><td>64</td><td>65</td><td>65</td></tr>
<tr><td>Time since menopause</td><td>17</td><td>18</td><td>18</td></tr>
<tr><td>% vertebral fxs</td><td>30</td><td>28</td><td>32</td></tr>
<tr><td>L spine T score</td><td>-2.91</td><td>-2.96</td><td>-2.84</td></tr>
<tr><td>Mean L spine BMD</td><td>0.783</td><td>0.733</td><td>0.75</td></tr>
<tr><td>Fem neck BMD</td><td>0.636</td><td>0.625</td><td>0.637</td></tr>
<tr><td>Trochanter BMD</td><td>0.547</td><td>0.545</td><td>0.557</td></tr>
</table>
</td>
<td>Mean % Change in BMD
<table>
<tr><td></td><td>PL</td><td>2.5mg</td><td>5mg</td></tr>
<tr><td>L spine</td><td>0.0</td><td>1.4</td><td>4.1</td></tr>
<tr><td>Fem neck</td><td>-1.0</td><td>0.9</td><td>1.3</td></tr>
<tr><td>Trochanter</td><td>-0.6</td><td>1.7</td><td>2.7</td></tr>
</table>
P < 0.001 for comparison between PL and RIS

% Change in biochemical markers
<table>
<tr><td></td><td>PL</td><td>5mg</td></tr>
<tr><td>BSAP</td><td>8</td><td>-22</td></tr>
<tr><td>NTx/Cr</td><td>-11</td><td>-44</td></tr>
</table>
Incidence of Fractures
<table>
<tr><td></td><td>PL</td><td>2.5mg</td><td>5mg</td></tr>
<tr><td>Vertebral</td><td>14</td><td>13</td><td>7</td></tr>
<tr><td>Nonvertebral</td><td>9</td><td>5</td><td>5</td></tr>
</table>
</td>
</tr>
<tr>
<td>McClung 2001
N=9331
R, DB, PC, MC
Hip Intervention Program Study Group

Grants from Procter & Gamble and Aventis Pharma</td>
<td>PL for 3 years
RIS 2.5 or 5mg</td>
<td>1. Incidence of hip fractures
2. Incidence of nonvertebral osteoporotic fractures, BMD</td>
<td>
<table>
<tr><td></td><td colspan="2">70-79 y/o with osteoporosis</td><td colspan="2">>80y/o with ≥1 risk factor for hip fracture</td></tr>
<tr><td></td><td>PL</td><td>RIS</td><td>PL</td><td>RIS</td></tr>
<tr><td>Age</td><td>74</td><td>74</td><td>83</td><td>83</td></tr>
<tr><td>Time since menopause</td><td>28</td><td>28</td><td>37</td><td>37</td></tr>
<tr><td>Fem neck T score</td><td>-3.7</td><td>-3.7</td><td></td><td></td></tr>
<tr><td>% vertebral fractures</td><td>39</td><td>38</td><td>45</td><td>44</td></tr>
</table>
</td>
<td>Incidence of Hip Fractures %
<table>
<tr><td></td><td>PL</td><td>RIS</td></tr>
<tr><td>Overall</td><td>3.9</td><td>2.8</td></tr>
<tr><td>70-79 w/osteo</td><td>3.2</td><td>1.9</td></tr>
<tr><td>W/baseline vertebral fxs</td><td>5.7</td><td>2.3</td></tr>
<tr><td>W/O baseline vertebral fxs</td><td>1.6</td><td>1.0</td></tr>
<tr><td>≥80 with ≥1 risk factor for hip fx</td><td>5.1</td><td>4.2</td></tr>
</table>
Nonvertebral Fracture Incidence
<table>
<tr><td></td><td>PL</td><td>RIS</td></tr>
<tr><td>Overall</td><td>11.2</td><td>9.4*</td></tr>
<tr><td>W/osteo</td><td>10.7</td><td>8.4</td></tr>
<tr><td>W/baseline vertebral fxs</td><td>16.1</td><td>10.3</td></tr>
<tr><td>W/ risk factors</td><td>11.9</td><td>10.8</td></tr>
</table>
P = 0.02

Mean % change in BMD
<table>
<tr><td></td><td>RIS</td></tr>
<tr><td>Fem Neck</td><td>2.1 (2.5mg) 3.4(5mg)</td></tr>
<tr><td>Trochanter</td><td>3.8 (2.5mg) 4.8 (5mg)</td></tr>
</table>
</td>
</tr>
</table>

Risedronate in Primary Osteoporosis-Combination Therapy

Trial	Dose	Measured Outcome	Baseline Characteristics			Results
Harris 2001 N=524 R, DB, PC, MC	0.625mg CEE + RIS 5mg or 0.625mg CEE + PL for 12 months	1. Change in L spine BMD at 12 mo 2. BMD at fem neck, torchanter, distal radius, midshaft radius, biochemical markers of bone formation, fracture assessment		HRT only (n=261)	RIS + HRT (n=263)	Mean % Change in BMD
			Age	59.8	58.0	
			Time since menopause	14.6	13.7	
			L spine BMD	0.964	0.979	
			% with prevalent vertebral fxs	28	29	
			% with T score < -1	63	60	
			BSAP Dpyr/Cr NTx/Cr	13.2 17.4 53.1	13.4 17.4 56.3	

Mean % Change in BMD

	HRT only	RIS + HRT
L spine	4.6	5.2
Fem neck	1.7	2.7*
Trochanter	3.2	3.7
Distal radius	1.7	1.6
Midshaft radius	0.4	0.7*

*p <0.01 comparison with HRT only

	HRT only	RIS + HRT
New vertebral fxs	2.6%	1.8%
Nonvertebral fxs	2.7%	0.8%
BSAP Dypr NTx	-36.8% -22.2% -48.9%	-44.4% -34.5% -61.7%

Risedronate-Prevention of Bone Loss in Early Menopause

Trial	Dose	Measured Outcome	Baseline Characteristics				Results
Mortensen 1998 N=111 R, DB, PC, MC Normal L spine BMD 6-60 mo post menopause 68 started in year 2	Year 1 PL RIS 5mg/d RIS 5mg/d x14d then off for 14 Year 2 options: 1. Discontinue from study 2. Complete a second year without therapy 3. Continue on blinded therapy for 1 year, then complete 1 year without therapy	1. Change in L spine BMD at 24 mo 2. BMD in fem neck, trochanter, Ward's triangle, Dpyr, total alk phos		PL (n=36)	Cyclic (n=38)	Daily (n=37)	Mean % Change in BMD
			Age	51.2	51.3	52.1	
			Time since menopause	3	2	3	
			L spine BMD	0.957	0.927	0.933	
			Fem neck BMD	0.743	0.713	0.735	
			Dpyr/Cr	18.8	21	18.2	
			Caucasian %	100	100	100	

Mean % Change in BMD

	PL	Cyclic	Daily
L spine	-4.3	-1.6	1.4
Fem neck	-2.4		1.3
Trochanter	-2.8		2.6

P<0.05 for comparison between PL and RIS daily

Dpyr	↔	-15	-31

	PL	Cyclic	Daily
Vertebral		1	1
Nonvertebral	3	3	

Risedronate- Corticosteroid-Induced Osteoporosis

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Cohen 1999
N=228
R, DB, PC, MC
≥7.5mg prednisone or equivalent within prior 3 months
Prevention Study

Grant support from Procter & Gamble Pharmaceuticals and Hoechst Marion Roussel</td>
<td>PL
RIS 2.5 or 5mg for 12 mo</td>
<td>1. BMD L spine
2. BMD fem neck, trochanter, distal radius, fractures, biochemical markers</td>
<td>
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>Age</td><td>57.2</td><td>59.5</td><td>61.9</td></tr>
<tr><td>Men %
Premenopausal
Postmenopausal</td><td>32.5
19.5
48.1</td><td>33.3
22.9
44</td><td>35.5
18.4
46.1</td></tr>
<tr><td>L spine BMD</td><td>1.066</td><td>1.032</td><td>1.082</td></tr>
<tr><td>L spine T score</td><td>-0.7</td><td>-0.96</td><td>-0.4</td></tr>
<tr><td>% Vertebral fx</td><td>28.9</td><td>25.7</td><td>36</td></tr>
</table>
</td>
<td>Mean % Change in BMD at 12 mo
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>L spine</td><td>-2.8</td><td>-0.1</td><td>0.6</td></tr>
<tr><td>Fem neck</td><td>-3.1</td><td>-0.4</td><td>0.8</td></tr>
<tr><td>Trochanter</td><td>-3.1</td><td>-0.2</td><td>1.4</td></tr>
<tr><td>Distal radius</td><td>0.5</td><td>1.5</td><td>3.2</td></tr>
<tr><td>Midshaft radius</td><td>-0.3</td><td>-1.0</td><td>0.1</td></tr>
</table>
5mg- p < 0.001 for comparison between PL and RIS at L spine, femoral neck, and trochanter
2.5mg – p < 0.005 for comparison between PL and RIS at L spine and trochanter

Fractures
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>Nonvertebral</td><td>5.2%</td><td>4</td><td>3.9</td></tr>
<tr><td>Vertebral fxs #</td><td>35</td><td>6</td><td>5</td></tr>
<tr><td># pts with new fxs</td><td>9/52</td><td>3/27</td><td>3/53</td></tr>
<tr><td># of pts with ≥2 new vertebral fractures</td><td>7</td><td>1</td><td>1</td></tr>
</table>
</td>
</tr>
<tr>
<td>Reid 2000
N=290
R, DB, PC, MC
(Mean daily dose of ≥7.5mg prednisone or equivalent for at least 6 months)
Treatment Study

Support by Procter & Gamble Pharmaceuticals and Hoechst Marion Roussel</td>
<td>PL for 12 mo
RIS 2.5 or 5mg</td>
<td>1. BMD
2. Fracture incidence</td>
<td>
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>Age</td><td>59</td><td>59</td><td>58</td></tr>
<tr><td>Sex (%)
Male
Premenopausal
Postmenopausal</td><td>
38
7
55</td><td>
39
10
51</td><td>
36
9
55</td></tr>
<tr><td>Duration of steroids (mo)</td><td>62</td><td>56</td><td>57</td></tr>
<tr><td>L spine BMD</td><td>0.93</td><td>0.96</td><td>0.94</td></tr>
<tr><td>Mean T score</td><td>-1.7</td><td>-1.4</td><td>-1.7</td></tr>
<tr><td>% with vertebral fxs</td><td>37</td><td>32</td><td>35</td></tr>
</table>
</td>
<td>Mean % Change in BMD
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>L spine</td><td>0.4</td><td>1.9</td><td>2.9</td></tr>
<tr><td>Fem neck</td><td>-0.3</td><td>-0.2</td><td>1.8</td></tr>
<tr><td>Trochanter</td><td>1.0</td><td>0.1</td><td>2.4</td></tr>
<tr><td>Distal radius</td><td>-2.0</td><td>-0.5</td><td>-0.6</td></tr>
<tr><td>Midshaft radius</td><td>-0.3</td><td>-0.1</td><td>-0.5</td></tr>
</table>
P < 0.001 at L spine, p = 0.004 at femoral neck, p = 0.01 at trochanter
Fractures
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>#(%) new vertebral fractures</td><td>9(15)</td><td>3(5)</td><td>3(5)</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Trial</th><th>Dose</th><th>Measured Outcome</th><th>Baseline Characteristics</th><th>Results</th></tr>
<tr>
<td>Wallach 2000
N=518
R, DB, PC, MC
(mean daily dose of ≥ prednisone or equivalent)
Results of Cohen and Reid were combined for analysis of fracture risk</td>
<td>PL for 12 mo
RIS 2.5 or 5mg</td>
<td>1. BMD L spine
2. BMD in fem neck, trochanter, distal radium, midshaft radius, biochemical markers</td>
<td>
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>Age</td><td>58</td><td>59.4</td><td>59.3</td></tr>
<tr><td>Sex (%)
Male
Premenopausal
Postmenopausal</td><td>
35
13
52</td><td>
37
15
48</td><td>
36
13
51</td></tr>
<tr><td>Duration of steroids (%)
≤3 mo
3-6mo
>6mo</td><td>
42
2
56</td><td>
42
4
54</td><td>
39
5
56</td></tr>
<tr><td>L spine BMD</td><td>0.989</td><td>0.991</td><td>1.003</td></tr>
<tr><td>L spine T score</td><td>-1.3</td><td>-1.2</td><td>-1.2</td></tr>
<tr><td>Prevalent vertebral fx %</td><td>34</td><td>28</td><td>35</td></tr>
<tr><td>NTx/Cr
BSAP</td><td>51.5
9.4</td><td>43
9.5</td><td>50.5
9.7</td></tr>
</table>
</td>
<td>
Mean % Change from baseline in BMD
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>L spine</td><td>-1.0</td><td>1.3</td><td>1.9</td></tr>
<tr><td>Fem neck</td><td>-1.5</td><td>-0.3</td><td>1.3</td></tr>
<tr><td>Trochanter</td><td>-0.8</td><td>-0.01</td><td>2.0</td></tr>
<tr><td>Distal radius</td><td>-1.2</td><td>0.01</td><td>0.4</td></tr>
<tr><td>Midshaft radius</td><td>-0.3</td><td>-0.3</td><td>-0.3</td></tr>
</table>
P < 0.001 for comparison between PL and RIS at L spine, femoral neck, and trochanter

Vertebral Fractures
<table>
<tr><td></td><td>PL</td><td>2.5</td><td>5</td></tr>
<tr><td>% with new vertebral fxs
Male
Premenopausal
Postmenopausal</td><td>16
24
0
16</td><td>7
0
0
12</td><td>5
9
0
5</td></tr>
<tr><td># of vertebral fractures</td><td>55</td><td>14</td><td>8</td></tr>
<tr><td>% of patients with ≥2 new vertebral fxs</td><td>9</td><td>2</td><td>1</td></tr>
</table>
P = 0.01 for 5mg p = 0.08 for 2.5mg
</td>
</tr>
</table>

Risedronate- Osteoporosis in Men

Trial	Dose	Measured Outcome	Baseline Characteristics	Results
Reid 2001 N=184 R, DB, PC, MC Analysis of males from the prevention and treatment trials in corticosteroid-induced osteoporosis	PL for 12 mo RID 2.5 or 5mg	BMD, Vertebral fractures, biochemical markers	See table below	See table below

Baseline Characteristics

	PL	2.5	5
Total	60	61	63
Prevention	25	25	27
Treatment	35	36	36
Age yrs	54.9	59.2	58.8
Duration of steroids %			
≤3mo	40	41	38.1
3-6mo	1.7	3.3	64
>6mo	58.3	55.7	55.5
L spine BMD			
Prevention	1.123	1.097	1.194
Treatment	0.984	1.002	0.959
L spine T score			
Prevention	-0.47	-0.89	0.15
Treatment	-1.67	-1.42	-1.89
Prevalent vertebral fractures %	36.7	38.3	46.8
Biochemical markers			
NTx/Cr	59.2	65	53.3
BSAP	10.8	10.3	10.7

Results

Mean % Change in BMD

	PL	2.5	5
Treatment:			4.8
L spine		Similar to	2.1
Fem neck		5mg	2.6
Trochanter			
Prevention:			
L spine	-3.4	Similar to	maintained
Fem neck	-3.3	5mg	maintained
Trochanter	-3.4		maintained

Treatment: p <0.001 for comparison between PL and RIS 5mg at L spine
Prevention: p < 0.01 for comparison between PL and RIS at all sites

Vertebral Fractures

	PL	2.5	5
V. fractures (# of patients)			
Prevention	4		1
Treatment	5		2
# of fractures	18		3

Combining both risedronate groups for analysis produced a 82.4% reduction in vertebral fracture risk compared with placebo.

Median % Change in Biochemical Markers

	PL	2.5	5
NTx/Cr	-61	-46.5	-17.1
BSAP	-11	-4	-20.2

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[3] Osteoporosis Task Force. American association of clinical endocrinologists 2001 medical guidelines for clinical practice for the prevention and management of postmenopausal osteoporosis. Endocrine Practice 2001; 7(4 July/August):293-312.
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[17] Cummings SR, Black D, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al for the Fracture Intervention Trial Research Group. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 1998;280:2077-2082.
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