# *Therapeutic Class Overview*
# *Bisphosphonates*

**Therapeutic Class**

- **Overview/Summary:** Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.[1] According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person.[2] Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.[1] Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.[3] Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death.[1] Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.[3] The bisphosphonates are primarily Food and Drug Administration (FDA)-approved for the prevention and/or treatment of osteoporosis in postmenopausal women, in men, and in patients taking prolonged courses of glucocorticoids. Bisphosphonates inhibit osteoclast activity by binding to bone surfaces that are undergoing active bone resorption resulting in the impairment of the ability for osteoclasts to form the ruffled border, adhere to the bony surface, and produce the protons necessary to continue bone resorption.[4-11] In general, the bisphosphonates are available for oral once-daily, once-weekly, or once-monthly administration. Currently, alendronate (tablet), etidronate, and ibandronate (150 mg tablet) are the only bisphosphonates available generically. Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures. While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis. At this time, evidence is insufficient to determine whether one bisphosphonates is "superior" to another.[1,3,13-16] Bisphosphonates are the most widely used drugs for the management of Paget's disease.[17]

**Table 1. Current Medications Available in Therapeutic Class**[4-11]

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Single-Entity Agents** | | | |
| Alendronate (Binosto®, Fosamax®) | Prevention of osteoporosis in postmenopausal women (Fosamax®).<br><br>Treatment of glucocorticoid-induced osteoporosis (Fosamax®).<br><br>Treatment to increase bone mass in men with osteoporosis.<br><br>Treatment of osteoporosis in postmenopausal women.<br><br>Treatment of Paget's disease of bone (Fosamax®). | Effervescent tablet (Binosto®):<br>70 mg<br><br>Solution (Fosamax®):<br>70 mg<br><br>Tablet (Fosamax®):<br>5 mg<br>10 mg<br>35 mg<br>40 mg<br>70 mg | ✔ (tablet) |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Etidronate (Didronel®) | Prevention and treatment of heterotopic ossification.*<br><br>Treatment of Paget's disease of bone. | Tablet:<br>200 mg<br>400 mg | ✔ |
| Ibandronate (Boniva®) | Prevention of osteoporosis in postmenopausal women (tablet).<br><br>Treatment of osteoporosis in postmenopausal women. | Injection:<br><br>Tablet:<br>150 mg | ✔ |
| Risedronate (Actonel®, Atelvia®) | Prevention of glucocorticoid-induced osteoporosis (Actonel®).<br><br>Prevention of osteoporosis in postmenopausal women (Actonel®).<br><br>Treatment of glucocorticoid-induced osteoporosis (Actonel®).<br><br>Treatment to increase bone mass in men with osteoporosis (Actonel®).<br><br>Treatment of osteoporosis in postmenopausal women.<br><br>Treatment of Paget's disease of bone (Actonel®). | Delayed-release tablet (Atelvia®):<br>35 mg<br><br>Tablet (Actonel®):<br>5 mg<br>30 mg<br>35 mg<br>150 mg | ✔ (tablet) |
| **Bisphosphonates-Combination Products** | | | |
| Alendronate/ cholecalciferol (Fosamax Plus D®) | Treatment to increase bone mass in men with osteoporosis<br><br>Treatment of osteoporosis in postmenopausal women | Tablet:<br>70 mg/2,800 IU<br>70 mg/5,600 IU | - |

IU=international units
*Following total hip replacement or due to spinal cord injury.

**Evidence-based Medicine**

- Clinical trials have demonstrated safety and efficacy their respective Food and Drug Administration-approved indications.[18-76]
- Head-to-head trials have not consistently demonstrated on one bisphosphonate to be more effective than another with regard to efficacy. Data from trials specifically examining fractures indicates that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo.[16,22,29,33]
- Evidence suggests that alendronate results in greater increases on BMD when compared to risedronate. Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate.[35-37]
- There is data to support alendronate and risedronate having similar efficacy.[20,42]
- Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate, in one trial, while another showed ibandronate to be similar in efficacy to alendronate. The included data also shows that alendronate and risedronate are effective in patients with glucocorticoid-induced osteoporosis.[12-14,38,40]
- Risedronate delayed release once weekly was compared to risedronate instant release daily in a new trial and found to be non-inferior.[73]
- Several recent studies suggest that higher doses with longer dosing intervals (monthly) increase adherence, without decreasing overall efficacy or increasing side effects.[73,74]

- Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. Three identified trials demonstrated that alendronate, risedronate, and tiludronate are more effective options than etidronate for the treatment of Paget's disease.[64,67]
- Overall, the most common adverse events associated with bisphosphonates are related to the gastrointestinal tract.[12-68]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:[1,3,13-17]
    - All drugs Food and Drug Administration-approved for use in osteoporosis are recommended as appropriate treatment options.
    - While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.
    - At this time, evidence is insufficient to determine whether one bisphosphonates is "superior" to another.
    - Bisphosphonates have good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures.
- Other Key Facts:
    - Alendronate (tablet, solution), etidronate, and ibandronate (tablet, solution), and risedronate (150 mg tablet) are the bisphosphonates currently available generically.

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# *Therapeutic Class Review*
# *Oral Bisphosphonates*

## Overview/Summary

Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.[1] According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person.[2] Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.[1] Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.[3] Osteoporotic fractures commonly occur in the wrist, spine, or hip and can result in complications such as chronic pain, disability, depression or even death.[1] Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.[3]

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## Medications

**Table 1. Medications Included Within Class Review**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| **Single-Entity Agents** | | |
| Alendronate (Binosto®, Fosamax®*) | Bisphosphonate | ✔ |
| Etidronate (Didronel®) | Bisphosphonate | ✔ |
| Ibandronate (Boniva®*) | Bisphosphonate | ✔ |
| Risedronate (Actonel®*, Atelvia®) | Bisphosphonate | ✔ |
| **Combination Products** | | |
| Alendronate/cholecalciferol (Fosamax Plus D®) | Bisphosphonate/ calcium regulator | - |

*Generic available in at least one dosage form and/or strength.

## Indications

**Table 2. Food and Drug Administration (FDA)-Approved Indications**[4-12]

| Generic Name | Prevention and Treatment of Heterotopic Ossification* | Prevention of Glucocorticoid-induced Osteoporosis | Prevention of Osteoporosis in Postmenopausal Women | Treatment of Glucocorticoid-induced Osteoporosis | Treatment to Increase Bone Mass in Men with Osteoporosis | Treatment of Osteoporosis in Postmenopausal Women | Treatment of Paget's Disease of Bone |
|---|---|---|---|---|---|---|---|
| **Single-Entity Agents** | | | | | | | |
| Alendronate | | | ✔ (Fosamax®) | ✔ (Fosamax®) | ✔ | ✔ | ✔ (Fosamax®) |
| Etidronate | ✔ | | | | | | ✔ |
| Ibandronate | | | ✔ (tablet) | | | ✔ | |
| Risedronate | | ✔ (Actonel®) | ✔ (Actonel®) | ✔ (Actonel®) | ✔ (Actonel®) | ✔ | ✔ (Actonel®) |
| **Combination Products** | | | | | | | |
| Alendronate/ cholecalciferol | | | | | ✔ | ✔ | |

*Following total hip replacement or due to spinal cord injury.

In addition to the Food and Drug Administration-approved indications, the bisphosphonates have the potential to be used off-label in the conditions outlined below.[12]

- Alendronate: management of arthroplasty of knee and fibrous dysplasia of bone, treatment of Crohn's disease-related osteoporosis, cystic fibrosis-related osteopenia, fibrous dysplasia of the bone, osteoporosis related to growth hormone deficiency, hypercalcemia of malignancy, juvenile idiopathic generalized osteoporosis, hypervitaminosis D and osteoporosis related to male hypogonadism.
- Etidronate: maintenance of hypercalcemia of malignancy, osteoporosis.
- Ibandronate: treatment of bone metastases, osteoporosis related to transplantation, and hypercalcemia of malignancy.
- Risedronate: decreased bone mineral density related to inflammatory bowel disease and postmenopausal osteoporosis related to inflammatory bowel disease.

## Pharmacokinetics

**Table 3. Pharmacokinetics**[4-12]

| Generic Name | Onset (months) | Bioavailability (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|---|
| **Single-Entity Agents** | | | | | |
| Alendronate* | 1 | 0.59 (men); 0.7 (women) | 50 | None | 1.9 |
| Etidronate | Not reported | 3 | 50 | None | 1 to 6 |
| Ibandronate | 1 to 3† | 0.6 | 50 to 60 | None | 37 to 157 |
| Risedronate | 0.47 | 0.63 | 50 | None | 561 |
| **Combination Products** | | | | | |
| Alendronate/ cholecalciferol | 1/not reported | 0.59 (men); 0.64 (women) | 50.0/2.4 | None/ 25(OH)D | 1.9/14.0 |

*Binosto® 70 mg effervescent tablet and alendronate 70 mg tablet are bioequivalent.
†Bone turnover with oral ibandronate.

## Clinical Trials

Clinical trials demonstrating the safety and efficacy of the bisphosphonates in their respective Food and Drug Administration-approved indications are outlined in Table 4.[18-76] Clinical trials evaluating alendronate effervescent tablet (Binosto®) have not been published. Alendronate effervescent tablet is considered bioequivalent to the 70 mg tablet formulations of alendronate.[5]

Clinical trials included within this review evaluate the efficacy of bisphosphonate agents in increasing bone mineral density (BMD) and/or decreasing bone turnover markers. Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD in order to reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focuses on the same treatment outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.

Head-to-head trials have not consistently demonstrated one bisphosphonate to be more effective than another with regard to efficacy. Data from trials specifically examining fractures indicates that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo.[24,30,37,41,42] Evidence suggests that alendronate results in greater increases in BMD when compared to risedronate.[43-45] Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate.[51] In addition, there is data to support alendronate and risedronate having similar efficacy.[28,50] Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate, in one trial, while others showed ibandronate to be similar in efficacy to alendronate.[46,48] The included data also shows that alendronate and risedronate are effective in patients with glucocorticoid-induced osteoporosis.[18-23] Risedronate delayed release once weekly was compared to risedronate instant release daily in a new trial and found to be non-inferior.[72] Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. Two identified trials demonstrated that alendronate and risedronate are more effective options than etidronate for the treatment of Paget's disease.[74,75] Several recent studies also suggests that higher doses with longer dosing intervals (monthly) increase adherence, without decreasing overall efficacy or increasing side effects.[70,72]

Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.

**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Prevention and/or Treatment of Glucocorticoid-induced Osteoporosis** | | | | |
| Okada et al[18]<br><br>Alendronate 5 mg QD plus alfacalcidol 1 mg QD<br><br>vs<br><br>alfacalcidol 1 mg QD<br><br>Patients received daily calcium supplements. | AC, OC, PRO, RCT<br><br>Premenopausal women (17 to 47 years of age) who were glucocorticoid naïve and had a systemic autoimmune disease requiring treatment with high-dose glucocorticoids (starting dose of prednisolone ≥1 mg/kg/day), and this treatment was expected to continue for at least 12 months with the daily dose after 6 months ≥7.5 mg/day | N=47<br><br>18 months | Primary:<br>Percentage change from baseline in BMD and metabolic bone markers after six, 12, and 18 months of treatment<br><br>Secondary:<br>Not reported | Primary:<br>After six months, the alfacalcidol group exhibited a -10.5% decrease in lumbar spine BMD while the combination group only exhibited a -2.1% decrease (P<0.001). At 12 months, the combination group had increased lumbar spine BMD by 1.7% from baseline while the alfacalcidol group had decreased a total of -9.9% (P<0.001). Lumbar spine BMD was also significantly higher after 18 months with the combination regimen compared to the alfacalcidol regimen (P<0.001).<br><br>There were no significant differences in the metabolic bone markers between the treatment groups (P values not reported).<br><br>Secondary:<br>Not reported |
| Mok et al[19]<br><br>Risedronate 5 mg QD<br><br>vs<br><br>placebo<br><br>Patients received daily calcium supplements. | DB, PC, RCT<br><br>Ambulatory patients 18 to 75 years of age with various medical conditions that required high-dose glucocorticoid treatment (oral prednisolone ≥0.5 mg/kg/day or equivalent for at least | N=120<br><br>6 months | Primary:<br>Percentage change in BMD of the lumbar spine and hip from baseline to six months<br><br>Secondary:<br>Occurrence of new vertebral fractures | Primary:<br>At six months patients in the risedronate group demonstrated a significant increase in mean spinal BMD of 0.7% (P=0.03) while patients in the placebo group exhibited a non-significant decrease of -0.7% (P=0.12). Both groups demonstrated a decrease in hip BMD, -0.8 and -1.3% in the risedronate and placebo groups, respectively (P<0.05, P<0.01).<br><br>Secondary:<br>No new fractures developed in any patients in either treatment group. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | 6 weeks or IV pulse methylprednisolone) irrespective of baseline BMD | | | |
| Reid et al[20]<br><br>Risedronate 5 mg QD<br><br>vs<br><br>zoledronic acid 5 mg injection<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, DD, MC, NI, RCT<br><br>Patients 18 to 85 receiving at least 7.5 mg oral prednisolone daily (or equivalent) and were expected to receive glucocorticoids for another 12 months | N=833<br><br>1 year | Primary:<br>Change from baseline in BMD of the lumbar spine at 12 months<br><br>Secondary:<br>Change from baseline in BMD at the total hip, femoral neck, trochanter, and distal radius; occurrence of thoracic and lumbar vertebral fractures at 12 months; relative change from baseline in β-CTX and P1NP | Primary:<br>Both zoledronic acid and risedronate increased lumbar spine BMD in the prevention and treatment subgroups. Based on the results, it was determined that the criteria for the NI of zoledronic acid were met. By 12 months, zoledronic acid had increased lumbar spine BMD more than risedronate in both the treatment (LSM, 4.06% vs LSM, 2.71%; mean difference, 1.36%; 95% CI, 0.67 to 2.05) and prevention subgroups (LSM, 2.60% vs LSM, 0.64%; mean difference, 1.96%; 95% CI, 1.04 to 2.88).<br><br>Secondary:<br>Zoledronic acid significantly increased BMD at the femoral neck compared to risedronate, in both the treatment (LSM, 1.45% vs LSM, 0.39%; mean difference, 1.06%; 95% CI, 0.32 to 1.79) and prevention (LSM, 1.30% vs LSM, -0.03%; mean difference, 1.33%; 95% CI, 0.41 to 2.25) subgroups.<br><br>Similar results were seen at the trochanter for the treatment (LSM, 1.97% vs LSM, 0.63%; mean difference, 1.34%; 95% CI, 0.59 to 2.08; P=0.0005) and prevention subgroups (LSM, 2.75% vs LSM, 0.48%; mean difference, 2.27%; 95% CI, 1.15 to 3.39; P<0.0001), and total hip for the treatment (LSM, 1.65% vs LSM, 0.45%; mean difference, 1.21%; 95% CI, 0.71 to 1.70; P<0.0001) and prevention (LSM, 1.54% vs LSM, 0.03%; mean difference, 1.51%; 95% CI, 0.78 to 2.23; P<0.0001) subgroups. However, at the distal radius zoledronic acid increased BMD compared to risedronate in the treatment (LSM, 0.85% vs LSM, 0.09%; mean difference, 0.76%; 95% CI, 0.11 to 1.40; P=0.0223) but not the prevention group (LSM, 0.06% vs LSM, 0.47%; mean difference, -0.42%; 95% CI, -1.17 to 0.34; P=0.2784).<br><br>There was no significant difference between drug groups, both in the |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | treatment and prevention subgroups, in the number of patients with new vertebral fractures (five patients taking zoledronic acid and three patients taking risedronate; P value not reported).<br><br>Reductions in both biomarkers at 12 months were significantly greater in patients on zoledronic acid than in those on risedronate, in both the treatment and prevention subgroups (P value not reported). |
| Sambrook et al[21]<br><br>Risedronate 5 mg QD<br><br>vs<br><br>zoledronic acid 5 mg injection<br><br>Patients were stratified into two groups based on the duration of glucocorticoid therapy at baseline (the "prevention" group used high-dose glucocorticoid therapy for ≤3 months and the "treatment" group used high-dose glucocorticoid therapy for >3 months).<br><br>All patients received calcium 1,000 mg and vitamin D 400 to 1200 IU daily during the study. | AC, DB, DD, MC, PG, RCT<br><br>Patients 18 to 85 years of age requiring high-doses of glucocorticoid therapy due to underlying clinical conditions with expected continuation for at least one year (≥7.5 mg/day of prednisolone or equivalent) | N=265<br><br>12 months | Primary:<br>Percent change in BMD of lumbar spine from baseline to 12 months<br><br>Secondary:<br>Percent change in BMD at other sites (total hip and femoral neck) from baseline to 12 months, relative change in biomarkers of bone turnover (β-CTx) and procollagen type 1 aminoterminal propeptide and safety assessments | Primary:<br>Zoledronic acid significantly increased the lumbar BMD at 12 months compared to risedronate in both the osteoporosis prevention group (2.46 vs -0.24%; P=0.0024) and the osteoporosis treatment group (4.69 vs 3.27%; P=0.0232).<br><br>Secondary:<br>At 12 months, there was no statistically significant difference in the percent change from baseline between zoledronic acid and risedronate with regard to BMD change at the total hip (P=0.0230) or femoral neck (P=0.0819) in the osteoporosis prevention subpopulation. Similarly, in the treatment subpopulation, there was no statistically significant change in BMD at the femoral neck (P=0.1754), but the change at the total hip favored zoledronic acid over risedronate (1.82 vs 0.18%; P=0.004).<br><br>The serum β-CTx levels were significantly higher at 12 months with zoledronic acid compared to risedronate in both the treatment subpopulation (P≤0.001) and the prevention subpopulation (P≤0.05).<br><br>Treatment with zoledronic acid significantly increased serum levels of procollagen type 1 aminoterminal propeptide in the treatment subgroup (P≤0.05). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Devogelaer et al[22]<br><br>Zoledronic acid 5 mg once yearly<br><br>vs<br><br>risedronate 5 mg QD<br><br>Patients received 400 to 1,200 IU of vitamin D and 1,000 mg of elemental calcium per day | MC, DB, DD, AC, PG, RCT<br><br>Patients 18 to 85 years of age being treated with at least 7.5 mg oral prednisone daily (or equivalent) and expected to continue for at least 12 months | N=833<br><br>1 year | Primary:<br>Changes in b-C-terminal telopeptides of type 1 collagen (b-CTx), N-terminal telopeptide of type I collagen (NTx), procollagen type 1 N-terminal propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP) from baseline<br><br>Secondary:<br>Effect on pre- and postmenopausal women, prednisone-equivalent dose effect, patient preference for treatment regimen | Primary:<br>There were significantly greater reductions (P<0.05) in serum b-CTx and urine NTx levels in both male and female subjects on zoledronic acid therapy compared with those on risedronate therapy in the treatment and prevention subpopulations at day 10 and months 3, 6 and 12, with the exception of NTx for the male prevention subpopulation at month 12.<br><br>There were significantly greater reductions (P<0.05) in both serum P1NP and BSAP concentrations with zoledronic acid treatment compared with risedronate treatment for both male and female subgroups at different post-baseline time points. Serum P1NP levels also decreased more significantly with zoledronic acid therapy compared with risedronate at all post-baseline time points in females of the prevention subpopulation. For the male and female subgroups of the treatment subpopulation that were on RIS therapy, P1NP concentrations did not change much from baseline to day 10; however, they decreased significantly at months 3, 6 and 12. In the prevention subpopulation, BSAP levels were reduced more significantly with zoledronic acid at months 3 and 6 in females and at month 3 in males.<br><br>Secondary:<br>Analyses of results on the basis of menopausal criteria demonstrated that there was a significantly greater reduction in the concentrations of the biomarkers with zoledronic acid treatment compared with risedronate in both pre- and postmenopausal women<br><br>Results of the treatment effect at 12 months revealed that zoledronic acid-treated subjects had significantly greater reductions in b-CTx, NTx, BSAP and P1NP compared with RIS-treated subjects (P<0.05) for both treatment and prevention subpopulations, which was independent of prednisone-equivalent dose at the end of the study.<br><br>A once-yearly infusion was preferred by the majority of patients regardless of subpopulation, gender or menopausal status. |
| Gluer et al[23] | RCT, OL, MC, AC | N=92 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Teriparatide 20 µg once weekly<br><br>vs<br><br>risedronate 35 mg once weekly | Men ≥ 25 years of age who have taken glucocorticoids for ≥3 months and had an areal BMD T-score ≤-1.5 | 1.5 years | Compare lumbar spine (L1 to L3) BMD<br><br>Secondary:<br>BMD and microstructure at the 12th thoracic vertebra, biomechanical effects for axial compression, anterior bending, and axial torsion, aBMD, biochemical markers, and safety | Trabecular BMD at L1 to L3 had significantly increased for both treatments, with significantly greater increases with teriparatide, 16.3% versus 3.8% (P=0.004).<br><br>Secondary:<br>HRQCT trabecular and cortical variables significantly increased for both treatments with significantly larger improvements for teriparatide for integral and trabecular BMD and bone surface to volume ratio (BS/BV) as a microstructural measure. Vertebral strength increases at 18 months were significant in both groups (teriparatide: 26.0% to 34.0%; risedronate: 4.2% to 6.7%), with significantly higher increases in the teriparatide group for all loading modes (0.005<P<0.015).<br><br>Adverse events were similar between groups. None of the patients on teriparatide but five (10.6%) on risedronate developed new clinical fractures (P=0.056) |
| **Prevention and/or Treatment of Osteoporosis** | | | | |
| Sawka et al[24]<br><br>Alendronate 10 mg QD<br><br>vs<br><br>placebo<br><br>Patients received daily calcium and vitamin D supplements.<br><br>In study B only patients in the control group received daily oral supplementation with alfacalcidol 1 µg. | BA<br><br>Study A:<br>men with BMD T-score -2 at femoral neck and T-score -1 at the lumbar spine or men with T-score -1 at the femoral neck and at least 1 vertebral or osteoporotic fracture<br><br>Study B:<br>Men with BMD T-score -2.5 at femoral neck or lumbar spine, excluding | Study A:<br>N=241<br><br>2 years<br><br>Study B:<br>N=134<br><br>3 years | Primary:<br>Incidence of vertebral and nonvertebral fractures<br><br>Secondary:<br>Not reported | Primary:<br>In study A, 2.7% of patients receiving alendronate and 7.4% of patients receiving placebo sustained a vertebral fracture at two years. However, in study B, 10.3 and 24.2% of patients in the alendronate and placebo groups respectively, sustained a vertebral fracture at three years (P values not reported).<br><br>The incidence of nonvertebral fractures was 4.1 vs 5.3% of patients taking alendronate and placebo, respectively in study A. The incidence in study B was 8.8 vs 12.1%, respectively (P values not reported).<br><br>When the results of these two trials were pooled, incorporating prior information from postmenopausal women, the OR of vertebral fractures in alendronate-treated men was 0.44 (95% CRI, 0.23 to 0.83; P value not reported) and the OR of nonvertebral fracture was 0.60 (95% CRI, 0.29 to 1.44; P value not reported). Further analysis, without incorporating data from women, resulted in an OR of vertebral fracture of 0.36 (95% CI, 0.17 to 0.77; P value not reported) and an OR for |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | hypogonadal men | | | nonvertebral fracture of 0.73 (95% CI, 0.32 to 1.67; P value not reported).<br><br>Secondary:<br>Not reported |
| Boonen et al[25]<br><br>Risedronate 35 mg weekly<br><br>All patients received 1,000 mg elemental calcium and Vitamin D 400 to 500 IU daily. | ES, MC, OL, RCT<br><br>Men ≥30 years of age with osteoporosis (lumbar T-score ≤-2.5 and femoral neck T-score ≤-1 standard deviation, or lumbar spine T-score ≤-1 and femoral neck T-score ≤-2 standard deviation) | N=218<br><br>2 years | Primary:<br>Safety assessment<br><br>Secondary:<br>Change in BMD, bone turnover markers and incidence of new vertebral fractures | Primary:<br>In the open-label phase, a similar percentage of adverse events were reported between patients who initially received placebo (placebo/risedronate) in the double-blind phase compared to patients receiving risedronate (risedronate/risedronate).<br><br>A higher percentage of patients in the placebo/risedronate group (6.0%) withdrew from the open-label extension study due to an adverse events compared to the risedronate/risedronate group (2.6%; P=0.2539).<br><br>A higher percentage of patients in the placebo/risedronate group experienced a “moderate to severe” upper gastrointestinal adverse event compared to the risedronate/risedronate group (7.5 vs 1.3%; P=0.0297); however, the total number of incidences were low.<br><br>The most frequently reported adverse event was nasopharyngitis (7.9%) in the risedronate/risedronate group and atrial fibrillation (6.0%) in the placebo/risedronate group. Headache was reported by more patients in the risedronate/risedronate group (6.0%) compared with no patients in the placebo/risedronate group. The incidences of these adverse events were not statistically different among treatment groups (P>0.05 for both).<br><br>There were no clinically-relevant unexpected changes, or abnormal laboratory results or significant findings (including vital signs, physical examination findings, and anthropometry) that affected patient safety during the study.<br><br>Secondary:<br>Patients in the risedronate/risedronate group experienced a significant increase in lumbar spine BMD from month 24 to month 48 (1.44%; |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 95% CI, 0.54 to 2.35%) as did the placebo/risedronate group (5.04%; 95% CI, 3.88 to 6.21%). The between-group difference in lumbar spine BMD changes from month 24 to month 48 was significantly different favoring the placebo/risedronate group (P<0.0001).<br><br>At 48 months, there was a significant increase from baseline in lumbar spine BMD in the risedronate/risedronate group (7.87%; 95% CI, 6.62 to 9.13%), and a more modest increase in the placebo/risedronate group (6.27%; 95% CI, 4.65 to 7.90%). The risedronate/risedronate group had a greater percentage change from baseline compared to the placebo/risedronate group in lumbar spine BMD at months 24 and 36, and at endpoint (P<0.05 for all three time points).<br><br>The percentage increase in the total proximal femur BMD was significant for the placebo/risedronate group from month 24 to month 48 (1.28%; 95% CI, 0.51 to 2.04%), but not for the risedronate/risedronate group (0.35%; 95% CI, −0.25 to 0.95%). The between-group difference from month 24 and month 48 was significantly significant favoring the placebo/risedronate group (P=0.0241).<br><br>The percentage increase in the femoral neck BMD from month 24 to month 48 was not statistically significant for the placebo/risedronate treatment group (0.65%; 95% CI, −0.47 to 1.76%) or risedronate/risedronate (0.22%; 95% CI, −0.65 to 1.09%) group. The between-group difference from month 24 and month 48 was not significantly different.<br><br>The percent change in femoral trochanter BMD was significant from month 24 to month 48 in the placebo/risedronate (2.11%; 95% CI, 1.00 to 3.21%) and the risedronate/risedronate (0.90%; 95% CI, 0.05 to 1.76%) groups. The between-group difference from month 24 and month 48 was significantly different (P<0.05).<br><br>A significant reduction in urinary NTX/Cr occurred from month 24 to months 30, 36 and 48, and at endpoint for the placebo/risedronate |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | group. No significant changes from month 24 in urinary NTX/Cr were observed for the risedronate/ risedronate group. A significant decrease in percentage change from baseline in urinary NTX/Cr was observed for both groups at all time points.<br><br>A significant decrease from month 24 in bone ALP was observed at months 36, 48, and at endpoint for the placebo/risedronate group. Bone ALP increased significantly from month 24 at all time points for the risedronate/risedronate group. At month 48, a significant (P<0.05) decrease in percent change from baseline in bone ALP was observed for both groups. There were no significant differences in percent change from baseline between the two groups in NTX/Cr, CTX and bone ALP by month 48.<br><br>Zero patients in the placebo/risedronate group and six (4.1%) patients in the risedronate/risedronate group experienced at least one vertebral fracture from month 24 to month 48 (P=0.18). A similar percentage of patients experienced a clinical fracture in the placebo/risedronate group (3%) and risedronate/risedronate group (2%; P=0.64). |
| Binkley et al[26]<br><br>Alendronate/ cholecalciferol 70 mg/2,800 IU once weekly plus cholecalciferol 2,800 IU once weekly (ALN+D5600)<br><br>vs<br><br>alendronate/ cholecalciferol 70 mg/ 2,800 IU (ALN+D2800)<br><br>All patients received daily | AC, DB, DD, ES, MC, RCT<br><br>Men and postmenopausal women with serum 25(OH)D ≥9 ng/mL and osteoporosis (lumbar spine or femoral neck BMD at least 2.5 SD below the young reference mean) | N=652<br><br>24 weeks (extension of a previous 15 week trial) | Primary:<br>Proportion of patients who developed hypercalciuria (24-hour urine calcium >300 mg in women or >350 mg in men, and an increase >25% vs baseline) at week 39<br><br>Secondary:<br>Proportion of patients with vitamin D insufficiency | Primary:<br>The proportion of patients with hypercalciuria at week 39 was 4% for the ALN+D5600 group and 3% for the ALN+D2800 group (P=0.354).<br><br>Secondary:<br>At week 39, the ALN+D2800 group had a larger proportion of patients with vitamin D insufficiency compared to the ALN+D5600 group (6 vs 3%; P=0.115).<br><br>The ALN+D5600 group had significantly larger increases in serum 25(OH)D levels at week 39 vs the ALN+D2800 group (6.1 ng/mL; 95% CI, 5.2 to 7.0 vs 4.0 ng/mL; 95% CI, 3.1 to 4.8; P<0.001).<br><br>The significant reductions in BSAP and urine NTX/Cr observed at week 15 were maintained throughout the 24 week extension (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| supplementation with oral calcium (500 to 600 mg). | | | (25(OH)D <15 ng/mL) at week 39; mean changes in serum 25(OH)D within and between treatment groups, changes from baseline in BTMs (BSAP, urine NTX/Cr); mean percent changes from baseline in serum calcium, serum phosphate and serum parathyroid hormone | There was no significant change in serum calcium levels and no significant difference in the percentage changes from week 0 to week 39 in serum parathyroid hormone levels between treatment groups (P values not reported). Both groups demonstrated significant reductions in serum phosphate levels, but the mean changes between the treatment groups were not significant (P values not reported). |
| Orwoll et al[27]<br><br>Zoledronic acid 5 mg injection<br><br>vs<br><br>alendronate 70 mg once weekly | AC, DB, MC, PG, RCT<br><br>Men 25 to 85 years of age with primary osteoporosis or osteoporosis associated with hypogonadism | N=302<br><br>Duration not specified | Primary:<br>Change in baseline lumbar spine BMD<br><br>Secondary:<br>Change in baseline lumbar spine, total hip, femoral neck, and total body BMD at six, 12, and 24 months; change baseline BTMs; change in baseline laboratory parameters; safety | Primary:<br>Both treatments increased BMD at the lumbar spine at 24 months. Increases were 6.1 and 6.2% with zoledronic acid and alendronate (difference, 0.13%; 95% CI, 1.12 to 0.85). The NI of zoledronic acid vs alendronate was established; however, “superiority” was not.<br><br>Secondary:<br>Both treatments increased BMD at the lumbar spine, total hip, femoral neck, and trochanter over 24 months, with no significant differences between the two treatments at any time. NI of zoledronic acid vs alendronate was established at the total hip (difference, 0.496%; 95% CI, 1.295 to 0.304) and femoral neck (difference, 0.576%; 95% CI, 1.006 to 2.157) at 24 months. There was also no difference between the treatments in the proportions of patients who responded to treatment.<br><br>At 12 and 24 months both treatments decreased BTMs. The decreases were more pronounced at months three, six, 15, and 18 months with zoledronic acid compared to alendronate. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | All patients experienced a decrease in height, with no difference between the two treatments. Sex steroid and sex hormone binding globulin levels had no clear effect on BMD.<br><br>There were four and six new fractures with zoledronic acid and alendronate (P=0.5349). The overall incidence of adverse events was similar between the two treatments (93.5 vs 93.2%). The most frequently occurring adverse events (≥5.0%) were pyrexia, myalgia, arthralgia, chills, fatigue, headache, influenza-like illness, malaise, backache, and pain. All these occurred within three days of zoledronic acid administration in at least five percent of patients. The overall frequency of serious adverse events was 17.6 and 20.9%, with no meaningful differences between the two treatments. |
| Cadarette et al[28]<br><br>Alendronate 10 or 70 mg<br><br>vs<br><br>risedronate 5 or 35 mg<br><br>vs<br><br>nasal calcitonin, dose not specified<br><br>vs<br><br>raloxifene, dose not specified | OS, RETRO<br><br>Low-income patients >65 years of age with a new prescription for an oral bisphosphonate (alendronate or risedronate), nasal calcitonin, or raloxifene | N=43,135<br><br>2 years | Primary:<br>Incidence of non-vertebral fractures within the first year of treatment<br><br>Secondary:<br>Incidence of non-vertebral fractures within 6 and 24 months of treatment | Primary:<br>There was no difference in non-vertebral fracture risk within 12 months between risedronate (HR, 1.01; 95% CI, 0.85 to 1.21; P=0.88) or raloxifene (HR, 1.18; 95% CI, 0.96 to 1.46; P=0.121) when compared to alendronate. The risk of non-vertebral fractures was significantly higher with calcitonin compared to alendronate (HR, 1.4; 95% CI, 1.2 to 1.63; P<0.001).<br><br>Secondary:<br>At six months, there was no difference in the risk of non-vertebral fractures with either risedronate (HR, 1.07; 95% CI, 0.85 to 1.36; P=0.56) or raloxifene (HR, 1.18; 95% CI, 0.88 to 1.58; P=0.26) compared to alendronate. Calcitonin had a significantly higher risk of non-vertebral fracture compared to alendronate (HR, 1.42; 95% CI, 1.16 to 1.74; P<0.001). Similarly, at 24 months, risedronate and raloxifene did not have a difference in the risk (HR, 0.96; 95% CI, 0.84 to 1.11; P=0.56 and HR, 1.00; 95% CI, 0.85 to 1.18; P=1.00, respectively), while calcitonin was at a significantly higher risk of non-vertebral fractures (HR, 1.28; 95% CI, 1.14 to 1.43; P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Freemantle et al[29]<br><br>Osteoporosis therapies (denosumab, alendronate, risedronate, ibandronate, zoledronic acid, etidronate, strontium ranelate*, teriparatide, raloxifene)<br><br>vs<br><br>placebo | MA (34 trials; 21 utilized in primary analysis)<br><br>Postmenopausal women | N=not reported<br><br>Duration varied | Primary:<br>Efficacy of osteoporosis therapies in reducing fractures<br><br>Secondary:<br>Not reported | Primary:<br>Direct comparisons for each active comparator to placebo from the random effects MA demonstrated that all agents demonstrated significant reductions in the risk of new vertebral fractures, with the exception of etidronate. Denosumab, risedronate, and zoledronic acid also showed significant reductions for nonvertebral and hip fractures compared to placebo, while alendronate, strontium ranelate, and teriparatide only showed significant differences compared to placebo for nonvertebral fractures.<br><br>In the mixed treatment comparison of each active comparator to placebo, the RR for new vertebral fractures were consistent with those obtained directly from the MA. The only treatments that showed a reduction in nonvertebral fracture risk were teriparatide and risedronate.<br><br>Secondary:<br>Not reported |
| Nakamura et al[30]<br><br>0.5 mg per month IV ibandronate plus oral placebo QD<br><br>vs<br><br>1.0 mg per month IV ibandronate plus oral placebo QD<br><br>vs<br><br>2.5 mg QD oral risedronate plus IV placebo monthly | PRO, RCT, DB, AC, DD<br><br>Ambulatory patients ≥60 years of age with primary osteoporosis according to the Diagnosis Criteria of Primary Osteoporosis in Japan and must have: fragile bone fracture; BMD of the lumbar spine (L2 to L4), or proximal femur <80% of the young adult mean (T score of -1.7,-1.6 and-1.4 respectively); | N=1,265<br><br>3 years | Primary:<br>Noninferiority of ibandronate versus risedronate with regards to the incidence of nontraumatic morphometric vertebral fractures at three years<br><br>Secondary:<br>Incidences of nontraumatic new vertebral fractures, all osteoporotic nonvertebral fractures, | Primary:<br>The cumulative incidences of new or worsening vertebral fractures over three years were 19.9% (95% CI, 15.6 to 24.1), 16.1% (95% CI, 12.2 to 19.9) and 17.6% (95% CI, 13.6 to 21.6) for the ibandronate 0.5 mg, ibandronate 1 mg, and risedronate groups, respectively. Compared with the risedronate group, the HR for fracture incidences were 1.09 (95% CI, 0.77 to 1.54) and 0.88 (95% CI, 0.61 to 1.27) for ibandronate 0.5 mg and 1 mg, respectively.<br><br>Secondary:<br>The cumulative incidences of first new vertebral fractures were 16.8% (95% CI, 12.8 to 20.8), 11.6% (95% CI, 8.2 to 15.0), and 13.2% (95% CI, 9.6 to 16.9) for the ibandronate 0.5 mg, ibandronate 1 mg, and risedronate groups, respectively. The HR for the ibandronate groups compared with the risedronate group were 1.27 (95% CI, 0.86 to 1.89) and 0.87 (95% CI, 0.57 to 1.33) for the 0.5 mg and 1 mg doses, respectively; the difference between the 0.5 mg and 1 mg ibandronate doses was not statistically significant (P=0.062). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| All patients received 305 mg calcium and 200 IU vitamin D QD | and one to five radiographically confirmed vertebral fractures in the fourth thoracic spine to fourth lumbar spine | | osteoporotic nonvertebral fractures at the six major sites (femur, forearm, humerus, clavicle, tibia/fibula, pelvis), clinical vertebral fractures, and total clinical fractures; percentage change from baseline in lumbar spine (L2–L4), total hip, trochanter and femoral neck BMD; change from baseline in BTMs of urinary Cand N-telopeptide of type 1 collagen corrected by creatinine (uCTX and uNTX, respectively), serum bone-specific alkaline phosphatase (BALP) and osteocalcin (OC); and safety | The cumulative incidences of osteoporotic nonvertebral fractures were 9.0, 7.2, and 8.4% for the ibandronate 0.5 mg, ibandronate 1 mg, and risedronate groups, respectively. The difference between the ibandronate groups was not statistically significant. The respective values for the major six nonvertebral fractures were 5.3, 4.6, and 6.3%. Differences between the treatment groups were not statistically significant for any of the fracture end points.<br><br>At three years, the mean relative change from baseline in BMD values for the ibandronate 0.5, 1 mg and risedronate groups was 7.7, 9.0, and 7.6%, respectively, for the lumbar spine, and 2.2, 3.1, and 2.0%, respectively, for the total hip. Respective values at the trochanter were 3.8, 4.7, and 3.1%, and at the femoral neck were 2.1, 3.1, and 2.2%. Significant differences were noted in lumbar spine BMD between the 1 mg and 0.5 mg ibandronate dose groups at one year (P=0.030), two years (P=0.001), and three years (P=0.010), and in total hip BMD at two years (P=0.029) and three years (P=0.006). Intergroup differences in BMD between the ibandronate groups were not significant at the trochanter. BMD changes in women showed similar trends in all three treatment groups.<br><br>Significant differences were noted between the ibandronate groups at each time point for all BTMs (P<0.005). Women showed similar differnces as the overall population.<br><br>No significant differences were observed between the treatment groups with respect to the incidence of all adverse effects, serious adverse effects, adverse effects leading to death or adverse effects leading to withdrawal. |
| **Prevention and/or Treatment of Postmenopausal Osteoporosis** | | | | |
| Black et al[31] | DB, MC, PC, RCT | N=2,027 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Alendronate 5 mg QD for 24 months, followed by 10 mg QD<br><br>vs<br><br>placebo<br><br>Patients received daily calcium and vitamin D supplements. | Patients 55 to 81 years of age who had been postmenopausal for at least 2 years and had a femoral neck BMD ≤0.68 g/cm$^2$ | 36 months | Incidence of new vertebral fractures defined by morphometry as a decrease of 20% (and at least 4 mm) in at least one vertebral height between baseline and latest follow-up radiograph<br><br>Secondary:<br>Incidence of clinical fractures grouped into six non-exclusive categories: all, non-spine, hip, wrist, vertebral, and other | The risk of new radiographic vertebral fractures was 47% lower in the alendronate group compared to the placebo group; 15 and 8% of the placebo and alendronate groups, respectively, experienced a new vertebral fracture (P<0.001).<br><br>Secondary:<br>Significantly fewer patients receiving alendronate had clinical vertebral fractures compared to patients receiving placebo (2.3 vs 5.0%; HR, 55.0%; P<0.001). Also, the cumulative proportion of patients experiencing any clinical fracture was significantly lower in the alendronate group compared to the placebo group (13.6 vs 18.2%, respectively; HR, 0.72; 95% CI, 0.58 to 0.90; P value not reported). There were significant differences between groups in the cumulative proportions of patients experiencing hip (2.2 vs 1.1%; HR, 0.49; 95% CI, 0.23 to 0.99) and wrist fractures (4.1 vs 2.2%; HR, 0.52; 95% CI, 0.31 to 0.87) with the alendronate group experiencing fewer (P values not reported). However, the differences in fractures occurring in sites other than the spine, hip or wrist were similar between groups and did not achieve statistical significance (P values not reported). |
| Stakkestad et al[32]<br><br>Ibandronate 100 mg once monthly<br><br>vs<br><br>ibandronate 150 mg once monthly<br><br>Patients received daily calcium and vitamin D supplements. | DB, ES, MC, PR<br><br>Ambulatory, postmenopausal (≥5 years since menopause) women 55 to 80 years of age with osteoporosis (mean lumbar spine BMD T-score <-2.5 and ≥-5.0 | N=719<br><br>1 year<br><br>Extension of a previous 2 year study | Primary:<br>Relative change in mean lumbar spine BMD at 36 months from the end of the previous two-year study<br><br>Secondary:<br>Relative change at 12, 24, and 36 months in total hip BMD and bone resorption markers (CTX) | Primary:<br>After one year of treatment in the ES patients in the 150 and 100 mg groups demonstrated a 1.5 and 1.1%, respectively, increase in lumbar spine BMD, compared to their values at the end of the previous two-year study (P values not reported).<br><br>Secondary:<br>After one year of treatment in the ES patients in the 150 and 100 mg groups demonstrated a 0.30 and -0.08%, respectively, change in total hip BMD when compared to their values at the end of the previous two-year study (P values not reported). Median peak serum CTX decreased from values at the end of the two-year study by -42.3 and -31.3% in the 150 and 100 mg groups, respectively. Median trough serum CTX increased by 10.3 and 22.2% in both groups respectively (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Post-hoc analysis:<br>A post-hoc analysis of the two treatment groups was conducted to re-evaluate the primary and secondary endpoints. This analysis included only those patients who had received 100 or 150 mg of ibandronate continuously for the total three years of the study (two years of previous study plus one year of extension study).<br><br>After a total of three years treatment a total increase of 7.6% in lumbar spine BMD was observed in the 150 mg group and 6.4% in the 100 mg group (P<0.0001 vs baseline for both groups). The increase from year two to year three in lumbar spine BMD was 1.2 and 0.9% for the 150 and 100 mg groups, respectively (P<0.0001, P=0.003). At the total hip, the BMD increases over three years were 4.1 and 3.4% in the 150 and 100 mg groups, respectively (P<0.0001 vs baseline for both groups). |
| Hakala et al (abstract)[33]<br><br>Ibandronate 150 mg once monthly<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Postmenopausal women with inflammatory rheumatic disease, normal or osteopenic baseline mean lumbar spine BMD, and receiving 5 to 15 mg/day of prednisone equivalent | N=140<br><br>1 year | Primary:<br>Change in mean lumbar spine BMD<br><br>Secondary:<br>Change in bone turnover markers, safety | Primary:<br>Mean lumbar spine BMD increased by 2.6 and 3.2% from baseline to six to 12 months with ibandronate compared to 0.3 and -0.1% with placebo, respectively (P<0.001). Comparable mean increases were also observed in trochanter, femoral neck, and total hip BMDs at 12 months.<br><br>Secondary:<br>Reductions in serum levels of bone turnover markers were significantly more marked with ibandronate compared to placebo at months one, six, and 12.<br><br>Adverse events were reported at a similar frequency with both treatments. A higher proportion of serious adverse events were reported with ibandronate. |
| Chesnut et al[34]<br><br>Ibandronate 2.5 mg QD plus 500 mg calcium and 400 IU vitamin D daily | DB, MC, PC, PG, RCT<br><br>Patients 55 to 80 years of age and ≥5 years | N=2,946<br><br>3 years | Primary:<br>Rate of patients with new morphometric vertebral fractures at three years | Primary:<br>At three years, 37 and 39 patients in the daily and intermittent ibandronate groups, respectively, suffered at least 1 new vertebral fracture compared to 73 patients in the placebo group. The RR reductions compared to placebo, 62% (95% CI, 41 to 75; P=0.0001) and 50% (95% CI, 26 to 66; P=0.0006) for the 2.5 and 20 mg ibandronate |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>ibandronate 20 mg every other day for 12 doses every 3 months, by mouth placebo on days without active medication plus 500 mg calcium and 400 IU vitamin D daily<br><br>vs<br><br>placebo plus 500 mg calcium and 400 IU vitamin D daily | postmenopausal, with 1 to 4 prevalent vertebral fractures ($T_4$ to $L_4$) and BMD T-score -2.0 to -5.0 in at least 1 vertebra ($L_1 – L_4$) | | Secondary:<br>Rate of patients with new or worsening vertebral fractures, clinical vertebral fractures, and clinical osteoporotic nonvertebral fractures, relative changes in BMD at the lumbar spine and proximal femur, relative changes in biochemical markers of bone turnover, changes in height | groups, respectively, after three years.<br><br>Secondary:<br>Significant reductions in the risk of new or worsening vertebral fractures were observed in both the 2.5 and 20 mg ibandronate groups (RR reductions, 62%; 95% CI, 43 to 75; P=0.0001 and 50%; 95% CI, 26 to 65; P=0.0005, respectively). The incidence of clinical vertebral fractures was estimated to be 2.8% (95% CI, 1.6 to 3.9; P value not reported) for both ibandronate groups and 5.3% (95% CI, 3.7 to 6.9; P value not reported) in the placebo group. The differences in treatment effect between the ibandronate groups and placebo were statistically significant (P=0.0117 for 2.5 mg and P=0.0143 for 20 mg). However, the incidence of clinical nonvertebral fractures was low and similar between all groups (8.2% for placebo, 9.1% for 2.5 mg, and 8.9% for 20 mg; P value not reported).<br><br>At three years, ibandronate was associated with statistically significant and progressive increases in BMD at the lumbar spine and hip (total hip, femoral neck, and trochanter) compared to placebo. BMD at the lumbar spine increased by 6.5, 5.7, and 1.3% in the 2.5 mg, 20 mg, and placebo groups, respectively (P<0.0001 for each active treatment group vs placebo). At the hip, BMD increased by 3.4, 2.9, and 0.7%, respectively (P<0.0001 for each active treatment group vs placebo).<br><br>Both ibandronate treatment groups demonstrated a significant and sustained reduction in biochemical markers of bone turnover. After three months there was a pronounced reduction in markers of bone resorption (CTX/creatinine and NTX/creatinine) and bone formation (serum osteocalcin and BSAP) in both ibandronate groups vs the placebo group that was sustained for the duration of the study (P<0.0001 for all bone markers after three years). The magnitude of reduction in biochemical markers was similar between the two ibandronate groups.<br><br>After three years of treatment the placebo group sustained a mean stature loss of 5.6 mm, which was significantly greater than the loss |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | seen with 2.5 mg ibandronate (3.9 mm; P=0.0005) or 20 mg ibandronate (4.7 mm; P=0.0144). |
| Delmas et al[35]<br><br>Ibandronate 2 mg IV every 2 months<br><br>vs<br><br>ibandronate 3 mg IV every 3 months<br><br>vs<br><br>ibandronate 2.5 mg QD every 2 months<br><br>vs<br><br>ibandronate 2.5 mg QD every 3 months<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, DD, MC, NI, RCT<br><br>Women 55 to 80 years of age, at least 5 years postmenopausal with osteoporosis (mean lumbar spine [L2-L4] BMD T-score <-2.5, but ≥-5.0) | N=1,395<br><br>2 years<br>(1 year results presented here) | Primary:<br>Mean change from baseline at one year in BMD of at least two vertebrae in lumbar spine (L2-L4) that were not fractured or so affected by degenerative changes that accurate measurement would be jeopardized<br><br>Secondary:<br>Mean change from baseline in BMD of the proximal femur (total hip, femoral neck, hip trochanter) after one year, BMD responder rates, defined as the proportion of patients whose lumbar spine and/or total hip BMD were ≥ baseline measurement, at one year, median change from baseline in serum | Primary:<br>At one year, mean increases in lumbar spine BMD from baseline were similar in the IV every two month group (mean, 5.1%; 95% CI, 4.7 to 5.5) and IV every three month group (mean, 4.8%; 95% CI, 4.5 to 5.2). However, the oral treatment groups did not achieve comparable increases in BMD in comparison to the IV treatment groups (mean, 3.8%; 95% CI, 3.4 to 4.2). The mean treatment differences for change in lumbar spine BMD between IV and oral were 1.31% (95% CI, 0.76 to 1.86) for the every two month group and 1.03% (95% CI, 0.49 to 1.58) for the every three month group. Both IV treatment groups met the pre-defined criteria for NI to the daily oral regimen. Subsequent analysis demonstrated that both IV regimens were statistically "superior" to either of the oral regimens (P<0.001).<br><br>Secondary:<br>At 12 months, the increases in BMD of the proximal femur from baseline were similar in the IV every two month and every three month groups (2.6 and 2.4%, respectively, for total hip; 2.0 and 2.3%, respectively, for femoral neck; and 4.1 and 3.8%, respectively, for trochanter). These increases were significantly greater than those in the oral groups (1.8% for the total hip, 1.6% for the femoral neck, and 3.0% for the trochanter; P<0.05) for all comparisons except the IV every two months vs oral treatment at the femoral neck (P value reported as not significant).<br><br>Responder rates at the lumbar spine were 92.6, 92.1 and 84.9% for the IV every two month, every three month, and daily oral groups respectively (P<0.01 for both comparisons). Significantly more patients in the IV groups were responders at the total hip, 86.4 and 82.3% for the every two months and three months groups, respectively, when compared to the daily oral group (75.1%; P<0.01 for both comparisons). The proportion of responders at the combination of lumbar spine and total hip were also significantly greater in the IV groups, 80.9 and 76.2% in the every two months and every three months groups, respectively, |

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| | | | levels of CTX | when compared to the oral group (67.2%; P<0.01 for both comparisons).<br><br>After one year, the reductions in CTX were similar between all three treatment groups (-64.6%; 95% CI, -67.2 to -62.5 for the IV every two months group; -58.6%; 95% CI, -61.5 to -55.4 for the IV every three months group; -62.6%; 95% CI, -66.0 to -58.9 in the oral group). |
| Eisman et al[36]<br><br>Ibandronate 2 mg IV every 2 months<br><br>vs<br><br>ibandronate 3 mg IV every 3 months<br><br>vs<br><br>ibandronate 2.5 mg QD<br><br>vs<br><br>ibandronate 2.5 mg QD<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, DD, MC, NI, RCT<br><br>Women 55 to 80 years of age, at least 5 years postmenopausal with osteoporosis (mean lumbar spine [L2-L4] BMD T-score <-2.5, but ≥-5.0) | N=1,395<br><br>2 years | Primary:<br>Mean change from baseline in lumbar spine (L2-L4) BMD after one year<br><br>Secondary:<br>Mean change from baseline in lumbar spine (L2-L4) BMD and proximal femur BMD after two years; responder rates (defined as the proportion of patients achieving changes in lumbar spine and/or total hip BMD ≥ baseline at two years); proportion of patients achieving defined increases in lumbar spine (≥6%) or total hip BMD (≥3%); change from baseline in serum CTX | Primary:<br>Results at one year are reported elsewhere (See Delmas et al[42]).<br><br>Secondary:<br>At two years, greater mean increases in lumbar spine BMD were observed in the 2 and 3 mg IV groups (6.4%; 95% CI, 5.9 to 6.9 and 6.3%; 95% CI, 5.7 to 6.8, respectively) than in the 2.5 mg QD group (4.8%; 95% CI, 4.3 to 5.4; P<0.001 for both IV groups). There was no difference between the two IV regimens and each IV group met the pre-specified criteria for NI compared to the QD regimen.<br><br>Increases in proximal femur BMD (total hip, femoral neck, trochanter) were similar in the two IV groups and both groups were "superior" to the 2.5 mg QD group for increases at the total hip and trochanter (P<0.001). The increase in the IV groups at the femoral neck was NI to that achieved in the 2.5 mg QD group.<br><br>A significantly greater proportion of patients in the IV arms were classified as responders when compared to the QD group (P values not reported). More patients in the IV groups also achieved a ≥6% increase in lumbar spine BMD and ≥3% increase in total hip BMD than those patients in the QD group (P values not reported).<br><br>The decreases in serum CTX in all treatment groups observed within three months of treatment initiation were maintained throughout the study. The decreases in serum CTX reported at two years were 55.6, 53.4, and 59.9% in the 2 mg IV, 3 mg IV and 2.5 mg oral daily groups, respectively (P values not reported). |
| McClung et al[37] | DB, MC, PC, RCT | N=160 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Ibandronate 150 mg once monthly<br><br>vs<br><br>placebo<br><br>Patients received daily calcium and vitamin D supplements. | Ambulatory postmenopausal women 45 to 60 years of age with a baseline mean lumbar spine BMD T-score between -1.0 and -2.5 and baseline T-score >-2.5 in: the total hip, trochanter, and femoral neck | 1 year | Relative change from baseline in mean lumbar spine BMD at 12 months, adjusted for baseline lumbar spine BMD and time since menopause<br><br>Secondary: Relative change in mean BMD from baseline at the proximal femur (total hip, trochanter, and femoral neck) at 12 months; relative change in bone resorption marker CTX from baseline at three, six, and 12 months; percent responders at 12 months (defined as participants with BMD ≥ baseline at the lumbar spine, at all three proximal femur sites [total hip, trochanter, femoral neck], or at both the lumbar spine and all three proximal femur locations) | Patients in the ibandronate group demonstrated greater increases in mean lumbar spine BMD from baseline compared to patients in the placebo group. The adjusted relative change in mean lumbar spine BMD from baseline was 3.7% in the ibandronate group and -0.4% in the placebo group, a treatment difference of 4.12% (95% CI, 2.96 to 5.28; P<0.0001).<br><br>Increases in BMD from baseline were seen in all three proximal femur sites in the ibandronate group after one year; 1.49% (95% CI, 0.96 to 2.01) at the total hip, 2.87% (95% CI, 2.12 to 3.62) at the trochanter, and 1.09% (95% CI, 0.45 to 1.73) at the femoral neck. The placebo group demonstrated a decrease in BMD from baseline in all three proximal femur sites after 1 year; -0.93% (95% CI, -1.37 to -0.48) at the total hip, -0.91% (95% CI, -1.62 to -0.20) at the trochanter, and -0.75% (95% CI, -1.65 to 0.14) at the femoral neck.<br><br>CTX decreased from baseline in both treatment groups, with the ibandronate group demonstrating greater reductions vs placebo. At three months CTX had decreased by 56% in the ibandronate group and remained low for months six and 12. For the placebo group, CTX only decreased by approximately -4% at three months, with no appreciable further decreases at months six and 12 (P values not reported).<br><br>At one year, 88.2% of patients in the ibandronate group and 38.6% of patients in the placebo group, were considered responders at the lumbar spine (OR, 12.5; 95% CI, 5.1 to 30.6). After one year, 60.3% of ibandronate patients and 15.5% of placebo patients were considered responders at all three proximal femur sites (OR, 8.6; 95% CI, 3.8 to 19.4). The ibandronate group also had more patients that demonstrated a response at both the lumbar spine and all three proximal femur sites when compared to placebo (54.4 vs 8.5%; OR, 13.8; 95% CI, 5.1 to 36.8). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Kanis et al[38]<br><br>Risedronate 5 mg once daily<br><br>vs<br><br>placebo<br><br>Patients received daily calcium and vitamin D supplements. | DB, MC, PC, RCT, RETRO<br><br>Women aged <85 years of age, at least 5 years postmenopausal with at least 2 prevalent vertebral fractures irrespective of BMD | N=1,802<br><br>3 years | Primary:<br>Incidence of fracture<br><br>Secondary:<br>Vertebral fracture efficacy in patient subgroups categorized according to the presence of risk factors for osteoporosis at baseline | Primary:<br>The overall incidence of fracture was significantly lower in patients receiving risedronate compared to patients receiving placebo (RR, 0.56; 95% CI, 0.44 to 0.72; P<0.001).<br><br>Secondary:<br>Fracture rates were higher in the elderly, aged 70 years or more (RR, 1.67; 95% CI, 1.22 to 2.29; P=0.002) and those with a baseline T-score of ≤–2.5 SD at the lumbar spine (RR, 1.84; 95% CI, 1.19 to 2.85; P=0.006) or femoral neck (RR, 2.47; 95% CI, 1.79 to 3.42; P<0.001). Low weight (RR, 1.66; 95% CI, 1.20 to 2.31; P=0.002) and small stature (RR, 1.74; 95% CI, 1.26 to 2.40; P<0.001) were also risk factors. Other risk factors including smoking, prior nonvertebral fracture, and high biochemical indexes of bone resorption and formation were considered relatively weak risk factors, and did not result in statistical significance (RR,1.23; RR,1.21; RR,1.65; RR,1.21; respectively). |
| Dane et al[39]<br><br>Risedronate sodium 35 mg once weekly<br><br>vs<br><br>placebo<br><br>Patients received daily calcium and vitamin D supplements. | AC, PRO, RCT<br><br>Postmenopausal women (no menstrual bleeding for at least 1 year since the last menstruation) with osteopenia (T-score -1.0 to -2.5 SD) or osteoporosis (T-score ≤2.5 SD) | N=211<br><br>6 months | Primary:<br>Change in CTX from baseline to six months<br><br>Secondary:<br>Incidence of clinical or laboratory adverse events occurring during the six-month study period | Primary:<br>Significant decreases in CTX levels were observed in the osteopenic and osteoporotic treatment groups (those taking risedronate) after six months of treatment when compared to baseline (P<0.001 for both groups). This effect was not found in either the osteopenic or osteoporotic control groups (P=0.14 and P=0.49, respectively). At six months, urinary CTX decreased by -54.7% in the osteoporotic treatment group and increase by 4.8% in the osteoporotic control group (treatment difference, -59.5%; 95% CI, -70.2 to -48.6; P<0.001). At six months, urinary CTX decreased by -66.7% in the osteopenic treatment group and -7.9% in the osteopenic control group (treatment difference, -58.8%; 95% CI, -68.2 to -49.5; P<0.001).<br><br>Secondary:<br>There were no meaningful differences between the active treatment groups and the control groups in adverse events (P values not reported). |
| McClung et al[40]<br><br>Risedronate IR 5 mg | AC, DB, MC, PG, RCT | N=923<br><br>52 weeks | Primary:<br>Mean percent change from | Primary:<br>The mean percent change from baseline in lumbar spine BMD was 3.3% (95% CI, 2.89% to 3.72%) in the once weekly DR group and 3.1% |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| once daily<br><br>vs<br><br>risedronate DR 35 mg once weekly<br><br>Patients also received calcium (1,000 mg/day) and vitamin D (800 to 1000 IU/day) daily. | Postmenopausal women ≥50 years of age with at least three vertebral bodies in lumbar spine for evaluation, and a lumbar spine or total hip BMD corresponding to a T-score of -2.5 or lower or a T-score of -2.0 or lower with at least one prevalent fracture | | baseline in lumbar spine BMD<br><br>Secondary:<br>"Superiority" of risedronate DR compared to IR and change in BMD at lumbar spine, hip, total proximal femur, femoral trochanter and femoral neck | (95% CI, 2.66% to 3.47%) in the IR daily group. The difference between the IR daily group and the DR group was −0.233%, (95% CI, -0.812% to 0.345%), within the upper limit of the CI non-inferiority margin of 1.5%.<br><br>Secondary:<br>There was no statistically significant difference between the risedronate DR weekly group and the IR daily groups with regard to mean percent change from baseline in lumbar spine BMD at any time point.<br><br>Significant increases from baseline in BMD at sites in the hip were observed at 26 and 52 in both treatment groups (P values not reported).<br><br>At week 52, there were no statistically significant differences between the risedronate treatments in BMD at the total proximal femur, femoral trochanter and femoral neck (P values not reported). |
| McClung et al[41]<br><br>Risedronate IR 5 mg once daily<br><br>vs<br><br>risedronate 150 mg once monthly<br><br>Calcium (1,000 mg) and vitamin D (400 to 500 IU/day) were supplied to all subjects, although they were allowed to take up to 1,000 IU/day of vitamin D. | AC, DB, MC, PG, NI, RCT<br><br>Postmenopausal women ≥50 years of age with at least three vertebral bodies in lumbar spine for evaluation and a lumbar spine BMD T-score of -2.5 or lower or a T-score of -2.0 or lower with at least one prevalent fracture | N=1,294<br><br>2 years | Primary:<br>Mean change from baseline in lumbar spine BMD<br><br>Secondary:<br>Percent change from baseline in lumbar spine BMD at months 6 and 24, and at endpoint, the percent change from baseline in BMD of the total proximal femur, femoral neck, and femoral trochanter at months 6, 12, and 24, and at endpoint, the percentage of | Primary:<br>The mean percent changes in lumbar spine BMD were statistically significant in both treatment groups at each time point evaluated. The mean percent change at 24 months was 3.9 % (95% CI, 3.43 to 4.42) for the 5-mg daily group and 4.2 % (95% CI, 3.68 to 4.65) for the 150 mg monthly group. The between-treatment difference in mean percent change in lumbar spine BMD at month 24 was -0.24% (95 % upper confidence bound, 0.25 %), below the 2.0% needed to establish non-inferiority.<br><br>Secondary:<br>There was no statistically significant difference between treatment groups in mean percent change in BMD at the lumbar spine or regions of the proximal femur (total proximal femur, femoral neck and femoral trochanter) at any time point (P values not reported).<br><br>No statistically significant differences were observed between treatment groups with regard to the occurrence of new vertebral fractures (14 subjects [2.5 %] in the 5 mg daily group and 15 subjects [2.6%] in the 150 mg once monthly group). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | patients with new vertebral fractures at one and two years, percent change in biochemical markers of bone turnover at months 3, 6, 12, and 24 and at endpoint | Significant decreases from baseline in NTX/Cr, CTX, and BALP were observed at 3, 6, 12 and 24 months in both treatment groups. Changes from baseline in these biochemical markers were generally similar in both treatment groups. The small difference in CTX between groups was statistically significant at months 3, 6, and 12 but not at month 24 (P values not reported). |
| Ringe et al[42]<br><br>Risedronate 5 mg daily plus daily calcium and vitamin D supplements<br><br>vs<br><br>alfacalcidol 1 µg/day plus daily calcium and vitamin D supplements or daily calcium and vitamin D supplements | OL, PRO, RCT<br><br>Men with primary or secondary osteoporosis, as indicated by a baseline lumbar spine BMD T-score ≤-2.5 and a baseline femoral neck BMD T-score ≤2.0 | N=316<br><br>2 years | Primary:<br>Incidence of new vertebral fractures and changes in BMD at the lumbar spine, femoral neck, and total hip<br><br>Secondary:<br>Change in body height; change in back pain; incidence of non-vertebral fractures | Primary:<br>At year two the incidence of new vertebral fractures in the risedronate group was significantly lower than the incidence in the control group (9.2 vs 23.6%; P=0.0026). Risedronate reduced vertebral fractures by 61% over two years (P value not reported). Significant improvements were also seen in BMD at all three skeletal sites (lumbar spine, femoral neck, and total hip) compared to control (P<0.001 for all three locations). Mean lumbar spine BMD increased 6.5% in the risedronate group compared to 2.2% in the control group (P<0.001). In the control group mean total hip BMD did not increase between years one and two (P value not reported).<br><br>Secondary:<br>Average height loss at year two was significantly lower in the risedronate group compared to the control group (-0.35 vs -0.85 cm; P<0.0001).<br><br>At year two the back pain scores were significantly lower in the risedronate group compared to those in the control group, indicating the risedronate patients experienced less back pain (0.56 vs 1.09; P<0.0001).<br><br>At year two the risedronate group had a significantly lower incidence of nonvertebral fractures compared to the control group (11.8 vs 22.3%; P=0.032). Risedronate reduced nonvertebral fractures by 45.0% over two years (P value not reported). |
| Rosen et al[43] | AC, DB, MC, RCT | N=1,-35 | Primary:<br>Mean percent | Primary:<br>A significantly greater increase in hip trochanter BMD was observed at |

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| Alendronate 70 mg once weekly<br><br>vs<br><br>risedronate 35 mg once weekly<br><br>All patients were instructed to take 1,000 mg of elemental calcium and 400 IU of vitamin D daily. | Postmenopausal (≥6 months) women ≥40 years of age (≥25 years if surgically menopausal) who had a BMD of ≥2.0 SD below young normal mean bone mass in at least one of four sites (total hip, hip trochanter, femoral neck, or postero-anterior lumbar spine (L1 to L4]) | 1 year | change from baseline in hip trochanter BMD at 12 months<br><br>Secondary:<br>Mean percent change from baseline in total hip, femoral neck, and lumbar spine BMD at 12 months, mean percent change in all BMD endpoints, biochemical markers of bone turnover (NTx, CTx, BSALP, and P1NP) at 3, 6 and 12 months | 12 months with alendronate compared with risedronate (3.4 vs 2.1%; P<0.001). More rapid gains in BMD were seen with alendronate compared to risedronate as the difference in hip trochanter BMD was significant as early as month six (treatment difference, 1.3%; 95% CI, 0.8 to 1.8; P<0.001).<br><br>Secondary:<br>At 12 months, a significantly greater increase in BMD occurred among patients treated with alendronate compared to risedronate at the total hip (2.2 vs 1.2%, P<0.001), femoral neck (1.6 vs 0.9%; P=0.005]), and lumbar spine (3.7 vs 2.6%; P<0.001). Significant differences between treatment groups were observed as early as six months at the total hip (P<0.001]), femoral neck (P=0.035) and lumbar spine (P=0.002).<br><br>The reduction in bone turnover at 12 months was significantly greater (P<0.001) with alendronate compared to risedronate for all biochemical markers.<br><br>At 12 months, urinary NTx decreased by -52.8% in the alendronate group and -40.3% in the risedronate group (P<0.001). Serum CTx decreased by -73.8% in the alendronate group and -54.7% in the risedronate group (P<0.001); serum BSALP decreased by -40.6% in the alendronate group and -28.1% in the risedronate group (P<0.001]); and serum P1NP decreased by -63.9% in the alendronate group and -48.0% in the risedronate group (P<0.001). Reductions in biochemical markers of bone turnover were significantly reduced in both treatment group at both three and six months of treatment (P<0.001 for both). |
| Reid et al[44]<br><br>Alendronic acid 70 mg once weekly<br><br>vs<br><br>risedronic acid 35 mg | AC, DB, MC, RCT<br><br>Ambulatory, community dwelling women ≥40 years of age, at least 6 months postmenopausal with | N=936<br><br>12 months | Primary:<br>Percentage change from baseline in hip trochanter BMD at 12 months<br><br>Secondary:<br>Percentage change | Primary:<br>Mean percentage increases from baseline in hip trochanter BMD were significant (P≤0.001) at 12 months for both treatment groups; 3.56 and 2.71% in the alendronic acid and risedronic acid groups, respectively (treatment difference, 0.83%; 95% CI, 0.22 to 1.45; P=0.008).<br><br>Secondary:<br>Mean percentage increases in BMD at the lumbar spine, total hip and |

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| once weekly<br><br>Patients received daily calcium and vitamin D supplements. | a BMD ≥2.0 SD below young normal mean BMD in at least 1 of 4 sites (total hip, hip trochanter, femoral neck, or lumbar spine) | | from baseline in lumbar spine, total hip and femoral neck BMD at 12 months, biochemical markers of bone turnover (NTX, CTX, BSAP, P1NP) at three, six, and 12 months, safety and tolerability, including an assessment of upper gastrointestinal adverse events | femoral neck, at 12 months, were greater in the alendronic acid group in comparison to the risedronic acid group. Mean differences in BMD between alendronic acid and risedronic acid at 12 months were 0.75% (95% CI, 0.28 to 1.23; P=0.002) at the lumbar spine, 0.68% (95% CI, 0.30 to 1.06; P<0.001) at the total hip, and 0.56% (95% CI, 0.03 to 1.09; P=0.039) at the femoral neck.<br><br>Both treatment groups resulted in significant reductions in all four markers of bone turnover at month 12 (P<0.001). The alendronic acid group resulted in greater decreases in all four markers of bone turnover in comparison to the risedronic acid group at month 12 (P<0.001).<br><br>The proportion of patients with a serious adverse event was significantly lower in the alendronic acid group vs the risedronic acid group (5.1 vs 10.0%; P=0.006). Upper gastrointestinal adverse event profiles were not significantly different between the treatment groups. |
| Reid et al[45]<br><br>Alendronate 70 mg once weekly<br><br>vs<br><br>risedronate 35 mg once weekly<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, ES, MC, RCT<br><br>Ambulatory, community dwelling women ≥40 years of age at least 6 months postmenopausal with a BMD ≥2.0 SD below young normal mean BMD in at least 1 of 4 sites (total hip, hip trochanter, femoral neck, or lumbar spine) | N=798<br><br>24 months (extension of Reid et al[22]) | Primary:<br>Percentage change from baseline in hip trochanter BMD at 24 months<br><br>Secondary:<br>Percentage change from baseline in lumbar spine, total hip and femoral neck BMD at 24 months; proportion of patients with increases of hip trochanter and lumbar spine BMD ≥ 0 and ≥3% from baseline to 24 | Primary:<br>Increases from baseline in hip trochanter BMD at month 24 were significantly greater in patients treated with alendronate than patients treated with risedronate (5.2 vs 3.7%; P≤0.001). Increases in both treatment groups compared to baseline were significant (P value not reported).<br><br>Secondary:<br>Mean percentage increases in BMD at the lumbar spine, total hip and femoral neck, at 24 months, were greater in the alendronate group in comparison to the risedronate group (6.0 vs 4.2%; P≤0.001; 3.7 vs 2.4%; P≤0.001; and 3.2 vs 2.3%; P=0.002, respectively).<br><br>At 24 months, the proportion of patients with ≥0% increase in BMD was significantly greater in the risedronate group compared to the alendronate group at the hip trochanter (89 vs 79%; P≤0.001), total hip (91 vs 79%; P≤0.001), femoral neck (81 vs 71%; P=0.002), and the lumbar spine (95 vs 85%; P≤0.001). Similarly, alendronate resulted in a significantly greater proportion of patients achieving ≥3% increase in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | months; biochemical markers of bone turnover (NTX, CTX, BSAP, P1NP) at 24 months | BMD at 24 months compared to risedronate at the hip trochanter (70 vs 53%; P≤0.001), total hip (62 vs 42%; P≤0.001), femoral neck (52 vs 39%; P=0.001), and the lumbar spine (77 vs 61%; P≤0.001).<br><br>Both treatment groups significantly reduced bone resorption markers (urine NTX and serum CTX) from baseline to 24 months. Patients in the alendronate group demonstrated a significantly greater decrease in NTX (58.2 vs 45.0%; P<0.001) and CTX (69.3 vs 44.0%; P<0.001) compared to risedronate starting at three months and maintained at 24 months. Alendronate also resulted in significantly greater decreases in bone formation markers BSAP (45.1 vs 36.2%; P<0.001) and P1NP (66.4 vs 51.6%; P<0.001) than risedronate starting at 3 months and maintained at 24 months. |
| Bonnick et al[46]<br><br>Alendronate 70 mg once weekly<br><br>vs<br><br>risedronate 35 mg once weekly<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, ES, MC, RCT<br><br>Women aged ≥40 years at least 6 months postmenopausal with a BMD ≥2.0 SD below young normal mean bone density in at least 1 of 4 sites (total hip, hip trochanter, femoral neck, or lumbar spine) | N=833<br><br>24 months | Primary:<br>Mean percentage change from baseline in trochanteric BMD at 24 months<br><br>Secondary:<br>Mean percentage change from baseline in total hip, femoral neck, and lumbar spine BMD at 24 months between groups, mean percentage change from baseline in biochemical markers of bone turnover (NTX, CTX, BSAP, and P1NP) | Primary:<br>The alendronate group had significantly greater increases in trochanteric BMD at 24 months compared to the risedronate group (treatment difference, 2.1%; 95% CI, 1.4 to 2.8; P<0.001).<br><br>Secondary:<br>Increases in BMD from baseline at all time points were significant in both treatment groups. However, increases in BMD at all sites were greater in the alendronate group vs the risedronate group. At 24 months, the treatment difference was 1.7% (95% CI, 1.3 to 2.2) at the total hip, 1.9% (95% CI, 1.2 to 2.5) at the femoral neck, and 1.8% (95% CI, 1.2 to 2.5) at the lumbar spine (P<0.001).<br><br>Alendronate and risedronate both resulted in a significant decrease in bone resorption, measured by serum NTX and CTX. Alendronate reduced NTX and CTX by 56.6 and 73.4%, respectively, at 24 months. Risedronate reduced NTX and CTX by 43.9 and 53.1%, respectively, at 24 months. Alendronate achieved a significantly greater reduction starting at three months, with significance maintained at 24 months (P<0.001). Alendronate resulted in a significantly greater reduction in BSAP and P1NP compared to risedronate at 24 months (-62 vs -46%; P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Miller at al[47]<br><br>Ibandronate 150 mg once monthly<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>Patients received daily calcium and vitamin D supplements. | AC, DB, DD, MC, NI, PG, RCT<br><br>Postmenopausal (≥5 years since menopause) women 55 to 84 with mean lumbar spine (L2-L4) BMD T-score <-2.5 and ≥-5 | N=1,760<br><br>12 months | Primary:<br>Relative change from baseline in mean BMD of the lumbar spine and total hip at 12 months<br><br>Secondary:<br>Mean change from baseline at 12 months in trochanter and femoral neck BMD | Primary:<br>After 12 months, the relative changes in mean lumbar spine BMD were 5.1 and 5.8% for ibandronate and alendronate, respectively (for between group difference; 95% CI, -1.13 to -0.23; P values not reported). The mean relative changes in total hip BMD were 2.9 and 3.0%, for ibandronate and alendronate, respectively (for between group difference; 95% CI, -0.38 to 0.18; P values not reported).<br><br>Secondary:<br>After 12 months, both the ibandronate and alendronate group demonstrated a 4.2% gain in trochanter BMD (P values not reported). For femoral neck BMD, the ibandronate group increased by 2.1% at 12 months, the alendronate group by 2.3% (P values not reported). |
| Li et al[48]<br><br>Ibandronate 2 mg injection every 3 months<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>Patients received daily calcium and vitamin D supplements. | OL, RCT<br><br>Patients with postmenopausal osteoporosis | N=158<br><br>3 months | Primary:<br>Change in baseline BMD<br><br>Secondary:<br>Change in baseline BTMs, safety | Primary:<br>Both treatments significantly increased BMD at the lumbar spine (4.27 and 4.24%), femoral neck (3.48 and 2.72%), and trochanter (2.03 and 2.99%) (P<0.001 for all), with no differences between the two treatments at six and 12 months (P>0.05 for all).<br><br>Secondary:<br>SCTX (-80.6 and -43.2%) and alkaline phosphate (-19.5 and -16.4%) decreased with both treatments. Decreases in alkaline phosphate were similar with both treatments, and ibandronate significantly decreased SCTX compared to alendronate at six and 12 months (P<0.001).<br><br>New fractures occurred in two patients; one with alendronate and one with ibandronate. No serious adverse events were observed. Muscle pain and flu-like illness was more common with ibandronate, especially within two to three days after the infusion. The number of patients with symptoms after subsequent infusions decreased substantially with ibandronate. No cases of acute renal failure were reported. |
| Harris et al[49]<br><br>Ibandronate 150 mg once | OS, RETRO<br><br>Women ≥45 years of | N=64,182<br><br>Up to 1 year | Primary:<br>Relative risks of vertebral fracture, | Primary:<br>Ibandronate patients demonstrated a significantly lower risk of vertebral fractures compared to weekly bisphosphonate patients (adjusted RR, |

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| monthly<br><br>vs<br><br>alendronate 35 mg once weekly<br><br>or<br><br>alendronate 70 mg once weekly<br><br>or<br><br>risedronate 35 mg once weekly | age, newly prescribed monthly ibandronate or weekly bisphosphonates between April 1, 2005 and December 31, 2005 with continuous eligibility in the selected health plan | | hip fracture, nonvertebral fracture and any clinical fracture in treatment-adherent patients<br><br>Secondary:<br>Relative risks of vertebral fracture, hip fracture, nonvertebral fracture and any clinical fracture in patients regardless of adherence | 0.36; 95% CI, 0.18 to 0.75; P=0.006). Risks of hip fracture (adjusted RR, 1.06; 95% CI, 0.61 to 1.83; P=0.84), nonvertebral fracture (adjusted RR, 0.88; 95% CI, 0.71 to 1.09, P=0.255) and any clinical fracture (adjusted RR, 0.82; 95% CI, 0.66 to 1; P=0.052) were numerically similar and not significantly different between the two treatment groups.<br><br>Secondary:<br>There was no significant difference in risk of vertebral fractures (adjusted RR, 0.86; 95% CI, 0.62 to 1.19; P=0.361), hip fractures (adjusted RR, 1.03; 95% CI, 0.70 to 1.51; P=0.884), nonvertebral fractures (adjusted RR, 1.01; 95% CI, 0.87 to 1.17; P=0.904), or any clinical fractures (adjusted RR, 0.98; 95% CI, 0.86 to 1.12; P=0.807) in the ibandronate group compared to the weekly bisphosphonate group when adherence was not considered. |
| Delmas et al[50]<br><br>Risedronate 75 mg QD on two consecutive days per month<br><br>vs<br><br>risedronate 5 mg QD | AC, DB, MC, NI, PG, RCT<br><br>Women at least 50 years of age who were at least 5 years postmenopausal with osteoporosis (lumbar spine T-score <2.5 SD below mean value in normal young women, and <2.0 SD below the mean value in normal young women for subjects having at least one prevalent vertebral fracture) | N=1,231<br><br>1 year | Primary:<br>Percent change from baseline in lumbar spine BMD at month 12<br><br>Secondary:<br>Mean percent change from baseline in lumbar spine and hip BMD and the incidence of new vertebral fractures | Primary:<br>The mean change in lumbar spine BMD from baseline to month 12 was similar for both treatment groups, 3.4 and 3.6% for the two consecutive days per month and 5 mg daily groups, respectively (LSM difference, 0.2; 95% CI, -0.19 to 0.62). For both treatment groups, within-group changes from baseline to month 12 were statistically significant (P values not reported).<br><br>Secondary:<br>There were no statistically significant differences between treatment groups in the mean change in hip BMD with the exception of a small difference in femoral neck BMD at month 12 (LSM difference, -0.5; 95% CI, -0.88 to -0.04). The incidence of new vertebral fractures was infrequent and similar between the two groups, 1.14 and 1.33% for the two consecutive days per month and 5 mg daily groups, respectively (P=1.0). |
| Sarioglu et al[51] | RCT, SB | N=50 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Risedronate 5 mg QD plus 1,000 mg calcium and 400 IU vitamin D daily<br><br>vs<br><br>alendronate sodium 70 mg once weekly plus 1,000 mg calcium and 400 IU vitamin D daily | Postmenopausal women with osteoporosis under the age of 75 | 12 months | Change in BMD and BTMs<br><br>Secondary:<br>Not reported | At six months, risedronate resulted in increases in BMD compared to baseline at the spine, femoral neck, trochanter, and Ward's triangle (2.1%; P<0.05; 0.9%; P value not significant; 2.1%; P<0.05; 3.6%; P<0.01, respectively). At 12 months, risedronate resulted in significant increases in BMD compared to base line at the spine, femoral neck, trochanter, and Ward's triangle (3.0, 3.7, 4.5, 4.4%, respectively; P<0.01 for all sites). At six months, alendronate resulted in increases in BMD compared to baseline at the spine, femoral neck, trochanter, and Ward's triangle (0.8%; P value not significant; 2.3%; P<0.05; 3.0%; P<0.01; 3.0%; P<0.01, respectively). At 12 months, alendronate resulted in increases in BMD compared to base line at the spine, femoral neck, trochanter, and Ward's triangle (0.4%; P value not significant; 2.6%; P<0.05; 6.4%; P<0.001; 4.5%; P<0.05, respectively). However, the difference in percentage increases between both groups at six and 12 months was not statistically significant (P value reported as not significant).<br><br>Changes in serum osteocalcin, BSAP, and urine deoxypyridinoline showed significantly reduction starting at month three and persisting through month 12 (P<0.05). However, there was no statistically significant difference between the two groups (P value not reported).<br><br>Secondary:<br>Not reported |
| Silverman et al[52]<br><br>Risedronate 35 mg once weekly<br><br>vs<br><br>alendronate 35 or 70 mg once weekly | CO, RETRO<br><br>Women ≥65 years of age with any use of once weekly dosing of risedronate or once weekly dosing of alendronate | N=33,830<br><br>Up to 1 year | Primary:<br>Incidence of nonvertebral fractures collectively (hip, wrist, humerus, clavicle, pelvis, leg) and subjects with a hip fracture, both at six and 12 months<br><br>Secondary: | Primary:<br>A total of 507 patients had nonvertebral fractures during the 12-month observational period after starting bisphosphonate therapy: of this, 30% were in the wrist, 21% in the hip, 17% in the leg, 15% in the pelvis, 14% in the humerus and 3% in the clavicle. The fracture incidence was similar between both treatment groups over the first three months of therapy. However at six months, the risedronate group had a 19% lower incidence of nonvertebral fracture than the alendronate group (95% CI, 0 to 35; P=0.05). At 12 months, the risedronate also had an 18% lower incidence of nonvertebral fractures compared to alendronate (95% CI, 2 to 32; P=0.03). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | Not reported | During the first three months of therapy, the incidence of hip fractures was similar between groups. At six months, the risedronate group had a 46% lower incidence of hip fracture compared to the alendronate group (95% CI, 9 to 68; P=0.02). The risedronate group also had a 43% lower incidence of hip fractures at 12 months compared to alendronate (95% CI, 13 to 63; P=0.01).<br><br>Secondary:<br>Not reported |
| McClung et al[53]<br><br>Zoledronic acid 5 mg IV one time<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>All patients received daily supplementation with by mouth calcium (1,000 mg) and vitamin D (400 IU). | AC, DB, DD, MC, NI RCT<br><br>Women 45 to 79 years of age who were postmenopausal (cessation of menses for 18 months in those <50 years of age or for 12 months in those ≥50 years; or documented bilateral oophorectomy at least 1 year previously) and were previously treated with alendronate for at least 1 year immediately prior to randomization and had a T-score ≤-2.0 at the lumbar spine or femoral neck prior to initiation of | N=225<br><br>12 months | Primary:<br>Percent change from baseline at 12 months in lumbar spine BMD<br><br>Secondary:<br>Relative change from baseline at months three, six, nine, and 12 in BTM (NTX, β-CTX, BSAP, P1NP), patient preference for treatment regimen | Primary:<br>At 12 months, both the zoledronic acid group and the alendronate group had comparable increases in the lumbar spine BMD (0.167 vs 0.813%, respectively, mean difference, -0.646%; 95% CI, -1.400 to 0.108; P value not reported). Zoledronic acid met the predefined criteria (lower bound of 95% CI for the difference in percent change from baseline between the two groups >1.5%) for NI compared to the weekly alendronate group.<br><br>Secondary:<br>In the zoledronic acid group BTM levels were significantly reduced from baseline after three months, returned to baseline after six months, and increased to values within the premenopausal reference range thereafter. At month 12, NTX and β-CTX increased by 16 and 15%, respectively, in the zoledronic acid group, and decreased by 3 and 18%, respectively, in the alendronate group. P1NP and BSAP increased by 39 and 15%, respectively, in the zoledronic acid group, and decreased by 14 and 1%, respectively, in the alendronate group.<br><br>Two hundred and twenty one patients completed the preference survey. It was found that, overall, 78.7% of patients preferred the once-yearly infusion regimen, 9.0% of patients preferred the once-weekly capsule regimen, and 11.8% of patients considered the treatments equal (P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | alendronate therapy | | | |
| Saag et al[54]<br><br>Zoledronic acid 5 mg IV one time<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>All patients received daily supplementation with by mouth calcium (1,000 mg) and vitamin D (400 IU). | AC, DB, DD, MC, RCT<br><br>Postmenopausal women 45 to 79 years of age with BMD T-scores ≤-2 at lumbar spine or femoral neck no more than 3 months prior to screening | N=128<br><br>24 weeks | Primary:<br>Relative change from baseline in urine NTX at week one (defined as $\log_c$ ratio of post-baseline measurement divided by baseline measurement)<br><br>Secondary:<br>Relative change in urine NTX (at weeks two, four, eight, 12, and 24) and serum β-CTX (weeks one, two, four, eight, 12, and 24), patient preference for treatment regimen | Primary:<br>At week one, the zoledronic acid group had a significantly lower mean urine NTX than the alendronate group (15.2 vs 35.5 nmol BCE/mmol creatinine, respectively; P<0.0001).<br><br>Secondary:<br>Zoledronic acid had a significantly lower mean urine NTX value throughout the 24-weeks when compared to the alendronate group (P<0.0001 at weeks two, four, and eight; P<0.05 at weeks 12 and 24). The nadir, in urine NTX, was reached after one week with zoledronic acid and after 12 weeks with alendronate, with both groups beginning to show an increase in levels after that point. Zoledronic acid resulted in significantly greater reduction in serum β-CTX when compared to alendronate (P<0.0001 at weeks two, four, eight, and 12; P<0.01 at week 24).<br><br>It was found that, overall, 66.4% of patients preferred the once-yearly infusion regimen, 19.7% of patients preferred the once-weekly capsule regimen, and 13.9% of patients considered the treatments to be equal (P value not reported). |
| Lewiecki et al[55]<br><br>Denosumab 6, 14, and 30 mg SC every 3 months<br><br>vs<br><br>denosumab 14, 60, 100, and 210 mg SC every 6 months<br><br>vs | AC, DB, DR, ES, MC, PC, RCT<br><br>Postmenopausal women up to 80 years of age with BMD T-score of -1.8 to -4.0 at the lumbar spine or -1.8 to -3.5 at the femoral neck or total hip | N=412<br><br>12 months (24 months total duration) | Primary:<br>Efficacy, safety<br><br>Secondary:<br>Not reported | Primary:<br>Denosumab was associated with significant increases in BMD compared to placebo. At the lumbar spine, BMD increases ranged from 4.13 to 8.89% compared to -1.18% with placebo (P<0.001 for all). The changes in BMD at the lumbar spine for all denosumab doses were significantly greater compared to placebo (P<0.001) from month three to month 24. At 24 months, all doses of denosumab were associated with significant increases compared to placebo (P<0.001 for all) for BMD at the total hip, distal 1/3 radius, and total body.<br><br>At 24 months, alendronate also significantly increased BMD at the lumbar spine (P<0.001), total hip (P<0.001), distal 1/3 radius (P=0.009), and total body (P<0.001) compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| placebo<br><br>vs<br><br>alendronate 70 mg once weekly (OL) | | | | With denosumab, BMD significantly increased from 12 to 24 months by 2.75±0.66% at the lumbar spine (P<0.001), 1.50±0.47% at the total hip (P=0.001), and 2.23±0.69% at the femoral neck (P=0.001), with changes of 0.52±0.67% at the distal 1/3 radius (P=0.440) and 0.20±0.60% at the total body (P=0.737).<br><br>During the second year of treatment, denosumab maintained decreases in SCTX and UNTX compared to placebo. Significant (P<0.001 for all) decreases relative to placebo were observed for all doses, except denosumab 14 mg every six months, for which values approached baseline levels at the time-points just before the next denosumab dose.<br><br>Decreases in bone alkaline phosphate during the second year of treatment with denosumab remained consistent compared to the first year, and significantly greater compared to placebo (P≤0.002). Alendronate also maintained sustained decrease in BTMs during the second year of treatment.<br><br>The proportion of patients who experienced adverse events over two years was generally similar among placebo, denosumab, and alendronate groups. Upper respiratory tract infection was the most common adverse event with denosumab (placebo, 17.4%; denosumab, 24.2%; alendronate, 23.9%). Other adverse events that occurred with >20% frequency with any treatment was arthralgia, dyspepsia, and nausea. Six cases of serious adverse events of infections associated with hospitalization were observed with denosumab. One death, caused by gastric cancer, occurred in the denosumab 100 mg every six months cohort. Clinical fractures occurred in 1/46 (2.2%), 21/314 (6.7%) and 2/46 (4.3%) patients receiving placebo, denosumab, and alendronate, respectively. Osteoporotic fractures occurred in 0/46 (0%), 12/314 (3.8%) and 2/46 (4.3%) patients, respectively.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Brown et al[56]<br><br>Denosumab 60 mg SC every 6 months<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>All patients were instructed to receive daily calcium and vitamin D supplementation. | AC, DB, DD, MC, NI, PG, RCT<br><br>Ambulatory postmenopausal women in general good health, BMD T-score ≤-2.0 at the proximal femur or lumbar spine by DXA, and with ≥1 hip and ≥2 vertebrae that were evaluable by DXA | N=1,189<br><br>12 months | Primary:<br>Change in baseline total hip BMD<br><br>Secondary:<br>Change in baseline femoral neck, trochanter, lumbar spine, and 1/3 radius BMD; change in baseline SCTX and P1NP | Primary:<br>The change in BMD at the total hip was 3.5% with denosumab compared to 2.6% with alendronate (P<0.0001), for a treatment difference of 1.0% (95% CI, 0.7 to 1.2) at month 12.<br><br>Secondary:<br>Because NI for the primary efficacy endpoint was met, the secondary endpoints were inferentially evaluated.<br><br>Prespecified “superiority” testing demonstrated significantly greater increases in BMD with denosumab compared to alendronate at the total hip (data not reported), trochanter (4.5 vs 3.4%; P<0.0001), and distal 1/3 radius (1.1 vs 0.6%; P=0.0001). “Superiority” testing at the femoral neck (2.4 vs 1.8%; P=0.0001) and lumbar spine (5.3 vs 4.2%; P<0.0001) also demonstrated greater increases in BMD with denosumab compared to alendronate.<br><br>With denosumab, SCTX decreases were rapid with maximal decreases observed at one month (-89%) and significantly greater decreases compared to alendronate (-61%; P<0.0001). At three months, decreases were significantly greater with denosumab compared to alendronate (-89 vs -66%, respectively; P<0.0001). At six months, SCTX decreases approached that of alendronate, although the treatment difference remained significant (-77 vs -73%, respectively; P=0.0001). At nine months a decrease was again observed with denosumab (-89 vs -76%; P<0.0001). At 12 months the decreases were similar with both treatments (-74 vs -76%; P=0.52).<br><br>With denosumab, significantly greater decreases in P1NP were achieved compared to alendronate at all time points (P<0.0001). At one month, P1NP decreased by -26% with denosumab compared to -11% with alendronate. Maximal decreases in P1NP were observed with denosumab by three months (-76 vs -56%), and was maintained through 12 months (-72 vs -65%). For alendronate, the maximal decrease was observed at nine months (-65% for alendronate vs -78% for |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | denosumab). |
| Finkelstein et al[57]<br><br>Teriparatide 40 µg SC QD, initiated at month 6 and continued for 24 months<br><br>vs<br><br>alendronate 10 mg QD for 30 months<br><br>vs<br><br>alendronate 10 mg QD plus teriparatide 40 µg SC QD<br><br>All patients received daily calcium and vitamin D supplements. | PG, RCT<br><br>Men 46 to 85 years of age with low BMD at the lumbar spine or femoral neck that was ≥2 SD below the mean value for young normal men | N=83<br><br>30 months | Primary:<br>Change in baseline posteroanterior lumbar spine BMD<br><br>Secondary:<br>Change in baseline lateral spine, proximal femur, and radial shaft BMD; change in baseline total body BMD; serum alkaline phosphate; safety | Primary:<br>There was a significantly greater increase in BMD at the posteroanterior spine with teriparatide compared to alendronate and combination therapy (P<0.001 for both). The BMD at the posteroanterior spine significantly increased more with combination therapy compared to alendronate (P<0.001).<br><br>Secondary:<br>There was a significantly greater increase in BMD at the lateral spine with teriparatide compared to alendronate and combination therapy (P<0.001 for both). The BMD at the lateral spine significantly increased more with combination therapy compared to alendronate (P=0.02).<br><br>The BMD at the femoral neck significantly increased with teriparatide compared to alendronate (P<0.001) and combination therapy (P=0.01). There was no difference between alendronate and combination therapy (P=0.18).<br><br>The BMD at the radial shaft decreased slightly with teriparatide and increased slightly with alendronate and combination therapy (P=0.002 teriparatide vs alendronate; P=0.009 teriparatide vs combination therapy).<br><br>There were no differences among treatments in the changes in total body BMD (P=0.60 for the three-way comparison).<br><br>At 12 months, changes in serum alkaline phosphate were significantly greater with teriparatide compared to alendronate or combination therapy (P<0.001 for both comparisons).<br><br>The differences among the three treatments in the incidence of side effects were generally small. |
| Finkelstein et al[58] | PG, RCT | N=83 | Primary:<br>Change in baseline | Primary:<br>With teriparatide N-telopeptide, osteocalcin, and P1NP reached peak |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Teriparatide 40 µg SC QD, initiated at month 6 and continued for 24 months<br><br>vs<br><br>alendronate 10 mg QD for 30 months<br><br>vs<br><br>alendronate 10 mg QD plus teriparatide 40 µg SC QD<br><br>All patients received daily calcium and vitamin D supplements. | Men 46 to 85 years of age with low BMD of the lumbar spine or femoral neck that was ≥2 SD below the mean value for young normal men | 30 months | N-telopeptide, osteocalcin and P1NP<br><br>Secondary:<br>Not reported | values by month 12 and then declined toward baseline during the next 18 months.<br><br>With alendronate osteocalcin and P1NP decreased from baseline through month six, at which point both remained stable. However, the N-telopeptide reached its nadir within one to two months.<br><br>With combination therapy BTM levels declined in the first six months (while receiving alendronate alone) and then returned to baseline levels (N-telopeptide) or above (osteocalcin and P1NP) after teriparatide was added.<br><br>Changes in each marker were significantly different between teriparatide and alendronate (P<0.001 for all), teriparatide and combination therapy (P<0.03 for all), and alendronate and combination therapy (P<0.001 for all).<br><br>Secondary:<br>Not reported |
| Saag et al[59]<br><br>Teriparatide 20 µg SC QD<br><br>vs<br><br>alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | DB, MC, RCT<br><br>Patients 22 to 89 years of age with osteoporosis who had received glucocorticoids for ≥3 months (prednisone equivalent ≥5 mg/day) | N=428<br><br>18 months | Primary:<br>Change in baseline lumbar spine BMD<br><br>Secondary:<br>Change in baseline total hip BMD and BTMs, time to changes in BMD, incidence of vertebral and non-vertebral fractures, safety | Primary:<br>BMD at the lumbar spine significantly increased with teriparatide compared to alendronate (7.2 vs 3.4%; P<0.001). A significant difference between the groups was reached by six months (P<0.001).<br><br>Secondary:<br>At 12 months, BMD at the total hip significantly increased with teriparatide compared to alendronate (P<0.01). At 18 months, the change was 3.8 and 2.4% with teriparatide and alendronate (P=0.005).<br><br>With teriparatide, P1NP and SCTX were increased at one month and peaked at six months. With alendronate, these markers decreased at one month and remained suppressed at 18 months (P<0.001 for all comparisons between treatments at months one, six, and 18).<br><br>Markers of bone formation (SCTX and bone alkaline phosphate) |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | significantly increased with teriparatide and decreased with alendronate (no additional data reported).<br><br>Fewer new vertebral fractures occurred with teriparatide compared to alendronate (0.6 vs 6.1%, respectively; P=0.004). The incidence of non-vertebral fractures was similar between the two treatments (5.6 vs 3.7%, respectively; P=0.36).<br><br>Safety profiles were similar between the two treatments, with no significant differences in the overall incidence of adverse events (85 vs 79%; P=0.11) or the incidence of serious adverse events (21 vs 18%; P=0.44). There were some differences in specific adverse events between the two treatments with more patients receiving teriparatide experiencing nausea (P=0.02), gastritis (P=0.06), insomnia (P=0.01), injection site reactions (P=0.09), and at least one elevated calcium (P<0.001) and urate level (P=0.18). More patients receiving alendronate reported dyspepsia (P=0.07), and rash (P=0.05). |
| Saag et al[60]<br><br>Teriparatide 20 µg SC QD<br><br>vs<br><br>alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | ES of Saag et al[51]<br><br>Patients 22 to 89 years of age with osteoporosis who had received glucocorticoids for ≥3 months (prednisone equivalent ≥5 mg/day) | N=241<br><br>36 months | Primary:<br>Change in baseline BMD and BTMs, incidence of vertebral and non-vertebral fractures, safety<br><br>Secondary:<br>Not reported | Primary:<br>At 36 months, teriparatide significantly increased BMD at the lumbar spine (11.0 vs 5.3%), total hip (5.2 vs 2.7%), and femoral neck (6.3 vs 3.4%) compared to alendronate (P<0.001 for all).<br><br>With teriparatide, increases in P1NP and osteocalcin were significant from one to 36 months (P<0.01), and increases in SCTX were significant from one to six months (P<0.01). With alendronate, decreases in P1NP, osteocalcin, and SCTX were significant by six months and remained below baseline through 36 months (P<0.001)<br><br>Significantly fewer patients receiving teriparatide had vertebral fractures compared to patients receiving alendronate (1.7 vs 7.7%; P=0.007), with most occurring within the first 18 months. There was no difference in the incidence of non-vertebral fractures between the two treatments (7.5 vs 7.0%; P=0.843).<br><br>Significantly more patients receiving teriparatide had elevated pre-dose |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | serum calcium concentrations (21 vs 7%; P<0.001).<br><br>Secondary:<br>Not reported |
| Langdahl et al[61]<br><br>Teriparatide 20 µg SC QD<br><br>vs<br><br>alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | Pos-hoc analysis of Saag et al[51]<br><br>Patients 22 to 89 years of age with osteoporosis who had received glucocorticoids for ≥3 months (prednisone equivalent of ≥5 mg/day) | N=428<br><br>18 months | Primary:<br>Change in baseline lumbar spine BMD by gender and menopausal status<br><br>Secondary:<br>Change in baseline total hip BMD, incidence of vertebral and non-vertebral fractures, safety | Primary:<br>At 18 months, increases in BMD at the lumbar spine were significantly greater with teriparatide compared to alendronate in postmenopausal women (7.8 vs 3.7%; P<0.001), premenopausal women (7.0 vs 0.7%; P<0.001), and men (7.3 vs 3.7%; P=0.03). In postmenopausal and premenopausal women, the change in BMD at the lumbar spine was also significantly greater with teriparatide compared to alendronate after six and 12 months (P<0.05 for all).<br><br>Secondary:<br>At the total hip, there were numerically greater increases in BMD at all measured time points with teriparatide compared to alendronate in postmenopausal women, premenopausal women and men. The differences between the two treatments reached significance in premenopausal women (12 months; P<0.001 and 18 months; P<0.01).<br><br>Radiographic vertebral fractures occurred in one teriparatide- (one postmenopausal, zero men) and 10 alendronate-treated patients (six postmenopausal, four men) (P=0.05 for both). Non-vertebral fractures occurred in 12 teriparatide- (nine postmenopausal, two premenopausal, one man) and eight alendronate-treated patients (six postmenopausal, zero premenopausal, two men) (P values not significant).<br><br>The proportions of patients reporting adverse events with teriparatide and alendronate were consistent across subgroups. |
| Body et al[62]<br><br>Teriparatide 40 µg SC QD<br><br>vs | DB, MC, PG, RCT<br><br>Postmenopausal women with osteoporosis | N=146<br><br>14 months (median) | Primary:<br>Change in baseline lumbar spine BMD<br><br>Secondary:<br>Change in baseline | Primary:<br>Teriparatide significantly increased BMD at the lumbar spine compared to alendronate at all time points. The increase at three months was 2.7% greater with teriparatide compared to alendronate (P<0.001). The difference in BMD increase between the treatments was 5.4% at six months and 8.3% at 12 months (P<0.001). Teriparatide increased BMD |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | | | femoral neck and total hip BMD, change in baseline total body BMD, incidence of new non-vertebral fractures, safety | at the lumbar spine by 5.2% at three months, whereas alendronate required 12 months to increase lumbar spine BMD by 5.9%.<br><br>Secondary:<br>Compared to alendronate, teriparatide significantly increased BMD at the femoral neck (P≤0.001) and total hip (P≤0.05), and total body BMD (P≤0.05), but BMD at the distal radius significantly decreased (P≤0.001).<br><br>The incidence of non-vertebral fractures was significantly lower with teriparatide compared to alendronate (P<0.05).<br><br>Both treatments were well tolerated despite transient mild asymptomatic hypercalcemia with teriparatide. |
| McClung et al[63]<br><br>Teriparatide 20 µg SC QD<br><br>vs<br><br>alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | DB, MC, PG, RCT<br><br>Postmenopausal women with osteoporosis | N=203<br><br>18 months | Primary:<br>Change in baseline areal and volumetric lumbar spine and total hip BMD, change in baseline BTMs, safety<br><br>Secondary:<br>Not reported | Primary:<br>At 18 months, areal and volumetric BMD at the lumbar spine were significantly higher with teriparatide compared to alendronate (10.3 vs 5.5%; P<0.001 and 19.0 vs 3.8%; P<0.01, respectively). Areal BMD at the femoral neck significantly increased with both treatments (3.9 vs 3.5%, respectively). There was no difference in trabecular BMD at the femoral neck between the two treatments (4.9 and 2.2%, respectively). Cortical volumetric BMD at the femoral neck was significantly different between teriparatide and alendronate (-1.2 and 7.7%, respectively; P=0.05).<br><br>Teriparatide significantly increased BTM that peaked at six months (P1NP increased by 218%, and N-telopeptide increased by 58%; P<0.001); whereas, alendronate significantly decreased BTMs at six months (-67 and -72%, respectively; P<0.001). The different effects of both agents on bone remodeling were evident after one month of treatment, with significant differences between the two for each marker at one, three, six, and 12 months (P<0.001).<br><br>Secondary:<br>Not reported |
| Downs et al[64] | MC, PC, PRO, RCT | N=299 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Calcitonin 200 IU/day nasal spray<br><br>vs<br><br>alendronate 10 mg/day<br><br>vs<br><br>placebo<br><br>All patients received daily calcium and vitamin D supplements. | Women ≥5 years postmenopause with osteoporosis | 1 year | Change in baseline lumbar spine BMD<br><br>Secondary:<br>Change in baseline femoral neck and hip trochanter BMD, and BTMs | Alendronate significantly increased BMD at the lumbar spine compared to calcitonin (5.16 vs 1.18%; P<0.001). There was no difference between calcitonin and placebo (P value not reported).<br><br>Secondary:<br>Alendronate significantly increased BMD at the femoral neck (2.78 vs 0.58%; P<0.001) and hip trochanter (4.73 vs 0.47%; P<0.001) compared to calcitonin.<br><br>Calcitonin significantly increased BMD at the femoral neck at months six and 12 compared to placebo (P<0.0.01), but there was no difference at hip trochanter (P value not reported).<br><br>Significantly greater decreases in BTMs were observed with alendronate compared to calcitonin (serum bone alkaline phosphate, -43 vs -9%; P<0.001; N-telopeptide, -62 vs -11%; P<0.001). No differences were observed between calcitonin and placebo (P values not reported).<br><br>The incidences of adverse events were similar among the treatments. |
| Recker et al[65]<br><br>Raloxifene 60 mg QD<br><br>vs<br><br>alendronate 10 mg QD<br><br>All patients received daily calcium and vitamin D supplements. | DB, MC, RCT<br><br>Postmenopausal women BMD T-score -2.5 and -4.0 at the femoral neck, no prevalent vertebral fractures, and no prior bone-active agent use | N=1,412<br><br>312 days (mean duration; trial was planned for 5 years but stopped early due to difficulty in recruiting treatment-naïve women) | Primary:<br>Incidence of ≥1 new osteoporotic vertebral or non-vertebral fracture<br><br>Secondary:<br>Change in baseline BMD, incidence of newly diagnosed breast cancer, safety | Primary:<br>There was no difference in the number of patients experiencing at least one new osteoporotic vertebral or non-vertebral fracture between raloxifene and alendronate (2.9 vs 3.1%; P value not reported).<br><br>No patients receiving raloxifene and four receiving alendronate had moderate-to-severe vertebral fractures (P=0.04).<br><br>Secondary:<br>BMD at the lumbar spine, femoral neck, and total hip were significantly increased after two years (P<0.001), with significantly greater increases with alendronate at all sites compared to raloxifene (P<0.05 for all).<br><br>There was no difference in the number of patients who had at least one adverse event and discontinued treatment due to an adverse event between the two treatments. The only adverse events with an incidence |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | that differed between the two treatments were colonoscopy, diarrhea, and nausea, which were all more common with alendronate (P<0.05 for all). There was one case of a venous thromboembolism event and breast cancer reported with each treatment. |
| Sanad et al (abstract)[66]<br><br>Raloxifene 60 mg QD<br><br>vs<br><br>alendronate 70 mg once weekly<br><br>vs<br><br>raloxifene 60 mg QD plus alendronate 70 mg once weekly | DB, RCT<br><br>Postmenopausal women with osteoporosis | N=135<br><br>12 months | Primary:<br>Change in baseline BMD, BTMs, and lipid profiles; safety<br><br>Secondary:<br>Not reported | Primary:<br>BMD at the lumbar spine, femoral neck, and total hip significantly increased with all treatments; however, increases were significantly greater with combination therapy compared to raloxifene or alendronate therapy (P<0.0001 for both).<br><br>Decreases in N-telopeptide and bone alkaline phosphate with combination therapy and alendronate therapy were significantly greater compared to raloxifene therapy (P<0.0001).<br><br>Significant decreases in TC and LDL-C, and a significant increase in HDL-C occurred with raloxifene and combination therapy, but not with alendronate therapy (P values not reported).<br><br>There were no significant differences in the incidence of adverse events between the three treatments.<br><br>Secondary:<br>Not reported |
| Lee et al[67]<br><br>Ibandronate 150 mg once monthly<br><br>vs<br><br>placebo, alendronate 70 once weekly, or ibandronate 2.5 mg QD | MA, SR (8 RCTs)<br><br>Patients with postmenopausal osteoporosis | N=not reported<br><br>6 to 24 months (follow-up) | Primary:<br>Change in baseline BMD, safety<br><br>Secondary:<br>Not reported | Primary:<br>Ibandronate 150 mg once monthly vs placebo<br>Ibandronate significantly increased BMD at the lumbar spine after one year compared to placebo (3.7 vs -0.4%; P<0.0001). Another trial revealed ibandronate significantly increased BMD at the total hip and lumbar spine after one year (difference, 2.2%; P=0.005; difference, 4.3%; P<0.001). Ibandronate significantly increased BMD at the lumbar spine compared to placebo (WMD, 4.054; 95% CI, 1.987 to 6.121; P=0.0001).<br><br>Ibandronate 150 mg once monthly vs alendronate 70 mg once weekly<br>One trial revealed ibandronate was clinically comparable to alendronate |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | and increased BMD at lumbar spine and total hip at 12 months. Changes were 5.1 to 5.5% at the lumbar spine and 2.9 and 3.0% at total hip, respectively. Another trial, revealed comparable efficacy of ibandronate in terms of BMD response. The proportion of patients with BMD at lumbar spine and total hip were 90 and 87% with ibandronate and 92 and 90% with alendronate. No significant differences were observed between the two treatments in terms of side effects such as gastrointestinal adverse events, number of withdrawals, and withdrawals due to adverse events.<br><br>Ibandronate 150 mg once monthly vs ibandronate 2.5 mg QD<br>Significant increases in BMD at the lumbar spine were achieved with both treatments (6.6 and 5.0%; P<0.001 for both), with ibandronate 150 mg once monthly achieving significantly greater increases in BMD at the total hip, femoral neck, and trochanter (P<0.05). A similar proportion of patients withdrew from treatment between the two treatments. The incidences of adverse events, drug-related adverse events, and drug-related adverse events leading to withdrawal were similar between the two treatments.<br><br>Secondary:<br>Not reported |
| Lin et al[68]<br><br>Denosumab 60 mg SC every six months<br><br>vs<br><br>alendronate 70 mg once weekly | MA (4 DB, PC, RCTs)<br><br>Postmenopausal women with low bone mass | N=1,942<br><br>Duration varied | Primary:<br>Incidence of fracture, change in baseline BMD, safety<br><br>Secondary:<br>Not reported | Primary:<br>No significant difference in fracture risk was demonstrated between denosumab and alendronate after one year (OR, 1.42; 95% CI, 0.84 to 2.40; P=0.19).<br><br>Both treatments significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after six months of treatment. Denosumab could obtain greater bone mass increment compared to alendronate.<br><br>Denosumab and alendronate had similar safety profiles after one year. There was no difference between the treatments with regards to total adverse events (OR, 0.91; 95% CI, 0.72 to 1.15; P=0.66), serious |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | adverse events (OR, 0.91; 95% CI, 0.63 to 1.33; P=0.65), neoplasms (OR, 1.10; 95% CI, 0.65 to 1.86; P=0.62), and infections (OR, 0.95; 95% CI, 0.79 to 1.15; P=0.62).<br><br>Secondary:<br>Not reported |
| Recknor et al[69]<br><br>Denosumab 60 mg SC every six months<br><br>vs<br><br>ibandronate 150 mg orally monthly<br><br>All women received 500 mg calcium and 800 IU (or more) vitamin D QD | RCT, OL, PG, MC<br><br>Postmenopausal women with low bone density who have been treated previously with oral bisphosphonate therapy | N=833<br><br>1 year | Primary:<br>Percentage change from baseline in total hip BMD at month 12<br><br>Secondary:<br>Percentage change from baseline in femoral neck and lumbar spine BMD at month 12, safety | Primary:<br>The mean percentage change from baseline in total hip BMD was 2.3% (95% CI, 2.0 to 2.5) in denosumab-treated women and it was 1.1% (95% CI, 0.9 to 1.4) in ibandronate-treated women, resulting in a treatment difference of 1.1% (95% CI 0.8 to 1.5, P<0.001) at month 12.<br><br>Secondary:<br>There was a significant increase from baseline in BMD with denosumab compared with ibandronate at the femoral neck (1.7% compared to 0.7%; treatment difference 1.0%; P<0.001) and lumbar spine (4.1% compared to 2.0%; treatment difference 2.1%; P<0.001).<br><br>At month 12, a greater number of women treated with denosumab compared with ibandronate had BMD gains that were met or exceeded the least significant change at the total hip (49% compared to 30%; P<0.001), femoral neck (26% compared to 14%; P<0.001), and lumbar spine (65% compared to 41%; P<0.001).<br><br>A total of 245 women (59.6%) in the denosumab group and 230 women (56.1%) in the ibandronate group experienced one or more adverse event during the study (P=0.635). |
| Guanabens et al[70]<br><br>150 mg oral ibandronate monthly<br><br>vs<br><br>70 mg oral alendronate | RCT, OL, SC<br><br>Postmenopausal women with a diagnosis of primary biliary cirrhosis and osteoporosis (BMD T-score of ≤-2.5) or | N=42<br><br>2 years | Primary:<br>Efficacy at the lumbar spine, femoral neck, and hip; adherence; adverse events<br><br>Secondary: | Primary:<br>After 24 months, both monthly ibandronate and weekly alendronate were associated with a significant relative increase in BMD at the lumbar spine from 0.899±0.02 to 0.949±0.03 g/cm$^2$ (P<0.001) with ibandronate and from 0.875±0.02 to 0.913±0.03 g/cm$^2$ (P<0.001) with alendronate.<br><br>At the femoral neck, BMD increased by 1.2% and 2.7% in the ibandronate and alendronate groups, respectively (P=not significant). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| weekly<br><br>All patients received 1,000 mg calcium per day, 266 µg 25(OH)D every two weeks, and 14 to 16 mg/kg/day of ursodeoxycholic acid | osteopenia (BMD T-score between -1 and -2.5) and at least one fragility fracture | | Not reported | A greater increase in total hip BMD from baseline was observed among patients treated with alendronate, with changes from 0.805 ± 0.02 to 0.822±0.02 g/cm$^2$ (P=0.04) compared to those treated with ibandronate; although, the percentage change was not significantly different between the groups (2.0% and 1.2%, P=not significant).<br><br>There were no significant differences in the magnitude of the decreases for changes in bone turnover markers between the groups at any time point.<br><br>When comparing adherence to ibandronate and alendronate treatment, the Morisky-Green scale showed a significantly higher adherence to Ibandronate than alendronate (P=0.009).<br><br>The overall incidence of adverse events was similar in both treatment groups.<br><br>Secondary:<br>Not reported |
| McClung et al[71]<br><br>Risedronate 150 mg once monthly<br><br>vs<br><br>risedronate 5 mg QD | RCT, DB, MC, AC<br><br>Women ≥50 years of age with postmenopausal osteoporosis who are ambulatory | N=1292<br><br>2 years | Primary:<br>Mean percent change from baseline in lumbar spine BMD after one year<br><br>Secondary:<br>BMD at the hip, bone turnover markers, new vertebral fractures, and adverse events | Primary:<br>The mean percent change in lumbar spine BMD was 3.9% (95 % CI, 3.43% to 4.42%) and 4.2% (95% CI, 3.68% to 4.65%) in the daily and once-a-month groups, respectively. The once monthly regimen was determined to be non-inferior to the daily regimen.<br><br>Secondary:<br>The mean percent changes in BMD at the hip were similar in both dose groups, as were changes in biochemical markers of bone turnover. The incidence of adverse events, adverse events leading to withdrawal, and upper gastrointestinal tract adverse events were similar in the two treatment groups. |
| McClung et al[72] | RCT, DB, AC, PG, MC | N=922 | Primary:<br>Mean percent | Primary:<br>All three treatment groups experienced significant improvements from |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Risedronate 5 mg immediate release QD<br><br>vs<br><br>risedronate 35 mg delayed release once weekly before breakfast<br><br>vs<br><br>risedronate 35 mg delayed release once weekly following breakfast | Postmenopausal women ≥50 years of age who had osteoporosis and were ambulatory | 2 years | change from baseline in lumbar spine BMD after 52 weeks<br><br>Secondary:<br>Changes in BMD at the lumbar spine and regions of the proximal femur, changes in biochemical markers of bone turnover, and incidence of morphometric vertebral fractures at week 104 | baseline in lumbar spine BMD after one year of treatment<br><br>Secondary:<br>The least squares mean percent change from baseline in lumbar spine BMD at week 104 was 5.5% (95% CI, 5.0% to 6.0 %) in the delayed release following breakfast weekly group, 5.4% (95% CI, 4.9% to 5.9%) in the delayed release before breakfast weekly group, and 4.4% (95% CI, 3.8% to 4.9%) in the immediate release group. The least squares mean difference between the delayed release following breakfast group and the immediate release group was −1.15 (95% CI, −1.9 to −0.4), and the least squares mean difference between the delayed release before breakfast group and the immediate release group was −1.04 (95% CI, −1.8 to −0.3).<br><br>Progressive increases in BMD at proximal femur sites (total hip, femoral neck, and femoral trochanter) were observed during the second year of the study. Significant increases from baseline were observed at all-time points in all treatment groups (no P-values given). Both delayed release groups showed greater increases compare to the immediate release daily group at the femoral trochanter at week 104 and endpoint and at the total hip at week 104 (least squares mean difference of delayed release following breakfast group vs immediate release group at week 104=-0.64 (95% CI, −1.18 to −0.11). The response in the total hip was also greater at endpoint with the 35-mg delayed release following breakfast dose and at the femoral neck at week 104 and endpoint with the 35-mg delayed release before breakfast dose compared to the 5-mg immediate release dose.<br><br>Significant decreases from baseline in NTX/creatinine, CTX, and BAP were observed at all-time points in all treatment groups. The decreases in CTX in both delayed release groups were statistically greater than with the 5-mg immediate release dose at week 104 and endpoint. The changes in NTX/creatinine or BAP were not significantly different among treatment groups at the end of year 2. No differences were observed in any BMD or bone turnover marker (BTM) response between both of the |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | delayed release regimens at any time point.<br><br>New incident morphometric vertebral fractures occurred in five subjects in the immediate release daily group, two subjects in the delayed release following breakfast weekly group, and six subjects in the delayed release before breakfast weekly group (not statistically significant between delayed release and immediate release groups).<br><br>Overall, the adverse event profile was similar across the three treatment groups. The incidence of upper and lower gastrointestinal adverse events was similar across groups. However, the incidence of events related to upper abdominal pain was higher in the delayed release before breakfast group than in the other two groups; most of these events were judged to be mild or moderate. |
| **Treatment of Paget's Disease** | | | | |
| Khairi et al (abstract)[73]<br><br>Etidronate 5, 10, or 20 mg/kg/day | OS, PRO<br><br>Patients with symptomatic Paget's disease | N=109<br><br>6 to 24 months | Primary:<br>Not reported<br><br>Secondary:<br>Not reported | Primary:<br>Not reported<br><br>Secondary:<br>Not reported<br><br>Significant decreases in serum alkaline phosphatase and urinary hydroxyproline were noted after six months of therapy. There was no significant further improvement after this time point.<br><br>Some patients maintained biochemical remission after withdrawal of etidronate, while others experienced a relapse, related primarily to the pretreatment severity.<br><br>Clinical improvement was noted in 61% of the patients.<br><br>Similar findings were seen after a second course of etidronate.<br><br>No adverse events were reported with 5 mg/kg/day, and patients receiving 10 or 20 mg/kg/day reported severe diarrhea (n=3), bone pain |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | (n=13), and nontraumatic fractures (n=12).<br><br>Quantitative histomorphometry demonstrated mineralization delay in patients receiving 10 or 20 mg/kg/day, but not in patients receiving 5 mg/kg/day.<br><br>Etidronate 5 mg/kg/day was effective and appears to be safer than higher doses. |
| Siris et al[74]<br><br>Etidronate 400 mg/day<br><br>vs<br><br>alendronate 40 mg/day | DB, RCT<br><br>Patients with active Paget's disease | N=89<br><br>6 months | Primary:<br>Change in baseline serum alkaline phosphatase and urinary deoxypyridinoline excretion<br><br>Secondary:<br>Pain, functional impairment scores, and radiological osteolysis; safety | Primary:<br>Alendronate significantly reduced serum alkaline phosphatase (79 vs 44%) and urinary deoxypyridinoline (75 vs 51%) compared to etidronate (P<0.001 for both).<br><br>Normalization of serum alkaline phosphatase was significantly more frequent with alendronate (63.4 vs 17.0%; P<0.001).<br><br>Secondary:<br>With alendronate the mean change in pain scores decreased from baseline by 0.67 after six months (P value not significant). With etidronate, the scores increased by 0.21 by month six (P value not significant). There was no difference between the two treatments (P=0.07).<br><br>The findings from the analysis of the functional impairment scores were similar to those observed with pain intensity scores.<br><br>With regards to radiological osteolysis, 32.4% of patients receiving alendronate showed improvement compared to 8.8% of patients who showed worsening of osteolytic lesions. The corresponding proportions with etidronate were 26.5 and 14.7%, respectively. There was no difference between the two treatments (P value not reported).<br><br>Alendronate was well tolerated and had a safety profile similar to that of etidronate. The most commonly reported adverse events were abdominal pain, nausea, back pain, and leg pain. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Miller et al[75]<br><br>Etidronate 400 mg/day for 6 months<br><br>vs<br><br>risedronate 30 mg/day for 2 months | MC, RCT<br><br>Patients 18 to 85 years of age with radiographically or scintigraphically documented Paget's disease and serum alkaline phosphatase ≥2 times the upper limit of normal | N=123<br><br>12 to 18 months | Primary:<br>Change in baseline serum alkaline phosphatase<br><br>Secondary:<br>Change in baseline serum bone specific alkaline phosphatase and urinary deoxypyridinoline, pain, safety | Primary:<br>Both treatments significantly reduced serum alkaline phosphatase from baseline (P<0.01); however, the response with risedronate was significantly greater compared to etidronate (P<0.001).<br><br>By month 12, biochemical remission was achieved in 73 and 15% of patients receiving risedronate and etidronate (P<0.001). The median time to normalization was significantly shorter with risedronate (P<0.001). Patients receiving risedronate were less likely to relapse compared to patients receiving etidronate (P<0.05). By month 18, 53 and 14% of patients with available data had serum alkaline phosphatase that remained within the normal range with risedronate and etidronate (P value not reported).<br><br>Secondary:<br>The differences between treatments in normalization of serum bone-specific alkaline phosphatase and urinary deoxypyridinoline creatinine concentrations were consistent with those for serum alkaline phosphatase.<br><br>A significant improvement in pain from baseline was achieved with risedronate (P<0.01), but not etidronate and differences between the two treatments were not significant (P values not reported).<br><br>Adverse events with a possible relation to the study drug were recorded in 47% of patients receiving either treatment. Upper gastrointestinal adverse events were recorded in 20% of patients receiving either treatment. No cases of esophagitis were reported. Eight and six percent of patients receiving etidronate and risedronate withdrew from the trial due to an adverse event. |
| Reid et al[76]<br><br>Zoledronic acid 5 mg IV one time | AC, DB, MC, RCT<br><br>Pooled analysis of two identical studies; men and women >30 | N=357<br><br>6 months | Primary:<br>Proportion of patients who had a therapeutic response (defined | Primary:<br>Serum alkaline phosphatase demonstrated a greater, and more rapid, reduction in the zoledronic acid group compared to the risedronate group. The rates of normalization of alkaline phosphatase levels also differed significantly between groups (P<0.001) at all times from one |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>risedronate 30 mg QD for 60 days<br><br>All patients received 1,000 mg calcium and 400 to 1,000 IU vitamin D daily. | years of age with radiologically confirmed Paget's disease of bone | | as normalization of alkaline phosphatase level or reduction of at least 75% in alkaline phosphatase excess at six months)<br><br>Secondary:<br>Biochemical markers of bone resorption (serum levels of βCTX and the ratio of urinary αCTX to creatinine), biochemical markers of bone formation (serum levels of P1NP), and quality of life (measured by the Medical Outcomes Study SF-36 General Health Survey) | month onward. As a result, the rates of therapeutic response, at six months, in the zoledronic acid group was significantly greater than the risedronate group (96.0 vs 74.3%, respectively; P<0.001). The median time to the first therapeutic response in the zoledronic acid group was 64 and 89 days in the risedronate group (P<0.001).<br><br>Secondary:<br>Zoledronic acid resulted in a significantly greater reduction of bone resorption (as measured with β-CTX and ratio of urinary αCTX to creatinine) compared to risedronate at all time points (P<0.001 at all time points).<br><br>Serum levels of P1NP demonstrated a pattern similar to that seen with alkaline phosphatase but with a greater response (P<0.001 at all time points).<br><br>The zoledronic acid group demonstrated significant improvement over baseline scores on the physical-component summary of the SF-36, at both three and six months, when compared to risedronate (P<0.05). |

*Agent not available in the United States.
Drug regimen abbreviations: IU=international units, IV=intravenous, QD=once-daily, SC=subcutaneous
Study design abbreviations: AC=active control, BA=Bayesian analysis, CI=confidence interval, CO=cohort, CRI=credibility interval, DB=double-blind, DD=double-dummy, DR=dose ranging, ES=extension study, HR=hazard-ratio, LSM=least squares mean, MA=meta-analysis, MC=multicenter, NI=noninferiority, OC=open-controlled, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PR=partially randomized, PRO=prospective, RCT=randomized controlled trial, Retro=retrospective, RR=relative risk, SA=single administration, SB=single blinded, SC=single center, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: 25(OH)D=25-hydroxyvitamin D, β-CTX=C-telopeptide of type I collagen, BMD=bone mineral density, BSAP/BSALP=bone-specific alkaline phosphatase, BTM=bone turnover marker, CTX=C-telopeptide, DXA=dual energy X-ray absorptiometry, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, NTX=N-telopeptide of type I human collagen, phosphatase, P1NP=N-terminal propeptide of type 1 procollagen, SCTX=serum type-1 collagen cross-linked C-telopeptide, SF-36=Short Form-36, UNTX=urinary type-1 collagen cross-linked N-telopeptide corrected for creatinine

## Special Populations

**Table 5. Special Populations**[4-12]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| **Single-Entity Agents** | | | | | |
| Alendronate | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required.<br><br>Not recommended with creatinine clearances <35 mL/minute. | No dosage adjustment required. | C | Unknown; use with caution. |
| Etidronate | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | No dosage adjustment required. | C | Unknown; use with caution. |
| Ibandronate | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required with mild or moderate renal dysfunction.<br><br>Not recommended with creatinine clearances <30 mL/minute. | No dosage adjustment required. | C | Unknown; use with caution. |
| Risedronate | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required.<br><br>Not recommended with creatinine clearances <30 mL/minute. | No dosage adjustment required. | C | Unknown; use with caution. |
| **Combination Products** | | | | | |
| Alendronate/ cholecalciferol | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. | No dosage adjustment required.<br><br>Not | No dosage adjustment required. | C | Yes; use with caution. |

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | Safety and efficacy in children have not been established. | recommended with creatinine clearances <35 mL/minute. | | | |

## Adverse Drug Events

**Table 6. Adverse Drug Events (%)**[4-12]

| Adverse Events | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate* | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| **Cardiovascular** | | | | | |
| Chest pain | - | - | - | 5 | - |
| Dependent edema | - | - | - | - | - |
| Hypertension | - | - | 6.3 to 7.3 | 10.5 | - |
| **Gastrointestinal** | | | | | |
| Abdominal pain | 0.9 to 6.6 | - | 5.3 to 7.8 | 2.9 to 12.2 | 1.5 to 6.6 |
| Constipation | 0.3 to 3.1 | - | 2.5 to 4.1 | 4.9 to 12.9 | 0.8 to 3.1 |
| Diarrhea | 0.6 to 3.1 | 0.07 to 0.30 | 2.4 to 6.8 | 8.8 to 10.8 | 0.6 to 3.1 |
| Dry mouth | - | - | - | | - |
| Dyspepsia | 1.1 to 3.6 | - | 4.3 to 11.9 | 3.9 to 10.8 | - |
| Exacerbation of existing peptic ulcer disease | - | ✔ | - | - | - |
| Flatulence | - | - | - | - | - |
| Gastritis | - | - | - | - | - |
| Nausea | 0.6 to 3.6 | 0.07 to 0.30 | 4.3 to 5.1 | 3.6 to 10.5 | 0.6 to 3.6 |
| Vomiting | 0.2 to 1.0 | - | 2.7 | 4.9 | - |
| **Metabolic and Nutritional Disorders** | | | | | |
| Hypocalcemia | - | - | - | - | 18 |
| Peripheral edema | - | - | - | 7.7 | - |
| Vitamin D deficiency | - | - | - | - | - |
| **Musculoskeletal** | | | | | |
| Arthralgia | - | ✔ | 3.5 to 8.6 | 6.8 to 23.7 | - |
| Arthritis | - | ✔ | 3.2 | 9.6 | - |
| Arthrosis | - | - | - | - | - |
| Bone fracture | - | ✔ | - | - | - |
| Back pain | - | - | 4.3 to 13.5 | 6.8 to 28 | - |
| Bone pain | - | ✔ | - | 5.3 | - |
| Fracture | - | - | - | - | - |
| Joint disorder | - | - | 3.6 | 7 | - |
| Muscle spasm | - | - | - | 1 | - |
| Musculoskeletal pain | 0.4 to 4.1 | - | 0.8 to 5.7 | 2.0 to 6.7 | 0.4 to 4.1 |
| Neck pain | - | - | - | - | - |

| Adverse Events | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate* | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| Osteomalacia | - | ✔ | - | - | - |
| Pain | - | - | - | - | - |
| Pain in extremity | - | - | 1.3 to 7.8 | 3.9 | - |
| Shoulder pain | - | - | - | - | - |
| **Nervous System/Psychiatric** | | | | | |
| Amnesia | - | ✔ | - | - | - |
| Anorexia | - | - | - | - | - |
| Anxiety | - | - | - | - | - |
| Asthenia | - | - | 3.5 | 5.4 | - |
| Chills | - | - | - | - | - |
| Confusion | - | ✔ | - | - | - |
| Depression | - | ✔ | 2.2 | 6.8 | - |
| Dizziness | - | - | 1.0 to 3.7 | 2.6 to 7.1 | - |
| Fatigue | - | - | 1.1 | - | - |
| Hallucination | - | ✔ | - | - | - |
| Headache | 0.2 to 2.6 | - | 2.6 to 6.5 | 2.6 to 9.9 | 2.6 |
| Hypoesthesia | - | - | - | - | - |
| Insomnia | - | - | 0.8 to 2.6 | 5 | - |
| Involuntary muscle contractions | - | - | - | - | - |
| Nervousness | - | - | - | - | - |
| Pain | - | - | - | 14.1 | - |
| Paresthesias | - | ✔ | - | - | - |
| Somnolence | - | - | - | - | - |
| Vertigo | - | - | - | - | - |
| **Respiratory** | | | | | |
| Bronchitis | - | - | 2.5 to 10.0 | 3.9 to 10.0 | - |
| Coughing | - | - | - | - | - |
| Dyspnea | - | - | - | - | - |
| Exacerbation of asthma | - | ✔ | - | - | - |
| Increased cough | - | - | - | 5.9 | - |
| Nasopharyngitis | - | - | 3.5 to 6.0 | - | - |
| Pharyngitis | - | - | 2.5 | 6 | - |
| Pneumonia | - | - | 5.9 | - | - |
| Rhinitis | - | - | - | 6.2 | - |
| Sinusitis | - | - | - | 8.7 | - |
| Upper respiratory tract infection | - | - | - | 3.6 | - |
| **Urogenital** | | | | | |
| Urinary tract infection | - | - | 1.8 to 5.5 | 11.1 | - |
| **Other** | | | | | |
| Accidental injury | - | - | - | - | - |
| Acute phase infection | - | - | - | 1.3 to 2.3 | - |
| Agranulocytosis | - | ✔ | - | - | - |
| Alopecia | - | ✔ | - | - | - |

| Adverse Events | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate* | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| Anemia | - | - | - | - | - |
| Cataract | - | - | - | - | - |
| Conjunctivitis | - | - | - | - | - |
| Esophagitis | - | ✔ | - | - | - |
| Fatigue | - | - | - | - | - |
| Flushing | - | - | - | - | - |
| Glaucoma | - | - | - | - | - |
| Glossitis | - | ✔ | - | - | - |
| Hyperparathyroidism | - | - | - | - | - |
| Hypersensitivity reactions | - | ✔ | - | - | - |
| Increased sweating | - | - | - | - | - |
| Infection | - | - | 4.3 | 31.1 | - |
| Influenza | - | - | 3.8 to 8.0 | 7.2 | - |
| Influenza-like illness | - | - | 0.8 to 3.3 | 10.5 | - |
| Lethargy | - | - | - | - | - |
| Leukopenia | - | ✔ | - | - | - |
| Malaise | - | - | - | - | - |
| Pancytopenia | - | ✔ | - | - | - |
| Pruritus | - | - | - | - | - |
| Pyrexia | - | - | - | - | - |
| Rash | - | - | 1.3 to 2.8 | 7.9 | - |
| Rigors | - | - | - | - | - |
| Skin disorder | - | - | - | - | - |
| Syncope | - | - | - | - | - |
| Tooth disorder | - | - | - | - | - |
| Urinary tract infection | - | - | - | - | - |

*The safety of Binosto® effervescent tablet 70 mg is based on clinical trial data of alendronate 10 mg daily tablet and 70 mg weekly tablet.
✔ Incidence not specified.
- Event not reported.

## Contraindications

**Table 7. Contraindications**[4-12]

| Contraindication | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| Abnormalities of the esophagus that delay esophageal emptying, such as stricture or achalasia | ✔ | ✔ | ✔ | ✔ | ✔ |
| Clinically overt osteomalacia | - | ✔ | - | - | - |
| Hypersensitivity to any component of | ✔ | ✔ | ✔ | ✔ | ✔ |

| Contraindication | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| this product | | | | | |
| Hypocalcemia | ✔ | - | ✔ | ✔ | ✔ |
| Inability to stand or sit upright for at least 30 minutes | ✔ | - | - | ✔ | ✔ |
| Inability to stand or sit upright for at least 60 minutes | | | ✔ | | |
| Increased risk of aspiration | ✔ (effervescent tablet, oral solution) | - | - | - | - |

**Warnings/Precautions**

**Table 8. Warnings and Precautions**[4-12]

| Warning/Precaution | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| Abnormalities in renal function following intravenous infusion | - | ✔ | - | - | - |
| Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate treatment | ✔ | - | ✔ | ✔ | ✔ |
| Bone turnover suppressed and mineralization slowed | - | ✔ | - | - | - |
| Enterocolitis and diarrhea may occur with higher doses | - | ✔ | - | - | - |
| Glucocorticoid-induced osteoporosis | ✔ (Fosamax®) | - | - | ✔ | - |
| Hyperphosphatemia may occur as a result of drug-related increases in tubular absorption of phosphate | - | ✔ | - | - | - |
| Hypocalcemia or other disorders affecting mineral metabolism must be | ✔ | - | ✔ | ✔ | ✔ |

| Warning/Precaution | Single-Entity Agents | | | | Combination Products |
|---|---|---|---|---|---|
| | Alendronate | Etidronate | Ibandronate | Risedronate | Alendronate/ Cholecalciferol |
| corrected prior to initiation of therapy | | | | | |
| Laboratory test interactions; bisphosphonates interfere with the use of bone-imaging agents | - | - | - | ✔ | - |
| Maintain calcium and vitamin D intake to maintain adequate nutritional status | - | ✔ | - | - | - |
| Musculoskeletal pain has been reported in post-marketing studies of patients taking this medication | ✔ | ✔ | ✔ | ✔ | ✔ |
| Osteomalacia/Bone fracture | - | ✔ | - | - | - |
| Osteonecrosis of the jaw may occur spontaneously but is generally associated with tooth extraction and/or local infection with delayed healing | ✔ | ✔ | ✔ | ✔ | ✔ |
| Paget disease; response to therapy may be of slow onset and continue for months after discontinuation of therapy | - | ✔ | - | - | - |
| Patients sensitive to high sodium intake should use caution when taking this medication | ✔ (Binosto®) | - | - | - | - |
| Renal impairment; not recommended for use in patients with a creatinine clearance of <35 (or 30) mL/min | ✔ | - | ✔ | ✔ | ✔ |
| Upper gastrointestinal adverse reaction | ✔ | ✔ | ✔ | ✔ | ✔ |

**Drug Interactions**

**Table 9. Drug Interactions**[4-12,77]

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Bisphosphonates (all) | Calcium, aluminum, magnesium and any other multivalent cations | Absorption of bisphosphonates may be decreased by the concomitant administration of multivalent cations. Consider modifying the dosing regimen. |
| Bisphosphonates (all) | Nonsteroidal anti-inflammatory drugs | Concomitant administration of nonsteroidal anti-inflammatory drugs with bisphosphonates may increase the risk of gastric ulceration. |

## Dosage and Administration

All bisphosphonates should be taken upon arising for the day when the stomach is empty and absorption will not be affected by food, beverages, or medications. Alendronate, risedronate, and combination products should be taken at least 30 minutes prior the ingestion of the first food, beverage, or medication of the day. However, ibandronate should be taken at least 60 minutes prior to the ingestion of any food, beverage, or medication. All patients should not lie down for at least 30 minutes when taking alendronate, risedronate or combination products and at least 60 minutes for oral ibandronate. All bisphosphonates should be taken with a full glass of water to help facilitate delivery to the stomach and reduce the potential for esophageal irritation.[4-12]

**Table 10. Dosing and Administration**[4-12]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| **Single-Entity Agents** | | | |
| Alendronate | Prevention of osteoporosis in postmenopausal women:<br>Tablet: 5 mg QD or 35 mg once weekly<br><br>Treatment of glucocorticoid-induced osteoporosis:<br>Tablet: 5 or 10 mg QD<br><br>Treatment to increase bone mass in men with osteoporosis, treatment of osteoporosis in postmenopausal women:<br>Effervescent tablet, solution: 70 mg once weekly<br><br>Tablet: 10 mg QD or 70 mg once weekly<br><br>Treatment of Paget's disease of bone:<br>Solution, tablet: 40 mg QD for six months | Safety and efficacy in children have not been established. | Effervescent tablet:<br>70 mg<br><br>Solution:<br>70 mg<br><br>Tablet:<br>5 mg<br>10 mg<br>35 mg<br>40 mg<br>70 mg |
| Etidronate | Prevention and treatment of heterotopic ossification:<br>Tablet: 20 mg/kg/day for one month before and three months after total hip replacement surgery or 20 mg/kg/day for two weeks followed by 10 mg/kg/day for 10 weeks after spinal cord surgery<br><br>Treatment of Paget's disease of bone:<br>Tablet: initial, 5 to 10 mg/kg/day for six months or 11 to 20 mg/kg/day for three months; | Safety and efficacy in children have not been established. | Tablet:<br>200 mg<br>400 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | maximum, 20 mg/kg/day<br><br>Retreatment should be initiated only after an etidronate-free period of ≥90 days and there is biochemical, symptomatic, or other evidence of active disease process. | | |
| Ibandronate | Prevention of osteoporosis in postmenopausal women:<br>Tablet: 150 mg once monthly<br><br>Treatment of osteoporosis in postmenopausal women:<br>Tablet: 150 mg once monthly | Safety and efficacy in children have not been established. | Tablet:<br>150 mg |
| Risedronate | Prevention of glucocorticoid-induced osteoporosis, treatment of glucocorticoid-induced osteoporosis:<br>Tablet: 5 mg QD<br><br>Prevention of osteoporosis in postmenopausal women:<br>Tablet: 5 mg QD or 35 mg once weekly or 150 mg once monthly<br><br>Treatment to increase bone mass in men with osteoporosis<br>Tablet: 35 mg once weekly<br><br>Treatment of osteoporosis in postmenopausal women:<br>Delayed-release tablet: 35 mg once weekly<br><br>Tablet: 5 mg QD, 35 mg once weekly, or 150 mg once monthly<br><br>Treatment of Paget's disease of bone:<br>Tablet: 30 mg QD for two months | Safety and efficacy in children have not been established. | Delayed-release tablet:<br>35 mg<br><br>Tablet:<br>5 mg<br>30 mg<br>35 mg<br>150 mg |
| **Combination Products** | | | |
| Alendronate/ cholecalciferol | Treatment to increase bone mass in men with osteoporosis, treatment of osteoporosis in postmenopausal women:<br>Tablet: 70 mg/2,800 IU or 70 mg/5,600 IU once weekly | Safety and efficacy in children have not been established. | Tablet:<br>70 mg/2,800 IU<br>70 mg/5,600 IU |

IU=international units, QD=once-daily
*Must be administered by a healthcare provider.

## Clinical Guidelines

Current clinical guidelines are summarized in Table 11. Please note that guidelines addressing the prevention and treatment of osteoporosis and Paget's disease are presented globally, addressing the role of various medication classes.

**Table 11. Clinical Guidelines**

| Clinical Guidelines | Recommendations |
|---|---|
| National Osteoporosis Foundation: **Clinician's Guide to Prevention and Treatment of Osteoporosis (2013)**[1] | Synopsis of major recommendations<br>• The following recommendations apply to postmenopausal women and men ≥50 years of age.<br>• Patients should be counseled on the risk of osteoporosis and related fractures.<br>• Secondary causes of osteoporosis should be assessed in patients.<br>• Patients should be advised to supplement with adequate amounts of calcium (1,000 mg/day for men 50 to 70 years; ≥1,200 mg/day for women 51 years and older and men 71 years or older) and vitamin D (800 to 1,000 international units [IU]/day), including supplements if necessary for patients ≥50 years of age.<br>• Regular weight-bearing and muscle-strengthening exercises should be recommended to reduce the risk of falls and fractures.<br>• Tobacco smoking and excessive alcohol intake should be avoided.<br>• Bone mineral density (BMD) testing is recommended in women ≥65 years of age and men ≥70 years of age.<br>• In postmenopausal women and men 50 to 69 years of age, recommend BMD testing when you have concern based on their risk factor profile.<br>• A BMD test is recommended to those who have had a fracture, in order to determine the degree of disease severity.<br>• Vertebral imaging should be performed for certain patients based on BMD t-score<br>• Treatment should be initiated in patients with hip or vertebral (clinical or asymptomatic) fractures.<br>• Initiate therapy in those patients with BMD T-scores ≤-2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry, after appropriate evaluation.<br>• Initiate treatment in postmenopausal women and men ≥50 years of age with low bone mass (T-score -1.0 to -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the Untied States-adapted World Health Organization absolute fracture risk model.<br>• Current Food and Drug Administration (FDA)-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (teriparatide), and RANK ligand inhibitor (denosumab).<br>• No pharmacologic therapy should be considered indefinite in duration. After the initial treatment period, which depends on the pharmacologic agent, a comprehensive risk assessment should be performed. There is no uniform recommendation that applies to all patients and duration decisions need to be individualized<br>• BMD testing performed in dual-energy x-ray absorptiometry centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical solutions. |
| American Association of | Prevention of bone loss<br>• Maintain adequate calcium and vitamin D intake. Use calcium supplements, |

| Clinical Guidelines | Recommendations |
|---|---|
| Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2010)**[3] | if needed, to meet minimal required intake. Supplement vitamin D, if needed, to maintain serum levels of 25-hydroxyvitamin D 30 to 60 ng/mL.<br>• Limit alcohol intake (≤2 servings/day).<br>• Limit caffeine intake.<br>• Avoid or stop smoking.<br>• Maintain an active lifestyle, including weight bearing exercises for ≥30 minutes a day.<br><br>Nonpharmacologic treatment<br>• In addition to the preventative measures, patients should maintain adequate protein intake, use proper body mechanics, consider the use of hip protectors (individuals with a high risk of falling), take measures to reduce the risk of falling, and consider physical and occupational therapy.<br><br>Screening for osteoporosis<br>• Women ≥65 years of age and younger postmenopausal women at an increased risk of fracture should be screened for osteoporosis.<br><br>Diagnosis and evaluation of osteoporosis<br>• A central dual-energy x-ray absorptiometry measurement should be used to diagnosis osteoporosis.<br>• In the absence of fracture, osteoporosis is defined as a T-score ≤-2.5 in the spine, femoral neck or total hip.<br>• Osteoporosis is defined as the presence of a fracture of the hip or spine (in the absence of other bone conditions).<br>• Evaluation for secondary osteoporosis should occur.<br>• Clinicians should also evaluate prevalent vertebral fractures.<br><br>Pharmacologic therapy<br>• Patients with a history of a fracture of the hip or spine should receive pharmacologic therapy.<br>• Patients with a history of fractures but with a T-score ≤-2.5 should receive pharmacologic therapy.<br>• Patients with a T-score -1.0 to -2.5 and a FRAX® (a tool created by the World Health Organization) major osteoporotic fracture probability ≥20% or a hip fracture probability of at least 3% should receive pharmacologic therapy.<br>• Drugs with proven anti-fracture efficacy should be used.<br>• Use alendronate, risedronate, zoledronic acid, and denosumab as first-line therapy.<br>• Use ibandronate as a second-line therapy.<br>• Use raloxifene as a second- or third-line therapy.<br>• Use calcitonin as last line of therapy.<br>• Use teriparatide for patients with very high fracture risk or in patients who have failed bisphosphonate therapy.<br>• Combination therapy is not recommended.<br><br>Monitoring treatment<br>• Obtain a baseline dual-energy x-ray absorptiometry, and repeat every one to two years until findings are stable. Continue with follow up dual-energy x-ray absorptiometry every two years or at a less frequent interval. |

| Clinical Guidelines | Recommendations |
|---|---|
| | • Changes in spine or total hip BMD should be monitored.<br>• Follow-up of patients should be in the same facility, with the same machine, and, if possible, with the same technologist.<br>• Bone turnover markers may be used at baseline to identify patients with high bone turnover and can be used to follow the response to therapy.<br><br>Successful treatment<br>• Treatment can be considered successful if BMD is stable or increasing, and no fractures are present.<br>• Treatment can be considered successful if bone turnover makers are at or below the median value for premenopausal women for patients taking antiresorptive agents.<br>• One fracture is not necessarily evidence of failure. Consider alternative therapy or reassessment for secondary causes of bone loss for patients who have recurrent fractures while receiving therapy.<br><br>Duration of treatment<br>• For treatment with bisphosphonates, if osteoporosis is mild, consider a "drug holiday" after four to five years of stability. If fracture risk is high, consider a drug holiday of one to two years after 10 years of treatment.<br>• Follow BMD and bone turnover markers during a drug holiday period, and reinitiate therapy if bone density declines substantially, bone turnover markers increase, or a fracture occurs.<br><br>Referral to a clinical endocrinologist<br>• When a patient with normal BMD sustains a fracture without major trauma.<br>• When recurrent fractures or continued bone loss occurs in a patient receiving therapy without obvious treatable causes of bone loss.<br>• When osteoporosis is unexpectedly severe or has unusual features.<br>• When a patient has a condition that complicates management (e.g., renal failure, hyperparathyroidism, malabsorption). |
| American College of Physicians: **Pharmacologic Treatment of Low Bone Density or Osteoporosis to Prevent Fractures: A Clinical Practice Guideline From the American College of Physicians (2008)**[13] | Initiating treatment<br>• Pharmacologic treatment should be offered to men and women who have known osteoporosis and to those who have experienced fragility fractures.<br>o Good quality evidence demonstrates that bisphosphonates, estrogen, raloxifene, and teriparatide prevent vertebral fractures. Fair quality evidence demonstrates that calcitonin reduces vertebral fractures.<br>o Good quality evidence also supports that bisphosphonates and estrogen prevent non-vertebral and hip fractures. Calcitonin and raloxifene have not been demonstrated to reduce non-vertebral and hip fractures. The evidence related to teriparatide is mixed with one large trial demonstrating a reduction and two small trials not demonstrating a reduction in non-vertebral fractures. Teriparatide has not demonstrated a reduction in hip fractures.<br>• Pharmacologic treatment should be considered for men and women who are at risk for developing osteoporosis (patients with a T-score -1.5 to -2.5, are receiving glucocorticoids, or are >62 years).<br><br>Pharmacologic therapies for the prevention and treatment of osteoporosis<br>• The drugs currently FDA-approved for the prevention of osteoporosis include bisphosphonates, estrogen, and raloxifene. The drugs currently |

| Clinical Guidelines | Recommendations |
|---|---|
| | FDA-approved for the treatment of osteoporosis include bisphosphonates, calcitonin, raloxifene, and teriparatide.<br>• Selection of pharmacologic treatment options for osteoporosis in men and women should be based on assessment of the risks and benefits to the individual patients.<br>o Because good-quality evidence demonstrates that bisphosphonates reduce the risk for vertebral, non-vertebral, and hip fractures, they are reasonable options to consider as first-line therapy (particularly in patients at a high risk for a hip fracture). Of the other agents available for treatment of osteoporosis, estrogen reduces the incidence of vertebral, non-vertebral, and hip fractures, but is associated with other serious risks.<br>o The most common adverse events associated with bisphosphonates are related to the gastrointestinal tract. No evidence was found that bisphosphonates, calcitonin, calcium, teriparatide, and vitamin D differ in risk for serious cardiac events. Estrogen was associated with a greater risk for stroke, and the estrogen-progestin combination was associated with a greater probability of stroke and higher odds of breast cancer. Raloxifene was associated with a higher risk for pulmonary embolism, thromboembolic events, and mild cardiac events.<br>o Evidence is insufficient to determine whether one bisphosphonate is "superior" to another.<br>• No clear evidence demonstrates the appropriate duration of treatment with bisphosphonates. |
| North American Menopause Society: **Management of Osteoporosis in Postmenopausal Women: 2010 Position Statement of The North American Menopause Society (2010)**[14] | • All postmenopausal women should be encouraged to employ lifestyle practices that reduce the risk of bone loss and osteoporotic fractures: maintain a healthy weight, eat a balanced diet, obtain adequate calcium and vitamin D, participate in appropriate exercise, avoid excessive alcohol consumption, do not smoke, and utilize measures to prevent falls.<br>• Periodic reviews of calcium and vitamin D intake and lifestyle behaviors are useful.<br>• After menopause, a woman's risk of falls should be assessed annually and at any time her physical or mental status changes.<br>• The physical examination should include an annual measurement of height and weight, along with an assessment from chronic back pain, kyphosis, and clinical risk factors.<br>• BMD testing is indicated for all postmenopausal women with medical causes of bone loss, and all women ≥65 years of age.<br>• BMD testing should be considered for postmenopausal women ≥50 years of age who have one or more of the following risk factors: previous fractures (other than skull, facial bone, ankle, finger, and toe) after menopause, thinness (body weight <127 lbs or a body mass index <21 kg/$m^2$), history of hip fracture in a parent, current smoking, rheumatoid arthritis, and excessive alcohol intake.<br>• When BMD testing is indicated, dual-energy x-ray absorptiometry is the preferred technique. The total hip, femoral neck, and posterior-anterior lumbar spine should be measured, using the lowest of the three BMD scores.<br>• The routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.<br>• Vertebral fracture must be confirmed by lateral spine radiographs or |

| Clinical Guidelines | Recommendations |
|---|---|
| | vertebral fracture assessment visualization of fracture at the time of BMD testing. Vertebral fracture is confirmed by height loss >20% of the anterior, mid, or posterior dimension of a vertebra on imaging.<br>• An adequate intake of both calcium and vitamin D is important for bone health and is recognized as an important component of any osteoporosis prescription-drug regimen. North American Menopause Society follows the National Osteoporosis Foundation recommendations of calcium intake of 1,200 mg/day for adults ≥50 years of age, and vitamin $D_3$ of 800 to 1,000 IU/day.<br>• Osteoporosis drug therapy is recommended in the following populations: all postmenopausal women who have had an osteoporotic vertebral or hip fracture; all postmenopausal women who have BMD values consistent with osteoporosis at the lumbar spine, femoral neck, or total hip region; and all postmenopausal women who have T-scores -1.0 to -2.5 and a 10-year risk, based on the FRAX® calculator, of major osteoporotic fracture of at least 20% or of hip fracture of at least 3%.<br>• It is important to encourage adherence to the treatment plan and to identify barriers to nonadherence. Providing clear information to women regarding their risk for fracture and the purpose of osteoporosis therapy may be the optimal way to improve adherence.<br>• During therapy, it is appropriate to re-evaluate the treatment goals and the choice of medication on an ongoing basis through periodic medical examination and follow-up BMD testing. Measurement of BMD has limited use in predicting the effectiveness of antiresorptive therapies for reducing fracture risk. Also, fracture risk reductions from therapy occur much more rapidly than BMD changes. An appropriate interval for repeat BMD testing is after one to two years of treatment. There appears to be little value in repeat testing if a woman is stable.<br>• For untreated postmenopausal women, repeat dual-energy x-ray absorptiometry testing is not useful until two to five years have passed.<br>• Bisphosphonates are the first-line drugs for treating postmenopausal women with osteoporosis. They have reduced the risk of vertebral fractures by 40 to 70% and reduced the incidence of non-vertebral fracture, including hip fracture, by about half this amount.<br>• The selective estrogen-receptor modulator raloxifene is most often considered for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis. It prevents bone loss and reduces the risk of vertebral fractures, but its effectiveness in reducing other fractures is uncertain. Extraskeletal risks and benefits are important when considering raloxifene therapy.<br>• Teriparatide is best offered to postmenopausal women with osteoporosis who are at high risk for fracture. Daily subcutaneous injections have been shown to stimulate bone formation and improve bone density. Therapy is indicated for no more than 24 months.<br>• The primary indication for systemic estrogen or estrogen plus progestogen therapy is to treat moderate-to-severe menopause symptoms. When symptoms are controlled or cease, continued hormone therapy can still be considered for bone effects, weighing its benefits and risks against those of alternative therapies.<br>• Estrogen and estrogen plus progestogen therapy may be a treatment option for a few years of early postmenopause.<br>• Calcitonin is not a first-line drug for postmenopausal osteoporosis |

| Clinical Guidelines | Recommendations |
|---|---|
| | treatment, as its fracture efficacy is not strong and its BMD effects are less than those of other agents. However, it is an option for women with osteoporosis who are more than five years beyond menopause.<br>• Calcitonin therapy may reduce vertebral fracture risk in women with osteoporosis, although the evidence documenting fracture protection is not strong. It is not recommended for treating bone pain, except bone pain from acute vertebral compression fractures.<br>• Data are inadequate to make definitive recommendations regarding combination or serial anabolic and antiresorptive drug therapies.<br>• The treatment of osteoporosis needs to be long-term in most women.<br>• If drug-related adverse effects occur, appropriate management strategies should be instituted. If adverse effects persist, switching to another agent may be required.<br>• Decisions to discontinue or suspend therapy are based on the woman's risk of fracture and her response to treatment. Given the uncertainties of long-term drug safety, careful monitoring is required. Fracture risk after discontinuing therapy has not been adequately evaluated. |
| Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Osteoporosis (2013)**[15] | • Discuss risk factors for osteoporosis and primary prevention with all patients presenting for routine health visits.<br>• Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis.<br>• Lifestyle adjustments are universally recommended for bone health.<br>• Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis.<br>• Bisphosphonates are indicated for reduction of fracture (both vertebral and non-vertebral), in postmenopausal women and men, and in the setting of glucocorticoid use.<br>• Once-yearly intravenous zoledronic acid may be given to men and women within 90 days of a hip fracture<br>• Anabolic therapy with parathyroid hormone is indicated for patients with particularly high risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture.<br>• Nasal calcitonin is not considered third-line treatment for osteoporosis but may be useful in some populations.<br>• Estrogen treatment is not recommended first line and should only be used in postmenopausal osteoporosis in women at significant risk that cannot take non-estrogen therapies<br>• Consider selective estrogen receptor modulator treatment with raloxifene as it has shown vertebral risk reduction in postmenopausal osteoporosis.<br>• Consider receptor activator of nuclear factor K-B ligand inhibitor treatment with denosumab as it has been shown to reduce the cumulative incidence of new vertebral and hip fractures in postmenopausal osteoporosis.<br>• Consider means to improve medication compliance, as poor compliance with osteoporosis medications is a large problem. Adherence is associated with significantly fewer fractures.<br>• Follow-up central dual energy X-ray absorptiometry on the same machine as the baseline may be considered for patients on pharmacologic therapy no more than every 12 to 24 months.<br>• Patients on glucocorticoid therapy may require testing every six to 12 months. |
| American College of | Recommendations for assessment, counseling for lifestyle modifications, and |

| Clinical Guidelines | Recommendations |
|---|---|
| Rheumatology: **Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (2010)**[16] | follow-up of all patients receiving glucocorticoid therapy<br>• Patients starting glucocorticoids at any dose with an anticipated duration of three or more months should receive counseling for lifestyle modification and assessment. The following should be considered: weight bearing activities, smoking cessation, avoidance of excessive alcohol intake (greater than two drinks per day), nutritional counseling on calcium and vitamin D intake, fall risk assessment, baseline dual x-ray absorptiometry, serum 25-hydroxyvitamin D level, baseline height, assessment of prevalent fragility fractures, consideration for radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent, calcium intake (supplement plus oral intake of 1,200 to 1,500 mg/day*), and vitamin D* supplementation.<br>• An important strategy in reducing a patient's risk is to use the smallest dose of glucocorticoid for the shortest duration possible.<br><br>Recommendations for low- and medium-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years<br>• Pharmacologic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of three or more months, or prevalent glucocorticoid therapy of a duration of at least three months are as follows:<br>o Low-risk patient:<br>▪ Alendronate, risedronate, or zoledronic acid for ≥7.5 mg/day prednisone.<br>o Medium-risk patient:<br>▪ Alendronate or risedronate for any dose of glucocorticoids, or zoledronic acid for ≥7.5 mg/day prednisone.<br>• The glucocorticoid dose warranting therapeutic intervention represents the practitioner's intended average daily dose and varies according to the specific medication being considered.<br><br>Recommendations for high-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years<br>• Consistent with the National Osteoporosis Foundation guideline that suggests treatment when the 10-year risk of major osteoporotic fractures is ≥20%, it is recommended that these patients receive prescription osteoporosis therapy even in the absence of glucocorticoid use.<br>• Pharmacologic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of three or more months, or prevalent glucocorticoid therapy of a duration of at least three months are as follows:<br>o High-risk patient (any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients):<br>▪ Alendronate, risedronate, zoledronic acid, or teriparatide (for ≥5 mg/day prednisone with a duration of one month or less and for any dose of glucocorticoids with a duration greater than one month).<br><br>Recommendations for premenopausal women and men age <50 years<br>• Recommendations for premenopausal women and men <50 years with a history of fragility fracture are as follows: |

| Clinical Guidelines | Recommendations |
|---|---|
| | o One to three months of glucocorticoids:<br>▪ Non childbearing potential:<br>• Alendronate or risedronate if prednisone ≥5 mg/day, or zoledronic acid if prednisone ≥7.5 mg/day.<br>▪ Childbearing potential:<br>• Inadequate data for recommendations to be made.<br>o Three or more months of glucocorticoids:<br>▪ Non childbearing potential:<br>• Alendronate, risedronate, zoledronic acid, or teriparatide for any dose.<br>▪ Childbearing potential:<br>• Alendronate, risedronate, or teriparatide if prednisone ≥7.5 mg/day.<br>• For women of childbearing potential, drugs with shorter half-lives are recommended. |
| The Paget Foundation: **A Physician's Guide to the Management of Paget's Disease of Bone (2012)**[17] | Indications for treatment<br>• Symptoms due to metabolically active Paget's disease (e.g., bone pain related to a pagetic site or fatigue fracture, headache resulting from an affected skull, back pain from affected pagetic vertebrae, other neurological syndromes associated with pagetic changes) warrant treatment.<br>• Treatment is warranted in a patient planning to undergo elective surgery on a pagetic site (e.g., hip replacement) in an attempt to minimize the operative blood loss due to hypervascularity present in active pagetic bone. Postoperative treatment may be helpful in preventing acceleration of disease activity which has been reported after surgery or fractures.<br>• Treatment is indicated in the management of hypercalcemia, a rare occurrence when a patient with multiple bones affected by Paget's disease and a highly elevated serum alkaline phosphatase level undergoes prolonged immobilization.<br>• Many investigators believe that treatment is indicated as an attempt to decrease local progression and reduce the risk of future complications-even in asymptomatic patients whose sites of disease and degree of metabolic hyperactivity place them at risk of progression and complications. This group includes individuals who may be at risk for bowing deformities in their long bones, for hearing loss, optic nerve impingement, skull enlargement, neurological complications due to pagetic changes in their vertebrae; or for secondary arthritis as a complication of Paget's disease adjacent to major joints.<br>• There is no direct evidence that aggressive treatment of Paget's disease is associated with prevention of progression or reduction in risk for future complications.<br>• It is good clinical practice to treat both symptomatic patients whose symptoms may respond to a reduction in abnormal bone turnover as well as asymptomatic patients with active Paget's disease that is likely to cause future problems.<br><br>Therapy options<br>• Four main methods of treatment exist for a patient with Paget's disease: nonpharmacological therapy, pharmacological therapy using either bisphosphonates or calcitonins, pain management using analgesics, and surgery. |

| Clinical Guidelines | Recommendations |
|---|---|
| | • Nonpharmacological therapy focuses mainly on physical therapy as a means of improving muscle strength and mobility to help control some types of pain.<br>• Bisphosphonates are the most widely used drugs for the management of Paget's disease.<br>• The potent oral bisphosphonates, alendronate and risedronate, both reduce the biochemical indices for bone turnover into the normal range in many patients with moderate to severe Paget's disease. Etidronate and tiludronate are less potent than alendronate and risedronate. The intravenous bisphosphonates, pamidronate and zoledronic acid, have the advantage of infrequent administration.<br>• The use of subcutaneous injection of calcitonin is limited mostly to patients who do not tolerate bisphosphonates. The agent has been shown to reduce elevated indices of bone turnover by 50%, decrease symptoms of bone pain, reduce warmth over affected bones, improve some neurological complications, and promote healing of lytic lesions.<br>• In the cases of pain caused by bone deformity or arthritic or neurological complications, acetaminophen, nonsteroidal anti-inflammatory drugs, or cox-2 inhibitors may be helpful. Treatments should be administered in addition to the main pagetic therapy chosen.<br>• Different orthopedic interventions may be necessary in pagetic patients.<br>• Neurosurgery is rarely required to decompress the posterior fossa in patients with marked skull enlargement. |

*Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration for greater than three months.

## Conclusions

Bisphosphonates inhibit osteoclast activity by binding to bone surfaces that are undergoing active bone resorption resulting in the impairment of the ability for osteoclasts to form the ruffled border, adhere to the bony surface, and produce the protons necessary to continue bone resorption.[4-12] The bisphosphonates are primarily Food and Drug Administration (FDA)-approved for the prevention and/or treatment of osteoporosis in postmenopausal women, in men, and in patients taking prolonged courses of glucocorticoids; however, some agents are also approved for the treatment of Paget's disease. In general, the bisphosphonates are available for oral once-daily, once weekly, or once monthly administration. The most common adverse events associated with bisphosphonates are related to the gastrointestinal tract.[4-12] Currently, alendronate (tablet), etidronate, and ibandronate (150 mg tablet) are the only bisphosphonates available generically.

Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one bisphosphonate is more efficacious in increasing bone mineral density and decreasing bone turnover markers. Furthermore, data from trials specifically examining fractures indicates that the use of bisphosphonates is efficacious and significantly lowers the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo.[18-76]

Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures. While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis. At this time, evidence is insufficient to determine whether one bisphosphonate is superior to another.[1,3,13-16] Bisphosphonates are the most widely used drugs for the management of Paget's disease.[17]

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