Article:
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Supplementary information

Contents

1. Clinical effectiveness review

Supplementary Table 1: Table of excluded studies

First author	Reason for exclusion
Adachi et al., 2010[259]	Parallel publication no additional information
Adachi et al., 2010[260]	Parallel publication no additional information
Adachi et al., 2010[261]	Parallel publication no additional information
Adachi et al., 2011[262]	Parallel publication no additional information
Adami et al., 2004[263]	Not treatment of interest - not currently licenced dose
Bauer et al., 2010[264]	Parallel publication no additional information
Bauer et al., 2014[265]	Parallel publication no additional information
Black et al., 2000[266]	Parallel publication no additional information
Black et al., 2003[267]	Not comparator of interest
Black et al., 2005[268]	Not comparator of interest
Black et al., 2006[269]	Extension study, participants not in original randomised groups
Black et al., 2006[270]	Parallel publication no additional information
Black et al., 2010[271]	Parallel publication no additional information
Black et al., 2012[272]	Extension study, participants not in original randomised groups
Black et al., 2009[273]	Parallel publication no additional information
Black et al., 2010[274]	Parallel publication no additional information
Black et al., 2010[275]	Parallel publication no additional information
Black et al., 2011[276]	Parallel publication no additional information
Bone et al., 1997[277]	Not treatment of interest - not currently licenced dose
Boonen et al., 2009[278]	Parallel publication no additional information
Boonen et al., 2010[279]	Parallel publication no additional information
Boonen et al., 2010[280]	Parallel publication no additional information
Boonen et al., 2010[281]	Parallel publication no additional information
Boonen et al., 2011[282]	Parallel publication no additional information
Boonen et al., 2011[283]	Parallel publication no additional information
Boonen et al., 2012[284]	Parallel publication no additional information
Boonen et al., 2012[285]	Parallel publication no additional information
Boonen et al., 2012[286]	Parallel publication no additional information
Colon-Emeric et al., 2010[287]	Parallel publication no additional information
Cosman et al., 2012[288]	Parallel publication no additional information
Delmas et al., 2004[289]	Parallel publication no additional information
Devogelaer et al., 1996[290]	No outcomes of interest
Durchschlag et al., 2006[291]	No outcomes of interest
Eastell et al., 2009[292]	Not outcomes of interest
Eastell et al., 2012[293]	Parallel publication no additional information
Emkey et al., 2009[294]	Parallel publication no additional information
Felsenberg et al., 1999[295]	Not treatment of interest - not currently licenced dose
Felsenberg et al., 2005[295]	Parallel publication no additional information
Genant et al., 2010[296]	Parallel publication no additional information
Grey et al., 2009[297]	Population outside scope of appraisal not licenced indication
Grey et al., 2012[298]	Population outside scope of appraisal not licenced indication
Grey et al., 2014[299]	Population outside scope of appraisal not licenced indication
Guo-Ping et al., 2005[300]	Not comparator of interest
Hakala et al., 2012[301]	Population outside scope of appraisal not licenced indication
Haworth et al., 2010[302]	Population outside scope of appraisal not licenced indication
Haworth et al., 2011[303]	Population outside scope of appraisal not licenced indication
Hochberg et al., 2005[304]	Parallel publication no additional information
Hosking et al., 1998[305]	Not treatment of interest - not currently licenced dose
Hosking et al., 1998[305]	Not treatment of interest - not currently licenced dose

Hwang et al., 2011[306]	Parallel publication no additional information
Hwang et al., 2010[307]	Population outside scope of appraisal not licenced indication
Kasayama et al., 2005[308]	Not treatment of interest - not currently licenced dose
Klotz et al., 2011[309]	Parallel publication no additional information
Langenegger, Opazo & Garcia, 2011[310]	Population outside scope of appraisal not licenced indication
Lindsay et al., 1999[311]	Not treatment of interest – combination therapy with HRT
Lindsay et al., 1999[311]	Not treatment of interest - not currently licenced dose
Majimi et al., 2006[312]	Not treatment of interest - not currently licenced dose
McClung et al., 1998[312]	Not comparator of interest
McClung et al., 2004[313]	Not treatment of interest - not currently licenced dose
McClung et al., 2004[314]	No outcomes of interest
McClung et al., 2005[315]	Not treatment of interest - not currently licenced dose
Mellström et al., 2004[316]	Extension study, participants not in original randomised groups
Miller at al., 2004[317]	Population outside scope of appraisal not licenced indication
Mok et al., 2008[318]	Population outside scope of appraisal not licenced indication
Mortensen et al., 1998[21]	Population outside scope of appraisal not licenced indication
Mortensen et al., 1998[21]	Population outside scope of appraisal not licenced indication
Nakamura et al., 2013[319]	Not treatment of interest - not currently licenced dose
Orwoll et al., 2010[320]	Population outside scope of appraisal not licenced indication
Orwoll et al., 2010[321]	Population outside scope of appraisal not licenced indication
Ravn et al., 1999[322]	Not treatment of interest - not currently licenced dose
Reid et al., 2009[323]	Parallel publication no additional information
Reid et al., 2013[324]	Parallel publication no additional information
Rossini et al., 1994[325]	Not treatment of interest - not currently licenced dose
Roux et al., 2012[326]	Not outcomes of interest
Sambrook et al., 2004[327]	Not comparator of interest
Sambrook et al., 2011[328]	Parallel publication no additional information
Schwartz et al., 2010[329]	Parallel publication no additional information
Seeman et al., 1999[99]	Parallel publication no additional information
Seeman et al., 2009[330]	Parallel publication no additional information
Siris et al., 2008[331]	Parallel publication no additional information
Stakkestad et al., 2003[332]	Not treatment of interest - not currently licenced dose
Tee et al., 2012[333]	Population outside scope of appraisal not licenced indication
Thiébaud et al., 1997[334]	Not treatment of interest - not currently licenced dose
Uchida et al., 2005[335]	Not treatment of interest - not currently licenced dose
Washnich et al., 2004[336]	Not treatment of interest - not currently licenced dose
Westin et al., 2013[337]	Not treatment of interest - not currently licenced dose
Yildrim et al., 2005[338]	No outcomes of interest

Supplementary Table 2: Characteristics of included studies

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Alendronate vs. placebo					
Adami 1995[55] Italy Multicentre RCT, 11 centres Sponsor not reported	*Inclusion:* women at least 2 years past natural menopause; the majority were under 65 years. Each had lumbar spine bone mineral density (BMD) which was >2 SD below the mean for young. Evidence of previous vertebral fracture was not an entry criterion, and only 5% of subjects had prevalent fractures. *Exclusion:* evidence of any secondary cause of osteoporosis, other metabolic bone disease, hyper- or hypothyroidism. Medications affecting bone metabolism	PBO, n=71 ALN10mg/d, n=78 *Adjuvant:* Both groups, calcium 500mg/d	24 months BMD assessed at 24 months	*Primary:* change in LS lumbar spine BMD (L1-L4) *Secondary:* change in FN and trochanter spine BMD	*Fractures:* not an outcome *BMD:* DXA - (Hologic, Waltham, MA, USA; Lunar, Madison, WI, USA; Norland, WI, USA; and Sophos, Paris, France)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Black 1996 [57] (FIT I) USA Multicentre RCT, 11 centres Merck Research Labs.	*Inclusion:* Women aged between 55 and 81 years, postmenopausal for at least 2 years, had at least one vertebral fracture and FN BMD of 0.68 g/cm2 or less (≤2 SDs below normal young adult) *Exclusion:* Peptic-ulcer disease, dyspepsia requiring treatment, abnormal renal function, major medical problems that would preclude participation, severe malabsorption syndrome, hypertension, myocardial infarction, unstable angina, disturbed thyroid or parathyroid function, use of oestrogen, calcitonin, bisphosphonates or sodium fluoride.	PBO, n=1005 ALN10mg/d, n=1022 *Adjuvant:* Both groups, women with low calcium intake 500 mg/d calcium supplements and 250 IU/d vitamin D	36 months Lateral radiographs were obtained at baseline and at 24 months and 36 months	*Primary:* New vertebral fractures at 3 years - a new vertebral fracture if any of the ratios of vertebral heights was more than 3 SDs below the mean population norm for that vertebral level. *Secondary:* non-vertebral fractures (hip, wrist, and others); FN, LS and total hip BMD. Adverse events.	*Fractures:* Vertebrae were judged to be fractured by morphometric assessment using a translucent digitiser. Clinical fractures (non-spine clinical fractures, hip fractures, wrist fractures, and clinical vertebral fractures; and other clinical fractures) were reported by participants and confirmed by a required written report of a radiological procedure. *BMD:* DXA - QDR-2000 Hologic (Waltham, MA, USA)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Cummings 1998 [66] (FIT II) USA Multicentre RCT, 11 centres Merck Research Labs.	*Inclusion:* Women aged 55-80 years; postmenopausal for at least 2 years; FN BMD of 0.68 g/cm2 or less (≤2 SDs below normal young adult) *Exclusion:* Peptic-ulcer disease, dyspepsia requiring treatment, abnormal renal function, major medical problems that would preclude participation, severe malabsorption syndrome, hypertension, myocardial infarction, unstable angina, disturbed thyroid or parathyroid function, use of oestrogen, calcitonin, bisphosphonates or sodium fluoride.	PBO, n=2218 ALN10mg/d, n=2214 *Adjuvant:* Both groups, women with low calcium intake 500 mg/d calcium supplements and 250 IU/d vitamin D	48 months Lateral radiographs were obtained at baseline and at baseline and 48 months	*Primary:* Clinical fractures (vertebral and non-vertebral) confirmed by radiographs at 4.2 years. *Secondary:* Change in BMD of the hip and posterior-anterior spine and whole body; adverse events, from baseline in each group.	*Fractures:* Clinical fractures were defined as one diagnosed by a physician. Self-reports of fractures were confirmed by radiographic or other tests (not described). Traumatic fractures and fractures of the face/skull were excluded. Vertebral fractures were assessed by radiographs. Fracture was defined as 20% decrease in height and 4mm decrease in vertebral height *BMD:* DXA - QDR-2000 Hologic (Waltham, MA, USA)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Bone 2000[59] Countries not specified RCT, number centres not specified Merck Research Labs.	*Inclusion:* Postmenopausal osteoporotic women 42-82 years old, with hysterectomy; BMD<0.862g/cm2 on at least 3 vertebra, LS T score (SD) ≤-2.5 *Exclusion:* Metabolic bone disease, low vitamin D, oestrogen replacement therapy > 6mo, drugs that affect bone turnover, renal insufficiency, cardiac disease, upper GI disease	PBO, n=50 ALN10mg/d, n=92 *Adjuvant:* Both groups, 1000 mg/d calcium	24 months BMD assessed at 3, 6, 12, 18 and 24 months	*Primary:* Change BMD of the LS, at 24 months. *Secondary:* Change BMD of the total hip, FN, trochanter, and total body; biochemical markers of bone turnover; fractures; adverse events.	*Fractures:* Clinical fractures recorded as adverse events (assessment method not reported) *BMD:* Hologic QDR densitometers (QDR-1000, -1000/W, -1500 or -2000; Hologic, Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Carfora 1998 [62] Italy Single centre RCT Sponsor not reported	*Inclusion:* Postmenopausal women (for at least 5 years); age 44 to 80; at least 2.5 SD below the mean value in premenopausal white women. *Exclusion:* Women with other causes of Osteoporosis or vitamin D deficiency, Paget's disease, hyperparathyroidism, peptic ulcer, abnormal renal/hepatic function, abnormalities of LS	PBO, n=34 ALN10mg/d, n=34 *Adjuvant:* Both groups, 500mg/d calcium	30 months BMD assessed every 5 months, X-rays at baseline and end treatment	*Primary:* Change BMD of the spine at 2.5 years. *Secondary:* Fractures; biochemical markers of bone turnover; and adverse events.	*Fractures:* X-rays of the thoracic and lumbar spine to evaluate fractures. No further details reported. *BMD:* DXA – Hologic QD|R1000

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Chesnut 1995 [63] USA Multicentre RCT, 7 centres Merck Research Labs	*Inclusion:* women aged 42 to 75 years, at least 5 years postmenopausal, with lumbar spine BMD ≤0.88 g/cm" (approximately 2 SDs below young, normal US white female mean BMD values) *Exclusion:* medications affecting bone metabolism were excluded, the presence of spine or hip fractures attributable to osteoporosis.	PBO, n=31 ALN10mg, n=30 Also evaluated ALN5mg/d, n=32; 20mg, n=32; 40mg/PBO, n=32, 40/2.5mg, n=31 *Adjuvant:* Both groups, 500mg/d calcium	24 months BMD assessed every 3 months	*Primary:* change in BMD at LS, FN, TH, intertrochanter, Ward's triangle and the forearm, bine markers, adverse events *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA Hologic 1000w, Inc., Waltham, Massachusetts).

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Dursun 2001 [67] Turkey Single centre RCT Sponsor not reported	*Inclusion:* Postmenopausal women with BMD of 2 SD or more below young adult mean at either LS or FN *Exclusion:* History of drug /alcohol abuse, metabolic bone disease, GI/liver disease, renal failure/calculi, glucocorticoid therapy, malignancy, disorder of calcium metabolism and LS abnormalities preventing BMD evaluation.	Calcium 1000mg/d, n=50 ALN10mg + Ca 1000mg/d, n=51 Also evaluated calcitonin, n=50	12 months BMD and X-ray assessment at 6 and 12 months	*Primary:* Change of LS, FN, trochanter and ward's triangle BMD in each group at 12 months. *Secondary:* Number of factures; quality of life and pain; fractures; adverse events.	*Fractures:* X-rays of thoracic and lumbar vertebrae. A new vertebral fracture was defined as a decrease of 20% and at least 4mm in any vertebral height. *BMD:* DXA – model and manufacturer not reported

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Greenspan 2002 [69] USA Multicentre RCT, 25 centres Merck Research Labs.	*Inclusion:* Ambulatory women in long-term care ≥65 years, LS or total hip BMD T-score ≤-2.0 SD *Exclusion:* Disorders of bone mineralisation; low vitamin D; hyperthyroidism; GI disease; use of bone-active agents.	PBO, n=164 ALN10mg/day, n=163 *Adjuvant:* Both groups, 1000 mg/d calcium and 400 IU/d vitamin D supplements.	24 months BMD assessed at 6, 12, 18 and 24 months	*Primary:* Change BMD of the LS, FN, hip and hip trochanter; and biochemical markers of bone turnover, at 2 years. *Secondary:* Adverse events including fractures.	*Fractures:* Clinical fractures recorded as adverse events (assessment method not reported) *BMD:* DXA - Hologic (Waltham, Mass.)
Greenspan 2003 [70] USA Single centre RCT NIH grant NR	*Inclusion:* Community-dwelling women aged 65 or older *Exclusion:* FN BMD ≥0.9 g/cm2 (=0 SD of mean peak). Disease or drugs affecting bone metabolism.	PBO, n=93 ALN10mg/d, n=93 *Adjuvant:* Women with low calcium intake, calcium 600 mg/d 200 IU/d vitamin D Both groups, vitamin D 400 to 800 IU/d	36 months BMD assessed at 6, 12, 18, 24 and 36 months	*Primary:* Change of BMD of the hip, spine, FN, trochanter, and ultradistal radius *Secondary:* Fractures and adverse events.	*Fractures:* Fracture reduction was not a primary end point – recorded as adverse events (assessment method not reported) *BMD:* DXA - QDR4500A Hologic (Bedford, Mass)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Ho 2005 [73] China RCT, number centres not reported MSD Ltd OP	*Inclusion:* Women with osteoporosis aged <75 years, postmenopausal for >3 years, and lumbar spine BMD -2.5 SDs below local peak age. *Exclusion:* Treatment with bisphosphonates of fluorides, SERMs or oestrogen, calcitonin or any other drug that could affect bone metabolism	Calcium 500mg/d, n=29 ALN10mg + Ca 500mg/d, n=29 *Adjuvant:* calcium 500 mg/d	12 months BMD assessed at 3, 6 and 12 months	*Primary:* Change in BMD at LS, FN and TH; bone markers; adverse events *Secondary:* not reported	*Fractures:* Fracture not an outcome *BMD:*DXA Hologic QDR
Klotz 2013[75] (CORAL) Canada. Multicentre RCT, 30 centres Abbot Laboratories	*Inclusion:* Men with histologically confirmed prostate cancer in whom ≥1 yr. of ADT was indicated *Exclusion:* Hypocalcaemia, abnormal renal/liver function, metabolic bone disease, bilateral hip replacement, prior treatment with bisphosphonates or therapy with glucocorticoids	PBO, n=102 ALN70/w, n=84 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* Change in LS BMD. *Secondary:* change in total hip BMD; changes in bone markers	*Fractures:* not an outcome *BMD:* DXA – model not reported

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Liberman 1995[78] One multicentre study was conducted in the United States, and the other in Australia, Canada, Europe, Israel, Mexico, New Zealand, and South America Phase III multicentre RCT Merck Research Labs.	*Inclusion:* Postmenopausal women (for at least 5 years); age 45 to 80; with LS BMD at least 2.5 SD below the mean value of in premenopausal white women *Exclusion:* Other disorders of BMD, abnormal hepatic function, abnormality of lumbar spine precluding assess of BMD, history of hip fracture, and prior bisphosphonates treatment within 12 months.	PBO, n=397 ALN5,10,20mg, n=526 *Adjuvant:* Both groups, 500mg/d calcium	36 months BMD and lateral spine films assessed at 12, 24 and 36 months	*Primary:* New vertebral and non-vertebral fractures; Change of BMD of the LS, FN, trochanter, and total body, in each group at 3 years. *Secondary:* Adverse events.	*Fractures:* The occurrence of new vertebral fractures and the progression of vertebral deformities were determined by an analysis of digitized radiographs, and loss of height was determined by sequential height measurements *BMD:* DXA - Hologic QDR-1000 or 1000/W (Hologic, Waltham, Mass.), Lunar DPX-L (Lunar, Madison, Wis.), or Norland XR-26 (Norland, Fort Atkinson, Wis.)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Orwoll 2000 [85] USA and 10 other countries Multicentre RCT, 20 centres Merck Research Labs.	*Inclusion:* Men with BMD at FN <2 SD below the mean value in normal young men and BMD at the LS <1 SD below the mean or a BMD of at least 1 SD below the mean at the FN and at least 1 vertebral deformity or a history of osteoporotic fracture. *Exclusion:* Secondary causes of osteoporosis, other bone diseases, vitamin D deficiency, renal disease, cardiac disease, cancer, peptic ulcer/oesophageal disease	PBO, n=95 ALN10mg/d, n=146 *Adjuvant:* Both groups, 1000 mg/d calcium and 400 IU/d vitamin D	24 months BMD assessed at 6, 12, 18 and 24 months X-rays at 24 months	*Primary:* Changes in BMD of the LS (L1-L4), FN, hip, and total body, between treatment groups, at 2 years. *Secondary:* Incidence of vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* To detect both vertebral fractures, X-ray films were assessed. both semiquantitative and quantitative morphometric methods were used. Non-vertebral (any site) from patient reporting confirmed by X-ray *BMD:* DXA - Hologic, (Waltham, Mass.), or Lunar, (Madison, Wis.)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Pols 1999 [86] (FOSIT) Europe, Latin America, Australia, Canada, South Africa, China Multicentre RCT, 153 centres Merck Research Labs.	*Inclusion:* Women ≤85 years old postmenopausal for ≥ 3yrs with LS BMD ≥ 2SD below mean for postmenopausal woman 20% to 50% above ideal weight. *Exclusion:* Metabolic bone disease, disturbed parathyroid/thyroid function, GI disease, myocardial infarction, hypertension/angina, organ disease; treatment with bisphosphonates, fluoride, vitamin A, vitamin D	PBO, n=958 ALN10mg/d, n=950 *Adjuvant:* Both groups, 1000 mg/d calcium.	12 months BMD assessed 3, 6 and 12 months	*Primary:* Change in BMD of the LS (L1-L4), FN, trochanter, and total hip, between treatment groups, at 1 year. *Secondary:* Incidence of vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* The occurrence of clinical fractures was captured through adverse event reporting. documentation for each fracture consisting of radiographs and/or radiology reports, hospital discharge reports with clinical diagnosis and/or confirmation by the investigator/treating physician was sought after completion of the study *BMD:* Hologic QDR densitometers (QDR-1000, -1000/W, -1500 or -2000; Hologic, Waltham, MA) or Lunar DPX densitometers (DPX, DPX-L or DPX-a; Lunar, Madison, WI),

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Saag 1998 [93] USA and 15 other countries. Multicentre RCT, 15 centres in the USA, and 22 in other countries. Merck & Co.	*Inclusion:* Men and women, 17 to 83 years of age, with underlying diseases requiring long-term oral glucocorticoid therapy at a daily dose of at least 7.5 mg of prednisone or its equivalent irrespective of baseline BMD *Exclusion:* Metabolic bone disease, a low serum vitamin D, concomitant therapy with drugs that affect bone turnover, pregnancy or lactation, renal insufficiency , severe cardiac disease, and a history of recent major upper GI disease.	PBO, n=159 ALN10mg/d, n=157 Also evaluated ALN5mg/d, n=161 *Adjuvant:* All groups, calcium 800-1000 mg/d and vitamin D 250-500IU/d	48 weeks BMD assessed at 4, 12, 24, 36 and 48 weeks, X-ray at 48 weeks	*Primary:* Change in LS BMD, from base line to week 48 between the groups. *Secondary:* Changes in BMD at FN, trochanter and total body; biochemical markers of bone turnover; and the incidence of new vertebral fractures.	*Fractures:* Radiographs of the lateral lumbar and thoracic spine - semi quantitative visual assessment: grade 0, normal; grade 1, 20-25% reduction in height, 10-20% area; grade 2, 25- 40% reduction in height, 20 -40% area; grade 3, ≥40% reduction in height and area. Vertebral fractures with grades of 2 or higher were defined as prevalent fractures, and fractures that increased in severity by at least one grade were defined as incident fractures. *BMD:* DXA - Hologic (Waltham, Mass.) or Lunar (Madison, Wis.)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Adachi 2001[100] (Saag 1998 extension)	Patients continued to receive the double-blind study medication to which they had been randomized at the beginning of year 1	PBO, n=61 ALN10mg/d, n=55	24 months	*Primary:* Change in LS, from base line to week 48 between the groups. *Secondary:* Changes in BMD of the hip, FN, trochanter and total body; biochemical markers of bone turnover; and the incidence of new vertebral fractures.	
Shilbayeh 2004 [95] Jordan RCT, number centres not reported Sponsor not reported	*Inclusion:* Menopausal or early menopausal women with osteoporosis - BMD ≥ 2.5 SD below the young adult mean *Exclusion:* not reported	PBO, n=27 ALN10mg/d, n=36 *Adjuvant:* Both groups, calcium 500mg/d and Vitamin D 0.25 mcg/d	12 months BMD assessed at 12 months	*Primary:* change in BMD at the LS and FN; adverse events *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA - Lunar DPXL densitometer (Lunar, Madison, WI).

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Smith 2004 [96] Australia Multicentre RCT, 3 centres Merck, Sharp and Dohme	*Inclusion:* Patients with asthma and/or chronic obstructive airways disease with following risk factors: >2 courses of prednisolone in the last two years, forced expiratory volume in one second (FEV) < 50% predicted, any respiratory admission in the last five years, severely limited exercise tolerance (unable to walk > 100 m unaided), being a woman aged over 50 and sustaining a bone fracture after the age of 40 *Exclusion:* known renal disease or symptoms of dysphagia, dyspepsia, use of proton pump inhibitors or alcohol dependence) or history of bilateral hip replacements.	PBO, n=79 ALN10mg/d, n=66 *Adjuvant:* Both groups, calcium 600 mg/d	12 months BMD assessed at 12 months	*Primary:* change in BMD at the LS and FN and whole femur *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA - Lunar (Lunar, Madison, WI).

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Ibandronate vs. placebo					
Chesnut 2004[45]; Chesnut 2005 [46] (BONE) Europe and North America Multicentre RCT, 73 centres Hoffman-La Roche Ltd	*Inclusion:* patients, aged 55-80 years, ≥5 years post menopause, with one to four prevalent vertebral fractures (T4-L4), and with a BMD T-score of -2.0 to -5.0 in at least one vertebra (L1-L4) *Exclusion:* upper GI disorders, LS T score -5.0; >2 vertebral fractures; disease or medication affecting bone metabolism	PBO, n=982 IBN2.5mg/d, n=982 IBN 20mg eod, 12 doses/m, n=982 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	36 months Lateral radiographs performed annually, BMD assessed every 6 months for 2 years, then annually	*Primary:* new morphometric vertebral fracture *Secondary:* worsening fractures, clinical vertebral and osteoporotic non vertebral fractures; change in BMD at LS and femur; biomarkers	*Fractures:* Lateral radiographs of thoracic the spine. Diagnosis of fracture based on morphometric criteria confirmed by qualitative assessment by radiologist. Morphometric fracture – height reduction at least 20% and 4mm decrease *BMD:* DXA (Hologic QDR)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Lester 2008[76] (ARIBON) UK. Multicentre RCT, 2 centres Astra Zeneca and Roche	*Inclusion:* postmenopausal women with a histologically confirmed diagnosis of oestrogen receptor – positive breast cancer. Patients classified as osteopenic (T scores of >-2.5 and <-1.0 either at the LS and TH) were randomized *Exclusion:* menopause was induced chemotherapy or drug therapy; concurrent administration; abnormal renal function, disorders of bone metabolism, and previous bilateral hip fractures prostheses.	PBO, n=25 IBN150mg/m, n=25 *Adjuvant:* Both groups, anastrozole 1 mg/d, calcium 500 mg/d and vitamin D 400IU/d	24 months BMD assessed at 12 and 24 months	*Primary:* change in BMD at the LS and TH *Secondary:* changes in bone resorption and formation markers and adverse events, including any fracture	*Fractures:* recorded as adverse events (assessment method not reported) *BMD:* DXA – Lunar DPX

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
McClung 2009[82] USA. Multicentre RCT, 10 centres Roche	*Inclusion:* postmenopausal women aged 45–60 years with baseline mean lumbar spine (LS) BMD T-score between -1.0 and -2.5 and baseline T-score>-2.5 in total hip (TH), trochanter (TR) and femoral neck (FN) with no prior vertebral fractures. *Exclusion:* Women with prevalent vertebral or low-trauma osteoporotic fractures; patients receiving treatment affecting bone metabolism.	PBO, n=83 IBN150mg/m, n=77 *Adjuvant:* Both groups, 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD *Secondary:* Change in FN, total hip and trochanter BMD change in bone resorption marker serum	*Fractures:* fractures were confirmed by radiograph and reported as adverse events. *BMD:* DXA - (Hologic Inc., Bedford, MA).
Ibandronate dose ranging trials					

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Delmas 2006 [49] (DIVA) USA, Canada, Mexico, Europe, Australia and South Africa Multicentre non-inferiority RCT, 53 centres Hoffman-La Roche and GlaxoSmithKline	*Inclusion:* Postmenopausal women 55–80 years of age; at least 5 years since menopause with osteoporosis (mean lumbar spine [L2-L4] BMD T score < -2.5 to -5.0) *Exclusion:* prior treatment with bisphosphonates or any other drug affecting bone metabolism; upper GI disease; renal impairment	IBN2.5mg/d, n=470 IBN2mg/iv, 2/m, n=454 IBN3mgiv, 3/m, n=471 *Adjuvant:* All groups, 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD year 1 *Secondary:* change in LS (L2–L4) BMD year 2 and BMD at proximal femur; bone markers	*Fractures:* Clinical vertebral and non-vertebral fractures were monitored from adverse event reporting (all fractures were confirmed radiographically). *BMD:* DXA on GE Lunar [Madison, WI, USA] and Hologic [Bedford, MA, USA]
Eisman 2008 [50] (DIVA) (year 2 data)			24 months		

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Miller 2005[47] (MOBILE) RCT phase III, non-inferiority study, involving 65 centres in the United States, Canada, Europe, Australia, South Africa, Mexico, and Brazil Hoffman-La Roche and GlaxoSmithKline	*Inclusion:* Postmenopausal women 55–80 years of age; at least 5 years since menopause with osteoporosis (mean lumbar spine [L2-L4] BMD T score < -2.5 and -5.0) *Exclusion:* Patients with uncontrolled active or recurrent peptic ulcer disease were excluded. Additional exclusion criteria were a disease, disorder, or therapy known to influence bone metabolism; prior treatment with bisphosphonates; fluoride treatment and renal	IBN2.5mg, n=402 IBN50mg. 2 doses/m, n=402 IBN100mg/m, n=404 IBN150mg/m, n=401: *Adjuvant:* Both groups, calcium 500mg/d plus vitamin D ≤400 IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS (L2–L4) BMD *Secondary:* Change in TH, trochanter and FN BMD	*Fractures:* Clinical vertebral and non-vertebral fractures were recorded as adverse events. *BMD:* DXA on GE Lunar [Madison, WI, USA] and Hologic [Bedford, MA, USA]
Reginster 2006 [48] (MOBILE) (year 2 data)			24 months		

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Risedronate vs. placebo					
Boonen 2009[60] Eastern and Western Europe, Lebanon, Australia, and the United States. Phase III multicentre RCT Procter & Gamble Pharmaceuticals and Sanofi-Aventis Pharmaceuticals	*Inclusion:* Men ≥30 yr. of age with osteoporosis including LS T-score ≤ -2.5 and FN T-score ≤ -1 SD or LS T-score ≤ -1 and FN T-score ≤ -2 SD. *Exclusion:* Men with secondary osteoporosis except those with primary hypogonadism who declined testosterone replacement therapy.	PBO, n=93 RIS35mg/w, n=191 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400-500IU/d	24 months X-rays taken at 12 and 12 months; BMD assessed at 6, 12 and 24 months	*Primary:* change in LS BMD at month 24 *Secondary:* change in LS and proximal femur BMD at months 6, 12, and 24; incidence of new vertebral fractures; incidence of clinical fractures (vertebral and Non-vertebral) reported as AEs at months 12 and 24.	*Fractures:* New vertebral fractures were determined by X-ray using a semiquantitative method Clinical vertebral and Non-vertebral fractures were reported as adverse events *BMD:* DXA (Hologic)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Choo 2011[64] Canada. RCT, number centres not reported AstraZeneca Pharmaceuticals	*Inclusion:* non-metastatic prostate cancer patients receiving radiotherapy plus 2-3 years of Androgen Ablation Therapy. All had LS T scores > -2.5	PBO, n=52 RIS35mg/w, n=52 *Adjuvant:* Both groups, calcium and vitamin D supplements (amount not reported)	24 months BMD assessed at 12 and 24 months	*Primary:* change in LS, FN and proximal femur BMD, biomarkers for bone turnover	*Fractures*: not an outcome BMD of the lumbar spine, proximal femur, and femoral neck were measured by DXA at baseline, year 1 and year 2

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Cohen 1999 [65] USA Multicentre RCT, 28 centres Procter & Gamble / NIH	*Inclusion:* Men and women aged 18-85 years old on glucocorticoids ≥ 7.5mg/day within 3 months; women at least 1 year postmenopausal *Exclusion:* History of hyperparathyroidism, hyperthyroidism or osteomalacia, use of drugs known to affect bone metabolism	Premenopausal women: PBO, n=52 RIS5mg/d, n=49 Postmenopausal women PBO, n=15 RIS5mg/d, n=14 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	12 months X-rays and BMD assessed at 12 months	*Primary:* Change of BMD at the LS BMD FN BMD, and femoral trochanter BMD *Secondary:* Fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* Quantitative morphometry was used to identify prevalent (baseline) and incident (new) vertebral fractures. A new (incident) vertebral fracture was defined as a decrease of ≥15% (for intact vertebrae at baseline) or a decrease of ≥4 mm (for fractured vertebrae at baseline) *BMD:* DXA - Hologic (Waltham, MA) or Lunar (Madison, WI)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Fogelman 2000 [68] (BMD-MN) France, the UK, the Netherlands, Belgium, and Germany Multicentre RCT, 13 centres Procter & Gamble and Aventis	*Inclusion:* Women up to 80 years of age. Postmenopausal for at least 1 year; mean lumbar spine (L1-L4) T score of -2 or less. *Exclusion:* History of hyperparathyroidism, hyperthyroidism or osteomalacia, use of drugs known to affect bone metabolism	PBO, n=180 RIS5mg/d, n=179 Also evaluated RIS2.5mmg/d, n=184 *Adjuvant:* Both groups, calcium1000mg/d	24 months BMD assessed at 6, 12, 18, and 24 months; X-ray at 24 months	*Primary:* Incidence of vertebral and non-vertebral fractures; and percentage change of BMD of the spine *Secondary:* Adverse events; and biochemical markers of bone turnover.	*Fractures:* non-vertebral fractures and vertebral fractures assessed as adverse events by radiographs. A vertebral body was considered to be fractured if any of the vertebral height ratios fell below 3 SD of the mean for the study population, *BMD:* Lunar Corp. (Madison, WI, USA) or Hologic, Inc. (Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Hooper 2005 [74] Australia Multicentre RCT, 11 centres Procter & Gamble and Aventis	*Inclusion:* Postmenopausal women for 6 to 36 months, with lumbar-spine BMD of greater than -2.5 SD (< 0.76 g/cm2 *Exclusion:* History of hyperparathyroidism, hyperthyroidism, or osteomalacia; treatment with bone agents likely to affect bone metabolism.	PBO, n=126 RIS5mg/d, n=129 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	24 months BMD assessed at 3, 6, 12, 18 and 24 months; X-ray at 24 months	*Primary:* Changes in LS BMD *Secondary:* Change of BMD at the FN, and trochanter; incidence of vertebral and non-vertebral fractures; adverse events.	*Fractures:* Prevalence and incidence vertebral fractures assessed by morphometric analysis. An incident fracture was considered evident if anterior/middle vertebral height was ≥15% of normal vertebrae height *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)
Harris 1999 [72] (VERT-NA) USA Multicentre RCT, 110 centres Procter & Gamble	*Inclusion:* Ambulatory women no older than 85 years, ≥5 years since menopause, with at least 1 vertebral fracture at baseline. *Exclusion:* Use of drugs known to affect bone metabolism.	PBO, n=815 RIS5mg/d, n=813 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months X-ray at 12, 24 and 36 months; BMD assessed every 6 months	*Primary:* Incidence of vertebral and non-vertebral fractures; and percentage change of BMD of the spine *Secondary:* Adverse events; and biochemical markers of bone turnover.	*Fractures:* Quantitative and semiquantitative assessment was used to assess prevalent (baseline) and incident fractures. Fracture was considered evident if anterior/middle vertebral height was ≤0.8 of posterior. *BMD:* Lunar (Madison, WI) or Hologic (Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Ste-Marie (2004)[101] (VERT-NA extension)	Women who had successfully completed the original 3-year study and who had undergone baseline and month-36 iliac crest biopsies were eligible to enrol. Women continued on their assigned treatments (placebo or risedronate) for an additional 2 years	PBO, n=42 RIS5mg/d, n=44	60 months	*Primary:* Histologic and Histomorphometric Assessments *Secondary:* Change in BMD	*Fractures:* recorded as adverse events
Reginster 2000 [87] (VERT-MN) European and Australian centres Multicentre RCT, no. centres NR Procter & Gamble and Hoechst Marrion Roussel	*Inclusion:* Ambulatory women up to 85 years and at least 5 years postmenopausal; had at least 2 radiographically confirmed vertebral fractures. *Exclusion:* Receiving treatment known to affect bone metabolism	PBO, n=407 RIS5mg/d, n=407 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months BMD assessed every 6 months, X-rays every 12 months	*Primary:* Changes in LS BMD *Secondary:* Change of FN BMD of the FN and trochanter BMD; incidence of vertebral and non-vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* Quantitative and semiquantitative assessment was used to assess prevalent (baseline) and incident fractures. Fracture was considered evident if anterior/middle vertebral height was ≥15% of normal vertebrae height. *BMD:* Lunar (Madison, WI) or Hologic (Waltham, MA)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Sorensen 2003 [102] (VERT-MN extension) USA Multicentre RCT, 29 centres Procter & Gamble	*Inclusion:* Women remained on the treatments (placebo or risedronate, 5 mg daily) to which they had originally been assigned. Blinding was maintained for the patients and clinical centre personnel throughout the 5 years of study.	PBO, n=130 RIS5mg/d, n=135 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	60 months	*Primary:* Incidence of vertebral fractures *Secondary:* Incidence of non-vertebral fractures; changes in LS and FN BMD and, FN, femoral trochanter and radius; biochemical markers of bone turnover; adverse events.	

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Leung 2005 [77] China Multicentre RCT, 4 centres Aventis Pharma	*Inclusion:* postmenopausal for 5 or more years with spine BMD at L1–4 <2.5 SD of the local peak young mean value. *Exclusion:* any medical conditions or medication known to affect bone metabolism	PBO, n=34 RIS5mg/d, n=31 *Adjuvant:* Both groups, calcium 500mg/d plus vitamin D 400 IU/d	12 months BMD assessed at 3, 6 and 12 months	*Primary:* Change in FN, LS, TH and trochanter BMD; bone marker *Secondary:* not reported	*Fractures:* not an outcome *BMD*: DXA (Hologic QDR 4500 plus, Hologic Inc., Waltham, MA, USA).

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
McClung 2001[80] USA Multicentre RCT, 183 centres Procter & Gamble / Aventis	*Inclusion:* Women ≥70 years old; Low BMD at the femoral neck T score lower than -4 or lower than -3 with at least 1 non-skeletal risk factor for hip fracture. *Exclusion:* Any major illness, history of another metabolic bone disease, bilateral hip fracture, recent use of drugs known to affect bone	Women 70–79 years: PBO, n=1821 RIS2.5mg/d, n=1812 RIS5mg/d, n=1812 Women ≥80 years: PBO, n=1313 RIS2.5mg/d, n=1281 RIS5mg/d, n=1292 *Adjuvant:* Both groups, calcium 1000mg/d plus vitamin D ≤500 IU/d for women with low vitamin D	36 months BMD assessed every 6 months	*Primary:* Change in LS BMD *Secondary:* Change in BMD of the FN, proximal femur, trochanter, radius; vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* radiographically confirmed hip fractures and non-vertebral osteoporotic fractures. Non-vertebral osteoporotic fractures, defined as all radiographically confirmed fractures of the wrist, leg, humerus, hip, pelvis, or clavicle. *BMD: DXA* - (Lunar, Madison, Wis., or Hologic, Waltham, Mass.

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Reid 2000 [88] UK Multicentre RCT, 23 centres Procter & Gamble and/ Hoechst Marrion Roussel	*Inclusion:* Ambulatory men and women 18-85 years, who had taken glucocorticoids for at least 6 months. *Exclusion:* History of hyperparathyroidism, hyperthyroidism, or osteomalacia; treatment with bone agents likely to affect bone metabolism	PBO, n=96 RIS5mg/d, n=100 *Adjuvant:* Both groups, vitamin D 400 IU/d calcium 1000mg/d	12 months BMD assessed at 6 and 12 months; X-ray at 12 months	*Primary:* Change in LS BMD *Secondary:* Change in BMD of the FN, proximal femur, trochanter, radius; vertebral fractures; biochemical markers of bone turnover; adverse events.	*Fractures:* incident fractures were identified using quantitative morphometry defined as a reduction of ≥15% in vertebral height in a previously intact vertebra or a reduction of ≥4mm in a previously fractured vertebra *BMD:* DXA - Lunar (Madison, WI, USA.) or Hologic (Waltham, Massachusetts, U.S.A.)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Ringe 2006[91] Germany. Single-centre RCT Sponsor not reported	*Inclusion:* Men with primary or secondary osteoporosis with or without pre-existing prevalent vertebral fractures. Osteoporosis was defined as a LS (BMD) T-score of ≤-2.5 SD and FN BMD T-score of ≤-2.0 relative to a healthy young adult male. Primary OP; secondary OP: PBO, 92 (58.2%); 66 (41.8%) RIS5mg/d, 94 (59.5%); 64 (40.5%) *Exclusion:* Patients with known hypersensitivity to bisphosphonates, severe impairment of renal function, hypocalcaemia and a history of bisphosphonate or fluoride pre-treatment	PBO, n=158 RIS5mg/d, n=158 *Adjuvant:* PBO with fractures, calcium 500mg/d and alfacalcidol 1000mg/d PBO without factures, calcium 800mg/d and vitamin D 1000IU/d	12 months BMD and X-ray at 12 months	*Primary:* Change in LS BMD *Secondary:* incidence of new vertebral fractures; change in FN and TH BMD; change in body height; course of back pain; and the incidence of non-vertebral fractures.	*Fractures:* Radiographic X-rays of the spine. Assessment of vertebral fracture was performed using the semi-quantitative technique *BMD:* DXA (Lunar Corp., Madison, WI, USA).
Ringe 2009 [103] Follow-up to Ringe 2006[91]		PBO, n=158 RIS, n=158	24 months		

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Taxel 2010[97] USA. RCT, number centres not reported Proctor and Gamble/and Aventis	*Inclusion:* Men aged >55 years and within a month of receiving an initial injection of ADT for prostate cancer *Exclusion:* metastatic bone disease, chronic kidney, gastrointestinal or liver diseases, a previous cancer diagnosis, metabolic bone disorders medications that interfere with bone metabolism.	PBO, n=20 RIS35mg/w, n=20 *Adjuvant:* Both groups, calcium 600 mg/d and vitamin D 400IU/d	6 months BMD assessed at 6 months	*Primary:* FN and TH BMD *Secondary:* change in bone markers	*Fractures:* not an outcome *BMD* DXA (Lunar DXA-IQ, Madison, WI, USA)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Zoledronate vs. placebo					

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Black 2007[58] (HORIZON-PFT) International. Multicentre RCT. Number centres not reported. Novartis Pharma	*Inclusion:* Postmenopausal women between the ages of 65 and 89 with FN BMD T score of -2.5 or less, with or without evidence of existing vertebral fracture, or a T score of -1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Use of hormone therapy, raloxifene, calcitonin, tibolone, tamoxifen, ehydroepiandrosterone ipriflavone, and medroxyprogesterone was allowed. Patients in Stratum I (n=6113) were not taking any osteoporosis medications at the time of randomization, whereas patients in Stratum II (n=1652) were all taking an allowed medication. *Exclusion:* previous use of parathyroid hormone., sodium fluoride, anabolic steroids, growth hormone, glucocorticoids, or strontium	PBO, n=3876 ZOL5mg/y, n=3889 *Adjuvant:* Both groups, calcium 1000 - 1500mg/d and vitamin D 400-1200IU/d	36 months X-ray at 12, 24, and 36 months in Stratum I; baseline and 36 months in Stratum II; BMD assessed at 6, 12, 24 and 36 months	*Primary:* Stratum II, vertebral fractures Strata I & II, hip fracture. *Secondary:* any non-vertebral fracture, any clinical fracture, and clinical vertebral fracture. Changes in LS, FN and TH BMD; changes in markers of bone resorption and formation.	*Fractures:* Spinal lateral radiographs were, vertebrae from T4 to L4 were evaluated with the use of quantitative morphometry and standard methods. Incident morphometric vertebral fractures were defined as a reduction in vertebral height of at least 20% and 4 mm by quantitative morphometry, confirmed by an increase of one severity grade or more on semiquantitative analysis. Clinical fracture reports were obtained from patients at each contact. Non-vertebral fracture reports required central confirmation. Excluded were fractures of the toe, facial bone, and finger and those caused by excessive trauma. *BMD*: DXA – model not reported. Measurements of bone mineral density at the lumbar spine were obtained for a subgroup of patients.

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Reid 2010[104] (HORIZON-PFT)				Adverse events	
Lyles 2007[79] (HORIZON-RFT) International. Multicentre RCT number centres not reported Novartis Pharma	*Inclusion:* Men and women 50 years of age or older within 90 days after surgical repair of a hip fracture sustained with minimal trauma; ambulatory prior to fracture. *Exclusion:* calculated low creatinine clearance, low serum calcium, active cancer, metabolic bone disease, and a life expectancy of less than 6 months	PBO, n=1062 ZOL5mg/y, n=1065 *Adjuvant:* Both groups, calcium 1000 - 1500mg/d and vitamin D 800-1200IU/d	36 months BMD assessed every 12 months	*Primary:* new clinical fractures excluding facial and digital fractures and fractures in abnormal bone (e.g., bone containing metastases). *Secondary:* BMD of the non-fractured hip; new vertebral, non-vertebral, and hip fractures; safety	*Fractures:* Lateral radiography of the chest and lumbar spine. A non-vertebral fracture (not a vertebral, facial, digital, or skull fracture) was confirmed when a radiograph, a radiographic report, or a medical record documented a new fracture. A new clinical vertebral fracture was defined as new or worsening back pain with a reduction in vertebral body height of 20% (grade 1) or more, as compared with baseline radiographs, or a reduction in vertebral body height of 25% (grade 2) or more if no baseline radiograph was available. *BMD:* DXA – model not reported
Adachi 2011[105] (HORIZON-RFT)				Quality of life	

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Boonen 2012[61] Europe, South America, Africa, and Australia. RCT, number centres not reported Novartis	*Inclusion:* Men 50 to 85 years of age who had primary osteoporosis or osteoporosis associated with low testosterone levels with BMD T score ≤–1.5 at TH or FN and one to three prevalent vertebral fractures Men without fractures were eligible if they had a bone mineral density T score ≤–2.5 at TH, FN or LS *Exclusion:* four or more prevalent vertebral fractures; low serum vitamin D, renal insufficiency, hypercalcaemia or hypocalcaemia; hypersensitivity to bisphosphonates; medication affecting bone metabolism	PBO, n=611 ZOL5mg/y, n=588 *Adjuvant:* Both groups, calcium 1000-1500 mg/d and vitamin D 800-1200IU/d	24 months X-ray at 12 and 24 months; BMD assessed at 6, 12 and 24 months	*Primary:* proportion of men with one or more new morphometric vertebral fractures *Secondary:* proportion of men with one or more new morphometric vertebral fractures; one or more new moderate-to-severe, or new or worsening morphometric vertebral fractures; change in height; the time to first clinical fracture (vertebral or Non-vertebral); change in LS, FN and TH BMD; bone-turnover markers; safety	*Fractures:* Vertebral fractures were assessed by means of quantitative vertebral morphometry performed on lateral thoracic and lumbar spine, incident vertebral fracture was assessed by means of morphometry and defined as a reduction in vertebral height of 20% or more and 4 mm or more. Clinical fractures (vertebral and Non-vertebral) were reported by participants at each visit and were verified by radiographic report or surgical notes. Only confirmed fractures were included in the analysis *BMD:* DXA – model not reported. BMD and bone markers were analysed in a subgroup of 100 or more participants.

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
McClung 2009 [81] USA and France. Multicentre RCT, 25 centres Novartis	*Inclusion:* Women aged 45 and older who were postmenopausal LS BMD T score less than -1.0 and more than -2.5 and FN T score greater than -2.5 *Exclusion:* Participants with >1 vertebral fracture or any grade 2 or 3 vertebral fracture. Participants with low vitamin D, renal insufficiency, hyper- or hypocalcaemia, treatment medications affecting bone metabolism	PBO, n=202 ZOL5mg/y, n=198 *Adjuvant:* Both groups, calcium 500-1200 mg/d and vitamin D 400-800IU/d	24 months BMD assessment time points not reported	*Primary:* change in LS BMD at 12 months *Secondary:* change TH< FN, trochanter and distal radius at 12 and 24 months; bone markers	*Fractures:* not an outcome *BMD:* DXA Hologic or GE Lunar machine.

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Head-to-head – Alendronate vs. Ibandronate					
Miller 2008[83] (MOTION) The Americas, USA, Europe and South Africa. Multicentre RCT, 65 centres Hoffman La-Roche Ltd and GlaxoSmithKline	*Inclusion:* postmenopausal women aged 55 to <85 with LS (L2–L4) BMD T-score <–2.5 and ≥–5.0 SD *Exclusion:* upper GI disease, any diseases or medications known to influence bone metabolism.	ALN70mg/w, n=873 IBN150mg/m, n=887 *Adjuvant:* Both groups, calcium 500 mg/d and vitamin D 400IU/d	12 months BMD assessed at 12 months	*Primary:* change in LS and TH BMD. *Secondary:* change in trochanter BMD; bone markers	*Fractures:* recorded as adverse events (assessment method not reported) *BMD:* DXA – model not reported
Head-to-head – Alendronate vs. Risedronate					
Atmaca 2006 [56] Turkey RCT, n centres not reported Sponsor not reported	*Inclusion:* late postmenopausal women with osteoporosis with a mean age of 66.3 y (range, 60–85 y) and a T-score less than –2.5 *Exclusion:* any medical conditions or medication known to affect bone metabolism	RIS5mg/d, n=14 ALN10mg/d, n=14 *Adjuvant:* Both groups, calcium 600 mg/d and vitamin D 400IU/d	12 months BMD assessment time point not reported	*Primary:* change in FN, LS and distal radius BMD; bone markers *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA – Hologic QDR

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Muscoso 2004[84] Italy RCT, n centres not reported Sponsor not reported	*Inclusion:* osteoporotic female population submitted to a treatment with antiresorption drugs *Exclusion:* not reported	RIS5mg/d, n=1000 ALN10mg/d, n=100 Other treatments were: clodronate, n=800 and raloxifene, n=100 *Adjuvant:* all groups, calcium 1000 mg/d and vitamin D 800IU/d	24 months BMD assessment time point not reported	*Primary:* change in LS BMD; fractures *Secondary:* not reported	*Fractures:* not reported *BMD:* DXA – Lunar DPX

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Sarioglu 2006[94] Turkey RCT, n centres not reported Sponsor not reported	*Inclusion:* postmenopausal women with osteoporosis *Exclusion:* Patients over 75 years and taking treatment for osteoporosis. The presence of any disease which interferes with bone metabolism, recent use of drugs known to affect bone metabolism and history of esophagitis and peptic ulcer were also accepted as exclusion criteria.	RIS5mg/d, n=25 ALN10mg/d, n=25 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	12 months BMD assessment time point not reported	*Primary:* change in hip BMD *Secondary:* not reported	*Fractures:* not an outcome *BMD:* DXA – Lunar DPX

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Rosen 2005[92] (FACT) USA Multicentre RCT, 78 centres Merck	*Inclusion:* Postmenopausal women≥40years or ≥25y if surgically menopausal. BMD T score ≤-2.0 SD in at least 1 of the 4 sites (total hip, hip trochanter, femoral neck, or posterior lumbar spine) *Exclusion:* Hypocalcaemia, hypovitaminosis D, metabolic bone disease; bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Had taken oestrogen, oestrogen analogues within 6 months	ALN70mg/w, n=520 RIS35mg/w, n=533 Both groups, 1000 mg calcium and 400 IU vitamin D	12 months BMD assessed at 6 and 12 months	*Primary:* Change trochanter BMD *Secondary:* Change in BMD at total hip, FN, total hip and LS	*Fractures:* incidence of clinical fracture recorded as adverse events (assessment method not reported) *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Bonnick 2005[106] (FACT) (Extension to Rosen 2005[92]) USA Multicentre RCT, 72 of the original 78 centres Merck	*Inclusion:* Postmenopausal women≥40years or ≥25y if surgically menopausal. BMD T score ≤-2.0 SD in at least 1 of the 4 sites (total hip, hip trochanter, femoral neck, or posterior lumbar spine) *Exclusion:* Hypocalcaemia, hypovitaminosis D, metabolic bone disease; bisphosphonates w/in 1y or for ≥2y w/in 5y; use of PTH w/in1y. Had taken oestrogen, oestrogen analogues within 6 months	ALN70mg/w, n=411 RIS35mg/w, n=414 Both groups, 1000 mg calcium and 400 IU vitamin D	Extension to 24 months	*Primary:* Change trochanter BMD *Secondary:* Change in BMD at total hip, FN, total hip and LS	*Fractures:* Clinical fractures that occurred during the trial, regardless of association with trauma or skeletal site, were reported by investigators as clinical AEs (assessment method not reported) *BMD:* Hologic (Waltham, MA) or Lunar (Madison, WI)

Author details (trial acronym), country, number centres and sponsor	**Inclusion & Exclusion criteria**	**Numbers randomised and adjuvant supplements**	**Final follow-up and assessment time points**	**Primary & secondary outcomes**	**Fracture & BMD assessments**
Reid 2006[89] (FACTS) Europe, the Americas and Asia-Pacific. Multicentre RCT , 75 centres Merck & Co., Inc.	*Inclusion:* Postmenopausal >40 years of age with low bone density (-2.0 SD below the young normal mean at LS< FN or TH *Exclusion:* hypocalcaemia, hypovitaminosis D, or metabolic bone diseases, use of oestrogen, oestrogen analogues, tibolone or anabolic steroids, bisphosphonates, or parathyroid hormone	ALN70mg/w, n=468 RIS35mg/w, n=468 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	12 months BMD assessed at 6 and 12	*Primary:* change in trochanter BMD *Secondary:* change in LS, TH and FN BMD	*Fractures:* Fractures were reported as adverse events whether or not they were associated with trauma and without requirements of radiographic confirmation or adjudication *BMD:* DXA -using Hologic or Lunar densitometers
Reid 2008[107] (FACTS) (Extension to Reid 2006[89]) Seventy-two of the original 75 international sites Merck & Co., Inc.	*Inclusion:* all eligible women maintained their original randomised, blinded treatment allocation from year 1	ALN70mg/w, n=403 RIS35mg/w, n=395 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400IU/d	24 months		

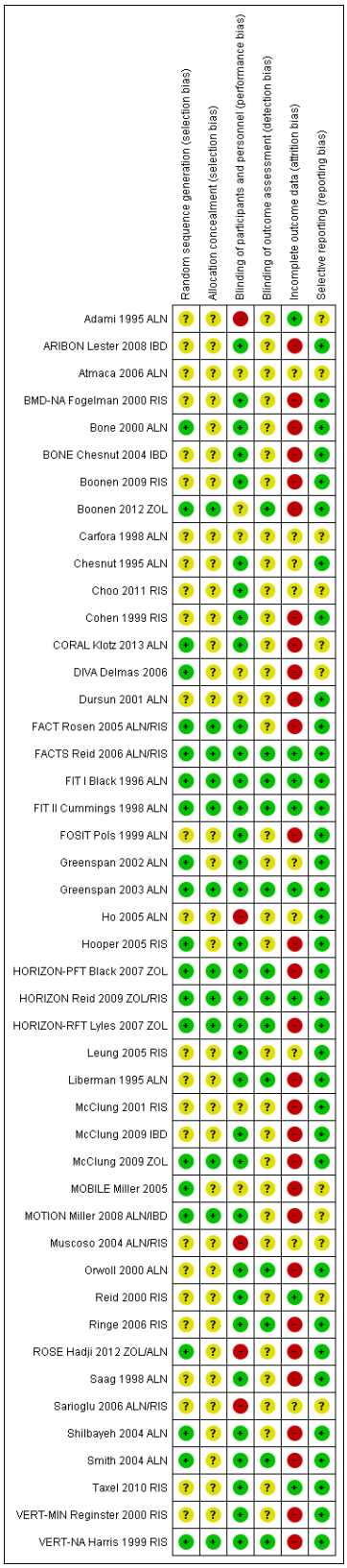
Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Head-to-head – Zoledronate vs. Alendronate					
Hadji 2010[108] (ROSE)				*Primary:* Quality of Life and compliance	
Hadji 2012[71] (ROSE) Germany Multicentre RCT, 95 centres Novartis Pharma	*Inclusion:* women aged 55–90 years who were considered postmenopausal with BMD T-score ≤-2.0 at TH or LS *Exclusion:* Patients who had received prior therapy with bisphosphonates, parathyroid hormone, strontium ranelate, raloxifene, calcitonin, high-dose glucocorticoids, patients with a fracture within 6 months secondary osteoporosis, primary hyperparathyroidism, Patients with inappropriate blood chemistry.	ZOL5mg/y, n=408 ALN70mg/w, n=196 *Adjuvant:* Both groups, calcium 1200 mg/d and vitamin D 800IU/d	12 months	*Primary:* to assess if zoledronic acid was superior to alendronate in reducing serum NTx levels. *Secondary:* comparison of P1NP levels ; safety and tolerability	*Fractures and BMD:* not outcomes assessed by the trial (assessed bone markers and quality of life)

Author details (trial acronym), country, number centres and sponsor	Inclusion & Exclusion criteria	Numbers randomised and adjuvant supplements	Final follow-up and assessment time points	Primary & secondary outcomes	Fracture & BMD assessments
Head-to-head – Zoledronate vs. Risedronate					
Reid 2009[90] (HORIZON) Australia, EU countries including UK, Hong Kong and USA. Multicentre RCT, 54 centres Novartis Pharma	*Inclusion:* Men and women aged 18–85 receiving at least 7.5 mg oral prednisolone daily (or equivalent) and were expected to receive glucocorticoids for at least another 12 months. *Exclusion:* previous treatment drugs that affect the skeleton, low serum vitamin D history of cancer or parathyroid disease, and renal impairment.	ZOL5mg/y treatment, =272; prevention, n=144 RIS5mg/d - treatment, n=273; prevention, n=144 *Adjuvant:* Both groups, calcium 1000 mg/d and vitamin D 400-1200IU/d	12 months BMD assessed at 6 and 12 months; X-ray at 12 months	*Primary:* change in LS BMD *Secondary:* change in BMD at FN, TH, trochanter, and distal radius; occurrence of thoracic and lumbar vertebral fractures	*Fractures:* thoracic and lumbar vertebral fractures were defined according to semiquantitative methods *BMD:* Hologic (Waltham, MA, USA) or GE Lunar (Madison, WI, USA)

ALN, alendronate; BMD, bone mineral density; DXA, dual X-ray absorptiometry; eod, every other day; FN, femoral neck; IBN, ibandronate; LS, lumbar spine; mg/d, milligrams per day; mg/m, milligrams per month; mg/iv, milligrams intravenous; mg/y, milligrams per year; NTx, N-telopeptide of collagen type I; P1NP, procollagen 1 C terminal extension peptide; PBO, placebo; PTH, parathyroid hormone; RCT, randomised controlled trial; RIS, risedronate; IU/d, international units per day; SD, standard deviation; TH, total hip; ZOL, zoledronate; 2/m, twice per month; 3/m, three times per month

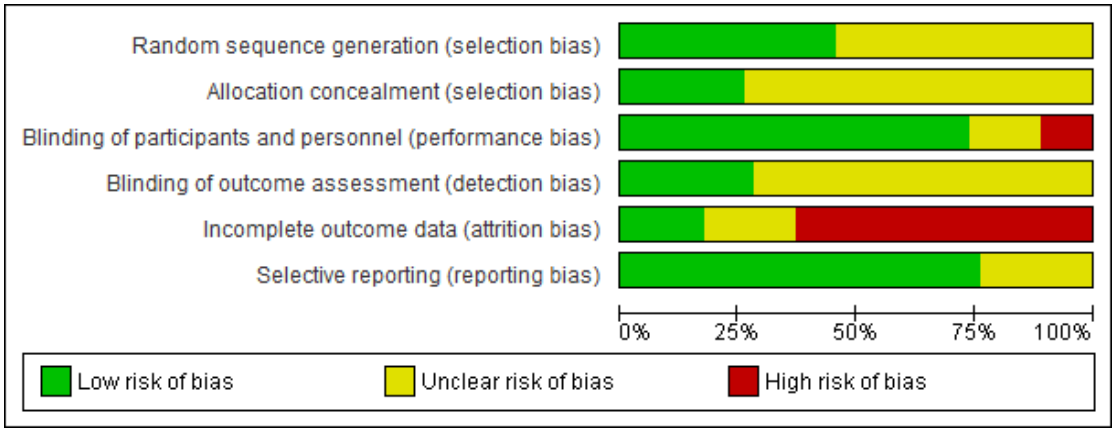
Trial acronyms: ARIBON, reversal of anastrozole (ARImidex) induced bone loss with oral monthly ibandronate (BONdronat) treatment during adjuvant therapy for breast cancer; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; DIVA, Dosing IntraVenous Administration; FACT, Fosamax Actonel Comparison Trial; FACTS, Fosamax Actonel Comparison Trial international study; FIT, Fracture Intervention Trial; FOSIT, FOSamax International Trial; HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial; HORIZON-RFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Recurrent Fracture Trial; ROSE, Rapid Onset and Sustained Efficacy; MOBILE, Monthly Oral iBandronate In LadiEs; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention; VERT-NA, Vertebral efficacy with Risedronate Therapy-North American; VERT-MN, Vertebral efficacy with Risedronate Therapy-Multi National

Supplementary Figure 1: Risk of bias summary: judgements about each risk of bias item for each included RCT



?, unclear risk of bias; +, low risk of bias, -, high risk of bias

Supplementary Figure 2: Risk of bias graph: judgements about each risk of bias item presented as percentages across all included RCTs



2. Statistical methods for the network meta-analysis

2.1. Statistical model for the network meta-analysis of fracture outcomes

The RCTs presented fracture data in terms of the number of individuals experiencing at least one fracture. For each fracture type, r_{ik} is defined as the number of events out of the total number of participants, n_{ik}, where the participants are receiving treatment t_{ik} in arm k of trial i. The data generation process is assumed to follow a Binomial likelihood such that

$$r_{ik} \sim bin(p_{ik}, n_{ik}), \quad (1)$$

where $p_{i,k}$ represents the probability of an event in arm k of trial i $(i = 1 \dots ns, k = 1 \dots na)$ after follow up time f_i. For all RCTs, the number of arms included in the analysis is 2 (i.e. $na = 2$) and the number of RCTs, ns, varies according to fracture type.

To account for different trial durations, an underlying Poisson process is assumed for each trial arm, so that T_{ik} (the time until a fracture occurs in arm k of study i) follows an exponential distribution, $T_{ik} \sim exp(\lambda_{ik})$, where λ_{ik} is the event rate in arm k of study i, assumed constant over time. The probability that there are no events at time f_i is given by the survivor function, $P(T_{ik} > f_i) = \exp(-\lambda_{ik} f_i)$. For each study, i, the probability of an event in arm k after follow up time f_i can be written as

$$p_{ik} = 1 - P(T_{ik} > f_i) = 1 - \exp(-\lambda_{ik} f_i), \quad (2)$$

which is dependent on follow up time. The probabilities of fracture are non-linear functions of event rates and so were modelled using the complementary log-log link function:

$$cloglog(p_{ik}) = \log(f_i) + \mu_i + \delta_{i,1k} I_{k \neq 1}. \quad (3)$$

Here, the μ_i are trial specific baselines, representing the log-hazards of fracture in the baseline treatment, which is assumed to be arm $k = 1$ for all trials. Note that for some trials, the baseline may be an active treatment rather than placebo. The trial-specific treatment effects, $\delta_{i,1k}$, are log-hazard ratios of fracture for the treatment in arm k, relative to the baseline treatment.

The trial-specific treatment effects, $\delta_{i,1k}$, were assumed to arise from a common population distribution with mean treatment effect relative to the reference treatment, which was defined as placebo for this analysis, such that

$$\delta_{i,1k} \sim N\left(d_{t_{i1} t_{ik}}, \tau^2\right), \quad (4)$$

where $\mathrm{d}_{\mathrm{t_{i1}t_{ik}}}$represents the mean effect of the treatment in arm k of study i (t_{ik}) compared to the treatment in arm 1 of study i (t_{i1}) and τ^2 represents the between study variance in treatment effects (heterogeneity) which is assumed to be the same for all treatments.

An exchangeable treatment effects model was used i.e. class effects model where the treatment effects are assumed to arise from a common distribution according to the class of drug. Under a

class effects model, the mean effects of each treatment are assumed to be exchangeable and assumed to arise from a Normal distribution with mean, D, with variance τ_D^2:

$$d_{t_{i1}t_{ik}} \sim N(D, \tau_D^2). \quad (5)$$

The model was completed by specifying prior distributions for the parameters. Where there were sufficient sample data, conventional reference prior distributions were used:

- Trial specific baseline, $\mu_i \sim N(0, 100^2)$,
- Between study standard deviation of treatment effects, $\tau \sim U(0,2)$.
- Mean bisphosphonate effect, $D \sim N(0, 100^2)$,
- Between treatment standard deviation, $\tau_D \sim U(0,2)$.

For hip and wrist outcomes where information for some treatments was either weak or absent, a weakly informative prior was used for the between treatment standard deviation such that: $\tau_D^2 \sim HN(0, 0.32^2)$.

Rational for choice of class effects model

Not all RCTs contributing wrist fracture data provide evidence about all bisphosphonates; in particular, there was no evidence about zoledronate in the wrist fracture network. To allow an assessment of the uncertainty associated with zoledronate, a class effects model was fitted from which the predictive distribution of a new intervention in the same class can be generated. This modelling approach also has the benefit of addressing data sparsity in the hip network without the need to use of a weakly informative prior for the baseline of ARIBON, Lester *et al.*, 2008[1] (as was required when fitting a standard independent random effects model).

For the reasons discussed above, the results presented in the main paper are based on the class effects model, however we note that using a standard independent random effects model results in broadly similar inferences (unpublished results).

Predicting effects in new RCTs

To account for heterogeneity in the effect of treatments between RCTs, results are also presented for the predictive distributions of the effect of treatment in a new (randomly chosen) study.

From equation (4), it follows that the study specific population log-hazard ratio, $\delta_{i,j}$, for study i, evaluating bisphosphonate j in reference to the control treatment can be written as

$$\delta_{i,j} = d_{1j} + \varepsilon_{ij}, \quad (6)$$

where $\varepsilon_{ij} \sim N(0, \tau^2)$. The predictive distribution for the effect of a particular bisphosphonate in a new study $\delta_{i,j}$ from the same class following, in a new study is:

$$\delta_{new,j} \sim N\left(d_{1j}, \tau^2\right) \quad (7)$$

The class effects model also allows generation of the predictive distribution of a new, randomly chosen treatment from the same class. From equation (5), it follows that the population log-hazard ratio for each treatment can be written as

$$d_{1j} = D + \xi_j, \quad (8)$$

where $\xi \sim N(0, \tau_D^2)$. Therefore, combining equations (6) and (8), the study-specific population log-hazard ratio, δ_{ij}, for study i evaluating bisphosphonate j is:

$$\delta_{ij} = D + \zeta_j + \varepsilon_{ij}, \quad (9)$$

For a new, randomly chosen bisphosphonate, the expectation is $E\left[\delta_{ij}\right] = E\left[D + \zeta_j + \varepsilon_{ij}\right] = D$, with variance:

$$V\left[\delta_{ij}\right] = V\left[D + \zeta_j + \varepsilon_{ij}\right] = \tau^2 + \tau_D^2 \quad (10)$$

Therefore, the predictive distribution for the effect of a new, randomly chosen study from the same class is:

$$\delta_{new} \sim N(D, \tau_D^2 + \tau^2), \quad (11)$$

which accounts for both between study, τ^2, and between treatment within class, τ_D^2, heterogeneity for any (including a new) treatment.

It is the predictive distribution of a new treatment within the class and the predictive distribution of a new study for a new treatment within the class that we use to characterise the uncertainty about the effect of zoledronate for wrist fractures.

2.2. Statistical model for the network meta-analysis of bone mineral density

Data for femoral neck BMD outcomes was presented in two different formats; either as the percentage change in femoral neck BMD for each treatment group, or as the mean difference in the percentage change between treatment groups. Two different data generation (i.e. likelihood) models are therefore required.

Percentage change in femoral neck BMD

The majority of RCTs presented data as the percentage change in femoral neck BMD, y_{ik}, and associated standard errors, se_{ik}, for arm k of trial i with study duration f_i years. The data generation process is assumed to follow a Normal likelihood such that

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2), \quad (12)$$

where the population variance of the mean, se_{ik}^2, is assume to be known and equal to the sample estimate. The parameters of interest, θ_{ik}, are modelled using the identity link function and, to account for differing trial lengths, study duration was included as a trial level covariate. The link function is given by:

$$\theta_{ik} = \mu_i + (\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i)I_{k\neq 1}, \quad (13)$$

where $\beta_{11} = 0$, and β_{1k} $(k = 2,..,na)$ are the treatment-specific interactions, describing the relationship between the effect of treatment on percentage change in femoral neck BMD and duration of study. The trial baselines, μ_i , represent the percentage change in femoral neck BMD from baseline in the reference arm. The treatment effects, $\delta_{i,1k}$, represent the difference between the percentage change in the treatment group and the reference group. Assumptions about the relationship between the interaction terms are described further in the meta-regression section.

Difference between treatments in mean change in femoral neck BMD

Some RCTs provided data in terms of the mean difference in percentage change in femoral neck BMD between two treatments, defined as

$$MD_{i,1k} = y_{ik} - y_{i1}, \quad (14)$$

together with the associated standard errors of the mean difference, $v_{i,1k}$, rather than the percentage change in femoral neck BMD for individual treatments. The difference between treatments in the mean change are also assumed to be Normally distributed such that:

$$MD_{i,1k} \sim N(\theta'_{ik}, v_{i1k}^2), \quad (15)$$

where the population standard error of the difference, v_{i1k}^2, is assumed to be known and equal to the sample estimate. From the mean differences, no trial-specific effects of the baseline treatment can be estimated. The linear predictor is then given by

$$\theta'_{ik} = (\delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})f_i)I_{k\neq 1} \quad (16)$$

The study-specific treatment effects, $\delta_{i,1k}$, have the same interpretation as those from the equation (13) and thus can be combined to estimate the mean effects for each treatment, regardless of the way the data were reported.

A class effects model was assumed such that the treatment effects of the individual bisphosphonates were assumed to be exchangeable and to arise from a Normal distribution with mean, D, with variance τ_D^2:

$$d_{t_{i1}t_{ik}} \sim N(D, \tau_D^2). \quad (17)$$

The model was completed by specifying prior distributions for the parameters, using conventional reference prior distributions:

- Trial specific baseline, $\mu_i \sim N(0, 100^2)$,
- Between study standard deviation of treatment effects, $\tau \sim U(0,100)$.
- Mean of related treatment effects, $D \sim N(0, 100^2)$,
- Between treatment standard deviation, $\tau_D \sim U(0,100)$.

2.3. Meta-regression

Where appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers. Meta-regression was used to test for interactions between the treatment effects and trial level covariates, as described in Dias *et al.*[2].

An interaction term, β, is introduced on the treatment effect by replacing

$$\tilde{\delta}_{i,1k} = \delta_{i,1k} + (\beta_{1t_{ik}} - \beta_{1t_{i1}})(x_i - \bar{x}), \quad (18)$$

where x_i is the trial-level covariate for trial i and may represent a subgroup, continuous covariate, or baseline risk (as described in more detail below), and $\beta_{11} = 0$. The regression is centred at the mean value of the covariate across the RCTs so that the interpretation of the treatment effect is as the effect at the average value of the covariate.

Different assumptions can be made about the relationship between the interaction terms for each treatment. For the main analysis, we assume a common interaction for each treatment relative to treatment 1, such that

$$\beta_{1,t_{ik}} = b, \quad (19)$$

for $k = 2, \ldots, na$. We also considered a model in which the interaction terms for each treatment were considered to be related but not identical (i.e. exchangeable) such that:

$$\beta_{1,t_{ik}} \sim N(b, \tau_B^2). \quad (20)$$

Meta-regression on baseline risk/response

Baseline risk/response can be used as a proxy for differences in patient characteristics across trials that, may be modifiers of treatment effect, and so introduce a potential source of heterogeneity in the NMA. Adjustment for baseline risk/response was assessed using the method of Achana et. al. [3]

Dependence on baseline risk is introduced through an interaction term, so that:

$$\tilde{\delta}_{i,1k} = d_{t_{i1}t_{ik}} + \beta_{t_{i1}t_{ik}}(\mu_{iP} - \bar{\mu}_P) + \varepsilon_{i,t_{i1}t_{ik}}, \quad (21)$$

where $\varepsilon_{i,t_{i1}t_{ik}} \sim N(0, \tau^2)$. The updated study specific treatment effects, $\tilde{\delta}_{i,1k}$, are now adjusted using the `true' but unobserved baseline risk/response in the placebo arm of trial i, μ_{iP}. The coefficient, $\beta_{t_{i1}t_{ik}}$, represents the change in the treatment effect (e.g. log HR or difference between treatments in mean change) per unit change in the baseline risk/response. The baseline risk/response is centred on $\bar{\mu}_P$, the observed mean (e.g. log HR or difference between treatments in mean change) in the placebo group, and $\beta_{11} = 0$.

For RCTs with an active treatment control, $(t_{i1} \neq P)$, there is no direct estimate of the placebo baseline risk/response. Under the consistency of evidence arising from the exchangeability assumption, the substitution $d_{t_{i1}t_{ik}} = d_{Pt_{ik}} - d_{Pt_{i1}}$ can be made, allowing equation (21) to be expressed as

$$\tilde{\delta}_{i,1k} = (d_{Pt_{ik}} - d_{Pt_{i1}}) + (\beta_{Pt_{ik}} - \beta_{Pt_{i1}})(\mu_{iP} - \bar{\mu}_P). \quad (22)$$

Although a placebo treatment may not be included in all RCTs, the assumption of exchangeability means that the treatment arms can be assumed missing at random without loss to efficacy, and the baseline risk/response in RCTs without a placebo arm can be estimated, borrowing strength from other RCTs [3].

As previously described, some RCTs report data on the mean differences in percentage change between two treatments. Under the model described in equations (15) and (16), study specific effects of the baseline treatment cannot be estimated. These RCTs still contribute to the model through estimation of the treatment effects, but do not directly contribute to estimation of the slope in the meta-regression.

For femoral neck BMD, the class effects model with baseline-response adjustment there was insufficient evidence to estimate parameters based on the sample evidence alone and so weakly informative priors were used for placebo arms of the RCTs with active treatment.

Reference List

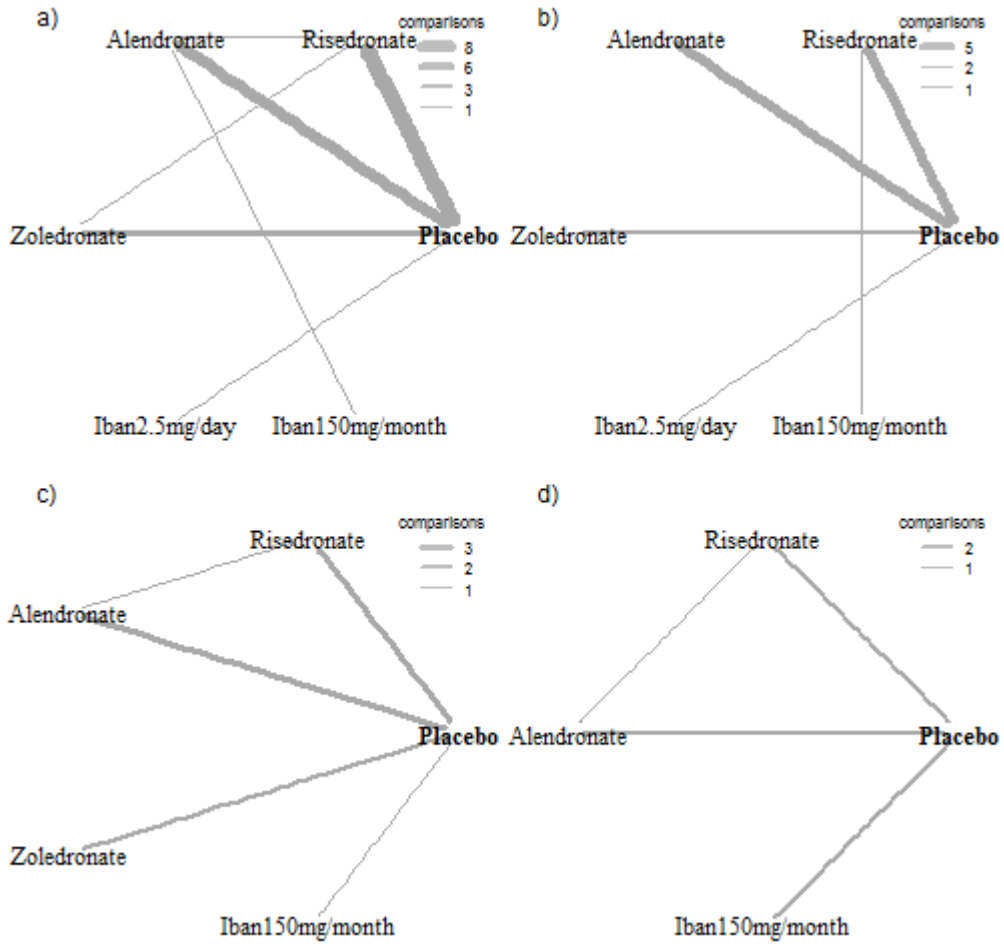
[1] Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clinical Cancer Research 2008;14:6336-42.

[2] Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence Synthesis for Decision Making 3: HeterogeneitySubgroups, Meta-Regression, Bias, and Bias-Adjustment. Medical Decision Making 2013;33:618-40.

[3] Achana FA, Cooper NJ, Dias S, Lu G, Rice SJ, Kendrick D et al. Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. Statistics in Medicine 2013;32:752-71.

3. Additional information, fracture outcomes

Supplementary Figure 3: Evidence network for fracture outcomes a) vertebral b) non-vertebral c) hip d) wrist.



Supplementary Table 3: Vertebral fractures. Pairwise HR and 95% credible intervals (lower triangle), predictive effects in a new study and 95% prediction interval (upper triangle). Treatment effects less than one favour the intervention.

Treatment	Placebo	Risedronate	Alendronate	Zoledronate	Ibandronate 2.5mg daily	Ibandronate 150 mg monthly
Placebo	1	0.51(0.28,0.86)	0.45(0.25,0.79)	0.40(0.23,0.76)	0.47(0.25,0.87)	0.46(0.21,0.97)
Risedronate	0.50(0.38,0.66)	1	0.89(0.42,1.98)	0.80(0.37,1.94)	0.92(0.42,2.10)	0.91(0.36,2.23)
Alendronate	0.45(0.35,0.58)	0.92(0.63,1.22)	1	0.90(0.42,2.08)	1.03(0.46,2.31)	1.01(0.40,2.46)
Zoledronate	0.41(0.28,0.55)	0.83(0.50,1.14)	0.92(0.59,1.25)	1	1.15(0.48,2.61)	1.11(0.44,2.87)
Ibandronate 2.5mg daily	0.46(0.32,0.68)	0.95(0.59,1.38)	1.01(0.68,1.58)	1.10(0.77,1.91)	1	0.98(0.38,2.51)
Ibandronate 150mg monthly	0.46(0.25,0.83)	0.95(0.46,1.61)	1.00(0.55,1.84)	1.07(0.64,2.40)	0.99(0.50,1.89)	1

Supplementary Table 4: Non-vertebral fractures. Pairwise HR and 95% credible intervals (lower triangle), predictive effects in a new study and 95% prediction interval (upper triangle). Treatment effects less than one favour the intervention.

Treatment	Placebo	Alendronate	Risedronate	Zoledronate	Ibandronate 2.5mg daily	Ibandronate 150 mg monthly
Placebo	1	0.80(0.55,1.08)	0.72(0.49,1.01)	0.75(0.53,1.05)	0.91(0.58,1.44)	0.81(0.49,1.43)
Alendronate	0.80(0.65,0.93)	1	0.90(0.56,1.48)	0.94(0.61,1.56)	1.15(0.69,1.96)	1.02(0.59,1.90)
Risedronate	0.72(0.54,0.89)	0.91(0.65,1.16)	1	1.05(0.66,1.72)	1.28(0.72,2.35)	1.12(0.64,2.28)
Zoledronate	0.75(0.61,0.90)	0.95(0.74,1.21)	1.04(0.81,1.46)	1	1.22(0.69,2.12)	1.07(0.61,2.06)
Ibandronate 2.5mg daily	0.90(0.67,1.35)	1.12(0.88,1.74)	1.26(0.93,2.15)	1.19(0.90,1.89)	1	0.91(0.46,1.64)
Ibandronate 150mg monthly	0.80(0.53,1.36)	1.01(0.67,1.69)	1.09(0.76,2.08)	1.05(0.71,1.86)	0.93(0.50,1.39)	1

Supplementary Table 5: Hip fractures. Pairwise HR and 95% credible intervals (lower triangle), predictive effects in a new study and 95% prediction interval (upper triangle). Treatment effects less than one favour the intervention.

Treatment	Placebo	Risedronate	Alendronate	Zoledronate	Ibandronate 150 mg monthly
Placebo	1	0.81(0.28,2.33)	0.77(0.27,2.23)	0.93(0.32,2.69)	0.87(0.27,3.01)
Risedronate	0.81(0.49,1.32)	1	0.95(0.23,3.96)	1.15(0.28,4.79)	1.08(0.24,5.03)
Alendronate	0.78(0.44,1.28)	0.98(0.53,1.60)	1	1.20(0.28,5.04)	1.12(0.26,5.48)
Zoledronate	0.92(0.55,1.61)	1.08(0.72,2.19)	1.11(0.74,2.48)	1	0.95(0.21,4.22)
Ibandronate 150mg monthly	0.86(0.43,2.00)	1.02(0.55,2.54)	1.05(0.61,2.86)	0.98(0.43,1.95)	1

Supplementary Table 6: Wrist fractures. Pairwise HR and 95% credible intervals (lower triangle), predictive effects in a new study and 95% prediction interval (upper triangle). Treatment effects less than one favour the intervention.

Treatment	Placebo	Risedronate	Alendronate	Ibandronate 150 mg monthly
Placebo	1	0.76(0.32,1.78)	0.83(0.35,1.82)	0.83(0.30,2.40)
Risedronate	0.76(0.45,1.24)	1	1.09(0.36,3.13)	1.08(0.34,3.95)
Alendronate	0.83(0.51,1.29)	1.04(0.69,1.91)	1	1.00(0.32,3.45)
Ibandronate 150mg monthly	0.82(0.41,1.89)	1.03(0.59,2.68)	1.00(0.51,2.12)	1

Supplementary Table 7: Vertebral fractures. Ranking of treatments. Mean rank, median rank with 95% credible intervals, SUCRA values.

	Rank, b						mean	median rank	SUCRA
Treatment, j	**1**	**2**	**3**	**4**	**5**	**6**	**rank**	**(95% CrI)**	**(%)**
Placebo	0	0	0	0	0.01	0.99	5.99	6(6,6)	0.22
Risedronate	0.05	0.1	0.17	0.28	0.4	0	3.88	4(1,5)	42.37
Alendronate	0.14	0.25	0.28	0.21	0.12	0	2.92	3(1,5)	61.66
Zoledronate	0.44	0.26	0.15	0.09	0.06	0	2.07	2(1,5)	78.68
Ibandronate 2.5mg daily	0.14	0.2	0.22	0.24	0.2	0	3.15	3(1,5)	57.07
Ibandronate 150 mg monthly	0.23	0.19	0.18	0.18	0.22	0.01	3	3(1,5)	60

Supplementary Table 8: Non-vertebral fractures. Ranking of treatments. Mean rank, median rank with 95% credible intervals, SUCRA values.

	Rank, b						mean	median rank	SUCRA
Treatment, j	**1**	**2**	**3**	**4**	**5**	**6**	**rank**	**(95% CrI)**	**(%)**
Placebo	0	0	0	0.09	0.28	0.63	5.53	6(4,6)	9.38
Risedronate	0.47	0.25	0.15	0.09	0.04	0	1.99	2(1,5)	80.26
Alendronate	0.09	0.18	0.34	0.28	0.11	0	3.14	3(1,5)	57.12
Zoledronate	0.23	0.34	0.24	0.13	0.06	0	2.47	2(1,5)	70.54
Ibandronate 2.5mg daily	0.04	0.06	0.1	0.18	0.36	0.26	4.52	5(1,6)	29.51
Ibandronate 150 mg monthly	0.18	0.16	0.17	0.22	0.16	0.11	3.34	3(1,6)	53.19

Supplementary Table 9: Hip fractures Ranking of treatments. Mean rank, median rank with 95% credible intervals, SUCRA values.

	Rank, b					mean	median rank	SUCRA
Treatment, j	**1**	**2**	**3**	**4**	**5**	**rank**	**(95% CrI)**	**(%)**
Placebo	0.06	0.08	0.15	0.22	0.48	3.98	4(1,5)	25.41
Risedronate	0.25	0.28	0.24	0.17	0.06	2.51	2(1,5)	62.23
Alendronate	0.36	0.27	0.19	0.13	0.05	2.24	2(1,5)	69.11
Zoledronate	0.11	0.17	0.22	0.29	0.21	3.34	4(1,5)	41.47
Ibandronate 150 mg monthly	0.22	0.21	0.2	0.19	0.19	2.93	3(1,5)	51.78

Supplementary Table 10: Wrist fractures Ranking of treatments. Mean rank, median rank with 95% credible intervals, SUCRA values.

	Rank, b				mean	median rank	SUCRA
Treatment, j	**1**	**2**	**3**	**4**	**rank**	**(95% CrI)**	**(%)**
Placebo	0.06	0.1	0.2	0.64	3.43	4(1,4)	18.91
Risedronate	0.43	0.31	0.21	0.06	1.89	2(1,4)	70.38
Alendronate	0.23	0.33	0.35	0.09	2.31	2(1,4)	56.49
Ibandronate 150 mg monthly	0.28	0.27	0.24	0.21	2.37	2(1,4)	54.22

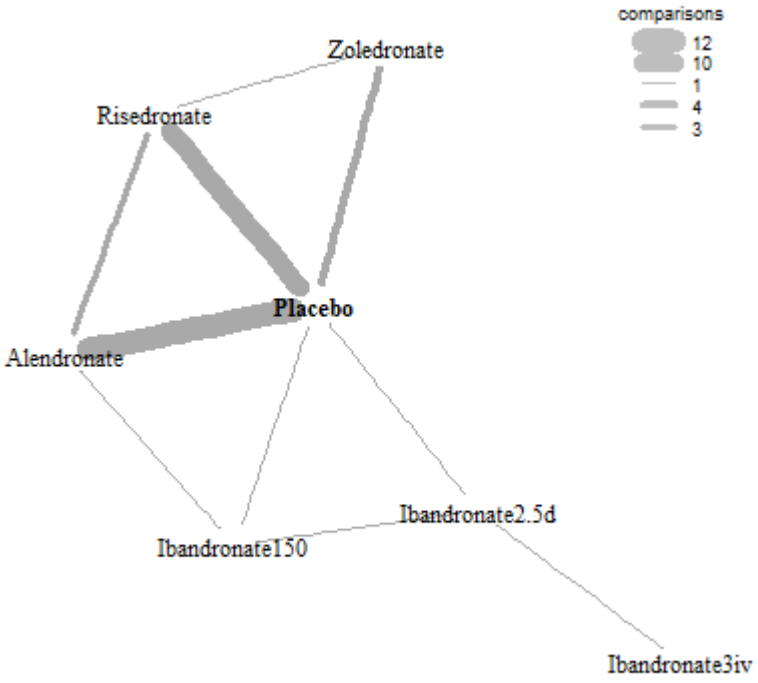
Supplementary Table 11: Assessment of inconsistency between direct and indirect evidence for vertebral fractures, assessed through node-splitting in the network meta-analysis

Treatment		All evidence	Direct comparison	Indirect comparison	Bayesian P-value
1	2	HR (95% CrI)	HR (95% CrI)	HR (95% CrI)	
Placebo	Risedronate	0.50 (0.38,0.66)	0.56 (0.41,0.75)	0.39 (0.14,0.66)	0.18
Placebo	Zoledronate	0.41 (0.28,0.56)	0.33 (0.22,0.50)	0.52 (0.31,1.23)	0.14
Risedronate	Zoledronate	0.84 (0.50,1.15)	1.80 (0.39,9.86)	0.77 (0.44,1.10)	0.29

Median values and 95% CrIs are from the posterior distribution of the hazard ratios from the NMA calculated using all the evidence, direct evidence only and indirect evidence only.

4. Additional information, percentage change in femoral neck BMD

Supplementary Figure 4: Evidence network for percentage change in femoral neck BMD.



Supplementary Table 12: Percentage change in femoral neck BMD. Pairwise HR and 95% credible intervals (lower triangle), predictive effects in a new study and 95% prediction interval (upper triangle). Treatment effects less than one favour the intervention.

	Placebo	**Alendronate**	**Risedronate**	**Ibandronate 150mg monthly**	**Ibandronate 2.5 mg daily**	**Zoledronate**	**Ibandronate 3mg iv**
Placebo	1	3.11(1.88,4.32)	2.37(1.14,3.62)	2.79(1.44,4.11)	2.32(0.83,3.78)	3.21(1.82,4.47)	2.86(1.27,4.38)
Alendronate	3.11(2.68,3.52)	1	-0.75(-2.42,0.98)	-0.33(-2.06,1.44)	-0.79(-2.67,1.05)	0.10(-1.70,1.77)	-0.24(-2.22,1.66)
Risedronate	2.36(1.90,2.84)	-0.74(-1.28,-0.18)	1	0.42(-1.40,2.20)	-0.05(-1.92,1.77)	0.86(-1.03,2.54)	0.49(-1.46,2.41)
Ibandronate 150mg monthly	2.79(2.04,3.48)	-0.31(-1.08,0.35)	0.41(-0.36,1.20)	1	-0.48(-2.26,1.36)	0.43(-1.47,2.22)	0.07(-1.85,2.01)
Ibandronate 2.5 mg daily	2.35(1.31,3.18)	-0.76(-1.82,0.06)	-0.02(-1.05,0.83)	-0.44(-1.38,0.34)	1	0.90(-1.11,2.82)	0.55(-1.33,2.38)
Zoledronate	3.20(2.51,3.85)	0.09(-0.60,0.78)	0.84(0.05,1.57)	0.40(-0.45,1.36)	0.85(-0.12,2.06)	1	-0.34(-2.29,1.64)
Ibandronate 3mg iv	2.86(1.69,3.94)	-0.23(-1.43,0.81)	0.48(-0.64,1.63)	0.07(-1.03,1.17)	0.52(-0.37,1.53)	-0.31(-1.62,0.79)	1

Supplementary Table 13: Femoral neck BMD. Ranking of treatments. Mean rank, median rank with 95% credible intervals, SUCRA values.

	Rank, b						mean	median rank	SUCRA
Treatment, j	**1**	**2**	**3**	**4**	**5**	**6**	**rank**	**(95% CrI)**	**(%)**
Placebo	0	0	0	0	0.01	0.99	5.99	6(6,6)	0.22
Risedronate	0.05	0.1	0.17	0.28	0.4	0	3.88	4(1,5)	42.37
Alendronate	0.14	0.25	0.28	0.21	0.12	0	2.92	3(1,5)	61.66
Zoledronate	0.44	0.26	0.15	0.09	0.06	0	2.07	2(1,5)	78.68
Ibandronate 2.5mg daily	0.14	0.2	0.22	0.24	0.2	0	3.15	3(1,5)	57.07
Ibandronate 150 mg monthly	0.23	0.19	0.18	0.18	0.22	0.01	3	3(1,5)	60

Supplementary Table 14: Assessment of inconsistency between direct and indirect evidence for percentage change in Femoral neck BMD, assessed through node-splitting in the network meta-analysis

Treatment		All evidence	Direct comparison	Indirect comparison	Bayesian P-value
1	2	TE (95% CrI)	TE (95% CrI)	TE (95% CrI)	
Placebo	Alendronate	3.11 (2.68,3.52)	3.25 (2.81,3.72)	2.79 (2.04,3.53)	0.29
Placebo	Risedronate	2.36 (1.90,2.84)	2.21 (1.62,2.77)	2.67 (1.93,3.37)	0.32
Placebo	Ibandronate 150 mg monthly	2.79 (2.04,3.48)	2.51 (0.97,4.04)	2.88 (2.04,3.68)	0.66
Placebo	Ibandronate 2.5 mg daily	2.35 (1.31,3.18)	1.18 (-0.81, 3.17)	2.60 (1.55,3.48)	0.21
Placebo	Zoledronate	3.20 (2.51,3.85)	3.42 (2.58,4.14)	2.96 (2.04,4.03)	0.48
Alendronate	Risedronate	-0.74 (-1.28,-0.18)	-0.68 (-1.51, 0.13)	-0.81 (-1.49,-0.11)	0.79
Alendronate	Ibandronate 150 mg monthly	-0.31 (-1.08,0.35)	-0.20 (-1.33, 0.94)	-0.45 (-1.56, 0.47)	0.71
Risedronate	Zoledronate	0.84 (0.05,1.57)	1.01 (-0.31, 2.34)	0.79 (-0.04, 1.65)	0.8
Ibandronate 150 mg monthly	Ibandronate 2.5 mg daily	-0.44 (-1.38,0.34)	-0.51 (-1.75, 0.74)	-0.46 (-2.08, 0.65)	0.99

Median values and 95% CrIs are from the posterior distribution of the mean difference between treatment comparisons from the NMA when the direct and indirect evidence was split using the node-splitting method.

Supplementary Table 15: Model fit information for all outcomes

outcome	absolute model fit		model comparison
	totresdev	data points	DIC
vertebral fractures	40.19	40	69.13
non-vertebral fractures	23.41	28	43.04
hip fractures	17.98	18	33.99
wrist fractures	12.50	12	23.06
femoral neck BMD	53.70	59	96.95