National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[G] Evidence reviews for adjuvant bisphosphonates

NICE guideline tbc

Evidence reviews

January 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Adjuvant bisphosphonates

This evidence report contains information on 1 review relating to adjuvant bisphosphonates.

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Review question 7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?

Introduction

Bisphosphonate treatment is used for prevention of skeletal-related events in people known to have advanced malignancies involving bone. It is used to reduce risk of fractures, slow disease progression and reduce pain due to malignant bone disease.

In early breast cancer, bisphosphonates are commonly recommended for the prevention or treatment of bone mineral density loss related to aromatase inhibitor therapy or ovarian suppression. Bisphosphonates can be administered by the intravenous (IV) route or taken orally. Identified risks of bisphosphonate treatment include renal function impairment, osteonecrosis of the jaw and hypocalcaemia.

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and affect T-cell function which in turn, could prevent or delay recurrence of bone disease, potentially making them effective as adjuvant treatments in early breast cancer.

To date, adjuvant bisphosphonate breast cancer trials have provided conflicting results and have not provided evidence of consistent benefit across all groups. The aim of this review is to examine more recent evidence on the effect of bisphosphonates on disease and treatment-related outcomes in early breast cancer.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer (M0) who have undergone surgery
Intervention	Bisphosphonates: • Alendronic acid/aledronate • Sodium clodronate • Pamidronate disodium • Ibandronic acid/ibandronate • Zoledronic acid/zoledronate • Risedronate sodium/risodronate
Comparison	• Bisphosphonates • No bisphosphonates
Outcome	**Critical** • Overall survival • Disease-free survival • Treatment-related morbidity **Important** • Bone health • Treatment-related mortality • HRQoL

HRQoL, Health related quality of life

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Twenty articles (number of participants, N=33,051) were included in the review (Coleman, 2011; Early Breast Cancer Trialists' Collaborative Group, 2015; Gnant, 2008; Gnant, 2011; Greenspan, 2008; Greenspan, 2015; Hadji, 2014; Hershman, 2010; Hines, 2009, Kim, 2011; Kristensen, 2008; Leal, 2010; Lester, 2008; McCloskey, 2010; Monda, 2017; Nuzzo, 2012; Paterson, 2012; Saarto, 2008; Sun, 2016; von Minckwitz, 2013); 18 reports of 17 randomised controlled trials (Austrian Breast & Colorectal Cancer Study Group [ABCSG]-12 [k=2], ARIBON [number of publications, k=1], Adjuvant Zoledronic acid redUce REcurrence [AZURE; k=1], Danish Breast Cancer Group [DBCG; k=1], German Adjuvant Intergroup Node Positive [GAIN; k=1], Hershman 2010 [k=1], HOBOE [k=1], International Standard Randomised Controlled Trials Number [ISRCTN] 83688026 [k=1], Korean Cancer Study Group [KCSG]-BR06-01 [k=1], Leal 2010 [k=1], Monda 2017 [k=1]; North Central Cancer Treatment Group [NCCTG] N02C1 [k=1], National Surgical Adjuvant Breast and Bowel Project [NSABP] B-34 [k=1], ProBONE II [k=1], REBBeCA [k=1], REBBeCA2 [k=1], Saarto 2008 [k=1], Saarto 2016 [k=1]) and one systematic review of randomised trials. The systematic review reported individual patient data from 26 trials (of 32 completed trials examining recurrence; 6 did not provide data); however, only the following trials were consistent with the review protocol: ABCSG-12, ARIBON, AZURE, DBCG, GAIN, HOBOE, KCSG-BR06-01, NCCTG N02C1, NSAPB B-34, ProBONE II. The North Central Cancer Treatment Group (NCCTCG) N03CC, Zometa-Femara Adjuvant Synergy Trial (Z-FAST), ZO-FAST and E-ZO-FAST trials were not eligible for inclusion as they compared immediate versus delayed zoledronic acid, rather than bisphosphonate treatment against no treatment; the Helsinki and the Breast Cancer Cancer Agency (BCCA) Vancouver, German Adjuvant Breast Cancer Study Group (GABG) and University of Saarland Germany trial populations had metastatic breast cancer and therefore were outside the scope of this guideline; the ANZAC, NATAN GBG 36 and Washington St Louis trials delivered bisphosphonate treatment alongside neoadjuvant chemotherapy and the timing of treatment (neoadjuvant versus adjuvant) was unclear in the Tel Aviv trial; and the SABRE trial included participants allocated to arm based on bone mineral density. Finally, there was no data available for the following trials: Borstkanker Onderzoek Groep (BOOG), Cancer and Leukemia Group B (CALGB) 79809, Columbia Bone Loss, California Pacific Medical Center Institutional Review Board (CPMC−IRB−14069), EXPAND, FemZone, Lyon Herriot, SCCG Bratislava and University of Wisconsin Zoledronate. Where the evidence reported in the published systematic review covered a larger sample, longer follow-up period, or an additional subgroup of interest compared to the evidence reported in the published articles identified above this evidence data was included in the guideline analysis.

Six trials compared zoledronic acid against no treatment control, 2 trials compared zoledronic acid against placebo, 1 trial compared risedronate against no treatment control, 3 trials compared risedronate against placebo, 1 trial compared ibandronate against no treatment control, 1 trial compared ibandronate against placebo, 2 trials compared sodium clodronate against placebo, 1 trial compared sodium clodronate against no treatment control, and 1 trial compared pamidronate against no treatment control. The systematic review reported relevant data for the following comparisons: zoledronic acid against no treatment control and

placebo, risedronate against placebo, ibandronate against no treatment control and placebo, and sodium clodronate against placebo.

Three trials (ABCSG-12, GAIN, NSABP B-34) and the systematic review reported data for critical outcomes by subgroups of interest: pre-menopausal (k=1), post-menopausal (k=2), ER/PR positive (k=2), ER/PR negative (k=2), node positive (k=3), node negative (k=2), grade 1/2 tumours (k=1), grade 3 tumours (k=1). Further subgroup analysis was reported in the systematic review but could not be included in the current analysis as which trials contributed to these analyses were not reported.

This review updates a question from the previous guideline CG80 (NICE 2009). Therefore, studies for this topic identified by the previous guideline would be incorporated into forest plots, GRADE evidence profiles, and evidence statements. However, studies are not incorporated where there is more recent data available from the same trial, unless different outcomes are reported, or where a change in protocol from the previous guideline means that studies no longer meet inclusion criteria. Seventeen articles included in the previous guideline were not incorporated into the current results for the following reasons: did not meet current inclusion criteria outlined in review protocol (k=10), more recent data available (k=3), insufficient presentation of results in original article to include in analysis (k=4). Additionally, 2 articles included in the previous guideline were picked up during the current literature search. This resulted in only 1 article (Atula, 2003) from the previous guideline being added to the current evidence. This trial compared sodium clodronate with placebo and did not report data for any subgroups of interest.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 3 to Table 10). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2: Summary of included studies

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
Coleman 2011	AZURE	• Female with stage II or III breast cancer • Performance status Karnofsky Index ≥60% or ECOG 0 and 1 • Exclusion: cancer diagnosis within the preceding 5 years; use of bisphosphonates during the previous year; diagnosis of osteoporosis or other bone disease likely to require bone-targeted treatment; serum creatinine greater than 1.5 times the upper limit of the normal range; clinically significant, active dental	Intervention arm (ZOL): zoledronic acid was administered immediately after each cycle of adjuvant chemotherapy in a 4-mg dose by intravenous infusion every 3 to 4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years. Radiotherapy and adjuvant cytotoxic and endocrine treatments were given in accordance with standard protocols at each participating institution. Trastuzumab was allowed

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		problems or planned jaw surgery	in patients with HER2-positive tumours. Daily oral supplements containing calcium and vitamin D were recommended for all patients during the first 6 months and were continued thereafter at the discretion of the treating physician. Control arm (no bisphosphonate): Radiotherapy and adjuvant cytotoxic and endocrine treatments were given in accordance with standard protocols at each participating institution. Trastuzumab was allowed in patients with HER2-positive tumours. Daily oral supplements containing calcium and vitamin D were recommended for all patients during the first 6 months and were continued thereafter at the discretion of the treating physician.
Early Breast Cancer Trialists' CollaborativeGroup 2015	ABCSG-12, ARIBON, AZURE, GAIN, HOBOE, KCSG-BR06-01, NCCTG N02C1, NSAPB B-34, ProBONE II	• Trials were eligible if they began before 2008 and randomly assigned women between a bisphosphonate of any type, dose, and schedule versus a control group (open label or placebo) with no bisphosphonate, all other treatments being similar in both groups.	Intervention arm 1: Sodium clodronate (<1 year, 2 years, and 3-5 years combined) Intervention arm 2: Aminobisphosphonate (<1 year, 1 year, 2 years, and 3-5 years combined; includes zoledronic acid, risedronate and ibandronate – separated in current analyses) Control arm: includes no treatment controls and placebo (separated in current analyses)
Gnant 2008	ABCSG-12	• Premenopausal women (≥19 years of age) with stage I/II ER+ and/or PR+ breast cancer; Karnofsky Index of 70 or greater; fewer than ten positive lymph nodes • Exclusion: T1a (except yT1a), T4d, or yT4 breast cancer; a history of other tumours or cytotoxic chemotherapy (preoperative	Intervention arm (ZOL): 3 years of goserelin (3.6mg subcutaneously every 28 days) and tamoxifen (20mg/day orally) or anastrozole (1mg/day orally) and zoledronic acid (initially 8mg intravenously every 6 months but reduced to 4mg due to decreased renal function reported in other studies)

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		chemotherapy was allowed); pre-operative radiotherapy; random assignment more than 8 weeks postoperatively; pregnancy or lactation (or both); oral contraception; serum creatinine concentration of 265 µmol/L or more, serum calcium concentration of less than 2 mmol/L or more than 3 mmol/L; bisphosphonate or long-term anticonvulsive therapy within 1 year of study entry; current or previous bone disease; long-term corticosteroid therapy; osteomalacia or osteogenesis imperfecta; pre-existing osteoperosis; any contraindications to trial medications	Control arm (no bisphosphonate): 3 years of goserelin (3.6mg subcutaneously every 28 days) and tamoxifen (20mg/day orally) or anastrozole (1mg/day orally) Patients randomised to tamoxifen, tamoxifen + zoledronic acid, anastrozole, or anastrozole + zoledronic acid Lumbar spine BMD assessed by dual-energy X-ray absorptiometry - machines were standardised between institutions
Gnant 2011	ABCSG-12	• Pre-menopausal women with stage I or II ER-positive and/or PR-positive breast cancer; fewer than ten positive lymph nodes; scheduled to receive standard therapy with goserelin. • Exclusion:T1a (except yT1a), T4d, and yT4 tumours; a history of other neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; contraindications for study drug	Intervention arm (ZOL): goserelin (3.6 mg subcutaneously every 28 days) plus either tamoxifen (20 mg per day orally) or anastrozole (1 mg per day orally) and zoledronic acid (4 mg intravenously every 6 months) for 3 years. Control arm (No bisphosphonate): goserelin (3.6 mg subcutaneously every 28 days) plus either tamoxifen (20 mg per day orally) or anastrozole (1 mg per day orally)
Greenspan 2008	REBBeCA	• Newly postmenopausal women who were treated with chemotherapy • Exclusion: Illness known to affect bone mineral metabolism or on medications known to affect bone mineral metabolism	Intervention arm (Ris): 35 mg risedronate taken once a week (initially for one year but trial extended to 2 years) Control arm (Placebo): matching placebo taken once a week (initially for one year but trial extended to 2 years) BMD assessed using dual energy x-ray absorptiometry
Greenspan 2015	REBBeCA2	• Postmenopausal women with hormone receptor positive breast cancer	Intervention arm (RIS): Aromatase inhibitor and 35mg oral risedronate

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		over age 55 years, with low bone mass currently receiving an aromatase inhibitor • Exclusion: treated with a bisphosphonate in the previous year; illnesses/medications known to affect bone and mineral metabolism	once weekly for 2 years. Daily calcium up to 1200 mg daily by diet and/or supplement Control arm (Placebo): Aromatase inhibitor and placebo once weekly for 2 years. Daily calcium up to 1200 mg daily by diet and/or supplement BMD measured using dual-energy x-ray absorptiometry
Hadji 2014	PROBONE II	• Premenopausal women with histologically confirmed, ER+ and/or HR+ invasive breast cancer; bone density T-score of ≥−2.5 (DEXA) • Exclusion: history of treatment or disease affecting bone metabolism; prior treatment with or hypersensitivity to bisphosphonates; abnormal renal function; current, active dental problems or a current/prior diagnosis of osteonecrosis of the jaw or recent (within 6 weeks)/planned dental or jaw surgery	Intervention arm (ZOL): No details provided for (neo)adjuvant (chemo)endocrine therapy. 8 cycles of zoledronic acid were given over 24 months (4mg IV every 3 months) Control arm (Placebo): No details provided for (neo)adjuvant (chemo)endocrine therapy. Eight infusions of placebo were administered at intervals of 3 months BMD assessed by dual-energy X-ray absorptiometry (DEXA)
Hershman 2010	No trial name	• Premenopausal women with newly diagnosed, breast cancer • Exclusion: T score of <2.0 at any site; fragility fracture; prior therapy with a bisphosphonate; lumbar spine anatomy precluding accurate BMD measurement, serum creatinine of at least 2 mg/dl; pregnancy	Intervention arm (ZOL): 4mg IV zoledronic acid over 15 min every 3 months for 12 months Control arm (Placebo): Placebo IV over 15 min every 3 months for 12 months BMD measured by dual-energy x-ray absorptiometry
Hines 2009	NCCTG N02C1	• Premenopausal women with an ECOG performance status of 0 (fully active) or 1 (ambulatory and able to carry out light work). • Exclusion: Hypercalcaemia; hypocalcaemia; inability to stand or sit upright for at least 30 minutes; known	Intervention arm (RIS): Chemotherapy (anthracyclines, taxanes, or cyclophosphamide), oral calcium 600 mg and vitamin D 400 U daily, and oral risedronate 35 mg weekly Control arm (Placebo): Chemotherapy (anthracyclines, taxanes,

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		swallowing disorder; BMD T score of 2.0 at the hip or LS; history of vertebral compression fracture; corticosteroid use at doses more than 5 mg/d of prednisone or equivalent for more than 2 weeks in the prior 6 months; previous treatment with bisphosphonates; diseases affecting bone metabolism; serum creatinine more than 2.0; malabsorption syndrome; menopausal oestrogen therapy; oral contraceptive use; bilateral oophorectomy; pregnancy; active nursing; of childbearing potential unwilling to employ adequate contraception; undergone (or planning) dental extraction, root canal, or dental implants during 3 months before registration	or cyclophosphamide), oral calcium 600 mg and vitamin D 400 U daily, and weekly placebo BMD measured by dual-energy x-ray absorptiometry (DEXA) devices.
Kim 2011	KCSG-BR06-01	• Premenopausal women over age 40 years with newly diagnosed breast cancer scheduled for four cycles of adjuvant AC followed by four cycles of paclitaxel or docetaxel • Exclusion: history of metabolic bone disease; received any bisphosphonate within 1 year of the start of the protocol; history of intake of pharmacologic amounts of any medications that can affect bone turnover; history of allergy to bisphosphonates; baseline BMD T-score of ≤-2.0 at the LS or hip; history of compression fractures; bilateral oophorectomy; were of child bearing potential but unwilling to employ adequate contraception; serum creatinine >1.6 mg/dl; undergone dental extraction or dental	Intervention arm (ZOL): adjuvant chemotherapy, daily oral supplements containing calcium and vitamin D, and 4 mg ZA intravenously over 15 min, starting on the day of first adjuvant chemotherapy, every 6 months for 12 months. Patients with hormone receptor-positive breast cancer were scheduled to receive adjuvant tamoxifen after the end of eight cycles of chemotherapy Control arm (No treatment): adjuvant chemotherapy, daily oral supplements containing calcium and vitamin D. Patients with hormone receptor-positive breast cancer were scheduled to receive adjuvant tamoxifen after the end of eight cycles of chemotherapy

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		implants ≤2 months before registration	BMD measured using local dual-energy x-ray absorption (DXA) devices
Kristensen 2008	DBCG	• Patients for the trial were recruited from the following three groups: A) premenopausal women without lymph node metastases but with grade 2 or 3 malignancy and a primary tumour ≤5 cm in diameter independent of hormone receptor status, B) premenopausal women with negative or unknown hormone receptor status and with either axillary lymph node metastases or a primary tumour >5 cm in diameter, C) postmenopausal women with hormone receptor negative tumours and with either axillary lymph node metastases or a primary tumour >5 cm in diameter	Intervention arm (PAM): All patients received CMF or CEF chemotherapy and oral pamidronate 150 mg twice daily for 4 years. Radiotherapy was given according to guidelines at participating centres and endocrine therapy was to be avoided. Control arm (No bisphosphonate): All patients received CMF or CEF chemotherapy. Radiotherapy was given according to guidelines at participating centres and endocrine therapy was to be avoided.
Leal 2010	No trial name	• Post-menopausal women with T4 or node positive breast cancer; diagnosis within five years of enrolment; ECOG performance status of 0 to 2; adequate bone marrow reserve, renal and hepatic function and normal calcium. • Exclusion: history of second or other cancers; risk of recurrence for the second malignancy over 5%; concurrent bisphosphonate use; T score of < −2.0 at the hip or spine (if not receiving tamoxifen)	Intervention arm (ZOL): Zoledronic acid 4mg IV every 12 weeks administered over at least 15 minutes for four cycles Control (No treatment): No details reported BMD measured by dual energy x-ray absorptiometry (DXA).
Lester 2008	ARIBON	• Postmenopausal women with a histologically confirmed diagnosis of oestrogen receptor – positive breast cancer. patients were classified as osteopenic if their T score was <-2.5 at either the LS or TH • Exclusion: menopause induced by either prior chemotherapy or by drug	Intervention arm (IBA): anastrozole 1 mg once a day and calcium and vitamin D supplements daily + ibandronate 150 mg every 28 days orally for 2 years. Control (Placebo): anastrozole 1 mg once a day and calcium and vitamin D supplements daily + placebo tablets of identical appearance to the

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		therapy; taking medications with effects on bone; abnormal renal function; disorders of bone metabolism; previous hip fractures or prostheses that would have made BMD assessments impossible.	ibandronate every 28 days orally for 2 years.
McCloskey 2010	ISRCT83688026	• Psychologically and physically suitable for 2 years of oral sodium clodronate or placebo • Exclusion: history of malignant disease or bisphosphonate use; significant renal or hepatic disease	Intervention arm (CLO): 1600 mg/d oral sodium clodronate for 2 years Control arm (Placebo): No details reported BMD measured by dual energy X-ray absorption using Hologic QDR1000 densitometers
Monda 2017		• Post-menopausal women; hormone receptor positive; mild to moderate risk of fracture • Exclusion: treatment-induced menopause; recent hormonal treatment; previous hip fracture or prosthesis; known bone-metabolism disorder; untreated hypo- or hypercalcaemia; previous treatment with medications that affect bone metabolism; liver or renal dysfunction	Intervention arm (Ris): 35 mg/week oral risedronate for 2 years; 1 mg anastrtozole daily and calcium (1,000 mg/day) and vitamin D (800 IU/day) supplements for 2 years Control arm (No treatment): 1 mg anastrtozole daily and calcium (1,000 mg/day) and vitamin D (800 IU/day) supplements for 2 years
Nuzzo 2012	HOBOE	• ER+ and/or PR+ • Exclusion: pregnant or lactating; abnormal kidney and/or liver function; evidence of active bone fracture; taken steroids on a regular basis in the previous 12 months or drugs interfering with bone metabolism in the previous 2 weeks; treated by or requiring invasive therapeutic procedures for dental diseases; previously received tamoxifen or an aromatase inhibitor	Intervention arm (ZOL): letrozole 2.5mg/day and zoledronic acid 4mg IV every 6 months for 5 years Control arm (No bisphosphonate): letrozole 2.5mg/day for 5 years
Paterson 2012	NSABP B-34	• Suitable physically to undergo 3 years of treatment with sodium clodronate or placebo • Exclusion: Renal, hepatic, or non-malignant bone	Intervention arm (CLO): Patients received 1600mg of adjuvant oral sodium clodronate daily. Appropriate local and systemic treatments

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		disease; history of malignant disease or bisphosphonate use	(chemotherapy, radiotherapy and endocrine therapy) were given at the investigator's discretion Control arm (Placebo): patients received placebo daily. Appropriate local and systemic treatments (chemotherapy, radiotherapy and endocrine therapy) were given at the investigator's discretion
Saarto 2008	No trial name	• Women with newly diagnosed node-positive breast cancer • Exclusion: Karnofsky performance index below 70%; other malignancies; peptic ulcer; creatinine over 150 umol/L; pregnancy	Intervention arm (CLO): surgery followed by postoperative radiotherapy. Premenopausal patients received six cycles CMF; postmenopausal patients were randomly assigned to receive antioestrogens, either 20 mg tamoxifen or 60 mg/d toremifene, for 3 years. All patients received 1600 mg/d of oral sodium clodronate for 3 years Control arm (No bisphosphonate treatment): surgery followed by postoperative radiotherapy. Premenopausal patients received six cycles CMF; postmenopausal patients were randomly assigned to receive antioestrogens, either 20 mg tamoxifen or 60 mg/d toremifene, for 3 years BMD measured by dual-energy, x-ray absorptiometry using a Hologic QDR-1000 densitometer
Sun 2016	No trial name	• Post-menopausal women with ER+ and or PR+ invasive breast cancer; life expectancy of ≥5 years; ECOG performance status of 0–2; baseline total LS or FN BMD T-score <-2.0; normal haematology, liver, and kidney function • Exclusion: existing LS or total hip (TH) fracture;	Intervention arm (ZOL): All patients received modified radical mastectomy or breast-conserving surgery. Patients with one or more pathological risk factors were administered 4 cycles of adjuvant chemotherapy. Patients started radiotherapy within 2-4 weeks of completion of chemotherapy. Endocrine

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		history of non-traumatic fractures or osteoporosis; recent treatment with drugs known to affect the skeleton; diseases known to influence bone metabolism; other malignancy within 5 years; renal dysfunction; uncontrolled infections; diabetes mellitus; thyroid dysfunction; seizure disorders associated with falls; HIV; malabsorption syndrome; mental illnesses; hypersensitivity to zoledronic acid, other bisphosphonates, letrozole, calcium, or vitamin D; contraindicated for the dual X-ray absorptiometry	therapy was started after completion of chemotherapy and all patients were instructed to take calcium and vitamin D daily. Zoledronic acid was administered every 6 months until disease recurrence intravenously over 30 minutes at a dosage of 4 mg. Control arm (No bisphosphonate treatment): All patients received modified radical mastectomy or breast-conserving surgery. Patients with one or more pathological risk factors were administered 4 cycles of adjuvant chemotherapy. Patients started radiotherapy within 2-4 weeks of completion of chemotherapy. Endocrine therapy was started after completion of chemotherapy and all patients were instructed to take calcium and vitamin D daily BMD measured using Norland dual-energy X-ray absorptiometry (DEXA) devices
von Minckwitz 2013	GAIN	• Female patients with breast cancer considered appropriate for intensive dose-dense chemotherapy (typically <65 years); needed to have histologic complete resection of the tumour and ≥10 resected axillary nodes with primary wound healing and no signs of infection; ECOG performance status <2; estimated life expectancy at least 10 years. • Exclusion: hypersensitivity to the compounds or incorporated substances; known dihydropyrimidine dehydrogenase deficiency; inadequate organ function; secondary	Intervention arm (IBA): patients were randomly assigned to either iddETC chemotherapy regimen or EC-TX chemotherapy regimen and received one 50-mg ibandronate tablet per day starting within 4 weeks after last administration of chemotherapy for a total duration of 2 years or until disease progression or unacceptable toxicity, patient's request to discontinue therapy, or withdrawal from the study. Radiotherapy, endocrine therapy and trastuzumab were administered according to AGO guidelines.

Study	Trial	• Additional inclusion/exclusion criteria	Interventions/comparison
		malignancy; time since axillary dissection >3 months; previously treated invasive breast carcinoma; previous or concurrent antitumor treatment; simultaneous therapy with sorivudine or brivudine as virostatics, immunosuppressive treatment or concurrent treatment with aminoglycosides; pregnancy or lactation; no adequate non-hormonal contraception in pre-menopausal patients; concurrent treatment with other experimental drugs	Control arm (No bisphosphonate): patients were randomly assigned to either iddETC chemotherapy regimen or EC-TX chemotherapy regimen. Radiotherapy, endocrine therapy and trastuzumab were administered according to AGO guidelines.

ABCSG, Austrian Breast & Colorectal Cancer Study Group; AC, doxorubicin, cyclophosphamide; AGO, German Gynecological Oncology Group (Arbeitsgemeinschaft Gynäkologische Onkologie); AZURE, Adjuvant Zoledronic acid redUce Recurrence; BMD, Bone mineral density; CEF, Cyclophosphamide Epirubicin Flourouracil; CMF, Cyclophosphamide Methotrexate Flourouracil; CLO, sodium clodronate; DBCG, Danish Breast Cancer Group; DEXA, dual-energy X-ray absorptiometry; ECOG, Eastern Cooperative Oncology Group; EC-TX, epirubicin, cyclophosphamide-docetaxel capecitabine; ER, oestrogen receptor; FN, femoral neck; GAIN, German Adjuvant Intergroup Node Positive; HER2, human epidermal growth factor receptor 2; IBA, ibandronate; iddETC, intense dose-dense epirubicin, paclitaxel, cyclophosphamide; ISRCTN, International Standard Randomised Controlled Trials Number; IV, intravenous; KCSG, Korean Cancer Study Group; LS, lumbar spine; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PAM, pamidronate; PR, progesterone receptor; RIS, risedronate; TH, total hip; ZOL, Zoledronic acid

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question is presented in Table 3 to Table 11. The included evidence ranges from high to very low; the main reason evidence was downgraded was due to imprecision around the estimate due to small number of events and wide confidence intervals. It was not possible to judge the overall quality of some evidence as the number events in certain subgroups was not reported.

Table 3: Summary clinical evidence profile: Comparison 1. Zoledronic acid versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: zoledronic acid			
DFS - Whole sample (5.6 year follow-up)	5.6yr DFS 77%	5.6yr DFS 78% (76% to 80%)	HR 0.95 (0.84 to 1.07)	5274 (1 study)	High
DFS - Post-menopausal (5.6 year follow-up)	5.6yr DFS 80%	5.6yr DFS 83% (80% to 85%)	HR 0.84 (0.72 to 0.98)	3622 (1 study)	High
DFS - Node positive (5.2 year follow-up)	NR	Cannot be calculated	HR 0.67 (0.45 to 0.99)	550 (1 study)	Moderate[1]
DFS - Node negative (5.2 year follow-up)	NR	Cannot be calculated	HR 0.66 (0.43 to 1.02)	1211 (1 study)	Number of events was not reported -

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: zoledronic acid			
					insufficient information to judge imprecision, and therefore overall quality
OS - Whole sample (5.6 year follow-up)	5.6yr OS 84%	5.6yr OS 85% (83% to 87%)	HR 0.93 (0.81 to 1.07)	5162 (1 study)	High
OS - Post-menopausal (5.6 year follow-up)	5.6yr OS 77%	5.6yr OS 79% (75% to 83%)	HR 0.9 (0.73 to 1.11)	1668 (1 study)	High
OS - Node positive (5.2 year follow-up)	NR	Cannot be calculated	HR 0.62 (0.34 to 1.14)	550 (1 study)	Moderate[1]
OS - Node negative (5.2 year follow-up)	NR	Cannot be calculated	HR 0.7 (0.33 to 1.5)	1211 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Treatment-related morbidity: osteonecrosis of the jaw (5 year follow-up)	0 per 1000	1 per 1000 (0 to 0)	RR 34.94 (2.1 to 580.49)	3359 (1 study)	Moderate[2]
Treatment-related morbidity: myalgia (1 year follow-up)	20 per 1000	52 per 1000 (14 to 193)	RR 2.58 (0.7 to 9.54)	301 (1 study)	Low[3]
Treatment-related morbidity: arthralgia (5.2 year follow-up)	134 per 1000	161 per 1000 (129 to 201)	RR 1.2 (0.96 to 1.5)	1803 (1 study)	Low[4]
Bone health – fractures (1 to 5 year follow-up)	48 per 1000	38 per 1000 (31 to 48)	RR 0.8 (0.64 to 1)	7065 (3 studies)	Moderate[5]
Bone health - LS BMD - LS BMD at follow-up (5.2 year follow-up)		The mean bone health – LS BMD at follow-up in the intervention groups was 0.07 higher (0.04 to 0.10 higher)		404 (1 study)	High
Bone health - LS BMD - Absolute change (1 year follow-up)		The mean bone health – LS BMD - absolute change in the intervention groups was 0.04 higher (0.01 to 0.07 higher)		55 (1 study)	Low[6,7]
Bone health - LS BMD - % change (1 year follow-up)		The mean bone health – LS BMD - % change in the intervention groups was 8.6 higher (7.38 to 9.82 higher)		112 (1 study)	Moderate[7]
Bone health - FN BMD - Absolute change (1 year follow-up)		The mean bone health – FN BMD - absolute change in the intervention groups was 0 higher (0.02 lower to 0.02 higher)		56 (1 study)	Low[6,7]
Bone health - FN BMD - % change (1 year follow-up)		The mean bone health – FN BMD - % change in the intervention groups		112 (1 study)	Moderate[7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: zoledronic acid			
		was 4.5 higher (2.8 to 6.2 higher)			
Bone health - ≥5% decline in LS BMD (1 year follow-up)	200 per 1000	40 per 1000 (10 to 174)	RR 0.2 (0.05 to 0.87)	100 (1 study)	Moderate[2]
Bone health - ≥5% decline in FN BMD (1 year follow-up)	240 per 1000	79 per 1000 (29 to 230)	RR 0.33 (0.12 to 0.96)	100 (1 study)	Moderate[2]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
BMD, Bone Mineral density; CI: Confidence interval; DFS: Disease free survival; FN, femoral neck; HR: Hazard ratio; LS, lumbar spine; OS, Overall survival; RR: Risk ratio
[1] Number of events not reported but unlikely to exceed 300 events due to sample size
[2] events <300
[3] <300 events in both arms and 95% CI crosses both thresholds for clinically significant differences based on GRADE default values (0.80 and 1.25)
[4] <300 events in both arms and 95% confidence intervals crosses boundary for no effect (1) and clinically important difference based on GRADE default values (1.25)
[5] 95% confidence interval touches threshold for no effect (1) and crosses boundary for clinically meaningful difference (0.8)
[6] Use of calcium and vitamin D was not routinely assessed or controlled for and control arm younger than intervention arm
[7] N<400

Table 4: Summary clinical evidence profile: Comparison 2. Zoledronic acid versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Placebo	Corresponding risk: Zoledronic acid			
DFS (5.6 year follow-up)	5.6yr DFS 100%	5.6yr DFS 100% (100% to 100%)	HR 1.09 (0.31 to 3.85)	71 (1 study)	Moderate[1]
Bone health - % change in LS BMD (2 year follow-up)		The mean bone health - % change LS BMD in the intervention groups was 7.56 higher (3.77 to 11.35 higher)		127 (2 studies)	Very low[2,3,4]
Bone health - % change in FN BMD (2 year follow-up)		The mean bone health - % change in FN BMD in the intervention groups was 2.57 higher (1.96 to 3.19 higher)		129 (2 studies)	Low[3,4]

Rates of DFS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
BMD: one mineral density; CI: Confidence interval; DFS: disease-free survival FN: femoral neck; HR: Hazard ratio; LS: lumbar spine; RR: Risk ratio;
[1]<300 events
[2] I squared 95%; high rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes. Estimated effect for both studies are in the same direction and exceed threshold for clinically important difference
[3] Some patients in Hershman 2010 received bisphosphonates as neoadjuvant therapy
[4] N<400

Table 5: Summary clinical evidence profile: Comparison 3. Risedronate versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: placebo	Corresponding risk: risedronate			
DFS (5.6 year follow-up)	5.6yr DFS 96%	5.6yr DFS 98% (93% to 100%)	HR 0.41 (0.09 to 1.86)	216 (1 study)	Moderate[1]
OS (5.6 year follow-up)	5.6yr DFS 96%	5.6yr DFS 98% (91% to 100%)	HR 0.48 (0.1 to 2.38)	216 (1 study)	Moderate[1]
Treatment-related morbidity: gastrointestinal (2 year follow-up)	241 per 1000	72 per 1000 (26 to 209)	RR 0.3 (0.11 to 0.87)	109 (1 study)	Moderate[1]
Treatment-related morbidity: arthralgia (1 year follow-up)	28 per 1000	4 per 1000 (0 to 77)	RR 0.14 (0.01 to 2.73)	212 (1 study)	Very low[2,3]
Treatment-related morbidity: constipation (1 year follow-up)	575 per 1000	501 per 1000 (391 to 645)	RR 0.87 (0.68 to 1.12)	212 (1 study)	Very low[2,4]
Treatment-related morbidity: nausea (1 year follow-up)	28 per 1000	47 per 1000 (12 to 192)	RR 1.67 (0.41 to 6.8)	212 (1 study)	Very low[2,5]
Treatment-related morbidity: abdominal pain (1 year follow-up)	283 per 1000	311 per 1000 (207 to 473)	RR 1.1 (0.73 to 1.67)	212 (1 study)	Very low[2,5]
Treatment-related morbidity: diarrhoea (1 year follow-up)	274 per 1000	282 per 1000 (183 to 438)	RR 1.03 (0.67 to 1.6)	212 (1 study)	Very low[2,5]
Bone health – fractures (2 year follow-up)	53 per 1000	88 per 1000 (16 to 497)	RR 1.68 (0.3 to 9.44)	72 (1 study)	Low[5]
Bone health - % change in LS BMD (1 to 2 year follow-up)		The mean bone health - % change LS BMD in the intervention groups was 2.43 higher (1.58 to 3.27 higher)		337 (3 studies)	Moderate[6]
Bone health - % change in FN BMD (1 to 2 year follow-up)		The mean bone health - % change in FN BMD in the intervention groups was 1.59 higher (1.26 to 1.91 higher)		242 (2 studies)	Moderate[6]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)

BMD, bone mineral density; CI: Confidence interval; DFS, Disease free survival; FN: femoral neck; HR: Hazard ratio; LS: lumbar spine; OS, Overall survival; RR: Risk ratio

[1] *<300 events*

[2] *Some patients received bisphosphonates as neoadjuvant treatment*

[3] *<300 events and 95% confidence interval crosses boundaries for no effect (1) and clinically important differences based on GRADE default values (0.8 and 1.25)*

[4] *<300 events and 95% confidence interval crosses boundary for no effect (1) and clinically meaningful difference based on GRADE default values (0.8)*

[5] *<300 events and 95% confidence interval crosses both boundaries for no effect (1) and clinically meaningful differences based on GRADE default values (0.8 and 1.25)*

[6] *N<400*

Table 6: Summary clinical evidence profile: Comparison 4. Ibandronate versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: ibandronate			
DFS - Node positive (3.3 year follow-up)	3.3yr DFS 86%	3.3yr DFS 87% (84% to 89%)	HR 0.95 (0.77 to 1.16)	2994 (1 study)	High
DFS - Pre-menopausal (3.3 year follow-up)	NR	Cannot be calculated	HR 1.02 (0.76 to 1.37)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Post-menopausal (3.3 to 5.6 year follow-up)	NR	Cannot be calculated	HR 0.89 (0.72 to 1.1)	1363 (2 studies)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Grade 1/2 (3.3 year follow-up)	NR	Cannot be calculated	HR 0.98 (0.7 to 1.37)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Grade 3 (3.3 year follow-up)	NR	Cannot be calculated	HR 0.91 (0.7 to 1.18)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER/PR+ (3.3 year follow-up)	NR	Cannot be calculated	HR 0.9 (0.59 to 1.38)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER/PR- (3.3 year follow-up)	NR	Cannot be calculated	HR 0.94 (0.74 to 1.2)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: ibandronate			
OS - Whole sample (5.6 year follow-up)	5.6yr DFS 94%	5.6yr DFS 94% (92% to 96%)	HR 1.03 (0.75 to 1.41)	3023 (1 study)	Moderate[1]
OS - Post-menopausal (5.6 year follow-up)	5.6yr DFS 93%	5.6yr DFS 93% (90% to 96%)	HR 0.98 (0.64 to 1.49)	1363 (1 study)	Moderate[1]
Treatment-related morbidity: gastrointestinal issues (3.25 year follow-up)	35 per 1000	62 per 1000 (43 to 90)	RR 1.76 (1.21 to 2.56)	2800 (1 study)	Moderate[1]
Treatment-related morbidity: renal/urinary issues (3.25 year follow-up)	5 per 1000	7 per 1000 (2 to 21)	RR 1.4 (0.48 to 4.09)	2350 (1 study)	Low[2]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DFS: Disease free survival; ER, oestrogen receptor; HR: Hazard ratio; OS: overall survival; PR: progesterone receptor; RR: Risk ratio
[1] <300 events
[2] <300 events and 95% confidence interval crosses both boundaries for no effect (1) and for clinically important differences based on GRADE default values (0.8 and 1.25)

Table 7: Summary clinical evidence profile: Comparison 5. Ibandronate versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: placebo	Corresponding risk: Ibandronate			
OS (post-menopausal only; 5.6 year follow-up)	5.6yr OS 92%	5.6yr OS 99% (84% to 100%)	HR 0.14 (0.01 to 2.16)	49 (1 study)	Moderate[1]
Treatment-related morbidity: arthralgia (2 year follow-up)	200 per 1000	240 per 1000 (84 to 686)	RR 1.2 (0.42 to 3.43)	50 (1 study)	Very low[2,3]
Treatment-related morbidity: upper GI symptoms (2 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 9 (0.51 to 158.85)	50 (1 study)	Very low[2,3]
Bone health – fractures (2 year follow-up)	120 per 1000	80 per 1000 (14 to 438)	RR 0.67 (0.12 to 3.65)	50 (1 study)	Very low[3,4]

Rates of OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; HR: Hazard ratio; OS: Overall Survival; RR: Risk ratio
[1] <300 events
[2] Attrition higher in placebo arm
[3] <300 events and 95% confidence interval crosses both boundaries for no effect (1) and for clinically important differences based on GRADE default values (0.8 and 1.25)
[4] Attrition higher in placebo arm and 2 discontinued study due to decrease in BMD which may minimise difference between groups

Table 8: Summary clinical evidence profile: Comparison 6. Sodium clodronate versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: placebo	Corresponding risk: Sodium clodronate			
DFS - Whole sample (7.5 year follow-up)	7.5yr DFS 81%	7.5yr DFS 83% (80% to 85%)	HR 0.91 (0.78 to 1.07)	3311 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: placebo	Corresponding risk: Sodium clodronate			
DFS - Post-menopausal (5.6 year follow-up)	5.6yr DFS 85%	5.6yr DFS 89% (85% to 91%)	HR 0.75 (0.58 to 0.97)	1833 (1 study)	Moderate[1]
DFS - ER/PR+ (7.5 year follow-up)	NR	Cannot be calculated	HR 0.94 (0.78 to 1.14)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER/PR- (7.5 year follow-up)	NR	Cannot be calculated	HR 0.84 (0.62 to 1.14)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Node positive (7.5 year follow-up)	NR	Cannot be calculated	HR 0.78 (0.59 to 1.03)	813 (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Node negative (7.5 year follow-up)	NR	Cannot be calculated	HR 0.99 (0.81 to 1.21)	2510 (1 study)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Whole sample (5.6 year follow-up)	5.6yr OS 85%	5.6yr OS 87% (85% to 89%)	HR 0.84 (0.72 to 0.99)	4402 (2 studies)	High
OS - Post-menopausal (5.6 year follow-up)	5.6yr OS 84%	5.6yr OS 86% (82% to 89%)	HR 0.89 (0.7 to 1.13)	1833 (1 study)	Moderate[1]
OS - ER/PR+ (7.5 year follow-up)	NR	Cannot be calculated	HR 0.9 (0.69 to 1.18)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - ER/PR- (7.5 year follow-up)	NR	Cannot be calculated	HR 0.72 (0.49 to 1.06)	NR (1 study)	Number of events/people in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: placebo	Corresponding risk: Sodium clodronate			
OS - Node positive (7.5 year follow-up)	NR	Cannot be calculated	HR 0.72 (0.51 to 1.01)	813 (1 study)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Node negative (7.5 year follow-up)	NR	Cannot be calculated	HR 0.94 (0.7 to 1.26)	2510 (1 study)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality
Treatment-related morbidity: gastrointestinal disorders (7.5 year follow-up)	562 per 1000	657 per 1000 (601 to 725)	RR 1.17 (1.07 to 1.29)	1079 (1 study)	Not possible to GRADE this outcome due to study included from previous guideline
Treatment-related morbidity: diarrhoea (7.5 year follow-up)	6 per 1000	17 per 1000 (8 to 36)	RR 2.82 (1.37 to 5.78)	3235 (1 study)	Moderate[1]
Treatment-related morbidity: hypocalcaemia (7.5 year follow-up)	1 per 1000	1 per 1000 (0 to 7)	RR 0.5 (0.05 to 5.55)	3235 (1 study)	Moderate[2]
Bone health – fractures (5.6 year follow-up)	116 per 1000	99 per 1000 (81 to 120)	RR 0.85 (0.7 to 1.03)	3323 (1 study)	Moderate[3]
Bone health - % change LS BMD (5 year follow-up)		The mean bone health - % change LS BMD in the intervention groups was 1.93 higher (0.96 to 2.9 higher)		851 (1 study)	High
Bone health - % change FN BMD (5 year follow-up)		The mean bone health - % change FN BMD in the intervention groups was 1.7 higher (0.46 to 2.94 higher)		851 (1 study)	High

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)

BMD: Bone mineral density; CI: Confidence interval; DFS: Disease free survival; ER: oestrogen receptor; FN: femoral neck; HR: Hazard ratio; LS: lumbar spine; OS: Overall survival; PR: progesterone receptor; RR: Risk ratio

[1] <300 events

[2] <300 events; not downgraded based on 95% CI due to very small differences in absolute risk

[3] 95% confidence interval crosses boundary for no effect (1) and clinically important difference based on GRADE default value (0.8)

Table 9: Summary clinical evidence profile: Comparison 7. Pamidronate versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: Pamidronate			
DFS – Whole sample (5.6 year follow-up)	5.6yr DFS 52%	5.6yr DFS 49% (41% to 56%)	HR 1.09 (0.89 to 1.35)	953 (1 study)	Moderate[3]
DFS – Post-menopausal (5.6 year follow-up)	5.6yr DFS 65%	5.6yr DFS 63% (52% to 72%)	HR 1.09 (0.78 to 1.51)	319 (1 study)	Low[2]
OS – Whole sample (5.6 year follow-up)	5.6yr OS 51%	5.6yr OS 50% (43% to 56%)	HR 1.04 (0.85 to 1.27)	953 (1 study)	Moderate[3]
OS – Post-menopausal (5.6 year follow-up)	5.6yr OS 71%	5.6yr OS 71% (65% to 75%)	HR 1.01 (0.74 to 1.37)	319 (1 study)	Low[2]
Treatment-related morbidity: nausea/vomiting (3 year follow-up)	722 per 1000	779 per 1000 (722 to 837)	RR 1.08 (1 to 1.16)	884 (1 study)	High
Treatment-related morbidity: abdominal pain (3 year follow-up)	221 per 1000	296 per 1000 (236 to 371)	RR 1.34 (1.07 to 1.68)	884 (1 study)	Moderate[1]
Bone health – fractures (4 year follow-up)	49 per 1000	63 per 1000 (38 to 107)	RR 1.30 (0.77 to 2.19)	953 (1 study)	Low[2]

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio
[1] <300 events
[2] <300 events and 95% confidence interval crosses boundary for no effect (1) and for clinically meaningful differences based on GRADE default values (0.8 and 1.25)
[3] 95% CI crosses boundary for both no effect (1) and minimally important difference (1.25) based on GRADE default value

Table 10: Summary clinical evidence profile: Comparison 8. Sodium clodronate versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: Sodium clodronate			
Bone health - % change LS BMD (10 year follow-up)		The mean bone health - % change LS BMD in the intervention groups was 4.8 higher (0.7 to 8.9 higher)		96 (1 study)	Low[1,2]
Bone health - % change FN BMD (10 year follow-up)		The mean bone health - % change FN BMD in the intervention groups was 2 higher (0.49 lower to 4.49 higher)		96 (1 study)	Low[1,2]

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio
[1] High rates of attrition and higher rates of chemotherapy in the control arm
[2] N<200
[3]<300 events

Table 11: Summary clinical evidence profile: Comparison 9. Risedronate versus no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: No treatment	Corresponding risk: Risedronate			
Bone health - LS BMD T-score (2 year follow-up)		The mean bone health - LS BMD T-score at 2 year follow-up in the intervention groups was 0.26 higher (0.03 to 0.49 higher)		71 (1 study)	Low[1]
Bone health - FN BMD T-score (2 year follow-up)		The mean bone health – FN BMD T-score at 2 year follow-up in the intervention groups was 0.33 higher (0.05 to 0.61 higher)		71 (1 study)	Low[1,3]
Bone health – fractures (2 year follow-up)	86 per 1000	12 per 1000 (1 to 223)	RR 0.14 (0.01 to 2.6)	71 (1 study)	Very low[1,4]
HRQoL - physical component summary of SF-36 (PCS-36; 2 year follow-up))		The mean HRQoL - physical component summary of sf-36 (PCS-36) in the intervention groups was 2.7 higher (4.51 lower to 9.91 higher)		71 (1 study)	Very low[5,6]
HRQoL - mental component summary of SF-36 (MCS-36; 2 year follow-up))		The mean HRQoL - mental component summary of sf-36 (MCS-36) in the intervention groups was 1.3 lower (7.49 lower to 4.89 higher)		71 (1 study)	Very low[3,5]

BMD: bone mineral density; CI: Confidence interval; HR: Hazard ratio; HRQoL: health-related quality of life; LS: lumbar spine; MCS: mental component summary; PCS: physical component summary; RR: Risk ratio; SF-36: 36-Item Short Form Survey

[1] High attrition

[3] N <400

[4] <300 events; 95% confidence interval crosses both no effect (1) and minimally important difference (1.25) based on GRADE default value

[5] High attrition and risk of detection bias

[6] N<400; 95% confidence interval crosses both no effect (0) and minimally important difference (0.5 x SD) based on GRADE default values

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Excluded studies

Search criteria and lists of excluded studies for the economic literature review across the whole guideline can be found in Supplement 1: Health economics.

Economic model

An economic analysis was developed to estimate the cost-effectiveness of bisphosphonates in the treatment of early and locally advanced breast cancer (see appendix J for the full report of the economic analysis).

Methods

The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (see Developing NICE guidelines: the manual). The model considered a fifty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

The analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis, in which three mutually exclusive health states were derived from the overall survival and progression free survival estimates:

- alive without progressed disease
- alive with progressed disease
- dead.

One of the primary aims of the analysis was to identify whether the use of bisphosphonates may be cost-effective in specific subgroups. In particular, the committee were interested in whether the use of bisphosphonates would be cost-effective in post-menopausal women and women with node positive breast cancer. Therefore, these subgroups were given separate consideration in the analysis (in addition to the modelling undertaken for the overall population).

Overall and disease free survival for each of the interventions was estimated using data on absolute and relative risk (using hazard ratios [HR]) from the systematic review of the clinical evidence conducted for this topic. Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of people that died of disease-specific and other causes.

The possibility of osteonecrosis of the jaw has been included in the economic model. Based on the systematic review of the clinical evidence conducted for this topic, it was assumed that osteonecrosis of the jaw would occur in 1% of people treated with zoledronic acid. No evidence was identified for the risk of osteonecrosis with the other bisphosphonates but it was assumed that there would be a similar level of risk. However, there is some evidence that the risk of osteonecrosis is lower when using oral bisphosphonates and it has therefore been assumed that the risk of osteonecrosis is 50% lower when given orally (i.e. absolute risk of 0.5%).

The analysis focused on the effect of bisphosphonates on cancer specific outcomes and as such did not consider the possible benefits associated with improvements in bone mineral density (such as a reduction in fractures). The analysis could therefore be considered conservative as the inclusion of such benefits would be likely to improve the cost-effectiveness of bisphosphonates.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices. The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Bisphosphonate costs were estimated for each of the bisphosphonates considered in the analysis. Zoledronic acid costs were estimated using drug costs from eMit, assuming that 4mg would be given every six months for three years (at a cost of £2.71 for a 4mg dose). Risedronate costs were estimated using drug costs from eMit assuming that 35mg would be given orally every three weeks for three years (at a cost of £0.10 per dose). Ibandronate costs were estimated using drug costs from eMit assuming that 50mg would be given every day for three years (at a cost of £0.28 per dose). Sodium clodronate costs were estimated using drug costs from eMit assuming that 1600mg would be given every day for three years (at a cost of £3.18 per dose). Delivery costs for bisphosphonates given intravenously were estimated to be £198.94 based on the cost to 'deliver simple parenteral chemotherapy at first attendance' from NHS Reference Costs 2015/16. It was assumed that bisphosphonates given orally would incur the cost of an annual GP visit (£36.00 based on an average consultation lasting 9.22 minutes).

Cost for the management of osteonecrosis of the jaw has been estimated from an analysis of resource use and cost associated with the management of osteonecrosis of the jaw in the US health care system (Najm 2014). The study was a retrospective review of medical records of 92 people with cancer and included data on medications, imaging and laboratory investigations, procedures and visits. It was estimated that the management of osteonecrosis cost $1,667 (based on all cancer types). Converting and inflating to UK 2015 prices, this equated to a cost of £1,266.04.

Subsequent treatment costs (following disease recurrence or progression) were estimated based on the average treatment that would be most likely to be used (based on the estimation of the guideline committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%). It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either delayed or at the time of mastectomy). It was further assumed that lymph node clearance would be performed for people with regional recurrence. It was also assumed that radiotherapy would be given in people that were not previously treated with radiotherapy (24% from Cameron 2017) and that everyone would receive adjuvant chemotherapy, trastuzumab and pertuzumab. It was assumed that distant recurrence would be treated with chemotherapy, trastuzumab and pertuzumab.

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi gated acquisition (MUGA) scans or cardiac MRI scans may be used. In the model, a weighted average cost per scan was calculated using weightings estimated by the guideline committee. It was assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced

from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that 5 cardiac monitoring scans would be required in the year that trastuzumab was received.

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every three to six months in the years one to three, every six to twelve months in years four to five and annually thereafter. The cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 for 3 months was applied based on the average resource use of people with cancer in the last three months of life.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values or quality of life (QoL) weights associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for people with breast cancer and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal (TA) for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (NICE TA424). It can be seen that people in the 'disease free' health state would have a QoL value of 0.847 which decreases to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer specific mortality. A QoL disutility for people with osteonecrosis of the jaw was sourced from a published economic evaluation of zoledronic acid in people with breast cancer and low oestrogen levels (Lamond 2015). It was assumed that the disutility would apply for one year.

Results

Base case results

The base case results of the analyses for each of the modelled populations are shown in Table 12 to Table 14. In the overall population, it can be seen that zoledronic acid and sodium clodronate were found to be more effective and more costly than no treatment. Zoledronic acid has an ICER above the NICE threshold of £20,000 per QALY and so was therefore not cost-effective while sodium clodronate has an ICER below the NICE threshold of £20,000 per QALY and was therefore cost-effective. Risedronate was found to be more effective and less costly than no treatment and was therefore dominant**.** Risedronate would also be preferred if comparing all strategies against each other as it is the most effective and least expensive of all the strategies.

In the node positive population, zoledronic acid and sodium clodronate were found to be more effective and more costly than no treatment. The ICERs for both treatments were below the NICE threshold of £20,000 per QALY and so both treatments are cost-effective when compared against no treatment. Comparing sodium clodronate and zoledronic acid, it can be seen that zoledronic acid would be preferred as it is less costly and more effective than sodium clodronate.

In the post-menopausal population, sodium clodronate and Ibandronate were found to be more effective and less costly than no treatment and were therefore dominant. Zoledronic acid was found to be more effective and more costly and was cost-effective with an ICER

below the NICE threshold of £20,000 per QALY. Comparing all strategies against each other in this population (using a 'dominance rank' approach), it was found that sodium clodronate would be the preferred strategy in cost-effectiveness terms.

While the results of the deterministic analysis are of some interest, it is important to remember when interpreting the results that many of the differences in clinical effectiveness were not statistically significant. This therefore limits the reliability of the base case estimates.

Table 12: Base case results for overall population (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£34,857	-	11.00	-	-
Zoledronic acid	£39,832	*£4,974*	11.10	*0.09*	£53,207
Risedronate	£29,812	*-£5,045*	11.76	*0.76*	Dominant
Sodium clodronate	£39,110	*£4,253*	11.23	*0.23*	£18,837

Table 13: Base case results for women with node positive breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£18,931	-	9.13	-	-
Zoledronic acid	£20,592	*£1,660*	9.83	*0.71*	£2,355
Sodium clodronate	£22,524	*£3,593*	9.59	*0.46*	£7,816

Table 14: Base case results for post-menopausal women with breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£18,931	-	9.13	-	**-**
Zoledronic acid	£19,180	*£248*	9.31	*0.18*	**£1,395**
Ibandronate	£16,510	*-£2,421*	9.16	*0.03*	**Dominant**
Sodium clodronate	£18,138	*-£793*	9.33	*0.20*	**Dominant**

Deterministic sensitivity results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are shown in Table 15 to Table 17. The tables show the cost-effectiveness result for each bisphosphonate in comparison to no treatment in each of the modelled scenarios.

In the analysis for the overall population (Table 15), it can be seen that zoledronic acid is not cost-effective in comparison to no treatment in the majority of modelled scenarios. However, it is cost-effective (and indeed dominant) in the scenario where the lower HR for disease free survival is used. Risedronate remains cost-effective in most scenarios but notably the conclusion is completely different when using the upper HRs for overall survival and disease free survival. Furthermore, it is not cost-effective when only statistically significant differences are considered. Sodium clodronate is cost-effective in most of the modelled scenarios but is not cost-effective when the upper HRs were used for overall survival and disease free survival or when only statistically significant treatment effects were included.

In the analysis for women with node-positive disease (Table 16), it can be seen that zoledronic acid remains cost-effective in comparison to no treatment in the majority of modelled scenarios. However, it is notably not cost-effective when the upper HR is used for overall survival or when only statistically significant differences are considered. Sodium clodronate is cost-effective in most of the modelled scenarios but it was not cost-effective when the upper HR for DFS was applied or when only statistically significant treatment effects were included.

In the analysis for postmenopausal women (Table 17), it can be seen that zoledronic acid, ibandronate and sodium clodronate remain cost-effective in comparison to no treatment in the majority of modelled scenarios. However, they were not cost-effective when the upper HR was used for DFS or when only statistically significant differences were considered.

Table 15: Deterministic sensitivity analysis results for overall population

	Comparisons against no treatment		
Change made	**Zoledronic acid**	**Risedronate**	**Sodium clodronate**
Base case	**£53,207**	**Dominant**	**£18,837**
Upper HR for OS	Dominated	***£6,532****	***£96,802***
Lower HR for OS	£28,189	£2,239	£16,908
Upper HR for DFS	£1,035,835	***£46,236***	***£37,899***
Lower HR for DFS	***Dominant***	Dominant	£3,482
Statistically significant treatment effects only	Dominated	***Dominated***	***£29,537***
Treatment effect duration of 10 years	£48,058	Dominant	£12,661
Treatment effect duration of 20 years	£47,214	Dominant	£9,912
Lifetime treatment effect duration	£49,529	Dominant	£9,160

** ICER result shows a scenario where the bisphosphonate was found to be less effective and less expensive than no treatment. Therefore, interpretation of the ICER result changes with values above £20,000 per QALY indicating cost-effectiveness.*

DFS: Disease free survival; OS, Overall survival

Table 16: Deterministic sensitivity analysis results for women with node positive breast cancer

	Comparisons against no treatment	
Change made	**Zoledronic acid**	**Sodium clodronate**
Base case	**£2,355**	**£7,816**
Upper HR for OS	£12,972	Dominant
Lower HR for OS	£7,910	£10,863
Upper HR for DFS	£16,748	***£24,869***
Lower HR for DFS	Dominant	Dominant
Statistically significant treatment effects only	***£793,678***	***£22,815***
Baseline risk from 'overall population'	Dominant	£5,541
Treatment effect duration of 10 years	£1,642	£4,826
Treatment effect duration of 20 years	£1,283	£3,447

Change made	Comparisons against no treatment	
	Zoledronic acid	Sodium clodronate
Lifetime treatment effect duration	£1,105	£2,977

Table 17: Deterministic sensitivity analysis results for postmenopausal women with breast cancer

Change made	Comparisons against no treatment		
	Zoledronic acid	Ibandronate	Sodium clodronate
Base case	**£1,395**	**Dominant**	**Dominant**
Upper HR for OS	£16,221	£5,200	£4,734
Lower HR for OS	£10,297	£10,892	£7,373
Upper HR for DFS	***£34,631***	***£122,160***	***£27,7519***
Lower HR for DFS	Dominant	Dominant	Dominant
Statistically significant treatment effects only	***Dominated***	***Dominated***	***£654,577***
Treatment effect duration of 10 years	Dominant	Dominant	Dominant
Treatment effect duration of 20 years	Dominant	Dominant	Dominant
Lifetime treatment effect duration	Dominant	Dominant	Dominant

Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values.

In the overall population, it was found that risedronate is strongly preferred as the optimal strategy with a high probability of being cost-effective. At the NICE threshold of £20,000 per QALY, risedronate has a 76% probability of being cost-effective while zoledronic acid has a 12% probability, sodium clodronate has a 7% probability and no treatment has 5% probability of being cost-effective. In women with node-positive breast cancer, zoledronic acid was found to be the preferred strategy at the NICE threshold of £20,000 per QALY with an 80% probability of being cost-effective while sodium clodronate has a 19% probability and no treatment has a 1% probability of being cost-effective. In post-menopausal women, there was no clearly preferred strategy. At the NICE threshold of £20,000 per QALY, sodium clodronate has the highest probability of being cost-effective (39%) closely followed by zoledronic acid (32%) and ibandronate (26%) while no treatment had a 12% probability of being cost-effective.

Conclusion

Conducting a robust economic analysis in this area is very difficult due to a lack of high quality clinical evidence showing clear differences between the approaches. Indeed, if only statistically significant treatment effects were used in the analysis then no treatment would be the preferred strategy.

Therefore it is difficult to draw any firm conclusion around cost-effectiveness in this area as the clinical evidence upon which it is based is too uncertain. However, one thing that does seem clear from the analysis is that the cost-effectiveness results largely mirror the clinical effectiveness inputs. Therefore if there was evidence that bisphosphonates improved overall and disease free survival then it is likely that their use would be cost-effective.

Evidence statements

Comparison 1. Zoledronic acid versus no treatment

Critical outcomes

Overall survival

- There is high quality evidence from 1 systematic review (N=5,162) that there is no clinically important effect of zoledronic acid on overall survival at 5.6 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 systematic review (N=1,668) that there is no clinically important effect of zoledronic acid on overall survival at 5.6 year follow-up for post-menopausal women with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=550) that that there is no clinically important effect of zoledronic acid on overall survival at 5.2 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=1,211) that there is no clinically important effect of zoledronic acid on overall survival at 5.2 year follow-up for people with node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Disease-free survival

- There is high quality evidence from 1 systematic review (N=5,274) that there is no clinically important effect of zoledronic acid on disease-free survival at 5.6 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 systematic review (N=3,622) that zoledronic acid produced clinically meaningful increases in disease-free survival at 5.6 year follow-up compared with no treatment control for post-menopausal women with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=550) that zoledronic acid produced clinically meaningful increases in disease-free survival at 5.2 year follow-up compared with no treatment control for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=1,211) that there is no clinically important effect of zoledronic acid on disease-free survival at 5.2 year follow-up for people with node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=3,359) that zoledronic acid produced clinically meaningful increases in osteonecrosis of the jaw at 5 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=301) that zoledronic acid produced clinically meaningful increases in myalgia at 1 year follow-up compared with no treatment control for people with invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,803) that there is no clinically important effect of zoledronic acid on arthralgia at 5.2 year follow-up for people with invasive breast cancer.

Important outcomes

Bone health

- There is moderate quality evidence from 3 RCTs (N=7,065) that there is no clinically important effect of zoledronic acid on bone fractures at 1 to 5 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=404) that there is no clinically important effect of zoledronic acid on lumbar spine bone mineral density at 5.2 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=55) that there is no clinically important effect of zoledronic acid on change in lumbar spine bone mineral density at 1 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=112) that zoledronic acid produced clinically meaningful increases in percentage change in lumbar spine bone mineral density at 1 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=56) that there is no clinically important effect of zoledronic acid on change in femoral neck bone mineral density at 1 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=112) that zoledronic acid produced clinically meaningful increases in percentage change in femoral neck bone mineral density at 1 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=100) that zoledronic acid produced clinically meaningful reductions in individuals experiencing ≥5% decline in lumbar spine bone mineral density at 1 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=100) that zoledronic acid produced clinically meaningful reductions in individuals experiencing ≥5% decline in femoral neck bone mineral density at 1 year follow-up compared with no treatment control for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2. Zoledronic acid versus placebo

Critical outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- There is moderate quality evidence from 1 systematic review (N=71) that there is no clinically important effect of zoledronic acid on disease-free survival at 5.6 year follow-up for people with invasive breast cancer.

Treatment-related morbidity

- No evidence was found for this outcome.

Important outcomes

Bone health

- There is very low quality evidence from 2 RCTs (N=127) that zoledronic acid produced clinically meaningful increases in percentage change in lumbar spine bone mineral density at 2 year follow-up compared with placebo for people with invasive breast cancer.
- There is low quality evidence from 2 RCTs (N=129) that zoledronic acid produced clinically meaningful increases in percentage change in femoral neck bone mineral density at 2 year follow-up compared with placebo for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 3. Risedronate versus placebo

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 systematic review (N=216) that there is no clinically important effect of risedronate on overall survival at 5.6 year follow-up for people with invasive breast cancer.

Disease-free survival

- There is moderate quality evidence from 1 systematic review (N=216) that there is no clinically important effect of risedronate on disease-free survival at 5.6 year follow-up for people with invasive breast cancer.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=109) that risedronate produced clinically meaningful reductions in gastrointestinal issues at 2 year follow-up compared with placebo for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=212) that risedronate produces clinically meaningful reductions in arthralgia at 1 year follow-up compared with placebo for people with invasive breast cancer. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=212) that there is no clinically important effect of risedronate on constipation at 1 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=212) that there is no clinically important effect of risedronate on nausea at 1 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=212) that there is no clinically important effect of risedronate on abdominal pain at 1 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=212) that there is no clinically important effect of risedronate on diarrhoea at 1 year follow-up for people with invasive breast cancer.

Important outcomes

Bone health

- There is low quality evidence from 1 RCT (N=72) that risedronate produces clinically meaningful increases in bone fractures at 2 year follow-up compared with placebo for people with invasive breast cancer. However, the effect was not statistically significant.
- There is moderate quality evidence from 3 RCTs (N=337) that risedronate produced clinically meaningful increases in percentage change in lumbar spine bone mineral density at 1 to 2 year follow-up compared with placebo for people with invasive breast cancer.
- There is moderate quality evidence from 2 RCTs (N=242) that risedronate produced clinically meaningful increases in percentage change in femoral neck bone mineral density at 1 to 2 year follow-up compared with placebo for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 4. Ibandronate versus no treatment

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 systematic review (N=3,023) that that there is no clinically important effect of ibandronate on overall survival at 5.6 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,363) that that there is no clinically important effect of ibandronate on overall survival at 5.6 year follow-up for post-menopausal women with invasive breast cancer.

Disease-free survival

- There is high quality evidence from 1 RCT (N=2,994) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for pre-menopausal women with invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT and 1 systematic review (N=1,363) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 to 5.6 year follow-up for post-menopausal women with invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for people with grade 1/2 invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for people with grade 3 invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is evidence from 1 RCT (N=NR) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for people with ER positive and/or PR positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that that there is no clinically important effect of ibandronate on disease-free survival at 3.3 year follow-up for people with ER negative and/or PR negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=2,800) that ibandronate produces clinically meaningful increases in gastrointestinal issues at 3.25 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2,350) that ibandronate produces clinically meaningful increases in renal/urinary issues at 3.25 year follow-up compared with no treatment control for people with invasive breast cancer. However, the effect was not statistically significant.

Important outcomes

Bone health

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 5. Ibandronate versus placebo

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 systematic review (N=49) that there is no clinically important effect of ibandronate on overall survival at 5.6 year follow-up for post-menopausal women with node positive invasive breast cancer.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (N=50) that there is no clinically important effect of ibandronate on arthralgia at 2 year follow-up for people with node positive invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=50) that ibandronate produces clinically meaningful increases in upper gastrointestinal symptoms at 2 year follow-up compared with placebo for people with invasive breast cancer. However, the effect was not statistically significant.

Important outcomes

Bone health

- There is very low quality evidence from 1 RCT (N=50) that ibandronate produces clinically meaningful reductions in fractures at 2 year follow-up compared with placebo for people with invasive breast cancer. However, the effect was not statistically significant.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 6. Sodium clodronate versus placebo

Critical outcomes

Overall survival

- There is high quality evidence from 1 RCT and 1 systematic review (N=4,402) that sodium clodronate produced clinically meaningful increases in overall survival at 5.6 year follow-up compared with placebo for women with invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,833) there is no clinically important effect of sodium clodronate on overall survival at 5.6 year follow-up for post-menopausal women with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of sodium clodronate on overall survival at 7.5 year follow-up for people with ER positive and/or PR positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of sodium clodronate on overall survival at 7.5 year follow-up for people with ER negative and/or PR negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=813) that there is no clinically important effect of sodium clodronate on overall survival at 7.5 year follow-up for people with node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=2,510) that there is no clinically important effect of sodium clodronate on overall survival at 7.5 year follow-up for people with node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Disease-free survival

- There is high quality evidence from 1 RCT (N=3,311) that there is no clinically important effect of sodium clodronate on disease-free survival at 7.5 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,833) that sodium clodronate produced clinically meaningful increases in disease-free survival at 5.6 year follow-up compared with placebo for post-menopausal women with invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of sodium clodronate on disease-free survival at 7.5 year follow-up for people with ER positive

and/or PR positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of sodium clodronate on disease-free survival at 7.5 year follow-up for people with ER negative and/or PR negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=813) that there is no clinically important effect of sodium clodronate on disease-free survival at 7.5 year follow-up for people with node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=2,510) that there is no clinically important effect of sodium clodronate on disease-free survival at 7.5 year follow-up for people with node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is evidence from 1 RCT (N=1,079) that there is no clinically important effect of sodium clodronate on gastrointestinal disorders at 7.5 year follow-up compared with placebo for people with invasive breast cancer. It was not possible to assess the quality of this evidenced due to study included from previous guideline.
- There is moderate quality evidence from 1 RCT (N=3,235) that sodium clodronate produced clinically meaningful increases in diarrhoea at 7.5 year follow-up compared with placebo for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=3,235) that sodium clodronate produced clinically meaningful reductions in hypocalcaemia at 7.5 year follow-up compared with placebo for people with invasive breast cancer. However, the effect was not statistically significant.

Important outcomes

Bone health

- There is moderate quality evidence from 1 RCT (N=3,323) that there is no clinically important effect of sodium clodronate on fractures at 5.6 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=851) that sodium clodronate produced clinically meaningful increases in percentage change in lumbar spine bone mineral density at 5 year follow-up compared with placebo for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=851) that sodium clodronate produced clinically meaningful increases in percentage change in femoral neck bone mineral density at 5 year follow-up compared with placebo for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 7. Pamidronate versus placebo

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 systematic review (N=953) that there is no clinically important effect of pamidronate on overall survival at 5.6 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 systematic review (N=319) that there is no clinically important effect of pamidronate on overall survival at 5.6 year follow-up for post-menopausal women with invasive breast cancer.

Disease-free survival

- There is moderate quality evidence from 1 systematic review (N=953) that there is no clinically important effect of pamidronate on disease-free survival at 5.6 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 systematic review (N=319) that there is no clinically important effect of pamidronate on disease-free survival at 5.6 year follow-up for post-menopausal women with invasive breast cancer.

Treatment-related morbidity

- There is high quality evidence from 1 RCT (N=884) that there is no clinically important effect of pamidronate on nausea/vomiting at 3 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=884) that pamidronate produced clinically meaningful increases in abdominal pain at 3 year follow-up compared with no treatment control for people with invasive breast cancer.

Important outcomes

Bone health

- There is low quality evidence from 1 RCT (N=953) that pamidronate produced clinically meaningful increases in fractures at 4 year follow-up compared with no treatment control for people with invasive breast cancer. However, the effect was not statistically significant.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 8. Sodium clodronate versus no treatment

Critical outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Important outcomes

Bone health

- There is low quality evidence from 1 RCT (N=96) that sodium clodronate produced clinically meaningful increases in percentage change in lumbar spine bone mineral density at 10 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=96) that there is no clinically important effect of sodium clodronate on percentage change in femoral neck bone mineral density at 10 year follow-up for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 9. Risedronate versus no treatment control

Critical outcomes

Overall survival

- No evidence was found for this outcome.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Important outcomes

Bone health

- There is low quality evidence from 1 RCT (N=71) that risedronate produced clinically meaningful increases in lumbar spine bone mineral density T-score at 2 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=71) that risedronate produced clinically meaningful increases in femoral neck bone mineral density T-score at 2 year follow-up compared with no treatment control for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=71) that risedronate produced clinically meaningful reductions in fractures at 2 year follow-up compared with no treatment control for people with invasive breast cancer; however, the effect was not statistically significant.

Treatment-related mortality

- No evidence as found for this outcome.

Health-related quality of life

- There is very low quality evidence from 1 RCT (N=71) that there is no clinically important effect of risedronate on physical health-related quality of life at 2 year follow-up.
- There is very low quality evidence from 1 RCT (N=71) that there is no clinically important effect of risedronate on mental health-related quality of life at 2 year follow-up.

Economic evidence statements

- There is evidence from a de novo cost-utility analysis that, in the overall population, zoledronic acid was not cost-effective in comparison to no treatment with an ICER of £53,207 per QALY while sodium clodronate was cost-effective with an ICER of £18,837 per QALY. Risedronate was found to be more effective and less costly than all other treatments and was therefore dominant. The analysis was directly applicable with minor limitations.
- There is evidence from a de novo cost-utility analysis that, in women with node- positive breast cancer, zoledronic acid and sodium clodronate were cost-effective in comparison to no treatment with ICERs of £2,355 and £7,816 per QALY, respectively. Zoledronic acid was found to be dominant when compared against sodium clodronate. The analysis was directly applicable with minor limitations.
- There is evidence from a de novo cost-utility analysis that, in postmenopausal women with breast cancer, zoledronic acid was cost-effective in comparison to no treatment with an ICER of £1,395 per QALY. Sodium clodronate and Ibandronate were more effective and less costly than no treatment and were therefore dominant. Sodium clodronate was the preferred strategy in cost-effectiveness terms when comparing all strategies against each other. The analysis was directly applicable with minor limitations.

Recommendations

G1. Offer bisphosphonates (zoledronic acid or sodium clodronate)[a] as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer.

G2. Consider bisphosphonates (zoledronic acid or sodium clodronate)[a] as adjuvant therapy for postmenopausal women with invasive breast cancer and a high risk[b] of recurrence.

G3. Discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal. Follow the Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines (MHRA/CHM) advice on bisphosphonates.

Research recommendation

Which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates?

a Although this use is common in UK clinical practice, at the time of consultation (January 2018), bisphosphonates did not have UK marketing authorisations for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

b Risk can be estimated using a range of standardised tools and clinical expertise.

Rationale and impact

Why the committee made the recommendations

There was good evidence that treatment with sodium clodronate and zoledronic acid improved disease-free and overall survival in postmenopausal women with node-positive invasive breast cancer.

There was little evidence on other bisphosphonates. The committee recommended considering zoledronic acid or sodium clodronate treatment for other high-risk populations, based on the evidence that sodium clodronate has overall survival benefits in mixed populations.

Although there is evidence that intravenous (IV) bisphosphonates have a higher risk of osteonecrosis of the jaw, oral bisphosphonates have a higher risk of gastrointestinal problems. There is also a risk of atypical femoral fractures and osteonecrosis of the external auditory canal with bisphosphonates. Because each drug and regimen has different risks, the potential benefits and risks should be discussed with women to help them make an informed choice.

The committee did not look at the evidence relating to the use of bisphosphonates for bone health or for the use of baseline dual-energy X-ray absorptiometry (DEXA) scanning, so did not make any new recommendations.

Impact of the recommendations on practice

Bisphosphonates are not consistently offered as adjuvant treatment, so this recommendation may lead to an increase in prescribing.

GPs may need to monitor people taking oral bisphosphonates, but this is likely to be an annual review so would not have a large workload impact. However, people may make more GP visits if they have side effects from bisphosphonate treatment.

The committee agreed that IV bisphosphonates would usually be administered at the same time as chemotherapy drugs for the first 6 months of treatment, so this would not result in extra hospital visits for this period. After that, extra visits for administration and monitoring may be needed.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

This review was concerned with potential role of bisphosphonates as adjuvant treatment (i.e., the effect of bisphosphonates on breast-cancer specific outcomes) rather than effect on bone health, which is already well established. Therefore overall survival, disease-free survival and treatment-related morbidity (particularly osteonecrosis of the jaw due to its severity) were prioritised as critical outcomes.

Survival outcomes are usually prioritised by patients but treatment-related morbidities are also critical as they affect patients' tolerance/acceptability of and adherence to treatment.

Bone health, treatment-related mortality and HRQoL were identified as important outcomes.

No evidence was found in this review for treatment-related mortality.

The quality of the evidence

The quality of the evidence was assessed using GRADE. For the outcomes of OS and DFS the evidence was moderate to high quality. However, it was not possible to judge the quality of evidence for a number of the subgroups as the number of people and/or number of events of interest were not reported in some papers, and so it was not possible to determine the imprecision around the estimate, and therefore the overall quality.

The first recommendation to offer bisphosphonates in postmenopausal node-positive women was driven by high quality evidence that sodium clodronate produces benefits in OS in mixed populations; high quality evidence that zoledronic acid produces DFS benefits in postmenopausal women; moderate quality evidence that zoledronic acid produces DFS benefits in node positive populations; and moderate quality evidence that sodium clodronate produces DFS benefits in postmenopausal women

There is a lack of evidence regarding OS and DFS for bisphosphonates other than zoledronic acid and sodium clodronate, particularly for specific subgroups. Therefore, the committee agreed to make a research recommendation to determine the long-term survival benefits for a wider number of bisphosphonates.

The second recommendation to consider zoledronic acid and sodium clodronate in postmenopausal women at high risk of recurrence was supported by the high quality evidence that sodium clodronate produces benefits in OS in mixed populations, but a strong ‘offer; recommendation could not be made due to the fact that for a number of other bisphosphonate comparisons a clinical benefit was not shown.

Treatment-related morbidity evidence was of mixed quality (high to very low) - but the evidence for osteonecrosis of the jaw (which is the most serious bisphosphonate-related morbidity) was of moderate quality.

Bone health evidence was of mixed quality (high to very low) but this outcome was not the primary focus of this question and was included to check whether newer evidence is not consistent with existing recommendations for the use of bisphosphonate treatment for bone loss.

There was a lack of evidence regarding health-related quality of life; the only available evidence was very low quality and showed no effect of bisphosphonate treatment.

Benefits and harms

The main benefits seen with zoledronic acid and sodium clodronate were in terms of OS and DFS compared to no treatment. Specifically, there was a 2% increase in OS (85 to 87%) and 4% increase in DFS (85 to 89%) at 5.6 years for those treated with sodium clodronate compared with placebo.

These benefits need to be balanced against the harms, and a 1% increase in osteonecrosis of the jaw was found with treatment with zoledronic acid compared with no treatment. There was no evidence available for the osteonecrosis rates following treatment with other bisphosphonates but it is known that the risk is greatest following IV bisphosphonates. In absolute terms, there would only be 1 additional incidence of osteonecrosis of the jaw for every 100 people treated with bisphosphonates, but jaw osteonecrosis is a very serious adverse event, can be life changing, and there is no effective treatment, with only conservative management available. As improvement in survival is of a similar order of magnitude (2%) the Committee agreed that it was important that the risk of jaw necrosis is discussed with people considering bisphosphonate treatments, and therefore made a recommendation to this effect. There is also a warning from the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines that atypical femoral fractures and osteonecrosis of the external auditory canal have been seen with bisphosphonates and so this warning was included in the recommendations.

The greatest evidence for benefit was for sodium clodronate which is administered orally once a day. However, this is typically less well tolerated due to much higher rates of GI side-effects, and hence adherence is lower than for IV bisphosphonates which only have to be administered every 3-6 months.

The committee agreed that any decision to initiate adjuvant bisphosphonate treatment will involve a trade-off between benefits and harms i.e., the risk of osteonecrosis and GI adverse effects versus the risk of breast cancer recurrence. For women with breast cancer with low risk of recurrence, the risks associated with treatment are unlikely to outweigh the benefits, whereas in high risk women bisphosphonate treatment is likely to be of benefit. This balance was used at the rationale for the second 'consider' recommendation.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. An economic analysis was undertaken for this question assessing the cost-effectiveness of various bisphosphonate regimens in overall, node positive and post-menopausal populations.

The base case results for the overall population showed that zoledronic acid was not cost-effective in comparison to no treatment while sodium clodronate and risedronate were cost-effective. Risedronate was found to be cost-effective when compared against sodium clodronate.

The base case results for the node-positive population showed that zoledronic acid and sodium clodronate were both cost-effective when compared against no treatment. Comparing sodium clodronate and zoledronic acid, zoledronic acid would be preferred as it is less costly and more effective than sodium clodronate.

The base case results for the postmenopausal population showed that ibandronate, zoledronic acid and sodium clodronate were cost-effective in comparison to no treatment. Comparing all strategies against each other, it was found that sodium clodronate would be the preferred strategy in cost-effectiveness terms.

The results show the potential for bisphosphonates to be cost-effective, especially in higher risk populations. However, while these results were of some interest, the committee were aware of the high degree of uncertainty around the clinical inputs upon which the analysis was based. Indeed, if only statistically significant treatment effects were used then no treatment would be the preferred strategy. However, the analysis gives an indication that the cost-effectiveness results largely mirror the clinical effectiveness inputs. Therefore if bisphosphonates were shown to improve overall and disease free survival then it is likely that their use would be cost-effective.

In terms of resource impact, the recommendations are likely to require an increase in resources as bisphosphonates are not consistently offered as an adjuvant treatment in current practice. This may include costs associated with any additional GP visits that may be required as well as bisphosphonate medication and delivery costs. However, the committee did not anticipate that the increase in resources would be significant because bisphosphonates are already being offered in many centres.

Other factors the committee took into account

The committee were aware that there was variation in the rates of osteonecrosis following bisphosphonate treatment reported in the literature. The EBCTCG meta-analysis, which could not be included in the current review in its entirety due to some included trials being inconstant with our protocol, reports that rates vary from less than 1% with oral bisphosphonates to 2% with more intensive zoledronic acid regimens. For example, in the AZURE study zoledronic acid was given every 3-4 weeks for 6 cycles, every 3 months for 8

cycles, then every 6 months for 5 cycles. However, the committee knew that in current clinical practice the treatment regimen for zoledronic acid is not so intense (usually every 6 months) and so the rates of osteonecrosis may be lower too.

The committee noted that the data from the EBCTCG meta-analysis included in the current review comes from AZURE study (with an intensive zoledronic acid regimen as detailed above), HOBOE and ABCSG-12 (both of which gave zoledronic acid on a 6 month schedule). There was no difference in the efficacy (in terms of DFS benefit) between AZURE and HOBOE/ABSG-12, and this therefore reinforced the acceptability of giving zoledronic acid as a less intense schedule to risk of osteonecrosis.

The committee were aware of guidelines from the Scottish Dental Clinical Effectiveness Programme (2017) regarding management of patients at risk of medication-related osteonecrosis of the jaw. This includes advising patients how to optimise their oral health (for example, use fluoride toothpaste and mouthwash, stop smoking, limit alcohol intake, report oral symptoms promptly), as this may help mitigate the risk of bisphosphonate-related osteonecrosis of the jaw.

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Appendices

Appendix A – Review protocols

Review protocol for 7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?

Field (based on PRISMA-P)	Content
Review question	What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine for which indications bisphosphonate therapy are evidence based and to better define the subgroups most likely to benefit, making recommendations on which bisphosphonate should be offered and to whom.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) who have undergone surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Bisphosphonates: • Alendronic acid/aledronate • Sodium clodronate • Pamidronate disodium • Ibandronic acid/Ibandronate • Zoledronic acid/Zoledronate • Risedronate sodium/Risodronate
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Bisphosphonates • No bisphosphonates
Outcomes and prioritisation	Critical (up to 3 outcomes) • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related morbidity (e.g., osteonecrosis of the jaw [MID: GRADE default values])

Field (based on PRISMA-P)	Content

	Important but not critical
	• Bone health
	  ○ Bone mineral density (MID: GRADE default values)
	  ○ Fractures (MID: GRADE default values)
	  ○ Changes in height (as measured by stadiometer or serial spine assessments [MID: GRADE default values])
	• Treatment-related mortality (MID: any statistically significant difference)
	• HRQoL (MID: values from the literature)
	5 year follow-up periods will be prioritised if multiple time points are reported.
	MID values from the literature:
	HRQoL:
	• FACT-G total: 3-7 points
	• FACT-B total: 7-8 points
	• TOI (trial outcome index) of FACT-B: 5-6 points
	• BCS of FACT-B: 2-3 points
	• WHOQOL-100: 1 point

Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only – excluding treatment-related morbidity): • Pre-menopausal • Post-menopausal • Lower priority subgroups: • Stage • Grade • Receptor status • Previous chemotherapy (yes/no)

Field (based on PRISMA-P)	Content
	• Men
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is a straightforward intervention review, limited to RCTs.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 2008 onwards as it is an update from the previous version of this guideline. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	Previous question: What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Offer bisphosphonates to patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK expert group (2008) (see Appendix 2).
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or appendix H (economic evidence tables).

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; RT, radiotherapy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies for 7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 21**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 25 September 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz

#	Searches
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Diphosphonates/ use prmz
34	exp Organophosphorus Compounds/ use prmz
35	exp Phosphoric Acids/ use prmz
36	exp bisphosphonic acid derivative/ use oemezd
37	exp organophosphorus compound/ use oemezd
38	exp phosphoric acid/ use oemezd
39	(bisphosphonat$ or diphosphonat$).af.
40	Alendronate/ use prmz
41	alendronic acid/ use oemezd
42	(alendron$ or aledron$ or fosamax or adrona or alendros or dronal).af.
43	Clodronic Acid/ use prmz
44	clodronic acid/ use oemezd
45	(clodron$ or bonefos or loron or ascredar or lodronat or lytos or ostac or clastoban or clasteon or difosfonal or ossiten or mebonat).af.
46	pamidronic acid/ use oemezd
47	(pamidron$ or APD or aredia).af.
48	ibandronic acid/ use oemezd
49	(ibandron$ or bondronat).af.
50	zoledronic acid/ use oemezd
51	(zoledron$ or zometa).af.
52	Risedronate Sodium/ use prmz
53	risedronic acid/ use oemezd
54	(risedron$ or risodron$ or actonel).af.
55	Etidronic Acid/ use prmz
56	etidronic acid/ use oemezd
57	(etidron$ or didron$ or difosfen or osteodidronel or osteum).af.
58	"disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
59	tiludronic acid/ use oemezd
60	(tiludron$ or skelid).af.
61	neridronic acid/ use oemezd
62	(neridron$ or AHDP).af.
63	olpadronic acid/ use oemezd
64	(olpadron$ or OPD).af.
65	"(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
66	incadronic acid/ use oemezd

#	Searches
67	(incadron$ or cimadronate or YM175 or YM 175).af.
68	minodronic acid/ use oemezd
69	(minodron$ or YM529 or YM 529).af.
70	or/33-69
71	32 and 70
72	limit 71 to yr="2008 -Current"
73	Limit 72 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

2 Date of last search: 25 September 2017

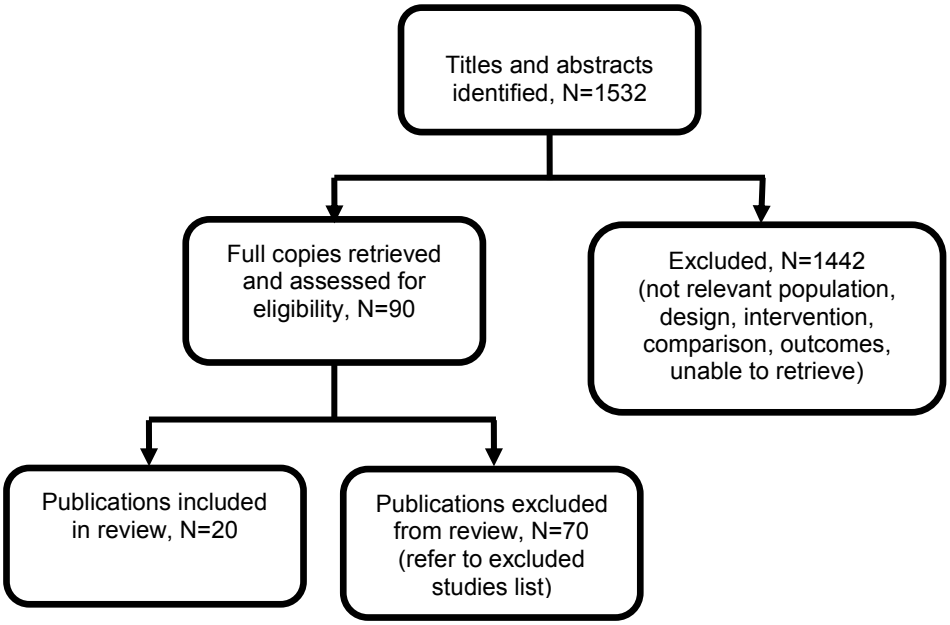
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Diphosphonates] explode all trees
#23	MeSH descriptor: [Organophosphorus Compounds] explode all trees
#24	MeSH descriptor: [Phosphoric Acids] explode all trees
#25	(bisphosphonat* or diphosphonat*):ti,ab,kw (Word variations have been searched)
#26	MeSH descriptor: [Alendronate] this term only

#	Searches
#27	(alendron* or aledron* or fosamax or adrona or alendros or dronal):ti,ab,kw (Word variations have been searched)
#28	MeSH descriptor: [Clodronic Acid] this term only
#29	(clodron* or bonefos or loron or ascredar or lodronat or lytos or ostac or clastoban or clasteon or difosfonal or ossiten or mebonat):ti,ab,kw (Word variations have been searched)
#30	(pamidron* or APD or aredia):ti,ab,kw (Word variations have been searched)
#31	(ibandron* or bondronat):ti,ab,kw (Word variations have been searched)
#32	(zoledron* or zometa):ti,ab,kw (Word variations have been searched)
#33	MeSH descriptor: [Risedronate Sodium] explode all trees
#34	(risedron* or risodron* or actonel):ti,ab,kw (Word variations have been searched)
#35	MeSH descriptor: [Etidronic Acid] explode all trees
#36	(etidron* or didron* or difosfen or osteodidronel or osteum):ti,ab,kw (Word variations have been searched)
#37	(tiludron* or skelid or neridron* or AHDP or olpadron* or OPD):ti,ab,kw (Word variations have been searched)
#38	(incadron* or cimadronate or YM175 or "YM 175"):ti,ab,kw (Word variations have been searched)
#39	(minodron* or YM529 or "YM 529"):ti,ab,kw (Word variations have been searched)
#40	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
#41	#21 and #40 Publication Year from 2008 to 2017

1

Appendix C – Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for adjuvant bisphosphonates



Appendix D – Clinical evidence tables

2 **Table 18: Clinical evidence table for adjuvant bisphosphonates**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Coleman, R. E., Marshall, H., Cameron, D., Dodwell, D., Burkinshaw, R., Keane, M., Gil, M., Houston, S. J., Grieve, R. J., Barrett-Lee, P. J., Ritchie, D., Pugh, J., Gaunt, C., Rea, U., Peterson, J., Davies, C., Hiley, V., Gregory, W., Bell, R., Breast-cancer adjuvant therapy with zoledronic acid, New England Journal of Medicine, 365, 1396-1405, 2011 **Ref Id** 570491 **Country/ies where the study was carried out** International (7 countries; NR) **Study type** RCT **Aim of the study**	**Sample size** 3360 **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Female patients (aged ≥18 years) with Stage II or III primary breast cancer with no evidence of metastatic disease. Patients should be scheduled to receive (neo)adjuvant chemotherapy and/or (neo)adjuvant hormonal therapy, and should have had or be scheduled to proceed to definitive surgery and/or radiotherapy. Performance status Karnofsky Index ≥60% or ECOG 0 and 1. **Exclusion criteria** Cancer diagnosis within the preceding 5 years, use of bisphosphonates during the previous year, or a diagnosis	**Interventions** **Intervention arm:** standard adjuvant systemic therapy + zoledronic acid **Control arm:** standard adjuvant systemic therapy	**Details** **Intervention arm (ZOL):** The zoledronic acid was administered immediately after each cycle of adjuvant chemotherapy in a 4-mg dose by intravenous infusion every 3 to 4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years. External-beam radiotherapy to the breast and chest wall, with or without irradiation of regional lymph nodes, and adjuvant cytotoxic and endocrine treatments were given in accordance with standard protocols at each participating institution. After regulatory approval of trastuzumab for adjuvant use, the drug was allowed in patients with HER2-positive tumours. Daily oral supplements containing calcium (400 to 1000 mg) and vitamin D (200 to 500 IU) were recommended for all patients during the first 6 months and were continued thereafter at the discretion of the treating physician.	**Results** **Treatment-related morbidity - osteonecrosis of the jaw:** ZOL 17/1681; No bisphosphonate 0/1678	**Selection bias: random sequence generation** Central, automated, computer-generated randomisation: Low **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to have a significant impact on results: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** All participants included in analysis except 1 that withdrew consent: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To determine whether adjuvant treatment with 4mg zoledronic acid plus chemotherapy and/or hormonal therapy is superior to chemotherapy and/or hormonal therapy alone in improving the disease-free and bone metastasis-free survival of women with breast cancer at high risk of relapse **Study dates** Recruited September 2003 to February 2006 **Source of funding** Novartis Pharmaceuticals and the National Cancer Research Network	of osteoporosis or other bone disease likely to require bone-targeted treatment. The serum creatinine level had to be less than 1.5 times the upper limit of the normal range. In 2005, after case reports of osteonecrosis of the jaw associated with bisphosphonates, an amendment was adopted to exclude patients with clinically significant, active dental problems or planned jaw surgery **Reported subgroups** Post-menopausal		**Control arm (no bisphosphonate):** External-beam radiotherapy to the breast and chest wall, with or without irradiation of regional lymph nodes, and adjuvant cytotoxic and endocrine treatments were given in accordance with standard protocols at each participating institution. After regulatory approval of trastuzumab for adjuvant use, the drug was allowed in patients with HER2-positive tumours. Daily oral supplements containing calcium (400 to 1000 mg) and vitamin D (200 to 500 IU) were recommended for all patients during the first 6 months and were continued thereafter at the discretion of the treating physician.		**Selective reporting** Low **Indirectness** None **Limitations** **Other information** AZURE trial - More up-to-date information on DFS, OS & bone fractures available in EBCTCG meta-analysis
Full citation Early Breast Cancer Trialists' Collaborative, Group, Coleman, R., Powles, T., Paterson, A., Gnant, M., Anderson, S., Diel, I., Gralow, J., von Minckwitz, G., Moebus, V., Bergh, J., Pritchard, K. I., Bliss, J., Cameron, D., Evans, V., Pan, H., Peto, R., Bradley, R., Gray, R., Adjuvant	**Sample size** Total sample 18,766 but only interested in individual patient data from the following trials (remaining trials inconsistent with protocol): ABCSG-12, ARIBON, AZURE, GAIN, HOBOE, KCSG-BR06-01, NCCTG N02C1, NSAPB B-34, ProBONE II **Characteristics**	**Interventions** **Intervention arm 1:** Sodium clodronate (<1 year, 2 years, and 3-5 years combined) **Intervention arm 2:** Aminobisphosphonate (<1 year, 1 year, 2 years, and 3-5 years combined; includes zoledronic acid, risedronate and ibandronate will need separating	**Details** No additional information reported	**Results** **Zoledronic acid vs. no treatment control** **Whole sample:** **DFS:** O-E: -13.46; V: 262.35	**A priori design** Unclear **Duplicate selection/extraction** Not reported: Unclear **Comprehensive literature search** Unclear (information not available in two of the

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials [Erratum: Lancet (2016) 387(10013): 30], Lancet, 386, 1353-61, 2015 **Ref Id** 570571 **Country/ies where the study was carried out** UK **Study type** Meta-analysis of RCTs **Aim of the study** To help clarify whether adjuvant bisphosphonates reduce the risk of bone and other metastases, and whether menopausal status affects efficacy **Study dates** Information was sought during 2012–14 - studies were eligible if they began before 2008 **Source of funding**	Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Trials were eligible if they began before 2008 and randomly assigned women between a bisphosphonate of any type, dose, and schedule versus a control group (open label or placebo) with no bisphosphonate, all other treatments being similar in both groups. **Exclusion criteria** No additional criteria reported **Reported subgroups** Post-menopausal; Can't extract data for other subgroups of interested as contributing trials not reported	in analysis to be consistent with our protocol) **Control arm:** includes no treatment controls and placebo (will need separating in analysis)		**OS:** O-E: -13.47; V: 185.67 **Bone health - fractures:** Zol 123/2581, control 151/2581 **Post-menopausal:** **DFS:** O-E: -26.42; V: 151.52 **OS:** O-E: -8.84; V: 83.87 **Zoledronic acid vs. placebo** **DFS:** O-E: 0.2; V: 2.4 **Risedronate vs. placebo** **DFS:** O-E: -1.5; V: 1.7	referenced papers and third is unavailable) **Publication status** Grey literature included **List of studies provided** Unclear - trials reported (including those where they could not obtain data) but references to published papers (where available) are not provided **Characteristics of included studies** Basic study characteristics not reported **Quality assessment** Not reported **Impact of quality assessment on conclusions** Not applicable as quality not reported **Appropriate methods for meta-analysis** Unclear - limited information provided about data synthesis

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Cancer Research UK, Medical Research Council				**OS:** O-E: -1.1; V: 1.5 **Ibandronate vs. no treatment control** **Whole sample:** **OS:** O-E: 1.2; V: 39.5 **Post-menopausal:** **DFS:** O-E: -4.8; V: 37.7 **OS:** O-E: -0.5; V: 21.2 **Ibandronate vs. placebo** **OS (post-menopausal only):** O-E: -1.0; V: 0.5	**Publication bias** Not assessed **Conflict of interest** Declaration of interest provided for the review but not included trials **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Sodium clodronate vs. placebo **Whole sample:** **OS:** O-E: -10.9; V: 93.1 **Bone health - fractures:** Clo 164/1662, placebo 193/1661 **Post-menopausal:** **DFS:** O-E: -16.4; V: 56.6 **OS:** O-E: -7.8; V: 66.3 **Pamidronate vs. no treatment** **Whole sample:**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				DFS: O-E: 7.9; V: 88.3 **OS:** O-E: 3.8; V: 96.8 **Bone health – fractures:** PAM 29/460; No treatment 24/493 **Post-menopausal:** **DFS:** O-E: 3.0; V: 35.4 **OS:** O-E: 0.3; V: 40.4	
Full citation Gnant, M., Mlineritsch, B., Luschin-Ebengreuth, G., Kainberger, F., Kassmann, H., Piswanger-Solkner, J. C., Seifert, M., Ploner, F., Menzel, C., Dubsky, P., Fitzal, F., Bjelic-Radisic, V., Steger, G., Greil, R., Marth, C., Kubista, E., Samonigg, H.,	**Sample size** 404 **Characteristics** Gender: 100% women Age: Median 45/4; Range 25.9 - 56.2 Ethnicity: NR	**Interventions** **Intervention arm:** goserelin + tamoxifen or anastrozole + zoledronic acid **Control arm:** goserelin + tamoxifen or anastrozole. No bisphosphonate treatment	**Details** **Intervention arm (ZOL):** 3 years of goserelin (3.6mg subcutaneously every 28 days) and tamoxifen (20mg/day orally) or anastrozole (1mg/day orally) and zoledronic acid (initially 8mg intravenously every 6 months but reduced to 4mg due to decreased renal function reported in other studies)	**Results** **Bone health - LS BMD (5 year follow-up):** Zol N=205, M=1.05, SD=0.13; Control N=199, M=0.98, SD=0.14	**Selection bias: random sequence generation** Centralised randomisation using computerised adaptive randomisation method of Pocock and Simon: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Wohlmuth, P., Mittlbock, M., Jakesz, R., Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy, The Lancet Oncology, 9, 840-849, 2008 **Ref Id** 570666 **Country/ies where the study was carried out** Austria; Germany **Study type** RCT **Aim of the study** To assess the efficacy of zoledronic acid for preventing bone loss associated with adjuvant endocrine therapy **Study dates** Enrolled June 1999 to May 2006 (taken from Gnant 2011) **Source of funding** AstraZeneca; Novartis	**Inclusion criteria** Premenopausal women (≥19 years of age) who had received surgery for stage I/II ER+ and/or PR+ breast cancer, Karnofsky Index of 70 or greater, fewer than ten positive lymph nodes **Exclusion criteria** Exclusion criteria included T1a (except yT1a), T4d, or yT4 breast cancer; a history of other tumours or cytotoxic chemo therapy (preoperative chemotherapy was allowed); pre-operative radiotherapy; random assignment more than 8 weeks postoperatively; pregnancy or lactation (or both); oral contraception; serum creatinine concentration of 265 µmol/L or more serum calcium concentration of less than 2 mmol/L or more than 3 mmol/L; bisphosphonate or long-term anticonvulsive therapy within 1 year of study entry; current or previous bone disease; long-term corticosteroid therapy; previous adjuvant chemotherapy; osteomalacia or osteogenesis imperfecta; pre-existing osteoperosis; and any contraindications to one of the trial medications.		**Control arm (no bisphosphonate):** 3 years of goserelin (3.6mg subcutaneously every 28 days) and tamoxifen (20mg/day orally) or anastrozole (1mg/day orally) Patients randomised to tamoxifen , tamoxifen + zoledronic acid, anastrozole, or anastrozole + zoledronic acid Lumbar spine (L1–L4) and trochanter (proximal femur) BMD was assessed by dual-energy X-ray absorptiometry - machines were standardised between institutions		**Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low, due to objective nature of results **Attrition bias** Outcomes available for all participants: Low **Selective reporting** Low **Indirectness** None **Limitations** Unclear whether any BMD improvement will be sufficient to prevent fractures in the future **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	Reported subgroups All pre-menopausal (but ovarian function suppressed by goserelin)				ABCSG-12 substudy
Full citation Gnant, M., Mlineritsch, B., Stoeger, H., Luschin-Ebengreuth, G., Heck, D., Menzel, C., Jakesz, R., Seifert, M., Hubalek, M., Pristauz, G., Bauernhofer, T., Eidtmann, H., Eiermann, W., Steger, G., Kwasny, W., Dubsky, P., Hochreiner, G., Forsthuber, E. P., Fesl, C., Greil, R., Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial, The Lancet Oncology, 12, 631-641, 2011 **Ref Id** 550098 **Country/ies where the study was carried out** Austria; Germany **Study type**	**Sample size** 1803 **Characteristics** Gender: 100% women Age: Median 45; Range 25-58 Ethnicity: NR **Inclusion criteria** Pre-menopausal women with stage I or II oestrogen-receptor-positive and/or progesterone-receptor-positive breast cancer. Must have had fewer than ten positive lymph nodes, and be scheduled to receive standard therapy with goserelin. Preoperative chemotherapy was allowed, and postoperative radiotherapy was administered according to institutional guidelines. **Exclusion criteria** Exclusion criteria were T1a (except yT1a), T4d, and yT4 tumours; a history of other	**Interventions** **Intervention arm:** Goserelin and tamoxifen or anastrozole + zoledronic acid **Control arm:** Goserelin and tamoxifen or anastrozole	**Details** **Intervention arm (ZOL):** goserelin (3.6 mg subcutaneously every 28 days) plus either tamoxifen (20 mg per day orally) or anastrozole (1 mg per day orally) and zoledronic acid (4 mg intravenously every 6 months) for 3 years. **Control arm (No bisphosphonate):** goserelin (3.6 mg subcutaneously every 28 days) plus either tamoxifen (20 mg per day orally) or anastrozole (1 mg per day orally)	**Results** **Whole sample:** **Treatment-related morbidity - arthralgia:** ZOL 145/900; No bisphosphonate 121/903 **Bone health - fracture:** ZOL 10/900; No bisphosphonate 15/903 **Node positive:** **DFS (median follow-up 62 months):** O-E: -9.90; V: 24.72 **OS (median follow-up 62 months):** O-E: -4.95; V: 10.35	**Selection bias: random sequence generation** Computer-generated, minimisation method: Low **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Low **Selective reporting**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT **Aim of the study** To compare the efficacy and safety of anastrozole or tamoxifen with or without zoledronic acid **Study dates** Enrolled June 1999 to May 2006 **Source of funding** AstraZeneca; Novartis	neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; and contraindications for study drugs. No patients received adjuvant chemotherapy. **Reported subgroups** All patients pre-menopausal			**Node negative:** **DFS (median follow-up 62 months):** O-E: -8.37; V: 20.14 **OS (median follow-up 62 months):** O-E: -2.35; V: 6.59	Low **Indirectness** None **Limitations** **Other information** ABCSG-12 trial. More up-to-date information for DFS & OS available in EBCTCG meta-analysis
Full citation Monda, V., Lupoli, G. A., Messina, G., Peluso, R., Panico, A., Villano, I., Salerno, M., Sessa, F., Marciello, F., Moscatelli, F., Valenzano, A., Molino, L., Lupoli, R., Fonderico, F., Tortora, A., Pisano, A., Ruberto, M., Gabriella, M., Cavaliere, G., Trinchese, G., Mollica, M. P., Cipolloni, L., Cibelli, G., Monda, M., Lupoli, G., Messina, A., Improvement of bone physiology and life	**Sample size** 84 **Characteristics** Gender: 100% female Age: mean 55.9 Ethnicity: NR **Inclusion criteria** Post-menopausal women with hormone receptor positive breast; mild to moderate risk of fracture (based on lumbar spine or femoral neck BMD T-score)	**Interventions** **Intervention arm:** anastrozole and oral risedronate **Control arm:** anastrozole alone	**Details** **Intervention arm (Ris):** patients received 1mg anastrtozole daily and calcium (1,000mg/day) and vitamin D (800 IU/day) supplements for 2 years; 35mg oral risedronate was given weekly early in the morning before and food or drink sue to poor absorption of oral bisphosphanates **Control arm (No bisphosphonate):** patients received 1mg anastrtozole daily and calcium (1,000mg/day) and	**Results** **Bone health - LS BMD T score (2 year follow-up):** Ris N=36, M=-1.9, SD=0.49; Control N=35, M=-2.16, SD=0.51 **Bone health - FN BMD T score (2 year follow-up):** Ris N=36, M=-1.72, SD=0.78; Control N=35, M=-2.05, SD=0.36	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
quality due to association of risedronate and anastrozole, Frontiers in Pharmacology, 8 (no pagination), 2017 **Ref Id** 682781 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To determine the effect of anastrozole and risedronate on bone health and quality of life in post-menopausal women with early breast cancer at mild to moderate risk of fragility fractures **Study dates** Not reported **Source of funding** Department of Biology, Universitá degli Studi di Napoli Federico II	**Exclusion criteria** Treatment-induced menopause; recent hormonal treatment; previous hip fracture or prosthesis; known bone-metabolism disorder; untreated hypo- or hypercalceamia; previous treatment with medications that affect bone metabolism; liver or renal dysfunction **Reported subgroups** N/A		vitamin D (800 IU/day) supplements for 2 years BMD was measured by DEXA scans (same operstor and densitomer) used at baseline and follow-up	**Bone health - fracture (2 year follow-up):** Ris 0/36; Control 3/35 **Health-related quality of life - physical component summary of SF-36 (PCS-36):** Ris N=36, M=40.7, SD=16; Control N=35, M=38, SD=15 **Health-related quality of life - mental component summary of SF-36 (MCS-36):** Ris N=36, M=38.6, SD=16; Control N=35, M=39.9, SD=10	No blinding but unlikely to significantly impact results **Detection bias** Low for bone health outcomes due to objective nature; high for HRQoL outcomes **Attrition bias** Loss to follow-up equivalent across arms (7 in control arm, 6 in intervention arm) but high given small sample size: Unclear **Selective reporting** Low **Indirectness** None **Limitations** Very small sample size **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Greenspan,S.L., Brufsky,A., Lembersky,B.C., Bhattacharya,R., Vujevich,K.T., Perera,S., Sereika,S.M., Vogel,V.G., Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial, Journal of Clinical Oncology, 26, 2644-2652, 2008 **Ref Id** 231696 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To examine the efficacy of risedronate in the prevention of bone loss in newly postmenopausal women with breast cancer treated with chemotherapy **Study dates**	**Sample size** 106 screened, 87 randomly assigned **Characteristics** Gender: 100% women Age: Risedronate Mean 50.1, SD 5.1; Placebo Mean 49, SD 5.9 Ethnicity: NR **Inclusion criteria** Newly postmenopausal women (≤ 8 years post-menopausal and verified by gonadotropin levels) with stage I–III breast cancer who were treated with chemotherapy **Exclusion criteria** Illness known to affect bone mineral metabolism or on medications known to affect bone mineral metabolism **Reported subgroups** All patients post-menopausal	**Interventions** **Intervention arm:** risedronate **Control arm:** placebo	**Details** **Intervention arm (Ris):** 35mg risedronate taken once a week (initially for one year but trial extended to 2 years) **Control arm (Placebo):** matching placebo taken once a week (initially for one year but trial extended to 2 years) BMD assessed using dual energy x-ray absorptiometry	**Results** **Bone health - percentage change in LS BMD (2 year follow-up):** Ris N=34, M=0.1, SD=1.1; Placebo N=38, M=-2.4, SD=1.1 **Bone health - percentage change in FN BMD (2 year follow-up):** Ris N=34, M=0.0, SD=0.6; Placebo N=38, M=-1.6, SD=0.8 **Bone health - fractures (2 year follow-up):** Ris 3/34; Placebo 2/38	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Low **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 5 women in intervention arm and 4 women in control arm did not continue to 2nd year of trial: Low **Selective reporting** Low **Indirectness** None **Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Not reported **Source of funding** Procter and Gamble					Underpowered to examine fracture efficacy. During the course of the study, due to a shift in the standard of care, women were switched from tamoxifen to AIs or started on an AI by their physicians (however rates of tamoxifen/AI use were not significantly different between arms) **Other information** REBBeCA trial
Full citation Greenspan, S. L., Vujevich, K. T., Brufsky, A., Lembersky, B. C., van Londen, G. J., Jankowitz, R. C., Puhalla, S. L., Rastogi, P., Perera, S., Prevention of bone loss with risedronate in breast cancer survivors: a randomized, controlled clinical trial, Osteoporosis international, 26, 1857-1864, 2015 **Ref Id** 570691	**Sample size** 280 screened, 109 randomised **Characteristics** Gender: 100% women Age: Mean 51, SD 1 Ethnicity: NR **Inclusion criteria** Postmenopausal women with hormone receptor positive breast cancer over age 55 years, with low bone mass (T-score between −1.0 and −2.5 at the spine or hip) currently	**Interventions** **Intervention arm:** aromatase inhibitor + risedronate **Control arm:** aromatase inhibitor + placebo	**Details** **Intervention arm (RIS):** Aromatase inhibitor (including anastrozole, letrozole, or exemestane) and 35mg oral risedronate once weekly for 2 years. Daily calcium up to 1200 mg daily by diet and/or supplement (supplement contained calcium carbonate 500 mg plus vitamin D 200 IU). **Control arm (Placebo):** Aromatase inhibitor (including anastrozole, letrozole, or exemestane) and placebo once weekly for 2	**Results** **Treatment-related morbidity - gastrointestinal:** Ris 4/55, Placebo 13/54 **Bone health - percentage change in PA Spine BMD (2 year follow-up):** Ris N=48, M=2.0, SD=3.46; Placebo N=47, M=-1.2, SD=3.43	**Selection bias: random sequence generation** Insufficient information: Unclear **Selection bias: allocation concealment** Low **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** RCT **Aim of the study** To examine the preservation of bone mass with an oral bisphosphonate in women with osteopenia or low bone mass taking adjuvant aromatase inhibitors **Study dates** Enrolled January 2008 to March 2013 **Source of funding** Procter and Gamble, the Alliance for Better Bone Health, Warner Chilcott and NIH grants K24DK062895, T32AG021885 and P30AG024827	receiving an AI including anastrozole, letrozole, or exemestane **Exclusion criteria** Treated with a bisphosphonate in the previous year, illnesses/medications known to affect bone and mineral metabolism such as glucocorticoids or certain antiseizure medications **Reported subgroups** All post-menopausal		years. Daily calcium up to 1200 mg daily by diet and/or supplement (supplement contained calcium carbonate 500 mg plus vitamin D 200 IU). Changes in BMD measured using dual-energy x-ray absorptiometry		**Detection bias** Low due to objective nature of outcomes **Attrition bias** Rates of attrition equivalent between arms (N=7 for both arms): Low **Selective reporting** Low **Indirectness** None **Limitations** Short duration (only 2 years). Not powered to assess efficacy of risedronate for preventing fractures. **Other information** REBBeCA2 trial
Full citation Hadji, P., Kauka, A., Ziller, M., Birkholz, K., Baier, M., Muth, M.,	**Sample size** 71 screened, 70 randomised **Characteristics**	**Interventions** **Intervention arm:** (neo)adjuvant (chemo)endocrine therapy + zoledronic acid	**Details** **Intervention arm (ZOL):** No details provided for (neo)adjuvant	**Results** **Bone health - percentage change LS BMD (2 year**	**Selection bias: random sequence generation** Not reported: Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Bauer, M., Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR⁺ breast cancer: The ProBONE II study, Osteoporosis international, 25, 1369-1378, 2014 **Ref Id** 570707 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To investigate the effect of adjuvant zoledronic acid on BMD and bone turnover markers in premenopausal women with early HR+ BC **Study dates** Randomised October 2005 to June 2009 **Source of funding** Novartis	Gender: 100% women Age: Mean 43, range 23-51 Ethnicity: 98.6% Caucasian, 1.4% Asian **Inclusion criteria** Premenopausal women ≥18 years of age with histologically confirmed, HR+ (defined as ≥10 % ER and/or PR positive cells or ≥10 fmol receptor protein/mg cytosol protein or insulin receptor substrate ≤2) invasive breast cancer (T1–4) and no evidence of metastases (M0). Participants receiving adjuvant therapy had to have no more than four positive lymph nodes; participants receiving neoadjuvant therapy had to be free of nodal involvement. Participants were also required to have a bone density T-score of ≥−2.5 (DXA) at study entry. **Exclusion criteria** History of treatment or disease affecting bone metabolism (e.g., Paget's disease, primary hypothyroidism); known visceral metastasis or bone metastases, known prior treatment with or hypersensitivity to	**Control arm:** (neo)adjuvant (chemo)endocrine therapy + placebo	(chemo)endocrine therapy. 8 cycles of zoledronic acid were given over 24 months (4mg IV every 3 months) **Control arm (Placebo):** No details provided for (neo)adjuvant (chemo)endocrine therapy. Eight infusions of placebo were administered at intervals of 3 months Bone mineral density was assessed by dual-energy X-ray absorptiometry (DXA); all DXA measurements were performed with the same Lunar Prodigy densitometer by the same technician using a standard protocol for the femoral neck, total hip, and lumbar spine. Calibration and standardization procedures were standard practice at the institution to maintain precision and accuracy of DXA measurements	**follow-up):** Zol N=34 , M=3.14 , SD=3.39; Placebo N=36, M=-6.43, SD=3.41 **Bone health - percentage change FN BMD (2 year follow-up):** Zol N=34, M=0.98, SD=2.65; Placebo N=36, M=-2.33, SD=3.70	**Selection bias: allocation concealment** Low **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 8 patients in intervention arm and 6 patients in control arm were not treated per-protocol. Reasons not reported: Unclear **Selective reporting** Low **Indirectness** Intervention: some patients received bisphosphonates as neoadjuvant treatment (proportion unclear): very serious

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	bisphosphonates; abnormal renal function; and current, active dental problems or a current/prior diagnosis of osteonecrosis of the jaw (ONJ) or recent (within 6 weeks)/planned dental or jaw surgery. **Reported subgroups** All pre-menopausal				**Limitations** Small sample size and short follow-up period. **Other information** ProBONE II trial
Full citation Hershman, D. L., McMahon, D. J., Crew, K. D., Shao, T., Cremers, S., Brafman, L., Awad, D., Shane, E., Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment, Journal of Clinical Endocrinology and Metabolism, 95, 559-566, 2010 **Ref Id** 538244 **Country/ies where the study was carried out** USA **Study type**	**Sample size** 85 **Characteristics** Gender: 100% women Age: Mean 44, SD 6 Ethnicity: 43% Hispanic, 41% Caucasian, 18% Black, 4% Asian **Inclusion criteria** Premenopausal women with newly diagnosed, histologically proven, non-metastatic breast cancer - enrolled after surgery but before initiating chemotherapy **Exclusion criteria** T score of <2.0 at any site, fragility fracture, prior therapy with a bisphosphonate, lumbar	**Interventions** **Intervention arm:** adjuvant chemotherapy + zoledronic acid **Control arm:** adjuvant chemotherapy + placebo	**Details** **Intervention arm (ZOL):** 4mg IV zoledronic acid over 15 min every 3 months for 12 months **Control arm (Placebo):** Placebo IV over 15 min every 3 months for 12 months Bone mineral density was measured by dual-energy x-ray absorptiometry. All instruments were calibrated before beginning the study with reference phantoms to read BMD within 1%. The subsequent calibration strategy included rescanning of the reference phantoms at 6-month intervals. Patients were assessed on the same machine for each follow-up visit.	**Results** **Bone health - percentage change in LS BMD (2 year follow-up):** Zol N=27, M=-0.6, SD=0.84; Placebo N=30, M=-6.3, SD=0.83 **Bone health - percentage change in FN BMD (2 year follow-up):** Zol N=27, M=0.04, SD=0.84; Placebo N=30, M=-2.4, SD=0.71	**Selection bias: random sequence generation** Random permuted blocks: Low **Selection bias: allocation concealment** Low **Selection bias: overall judgement** Low **Performance bias** Double-blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT **Aim of the study** To determine whether zoledronic acid, given every 3 months for 1 year to premenopausal women with breast cancer undergoing chemotherapy, prevented a reduction in BMD **Study dates** Not reported **Source of funding** National Cancer Institute (CA95597), American Society of Clinical Oncology, National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR052665), Novartis	spine anatomy precluding accurate bone mineral density measurement of at least three lumbar vertebrae, serum creatinine of at least 2 mg/dl, or pregnancy **Reported subgroups** All pre-menopausal				Rates of attrition similar in both arms - main reason was 24 month BMD measures being performed after 30 months: Low **Selective reporting** Low **Indirectness** None **Limitations** Small sample size **Other information**
Full citation Hines, S. L., Mincey, B. A., Sloan, J. A., Thomas, S. P., Chottiner, E., Loprinzi, C. L., Carlson, M. D., Atherton, P. J., Salim, M., Perez, E. A., Phase III randomized, placebo-controlled,	**Sample size** 216 **Characteristics** Gender: 100% women Age: Mean 43.5, SD 5.73 Ethnicity: NR	**Interventions** **Intervention arm:** chemotherapy + risedronate **Control arm:** chemotherapy + placebo	**Details** **Intervention arm (RIS):** Chemotherapy (anthracyclines, taxanes, or cyclophosphamide), oral calcium 600 mg and vitamin D 400 U daily, and oral risedronate 35 mg weekly	**Results** **Treatment-related morbidity - arthralgia:** Ris 0/106; Placebo 3/106	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
double-blind trial of risedronate for the prevention of bone loss in premenopausal women undergoing chemotherapy for primary breast cancer, Journal of clinical oncology, 27, 1047-1053, 2009 **Ref Id** 570741 **Country/ies where the study was carried out** North America **Study type** RCT **Aim of the study** To determine whether risedronate prevents bone loss in premenopausal women undergoing chemotherapy for breast cancer **Study dates** Enrolled March 2003 to March 2006 **Source of funding**	**Inclusion criteria** Eligible study participants were premenopausal women scheduled to undergo adjuvant or neoadjuvant chemotherapy for primary breast cancer (stages I to IIIB). Women must have been at least 18 years of age, with an Eastern Cooperative Oncology Group performance status of 0 (fully active) or 1 (ambulatory and able to carry out light work). **Exclusion criteria** Hypercalcaemia, hypocalcaemia, inability to stand or sit upright for at least 30 minutes, known swallowing disorder, BMD T score of 2.0 at the hip or LS, history of vertebral compression fracture, corticosteroid use at doses more than 5 mg/d of prednisone or equivalent for more than 2 weeks in the prior 6 months, previous treatment with bisphosphonates, diseases affecting bone metabolism, serum creatinine more than 2.0, malabsorption syndrome, menopausal estrogen therapy, oral contraceptive use, bilateral oophorectomy,		**Control arm (Placebo):** Chemotherapy (anthracyclines, taxanes, or cyclophosphamide), oral calcium 600 mg and vitamin D 400 U daily, and weekly placebo Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry (DXA) devices. The same device was used at baseline and 1 year; prevision assessments conducted by the participating NCCTG locations were performed locally.	**Treatment-related morbidity - constipation:** Ris 53/106; Placebo 61/106 **Treatment-related morbidity - nausea:** Ris 5/106; Placebo 3/106 **Treatment-related morbidity - abdominal pain:** Ris 33/106; Placebo 30/106 **Treatment-related morbidity - diarrhoea:** Ris 30/106; Placebo 29/106 **Bone health - percentage change LS BMD (1 year follow-up):** Ris N=85, M=-4.3, SD=5.19; Placebo N=85, M=-5.4, SD=6.44 **Bone health - percentage**	Low **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** Rates of and reasons for attrition are comparable across arms: Low **Selective reporting** Low **Indirectness** Intervention: some patients received bisphosphonates as neoadjuvant treatment (proportion unclear): very serious **Limitations** Study was underpowered **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
National Cancer Institute (NCI), Aventis	pregnancy, active nursing, of childbearing potential unwilling to employ adequate contraception, and having undergone dental extraction, root canal, or dental implants 3 months before registration. Women planning dental extraction, root canal, or dental implants during study treatment were also ineligible **Reported subgroups** All pre-menopausal			**change FN BMD (1 year follow-up):** Ris N=85, M=-2.2, SD=8.76; Placebo N=85, M=-2.4, SD=12.56	NCCTG N02C1 Trial
Full citation Kim,J.E., Ahn,J.H., Jung,K.H., Kim,S.B., Kim,H.J., Lee,K.S., Ro,J.S., Park,Y.H., Ahn,J.S., Im,Y.H., Im,S.A., Lee,M.H., Kim,S.Y., Zoledronic acid prevents bone loss in premenopausal women with early breast cancer undergoing adjuvant chemotherapy: A phase III trial of the Korean Cancer Study Group (KCSG-BR06-01), Breast Cancer Research and Treatment, 125, 99-106, 2011 **Ref Id** 99203	**Sample size** 116 **Characteristics** Gender: 100% women Age: Mean 44.8, SD 2.9 Ethnicity: NR **Inclusion criteria** Premenopausal women over age 40 years with newly diagnosed, histologically proven, non-metastatic breast cancer, and scheduled for four cycles of adjuvant AC (Adriamycin and cyclophosphamide) followed by four cycles of paclitaxel or docetaxel	**Interventions** **Intervention arm:** adjuvant chemotherapy + zoledronic acid **Control arm:** adjuvant chemotherapy	**Details** **Intervention arm (ZOL):** adjuvant chemotherapy (four cycles of adjuvant AC (Adriamycin and cyclophosphamide) followed by four cycles of paclitaxel or docetaxel), daily oral supplements containing calcium (500 mg) and vitamin D (cholecalciferol 1000 IU), and 4 mg ZA intravenously over 15 min, starting on the day of first adjuvant chemotherapy, every 6 months for 12 months. Patients with hormone receptor-positive breast cancer were scheduled to receive adjuvant tamoxifen after the end of eight cycles of chemotherapy	**Results** **Bone health - percentage change LS BMD (1 year follow-up):** Zol N=56, M=-1.1, SD=3.7; Control N=56, M=-7.5, SD=2.8 **Bone health - percentage change FN BMD (1 year follow-up):** Zol N=56, M=1.1, SD=5.6; Control N=56, M=-3.4, SD=3.3	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Korea **Study type** RCT **Aim of the study** To determine whether zoledronic acid (ZA) can prevent bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer **Study dates** Randomised January 2007 to December 2008 **Source of funding** Korean Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (0412-CR01-0704-001)	**Exclusion criteria** History of metabolic bone disease; received any bisphosphonate within 1 year of the start of the protocol; history of intake of pharmacologic amounts of any medications that can affect bone turnover; history of allergy to bisphosphonates; baseline BMD T-score of ≤-2.0 at the LS or hip; history of compression fractures; bilateral oophorectomy; were of child bearing potential but unwilling to employ adequate contraception; serum creatinine >1.6 mg/dl; undergone dental extraction or dental implants ≤2 months before registration **Reported subgroups** All premenopausal		**Control arm (No treatment):** adjuvant chemotherapy (four cycles of adjuvant AC (Adriamycin and cyclophosphamide) followed by four cycles of paclitaxel or docetaxel), daily oral supplements containing calcium (500 mg) and vitamin D (cholecalciferol 1000 IU). Patients with hormone receptor-positive breast cancer were scheduled to receive adjuvant tamoxifen after the end of eight cycles of chemotherapy. Zoledronic acid was started if there was a clinical fracture unrelated to trauma or 6 month follow-up BMD T-score ≤-2.5 standard deviations (SDs) at either the LS or total hip; no individuals in this group started ZA during the study period Bone mineral density was measured using local dual-energy x-ray absorption (DXA) devices at participating hospitals, with all instruments calibrated before the study using reference phantoms. Patients were assessed on the same machine at each follow-up visit		Low due to objective nature of outcomes **Attrition bias** Very little attrition: Low **Selective reporting** None **Indirectness** None **Limitations** Short follow-up period **Other information** KCSG-BR06-01 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Kristensen, B., Ejlertsen, B., Mouridsen, H. T., Jensen, M. B., Andersen, J., Bjerregaard, B., Cold, S., Edlund, P., Ewertz, M., Kamby, C., Lindman, H., Nordenskjold, B., Bergh, J., Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer, Acta oncologica, 47, 740-6, 2008 **Ref Id** 565656 **Country/ies where the study was carried out** Denmark; Sweden; Iceland **Study type** RCT **Aim of the study** To investigate whether oral pamidronate can prevent the occurrence of bone metastases and fractures	**Sample size** 953 **Characteristics** Gender: 100% women Age: Mean/Range NR; 47% aged 40-49 years, 23% aged 50-59 years, 16% aged ≤39 years, 15% aged 60-69 years Ethnicity: NR **Inclusion criteria** Women with resectable adenocarcinoma of the breast and without signs of distant metastases. Patients for the trial were recruited from the following three groups: A) premenopausal women without lymph node metastases but with grade 2 or 3 malignancy and a primary tumour ≤5 cm in diameter independent of hormone receptor status, B) premenopausal women with negative or unknown hormone receptor status and with either axillary lymph node metastases or a primary tumour >5 cm in diameter, C) postmenopausal women with hormone receptor negative tumours and with either axillary lymph node	**Interventions** **Intervention arm:** CMF/CEF chemotherapy + pamidronate **Control arm:** CMF/CEF chemotherapy	**Details** **Intervention arm (PAM):** All patients received CMF or CEF chemotherapy and oral pamidronate 150 mg twice daily for 4 years. Radiotherapy was given according to guidelines at participating centres and endocrine therapy was to be avoided. **Control arm (No bisphosphonate):** All patients received CMF or CEF chemotherapy. Radiotherapy was given according to guidelines at participating centres and endocrine therapy was to be avoided.	**Results** **Treatment-related morbidity - nausea/vomiting:** PAM 324/417; No bisphosphonate 337/467 **Treatment-related morbidity - abdominal pain:** PAM 123/417; No bisphosphonate 103/467	**Selection bias: random sequence generation** Randomisation method NR: Unclear **Selection bias: allocation concealment** Randomisation method NR: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 24 lost to follow-up and 182 had incomplete fracture records - rates similar between groups: Unclear **Selective reporting**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates January 1990 to January 1996 **Source of funding** Pharmacia (now Pfizer) and Ciba-Giegy (now Novartis)	metastases or a primary tumour >5 cm in diameter **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest				Survival outcomes not reported in sufficient detail for analysis **Indirectness** None **Limitations** **Other information** DBCG trial; more recent data on fractures available in EBCTCG meta-analysis
Full citation Leal,T., Tevaarwerk,A., Love,R., Stewart,J., Binkley,N., Eickhoff,J., Parrot,B., Mulkerin,D., Randomized trial of adjuvant zoledronic acid in postmenopausal women with high-risk breast cancer, Clinical Breast Cancer, 10, 471-476, 2010 **Ref Id** 267514 **Country/ies where the study was carried out** USA	**Sample size** 68 **Characteristics** Gender: 100% women Age: Zol Median 54.5, Range 41-83; Control Median 50.5, Range 37-65 Ethnicity: 98.5% Caucasian, 1.5% Hispanic **Inclusion criteria** Post-menopausal women with histologically-confirmed T4 or node positive adenocarcinoma of the breast; diagnosis had to have occurred within five years of	**Interventions** **Intervention:** Zoledronic acid **Control:** No bisphosphonate treatment	**Details** **Intervention arm (ZOL):** Zoledronic acid 4mg IV every 12 weeks administered over at least 15 minutes for four cycles **Control (No treatment):** No further details reported Bone mineral density was measured by dual energy x-ray absorptiometry (DXA). A Bone-fide® calibration phantom was measured by the densitometers at all participating facilities. Quality assurance phantom data from all participating facilities was evaluated; no	**Results** **Bone health - change in LS BMD (1 year follow-up):** Zol N=29, M= 0.05, SD=0.04; Control N=26, M=0.01, SD=0.07 **Bone health - change in FN BMD (1 year follow-up):** Zol N=30, M=0.01, SD=0.04; Control N=26, M=0.01, SD=0.05	**Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type RCT **Aim of the study** To examine changes in bone mineral density following a year of zoledronic acid in post-menopausal women with high risk breast cancer **Study dates** February 2000 to February 2007 **Source of funding** Novartis	enrolment. Patients were required to have an ECOG performance status of 0 to 2, age > 18 years, adequate bone marrow reserve, adequate renal and hepatic function and normal calcium. Prior adjuvant chemotherapy was permitted and choice of regimen was decided upon by the treating physician. Use of supplemental calcium and vitamin D was permitted at the discretion of the treating physician, but not routinely assessed or tracked. **Exclusion criteria** History of second or other cancers; risk of recurrence for the second malignancy over 5%; concurrent bisphosphonate use; T score of < −2.0 at the hip or spine (if not receiving tamoxifen) **Reported subgroups** All post-menopausal		densitometer shift or drift occurred during the course of this trial.		**Detection bias** Low due to objective nature of outcomes **Attrition bias** Reasons for attrition are similar but rates fairly high for sample size(6 in each arm): Unclear **Selective reporting** OS and DFS not included in sufficient detail for analysis **Indirectness** None **Limitations** Study underpowered; control arm younger than intervention arm (statistical significance not reported); use of calcium and vitamin D was not routinely assessed or controlled for; did not prospectively follow patients for subsequent fractures **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Lester,J.E., Dodwell,D., Purohit,O.P., Gutcher,S.A., Ellis,S.P., Thorpe,R., Horsman,J.M., Brown,J.E., Hannon,R.A., Coleman,R.E., Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer, Clinical Cancer Research, 14, 6336-6342, 2008 **Ref Id** 232221 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** To investigate the impact of oral ibandronate on BMD in women with osteopenia taking anastrozole	**Sample size** 131 recruited but only those who had osteopenia (N=50) were randomised **Characteristics** Gender: 100% women Age: Median 68; IQR for ibandronate 59-73; IQR for placebo 64-71 Ethnicity: NR **Inclusion criteria** Postmenopausal women with a histologically confirmed diagnosis of oestrogen receptor –positive breast cancer. Patients were classified as osteopenic if their T score was <-2.5 at either the LS or TH. **Exclusion criteria** Patients were excluded if their menopause was induced by either prior chemotherapy or by drug therapy. Other exclusion criteria included concurrent administration of medication(s) with effects on bone such as bisphosphonates or hormone replacement therapy, abnormal renal function, disorders of bone metabolism, and previous bilateral hip	**Interventions** **Intervention arm:** anastrozole, calcium and vitamin D supplements + ibandronate **Control arm:** anastrozole, calcium and vitamin D supplements + placebo	**Details** **Intervention arm (IBA):** All patients received anastrozole 1 mg once a day and calcium (500 mg) and vitamin D (400 IU) supplements daily + ibandronate 150 mg every 28 days orally for 2 years. Ibandronate capsules were taken in an upright position first thing in the morning on an empty stomach and washed down with 100 mL water to minimize the risk of oesophageal irritation; no food or drink (other than water) was consumed for at least 30 min after taking the study medication. **Control (Placebo):** All patients received anastrozole 1 mg once a day and calcium (500 mg) and vitamin D (400 IU) supplements daily + placebo tablets of identical appearance to the ibandronate every 28 days orally for 2 years. Placebo capsules were taken in an upright position first thing in the morning on an empty stomach and washed down with 100 mL water to minimize the risk of oesophageal irritation; no food or drink (other than water) was consumed for at least 30 min after taking the study medication.	**Results** **Treatment-related morbidity - arthralgia:** IBA 6/25; Placebo 5/25 **Treatment-related morbidity - upper GI symptoms:** IBA 4/25; Placebo 0/25 **Bone health - fractures:** IBA 2/25; Placebo 3/25	**Selection bias: random sequence generation** Method of randomisation NR: Unclear **Selection bias: allocation concealment** Method of randomisation NR: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Double-blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** Slightly higher rate of attrition in placebo group - 2 discontinued in placebo group due to reduced BMD, may minimise difference between groups: High **Selective reporting**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Recruited December 2003 to October 2005 **Source of funding** Astra Zeneca and Roche	fractures or bilateral hip prostheses that would have made BMD assessments impossible. **Reported subgroups** All patients post-menopausal and ER+				BMD not reported in sufficient detail to include in analysis although this was primary aim of study **Indirectness** None **Limitations** Small sample size - power calculations suggest this was adequate to detect expected difference in BMD but BMD not reported in sufficient detail to include in analysis. Unclear if sufficiently powered for the other outcomes **Other information** ARIBON trial
Full citation McCloskey, E., Paterson, A., Kanis, J., Tahtela, R., Powles, T., Effect of oral clodronate on bone mass, bone turnover and subsequent metastases in women with primary breast cancer, European journal of cancer, 46, 558-565, 2010	**Sample size** 851 **Characteristics** Gender: 100% women Age: Mean 52.9, SD 10.3 Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** standard therapy + oral sodium clodronate **Control arm:** standard therapy + placebo	**Details** **Intervention arm (CLO):** 1600mg/d oral sodium clodronate for 2 years **Control arm (Placebo):** No further details reported	**Results** **Bone health - percentage change in LS BMD (2 year follow-up):** Clo N=419, M=0.06, SD=7.55; Placebo N=432, M=-1.87, SD=6.87	**Selection bias: random sequence generation** Random numbers tables and random permutated blocks: Low **Selection bias: allocation concealment** Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 570963 **Country/ies where the study was carried out** UK, Canada, Scandinavia **Study type** RCT **Aim of the study** To evaluate the effect of oral sodium clodronate treatment on spine and hip bone mineral density during the 2-year treatment period and during 3 years of post-treatment follow-up **Study dates** Randomised 1989 to July 1995 (Taken from Powles 2002) **Source of funding** Bayer Schering Pharma	Histologically or cytologically confirmed operable primary breast cancer with no evidence of metastatic disease or significant renal, hepatic, or non-malignant bone disease. Need to be psychologically and physically suitable for 2 years of oral sodium clodronate or placebo (taken from Powles 2002) **Exclusion criteria** History of malignant disease or bisphosphonate use (taken from Powles 2002) **Reported subgroups** Pre-menopausal, post-menopausal		Bone mineral density was measured by dual energy X-ray absorption using Hologic QDR1000 densitometers. The BMD data were collected centrally at the study centre in Sheffield, using appropriate quality control procedures and identifying any scans that required review and/or re-analysis under blinded conditions.	**Bone health - percentage change in FN BMD (5 year follow-up):** Clo N=419, M=-2.35, SD=9.58; Placebo N=432, M=-4.05, SD=8.78	**Selection bias: overall judgement** Low **Performance bias** Double-blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** Paper only includes those with available BMD data. Attrition in wider study not reported: Unclear **Selective reporting** Low **Indirectness** None **Limitations** **Other information** ISRCT83688026 Trial
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Nuzzo, F., Gallo, C., Lastoria, S., Di Maio, M., Piccirillo, M. C., Gravina, A., Landi, G., Rossi, E., Pacilio, C., Labonia, V., Di Rella, F., Bartiromo, A., Buonfanti, G., De Feo, G., Esposito, G., D'Aniello, R., Maiolino, P., Signoriello, S., De Maio, E., Tinessa, V., Colantuoni, G., De Laurentiis, M., D'Aiuto, M., Di Bonito, M., Botti, G., Giordano, P., Daniele, G., Morabito, A., Normanno, N., de Matteis, A., Perrone, F., Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBOE study, Annals of oncology, 23, 2027-33, 2012 **Ref Id** 538563 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study**	483 - but only interested in letrozole (N=149) and letrozole + zoledronic acid (N=154) groups **Characteristics** Gender: 100% women Age: Median 49; Range 28-78 Ethnicity: NR **Inclusion criteria** Patients, at least 18 years old, with histologically confirmed breast cancer, either pre- or postmenopausal, without evidence of recurrence after eventual adjuvant chemotherapy, whose tumour expressed oestrogen or progesterone receptors in at least 1% of tumour cells at immunohistochemistry. Adjuvant trastuzumab for HER-2 positive tumours and adjuvant radiotherapy were allowed. **Exclusion criteria** Pregnant or lactating, abnormal kidney and/or liver function, evidence of active bone fracture, taken steroids on a regular basis in the previous 12 months or drugs interfering with bone metabolism (e.g. calcitonin,	**Intervention arm:** letrozole + zoledronic acid **Control arm:** letrozole	**Intervention arm (ZOL):** letrozole 2.5mg/day and zoledronic acid 4mg IV every 6 months for 5 years **Control arm (No bisphosphonate):** letrozole 2.5mg/day for 5 years	**Treatment-related morbidity - myalgia:** ZOL 8/153; No bisphosphonate 3/148	Centralised, computerised minimisation procedure: Low **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to have a significant impact on results: Low **Detection bias** Low due to objective nature of outcome **Attrition bias** Some loss of data due to non-completion of post-treatment BMD scan and discontinuation of treatment. Unclear if rates differ across groups **Selective reporting** BMD not reported in sufficient detail to

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To estimate the negative effect on bone of letrozole compared with tamoxifen and the positive effect of the addition of zoledronic acid to letrozole, in pre- and postmenopausal patients with hormone receptor-positive early breast cancer. **Study dates** Randomised March 2004 to December 2009 **Source of funding** Associazione Italiana per la Ricerca sul Cancro (AIRC), Novartis and Ipsen	mitramycin) in the previous 2 weeks. Patients treated by or requiring invasive therapeutic procedures for dental diseases and those who had previously received tamoxifen or an AI were not eligible. **Reported subgroups** None of interest				include in analysis despite being primary aim of study **Indirectness** None **Limitations** **Other information** HOBOE trial
Full citation Paterson, A. H. G., Anderson, S. J., Lembersky, B. C., Fehrenbacher, L., Falkson, C. I., King, K. M., Weir, L. M., Brufsky, A. M., Dakhil, S., Lad, T., Baez-Diaz, L., Gralow, J. R., Robidoux, A., Perez, E. A., Zheng, P., Geyer, C. E., Swain, S. M., Costantino, J. P., Mamounas, E. P.,	**Sample size** 3323 **Characteristics** Gender: 100% women Age: Median/Range NR; 65% ≥50 years Ethnicity: 83% Caucasian, 8% Black, 6% Hispanic, 3% Asian **Inclusion criteria**	**Interventions** **Intervention arm:** adjuvant sodium clodronate **Control arm:** placebo	**Details** **Intervention arm (CLO):** Patients received 1600mg of adjuvant oral sodium clodronate daily. Appropriate local and systemic treatments (chemotherapy, radiotherapy and endocrine therapy) were given at the investigator's discretion	**Results** **Whole sample:** **DFS (median follow-up 90 months for CLO, 91.5 for placebo):** O-E: -14.50; V: 153.76	**Selection bias: random sequence generation** Stratified coin minimisation approach: Low **Selection bias: allocation concealment** Masked to treatment assignment: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Wolmark, N., Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): A multicentre, placebo-controlled, randomised trial, The Lancet Oncology, 13, 734-742, 2012 **Ref Id** 571067 **Country/ies where the study was carried out** North America **Study type** RCT **Aim of the study** To ascertain whether oral sodium clodronate with standard adjuvant treatment might reduce the incidence of metastases in patients with primary operable breast cancer **Study dates** Randomised January 2001 to March 2004 **Source of funding**	Women with histologically confirmed operable breast cancer and no evidence of metastases suitable physically to undergo 3 years of treatment with sodium clodronate or placebo **Exclusion criteria** Renal, hepatic, or non-malignant bone disease; history of malignant disease or bisphosphonate use **Reported subgroups** ER/PR+; ER/PR-		**Control arm (Placebo):** patients received placebo daily. Appropriate local and systemic treatments (chemotherapy, radiotherapy and endocrine therapy) were given at the investigator's discretion	**Treatment-related morbidity - diarrhoea:** CLO 28/1612; Placebo 10/1623 **Treatment-related morbidity - hypocalcaemia:** CLO 1/1612; Placebo 2/1623 **ER/PR+:** **DFS:** O-E: -6.46; V: 104.43 **OS:** O-E: -5.62; V: 53.37 **ER/PR-:** **DFS:** O-E: -7.22; V: 41.42 **OS:** O-E: -8.28; V: 25.19	**Selection bias: overall judgement** Low **Performance bias** Double-blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 99.6% had follow-up data, rates of attrition similar across groups: Low **Selective reporting** Low **Indirectness** None **Limitations** Low adherence to study drug - at end of 3 year treatment 60% for placebo and 56% for sodium clodronate. Majority of patients were node negative so had better prognosis and lower recurrence in comparison with other bisphosphonate trials.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
NCI Department of Health and Human Services Public Health Service and Scherring AG				**Node positive:** **DFS:** O-E: -12.74; V: 51.27 **OS:** O-E: -10.81; V: 32.91 **Node negative:** **DFS:** O-E: -0.96; V: 95.40 **OS:** O-E: -2.75; V: 44.48	Older average age and early stage of patients enrolled in this study (compared with the general population of breast cancer patients and populations of comparable clinical trials), second primary malignant diseases were typically noted as first events, for which sodium clodronate had no observable effect. Inclusion of an endpoint unlikely to be affected by sodium clodronate, but which arises at a fairly high rate independent of the investigational agent, such as second primary malignant diseases, is likely to lower the ability to show a statistically clear benefit for breast cancer outcomes in patients for whom a real benefit could be present. **Other information** NSABP B-34 trial. More up-to-date OS information available in EBCTCG meta-analysis

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Saarto,T., Vehmanen,L., Blomqvist,C., Elomaa,I., Ten-year follow-up of 3 years of oral adjuvant clodronate therapy shows significant prevention of osteoporosis in early-stage breast cancer, Journal of Clinical Oncology, 26, 4289-4295, 2008 **Ref Id** 233009 **Country/ies where the study was carried out** Finland **Study type** RCT **Aim of the study** To investigate the efficacy of sodium clodronate in the prevention of treatment-related osteoporosis in women with early-stage breast cancer **Study dates**	**Sample size** 268 **Characteristics** Gender: 100% women Age: Mean 52.5, Range 28-72 Ethnicity: NR **Inclusion criteria** Women with newly diagnosed node-positive breast cancer **Exclusion criteria** Karnofsky performance index below 70%; other malignancies; peptic ulcer; creatinine over 150 umol/L; pregnancy **Reported subgroups** None of interest	**Interventions** **Intervention arm:** surgery, post-operative radiotherapy, chemotherapy for pre-menopausal patients and tamoxifen/toremifine, and oral sodium clodronate **Control arm:** surgery, post-operative radiotherapy and chemotherapy for pre-menopausal patients and tamoxifen/toremifine	**Details** **Intervention arm (CLO):** surgery (mastectomy/breast conserving surgery) followed by postoperative radiotherapy with 50 Gy megavoltage irradiation in 25 fractions to regional lymph nodes, and to operative scar or remaining breast after breast-conserving resection, which was done concomitantly with adjuvant therapy. Premenopausal patients received six cycles of cyclophosphamide, methotrexate, and fluorouracil chemotherapy, consisting of 600 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 600 mg/m^2 fluorouracil administered intravenously on day one and thereafter at 3-week intervals; postmenopausal patients were randomly assigned to receive antiestrogens, either 20mg tamoxifen or 60 mg/d toremifene, for 3 years. 1600mg/d of oral sodium clodronate for 3 years **Control arm (No bisphosphonate treatment):** surgery (mastectomy/breast	**Results** **Bone health - percentage change in LS BMD (10 year follow-up):** Clo N=44, M=-5.5, SD=10.7; No bisphosphonate treatment N=52, M=-10.3, SD=9.6 **Bone health - percentage change in FN BMD (10 year follow-up):** Clo N=44, M=-5.2, SD=6.3; No bisphosphonate treatment N=52, M=-7.2, SD=6.1	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** High: 172 were excluded from the analysis, primarily due to breast-cancer death or metastatic disease **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Treated 1990 to 1993 **Source of funding** Inkeri Elomaa			conserving surgery) followed by postoperative radiotherapy with 50 Gy megavoltage irradiation in 25 fractions to regional lymph nodes, and to operative scar or remaining breast after breast-conserving resection, which was done concomitantly with adjuvant therapy. Premenopausal patients received six cycles of cyclophosphamide, methotrexate, and fluorouracil chemotherapy, consisting of 600 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 600 mg/m^2 fluorouracil administered intravenously on day one and thereafter at 3-week intervals; postmenopausal patients were randomly assigned to receive antiestrogens, either 20mgtamoxifen or 60 mg/d toremifene, for 3 year Bone mineral density was measured by dual-energy, x-ray absorptiometry using a Hologic QDR-1000 densitometer		None **Limitations** Higher rates of pre-menopausal women, and therefore chemotherapy, in the control arm. **Other information**
Full citation Sun, S., Wang, F., Dou, H., Zhang, L., Li, J., Preventive effect of zoledronic acid on aromatase inhibitor-associated bone loss for	**Sample size** 120 **Characteristics** Gender: 100% women	**Interventions** **Intervention arm:** zoledronic acid **Control arm:** No bisphosphonate treatment	**Details** **Intervention arm (ZOL):** All patients received modified radical mastectomy or breast-conserving surgery. Patients with one or more pathological risk factors (e.g., positive	**Results** **Bone health - ≥5% decline in LS BMD (1 year follow-up):** Zol 2/50; Control 10/50	**Selection bias: random sequence generation** Not reported: Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
postmenopausal breast cancer patients receiving adjuvant letrozole, OncoTargets and therapy, 9, 6029-6036, 2016 **Ref Id** 571258 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** To compare the efficacy and safety between zoledronic acid combined with calcium and calcium alone to prevent aromatase inhibitor-associated bone loss for post-menopausal breast cancer patients receiving adjuvant letrozole **Study dates** Recruited January 2011 to February 2012	Age: Zol median 58, range 35-83; Control median 56, range 33-79 Ethnicity: NR **Inclusion criteria** Women >60 years with cessation of menses, women ≤60 years with spontaneous cessation of menses >12 months, women with bilateral oophorectomy, or women ≤60 years, with no spontaneous menses for <1 year but with postmenopausal estradiol levels; histopathological or cytological diagnosis as invasive breast cancer; stage I, II, or IIIA breast cancer; estrogen and/ or progesterone receptor positive; no evidence of recurrent or metastatic disease; life expectancy of ≥5 years; an ECOG performance status of 0–2; baseline total LS or FN BMD T-score <-2.0; normal haematology, liver, and kidney function; and good understanding and compliance by patients with the pilot program and provision of informed consent **Exclusion criteria**		nodes, positive surgical margin) were administered 4 cycles of adjuvant chemotherapy followed by the T regimen, which included Adriamycin 60mg/m² on day 1 and cyclophosphamide 600mg/m² on day 1 for four cycles, followed by paclitaxel 175mg/m² on day 1 for four cycles with 14 days per cycle. Patients stated radiotherapy 2-4 weeks of completion of chemotherapy (total planned dose 50Gy/25 fractions and additional 10-16Gy to the tumour bed). Endocrine therapy (letrozole 2.5mg daily for 5 years of until disease recurrence) was started after completion of chemotherapy and all patients were instructed to take calcium 500mg daily and vitamin D 400 IU. Zoledronic acid was administered every 6 months until disease recurrence intravenously over 30 minutes at a dosage of 4mg. Patients who discontinued letrozole or zoledronic acid were withdrawn from the study. Prohibited concomitant therapy included any other bisphosphonates, calcitonin, sodium fluoride, parathyroid hormone, mithramycin, gallium nitrate, or tibolone	**Bone health - ≥5% decline in FN BMD (1 year follow-up):** Zol 4/50; Control 12/50 **Bone health - vertebral compression fracture (1 year follow-up):** Zol 2/50; Control 3/50	**Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** 20 patients (10 in each arm) were not included in the analysis. Reasons in each arm not reported: Unclear **Selective reporting** Low **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors	Patients with clinical or radiological evidence of distant metastases; patients with existing LS or total hip (TH) fracture, or a history of non-traumatic fractures or osteoporosis; patients who received recent treatment with any drugs known to affect the skeleton, prior treatment with intravenous bisphosphonates or AIs, prior exposure (within the past 6 months) to anabolic steroids or growth hormone; patients with diseases known to influence bone metabolism, other malignancy within 5 years (except adequately treated basal or squamous cell carcinoma of the skin and in situ carcinoma of the cervix), renal dysfunction, uncontrolled infections, diabetes mellitus, thyroid dysfunction, seizure disorders associated with falls, HIV, malabsorption syndrome, or mental illnesses; patients with a known hypersensitivity to zoledronic acid, other bisphosphonates, letrozole, calcium, or vitamin D; and patients contraindicated for the dual X-ray absorptiometry **Reported subgroups**		**Control arm (No bisphosphonate treatment):** All patients received modified radical mastectomy or breast-conserving surgery. Patients with one or more pathological risk factors (e.g., positive nodes, positive surgical margin) were administered 4 cycles of adjuvant chemotherapy followed by the T regimen, which included Adriamycin 60mg/m² on day 1 and cyclophosphamide 600mg/m² on day 1 for four cycles, followed by paclitaxel 175mg/m² on day 1 for four cycles with 14 days per cycle. Patients stated radiotherapy 2-4 weeks of completion of chemotherapy (total planned dose 50Gy/25 fractions and additional 10-16Gy to the tumour bed). Endocrine therapy (letrozole 2.5mg daily for 5 years of until disease recurrence) was started after completion of chemotherapy and all patients were instructed to take calcium 500mg daily and vitamin D 400 IU. Patients who discontinued letrozole were withdrawn from the study. Prohibited concomitant therapy included any other bisphosphonates, calcitonin, sodium fluoride, parathyroid hormone, mithramycin, gallium nitrate, or tibolone		

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	All post-menopausal		BMD was measured using Norland dual-energy X-ray absorptiometry (DEXA) devices. Each DEXA device was cross-calibrated at baseline using four Bio-Imaging Bona Fide Phantoms and the stability of the DEXA devices was monitored quarterly.		
Full citation von Minckwitz, G., Mobus, V., Schneeweiss, A., Huober, J., Thomssen, C., Untch, M., Jackisch, C., Diel, I. J., Elling, D., Conrad, B., Kreienberg, R., Muller, V., Luck, H. J., Bauerfeind, I., Clemens, M., Schmidt, M., Noeding, S., Forstbauer, H., Barinoff, J., Belau, A., Nekljudova, V., Harbeck, N., Loibl, S., German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 3531-3539, 2013 **Ref Id**	**Sample size** 2,015 **Characteristics** Gender: 100% women Age: Median 49 for IBA, 50 for No bisphosphonate; Range 20-72 Ethnicity: NR **Inclusion criteria** Female patients considered appropriate for intensive dose-dense chemotherapy (typically <65 years) with histologically confirmed primary breast cancer. Patients needed to have histologic complete resection of the tumour and ≥10 resected axillary nodes with primary wound healing and no signs of infection. Stage pT1 to operable pT4a-c with at least one involved axillary or internal mammary lymph	**Interventions** **Intervention arm:** chemotherapy + ibandronate **Control arm:** chemotherapy + observation	**Details** **Intervention arm (IBA):** patients were randomly assigned to either iddETC chemotherapy regimen or EC-TX chemotherapy regimen and received one 50-mg ibandronate tablet per day starting within 4 weeks after last administration of chemotherapy for a total duration of 2 years or until disease progression or unacceptable toxicity, patient's request to discontinue therapy, or withdrawal from the study. Patients were advised to take the tablet 30 minutes before the first meal of each day with water not mixed with milk or calcium-enriched mineral water. Radiotherapy, endocrine therapy and trastuzumab were administered according to Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) guidelines.	**Results** **Whole sample (node positive):** **DFS (median follow-up 39 months):** O-E: -5.09; V: 89.98 **Treatment-related morbidity - gastrointestinal issues:** IBA 113/1832; No bisphosphonate 34/968 **Treatment-related morbidity - renal/urinary issues:** IBA 10/1382; No bisphosphonate 5/968 **Pre-menopausal:**	**Selection bias: random sequence generation** computer-generated permutated block randomization: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
567162 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** Primary aim to investigate the impact of adjuvant ibandronate on DFS in patients with early-stage, node-positive breast cancer **Study dates** Recruited August 2004 to July 2008 **Source of funding** Roche, Amgen, Novartis, Johnson & Johnson	node and no evidence of distant metastases. ECOG performance status had to be <2 and estimated life expectancy of at least 10 years. **Exclusion criteria** Known hypersensitivity to the compounds or incorporated substances; known dihydropyrimidine dehydrogenase deficiency; inadequate organ function; insufficient or uncompensated cardiac function (with left ventricular ejection fraction below the normal range of the institution), history of severe heart disease, myocardial infarction within the last 6 months, significant cardiac arrhythmias; evidence for infection including wound infections and chronic infections; secondary malignancy; time since axillary dissection >3 months; previously treated invasive breast carcinoma; previous or concurrent antitumor treatment for any reason; simultaneous therapy with sorivudine or brivudine as virostatics, immunosuppressive treatment or concurrent treatment with aminoglycosides; pregnancy or lactation period or no adequate non-hormonal contraception in pre-		**Control arm (No bisphosphonate):** patients were randomly assigned to either iddETC chemotherapy regimen or EC-TX chemotherapy regimen. Radiotherapy, endocrine therapy and trastuzumab were administered according to Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) guidelines.	**DFS (median follow-up 39 months):** O-E: 0.86; V: 43.18 **Post-menopausal:** **DFS (median follow-up 39 months):** O-E: -4.77; V: 45.24 **Grade 1 or 2:** **DFS (median follow-up 39 months):** O-E: -0.69; V: 34.08 **Grade 3:** **DFS (median follow-up 39 months):** O-E: -5.31; V: 56.35 **HR (ER and/or PR)+:**	Less than 1% in both groups excluded from ITT analysis; similar rates of discontinuation and missing data: Low **Selective reporting** Low **Indirectness** None **Limitations** Patients older than age 60 years, in which the effect of bisphosphonates is considered to be highest, were under-represented in the GAIN study because patients had to be eligible for dose-dense chemotherapy. **Other information** GAIN trial. More up-to-date OS information available in EBCTCG meta-analysis

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	menopausal patients; concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational not-marketed drug within 30 days before study entry. **Reported subgroups** All node positive; Pre-menopausal, post-menopausal, grade 1/2, grade 3, HR+, HR-			**DFS (median follow-up 39 months):** O-E: -2.24; V: 21.28 **HR (ER and/or PR)-:** **DFS (median follow-up 39 months):** O-E: -3.98; V: 64.35	

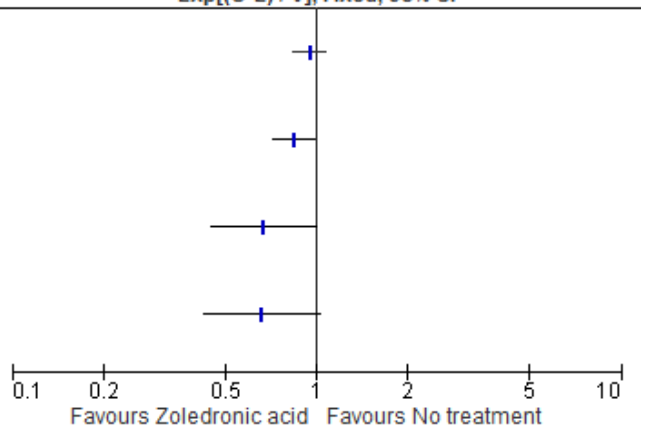
ABCSG, Austrian Breast & Colorectal Cancer Study Group; AC, doxorubicin, cyclophosphamide; AGO, German Gynecological Oncology Group (Arbeitsgemeinschaft Gynäkologische Onkologie); AI, aromatase inhibitor; AZURE, Adjuvant Zoledronic acid redUce Recurrence; BMD, Bone mineral density; CEF, Cyclophosphamide Epirubicin Flourouracil; CMF, Cyclophosphamide Methotrexate Flourouracil; CLO, sodium clodronate; DBCG, Danish Breast Cancer Group; DEXA, dual-energy X-ray absorptiometry; ECOG, Eastern Cooperative Oncology Group; EC-TX, epirubicin, cyclophosphamide-docetaxel capecitabine; ER, oestrogen receptor; fmol, femtomole; FN, femoral neck; GAIN, German Adjuvant Intergroup Node Positive; Gy, gray; HER2, human epidermal growth factor receptor 2; HRQoL: health-related quality of life; IBA, ibandronate; iddETC, intense dose-dense epirubicin, paclitaxel, cyclophosphamide; ISRCTN, International Standard Randomised Controlled Trials Number; IQR, interquartile range; IV, intravenous; KCSG, Korean Cancer Study Group; LS, lumbar spine; MCS: mental component summary; NCCTG, North Central Cancer Treatment Group; NCI, National Cancer Institute; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; ONJ, osteonecrosis of the jaw; PAM, pamidronate; PCS: physical component summary; PR, progesterone receptor; RCT, randomised controlled trial; RIS, risedronate; SD, standard deviation; SF-36, SF-36: 36-Item Short Form Survey; TH, total hip; ZOL, Zoledronic acid

Appendix E – Forest plots

Comparison 1. Zoledronic acid versus no treatment

Figure 2: Disease-free survival at approximately 5 year follow-up

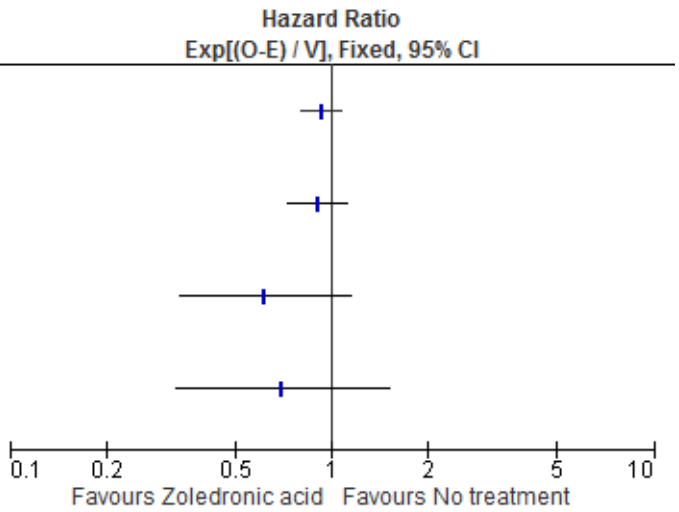
Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Whole sample							
EBCTCG	562	2637	601	2637	-13.46	262.35	0.95 [0.84, 1.07]
1.1.2 Post-menopausal							
EBCTCG	317	1807	364	1815	-26.42	151.52	0.84 [0.72, 0.98]
1.1.3 Node positive							
ABCSG-12	0	275	0	275	-9.9	24.72	0.67 [0.45, 0.99]
1.1.4 Node negative							
ABCSG-12	0	602	0	609	-8.37	20.14	0.66 [0.43, 1.02]



Note. Number of events in each arm not reported for ABCSG-12

Figure 3: Overall survival at approximately 5 year follow-up

Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.2.1 Whole sample							
EBCTCG	381	2581	413	2581	-13.47	185.67	0.93 [0.81, 1.07]
1.2.2 Post-menopausal							
EBCTCG	176	830	195	838	-8.84	83.87	0.90 [0.73, 1.11]
1.2.3 Node positive							
ABCSG-12	0	275	0	275	-4.95	10.35	0.62 [0.34, 1.14]
1.2.4 Node negative							
ABCSG-12	0	602	0	609	-2.35	6.59	0.70 [0.33, 1.50]



Note. Number of events in each arm not reported for ABCSG-12

Figure 4: Treatment-related morbidity: osteonecrosis of the jaw at 5 year follow-up

Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
AZURE	17	1681	0	1678	34.94 [2.10, 580.49]

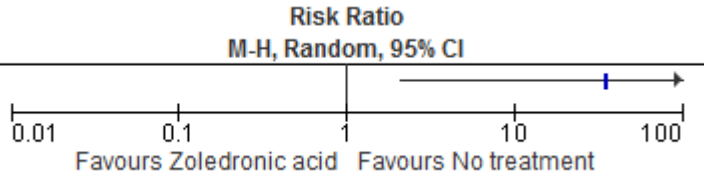


Figure 5: Treatment-related morbidity: myalgia at 1 year follow-up

Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
HOBOE	8	153	3	148	2.58 [0.70, 9.54]

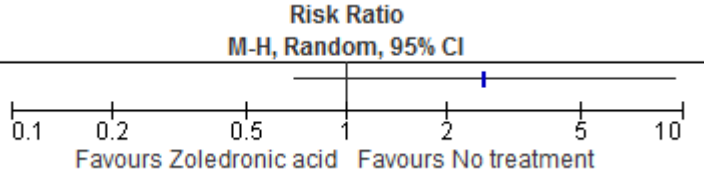


Figure 6: Treatment-related morbidity: arthralgia at 5.2 year follow-up

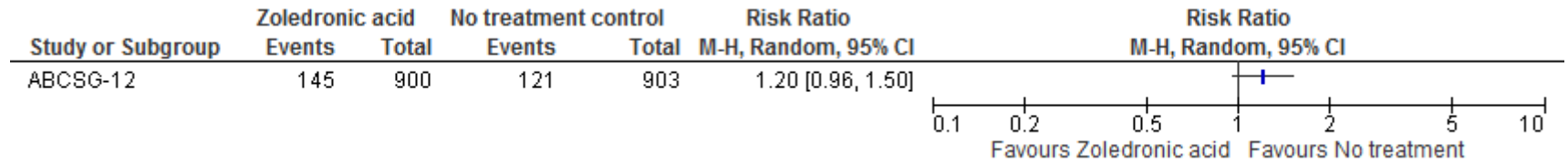


Figure 7: Bone health: fractures at 1 to 5 year follow-up

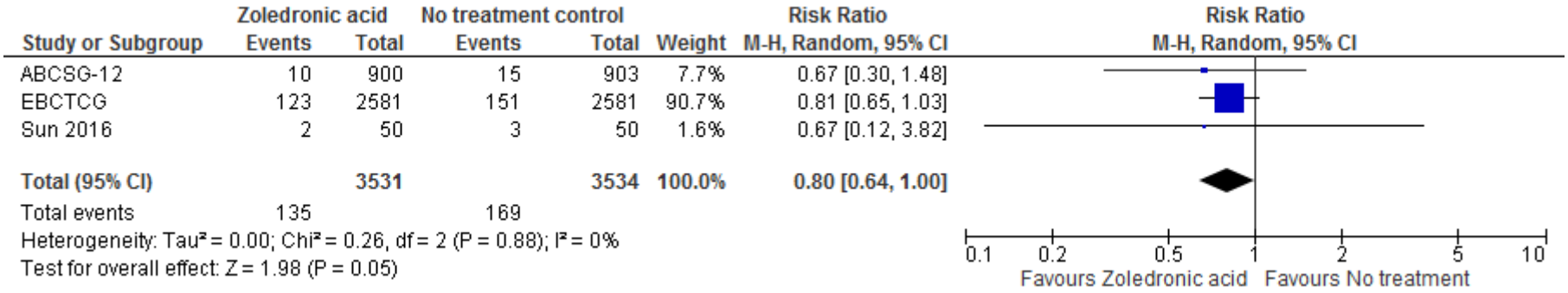


Figure 8: Bone health: LS BMD at 1 to 5.2 year follow-up

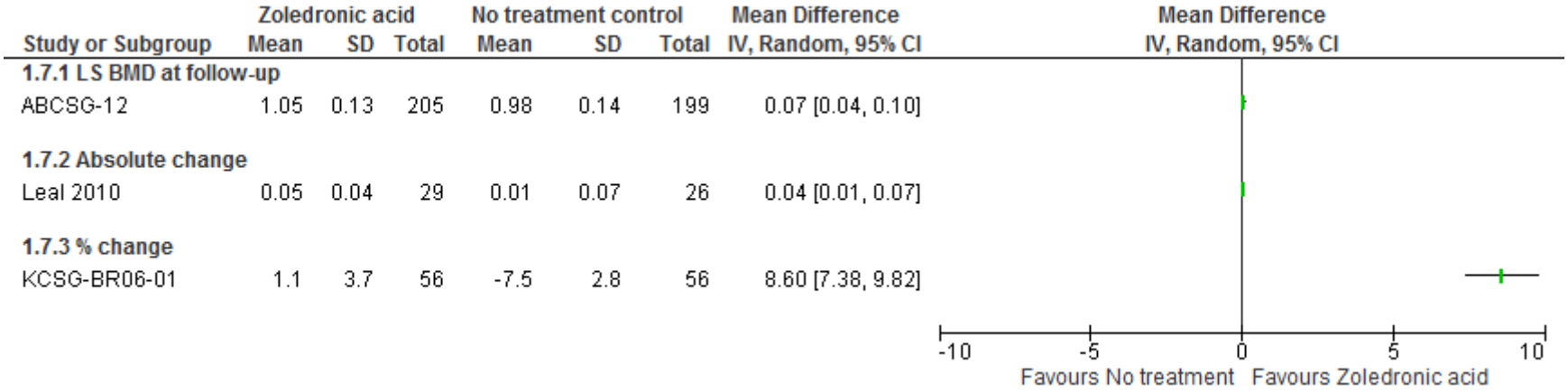


Figure 9: Bone health: FN BMD at 1 year follow-up

Study or Subgroup	Zoledronic acid Mean	SD	Total	No treatment control Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.8.1 Absolute change							
Leal 2010	0.01	0.04	30	0.01	0.05	26	0.00 [-0.02, 0.02]
1.8.2 % change							
KCSG-BR06-01	1.1	5.6	56	-3.4	3.3	56	4.50 [2.80, 6.20]

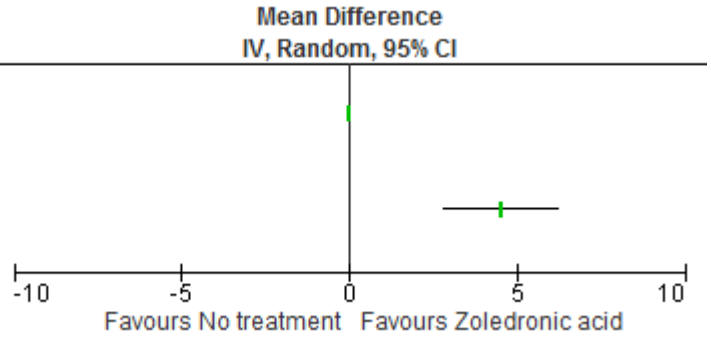


Figure 10: Bone health: ≥5% decline in LS BMD at 1 year follow-up

Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
Sun 2016	2	50	10	50	0.20 [0.05, 0.87]

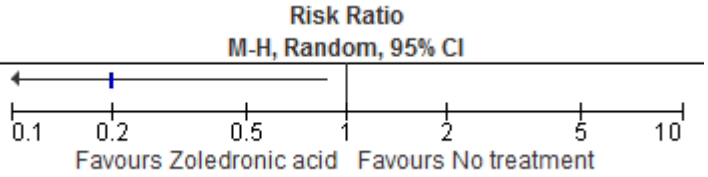
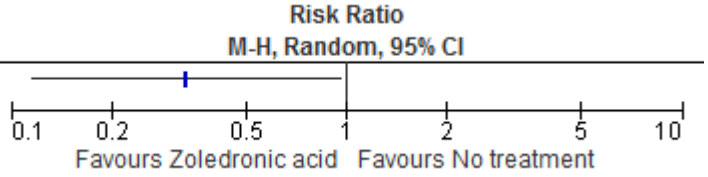


Figure 11: Bone health: ≥5% decline in FN BMD at 1 year follow-up

Study or Subgroup	Zoledronic acid Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
Sun 2016	4	50	12	50	0.33 [0.12, 0.96]



Comparison 2. Zoledronic acid versus placebo

Figure 12: Disease-free survival at approximately 5 year follow-up

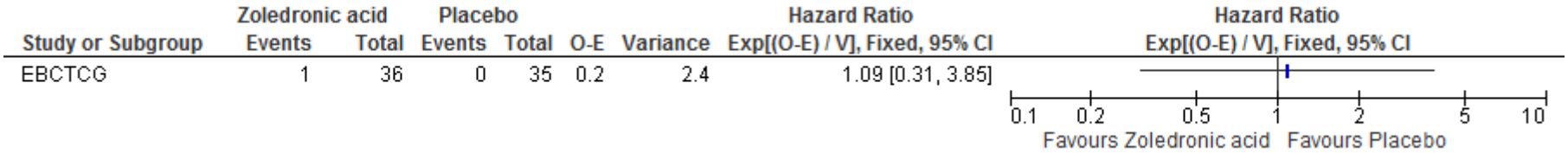


Figure 13: Bone health: % change in LS BMD at 2 year follow-up

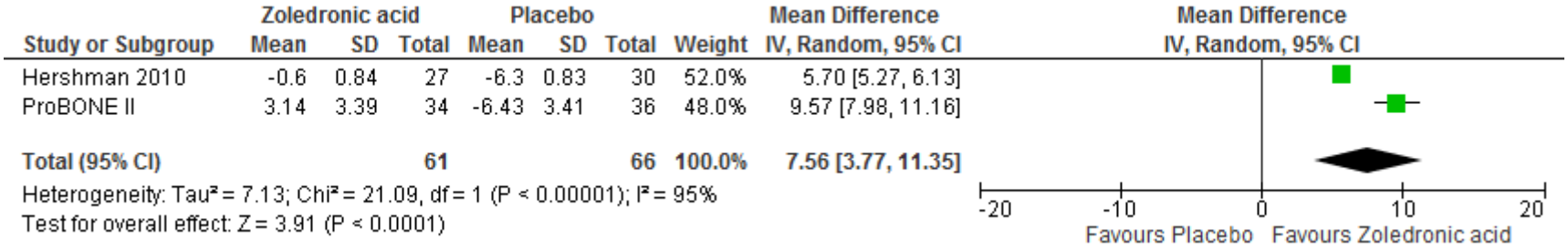
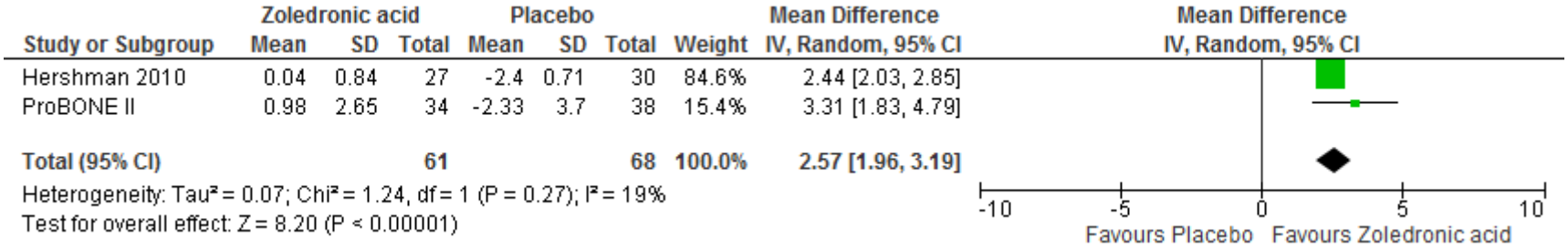


Figure 14: Bone health: % change in FN BMD at 2 year follow-up



Comparison 3. Risedronate versus placebo

Figure 15: Disease-free survival at approximately 5 year follow-up

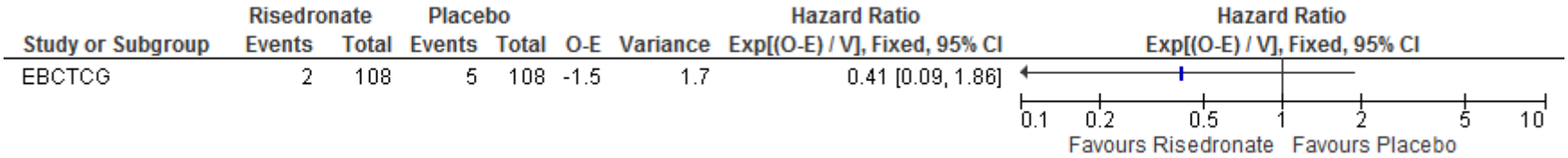


Figure 16: Overall survival at approximately 5 year follow-up

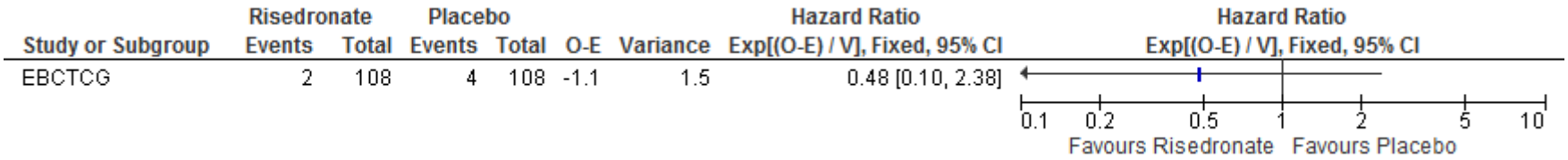


Figure 17: Treatment-related morbidity: gastrointestinal issues at 2 year follow-up

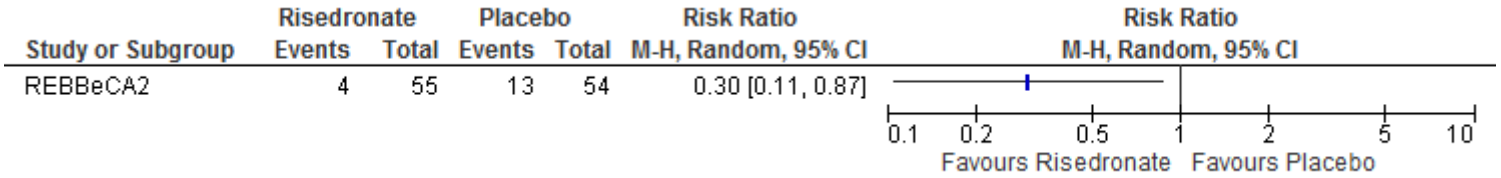


Figure 18: Treatment-related morbidity: arthralgia at 1 year follow-up

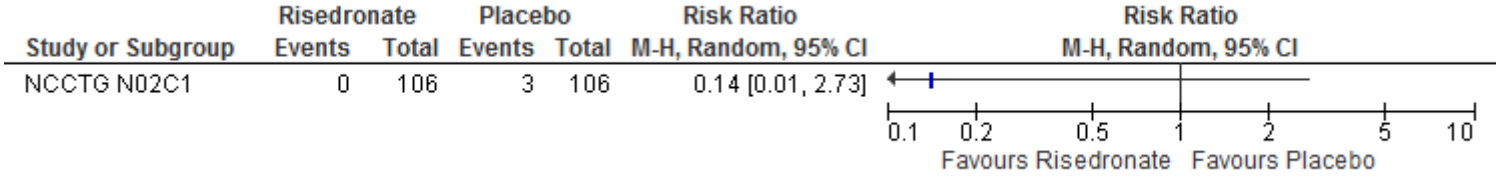


Figure 19: Treatment-related morbidity: constipation at 1 year follow-up

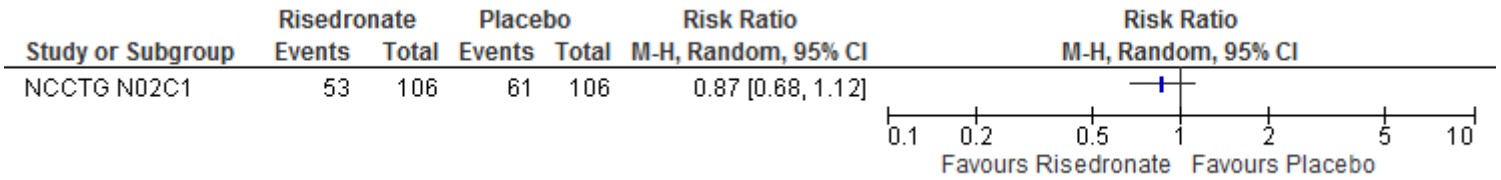


Figure 20: Treatment-related morbidity: nausea at 1 year follow-up

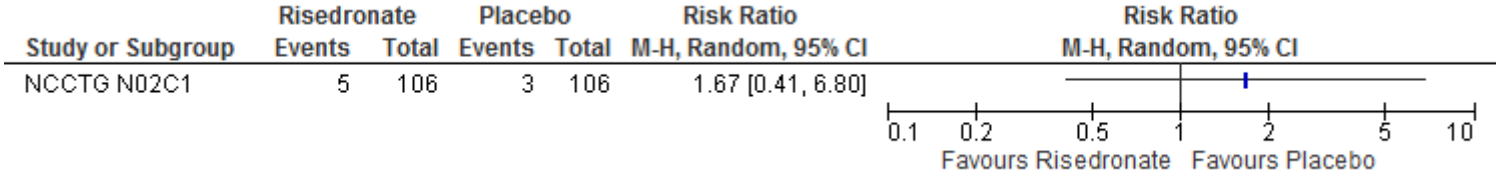


Figure 21: Treatment-related morbidity: abdominal pain at 1 year follow-up

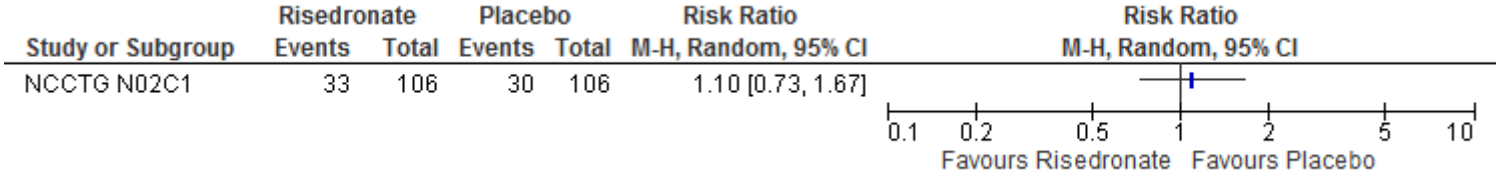


Figure 22: Treatment-related morbidity: diarrhoea at 1 year follow-up

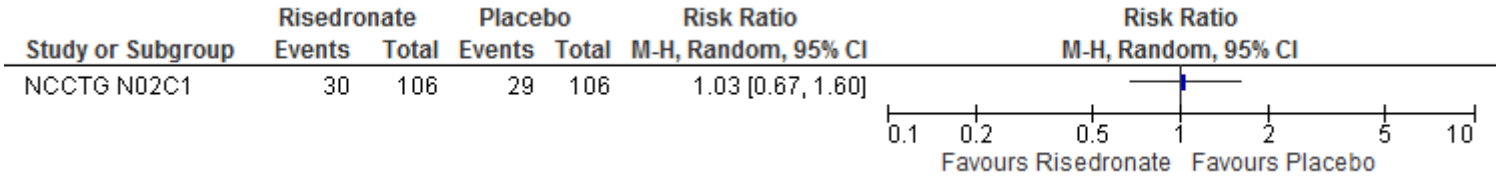


Figure 23: Bone health: fractures at 2 year follow-up

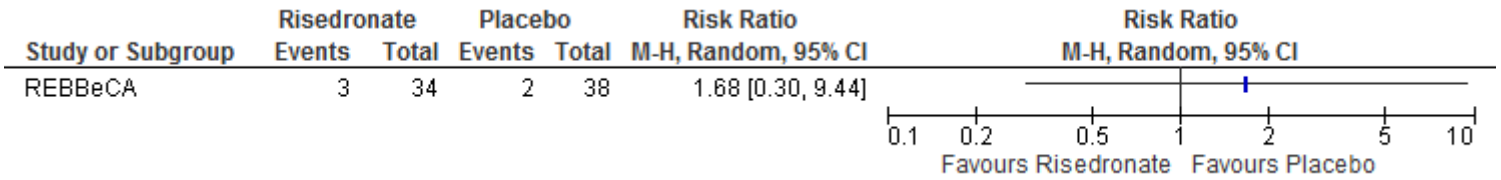


Figure 24: Bone health: % change in LS BMD at 1 to 2 year follow-up

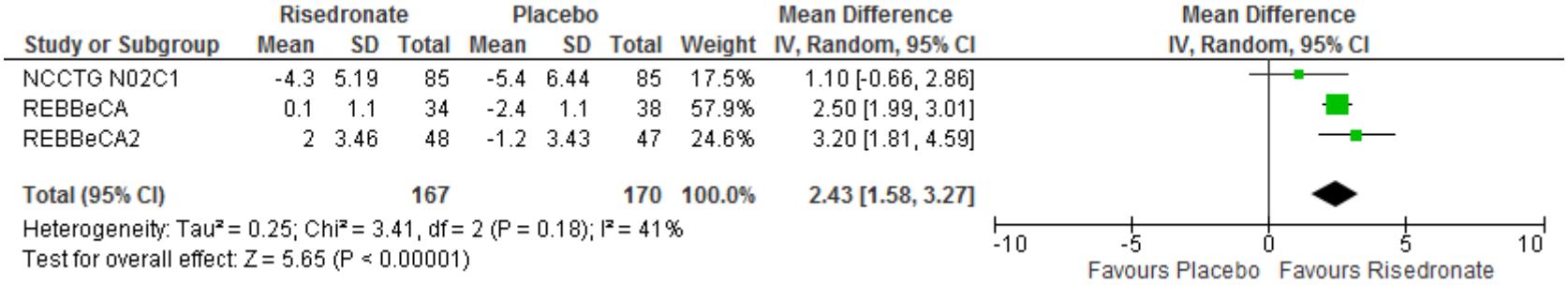
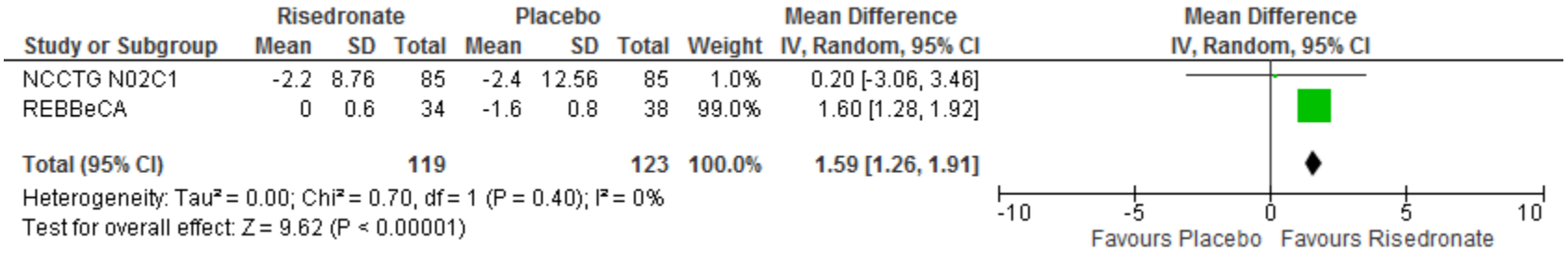


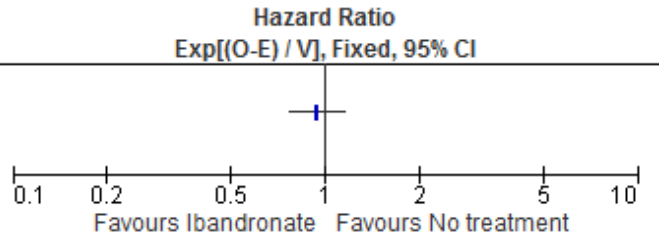
Figure 25: Bone health: % change in FN BMD at 1 to 2 year follow-up



Comparison 4. Ibandronate versus no treatment

Figure 26: Disease-free survival at 3.3 year follow-up – node positive subgroup

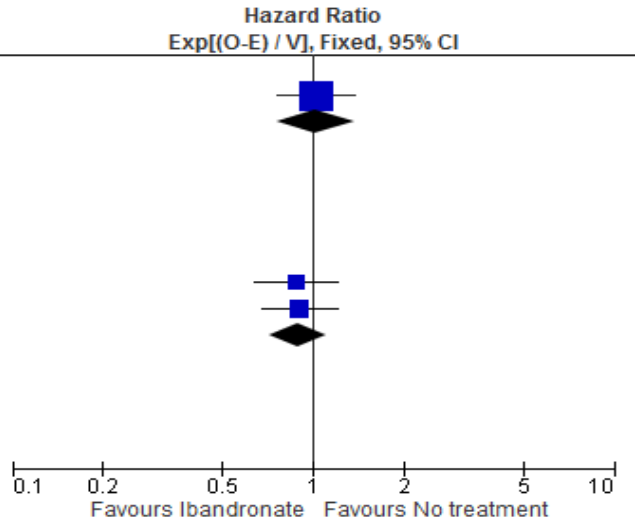
Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.5.1 Node positive							
GAIN	270	1996	135	998	-5.09	89.98	0.95 [0.77, 1.16]



Note. Number of events/participants in each arm not reported

Figure 27: Disease-free survival at 3.3 to 5.6 year follow-up – menopausal status subgroups

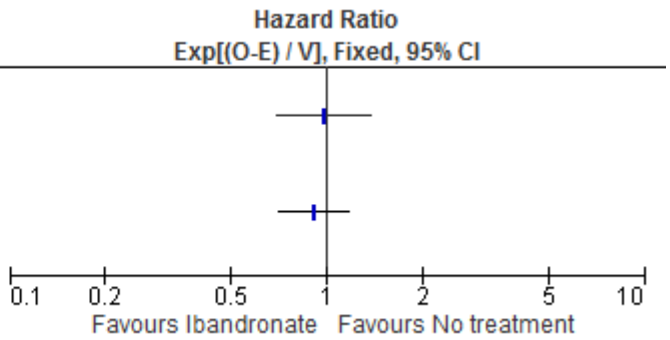
Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.6.2 Pre-menopausal								
GAIN	0	0	0	0	0.86	43.18	100.0%	1.02 [0.76, 1.37]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**1.02 [0.76, 1.37]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
4.6.3 Post-menopausal								
EBCTCG	117	895	64	468	-4.8	37.7	45.4%	0.88 [0.64, 1.21]
GAIN	0	0	0	0	-4.77	45.25	54.6%	0.90 [0.67, 1.20]
Subtotal (95% CI)		**895**		**468**			**100.0%**	**0.89 [0.72, 1.10]**
Total events	117		64					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 1.05 (P = 0.29)								



Note. Number of events/participants in each arm not reported in the GAIN trial

Figure 28: Disease-free survival at 3.3 year follow-up – Grade status subgroups

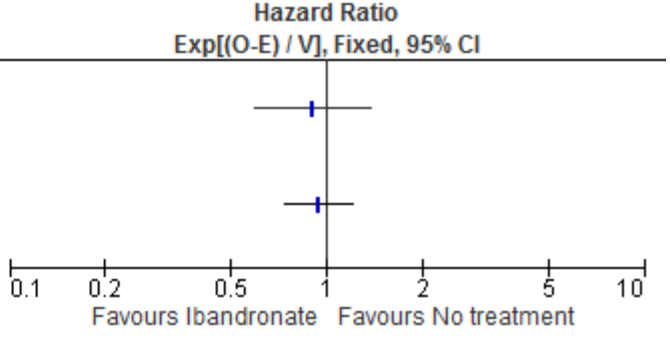
Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.7.4 Grade 1/2							
GAIN	0	0	0	0	-0.69	34.08	0.98 [0.70, 1.37]
4.7.5 Grade 3							
GAIN	0	0	0	0	-5.31	56.35	0.91 [0.70, 1.18]



Note. Number of events/participants in each arm not reported in the GAIN trial

Figure 29: Disease-free survival at 3.3 year follow-up – hormone receptor subgroups

Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.8.6 ER/PR+							
GAIN	0	0	0	0	-2.24	21.28	0.90 [0.59, 1.38]
4.8.7 ER/PR-							
GAIN	0	0	0	0	-3.98	64.35	0.94 [0.74, 1.20]



Note. Number of events/participants in each arm not reported in the GAIN trial

Figure 30: Overall survival at 5.6 year follow-up

Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.2.1 Whole sample							
EBCTCG	128	2015	59	1008	1.2	39.5	1.03 [0.75, 1.41]
4.2.2 Post-menopausal							
EBCTCG	66	895	33	468	-0.5	21.2	0.98 [0.64, 1.49]

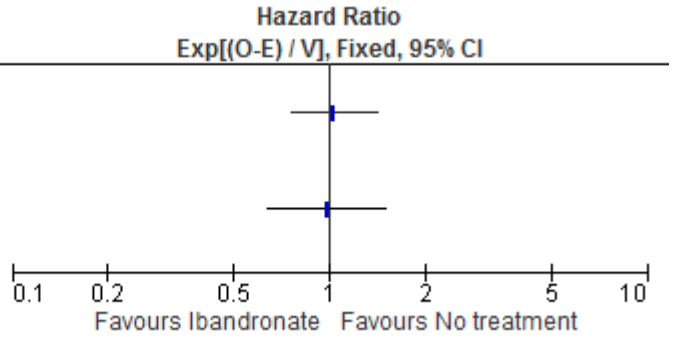


Figure 31: Treatment-related morbidity: gastrointestinal issues at 3.25 year follow-up

Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	Risk Ratio M-H, Random, 95% CI
GAIN	113	1832	34	968	1.76 [1.21, 2.56]

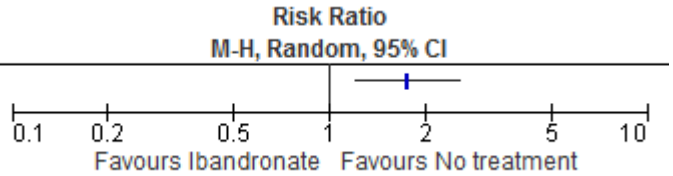
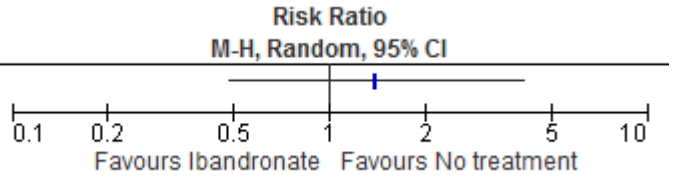


Figure 32: Treatment-related morbidity: renal/urinary issues at 3.25 year follow-up

Study or Subgroup	Ibandronate Events	Ibandronate Total	No treatment control Events	No treatment control Total	Risk Ratio M-H, Random, 95% CI
GAIN	10	1382	5	968	1.40 [0.48, 4.09]



Comparison 5. Ibandronate versus placebo

Figure 33: Overall survival at 5.6 year follow-up (post-menopausal)

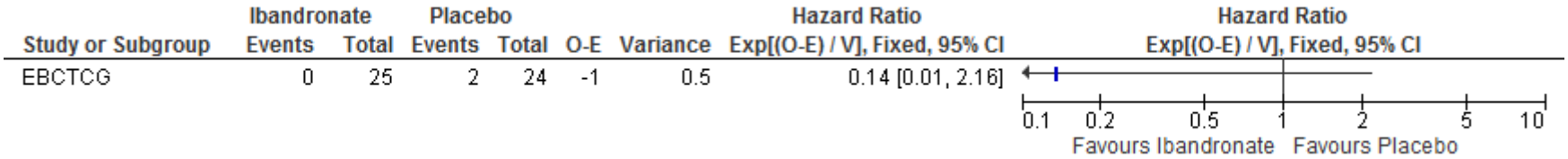


Figure 34: Treatment-related morbidity: arthralgia at 2 year follow-up

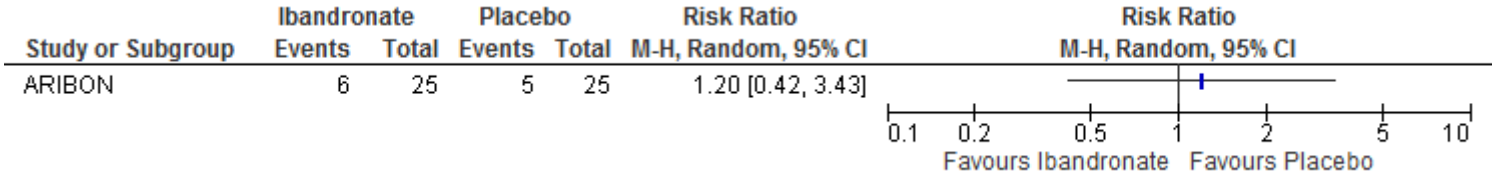


Figure 35: Treatment-related morbidity: upper GI symptoms at 2 year follow-up

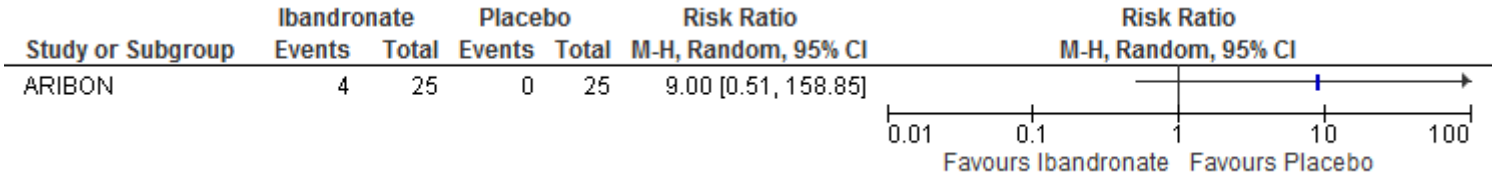
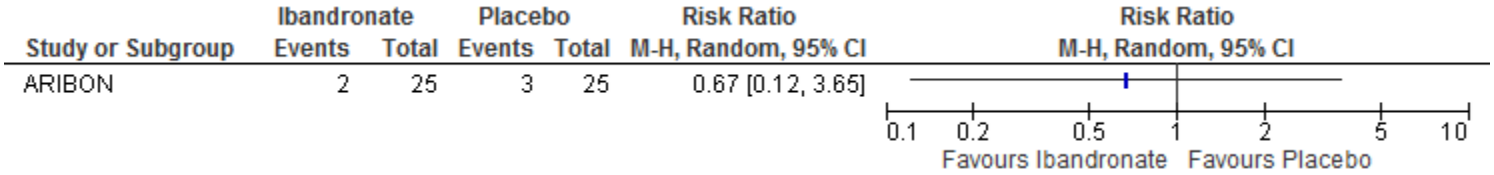


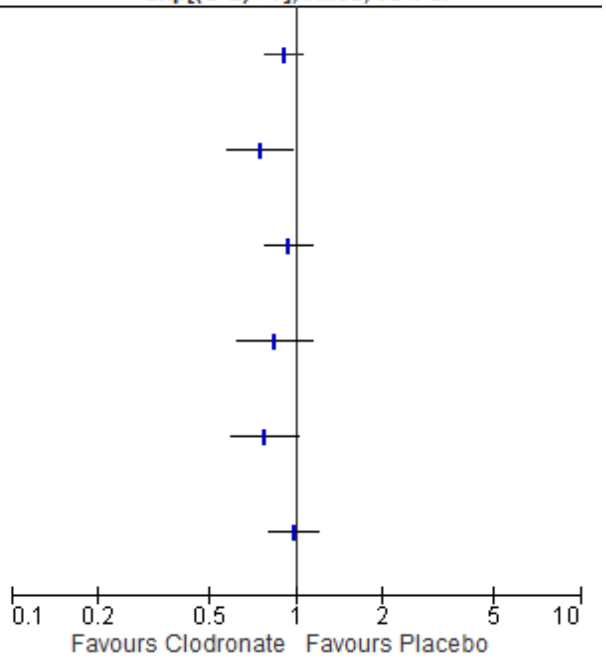
Figure 36: Bone health: fractures at 2 year follow-up



Comparison 6. Sodium clodronate versus placebo

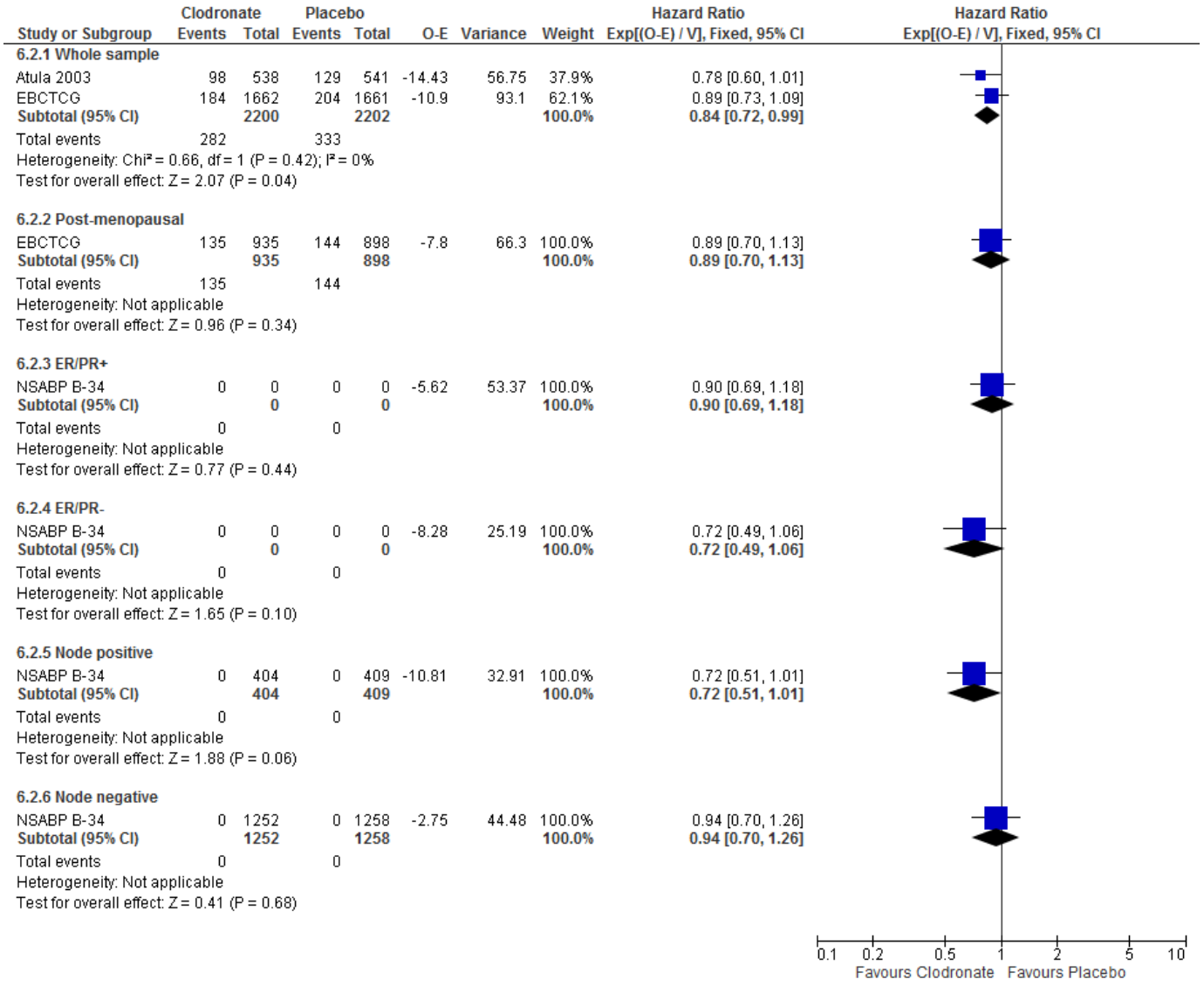
Figure 37: Disease-free survival at 5.6 to 7.5 year follow-up

Study or Subgroup	Clodronate Events	Clodronate Total	Placebo Events	Placebo Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
6.1.1 Whole sample							
NSABP B-34	286	1655	312	1656	-14.5	153.76	0.91 [0.78, 1.07]
6.1.2 Post-menopausal							
EBCTCG	109	935	133	898	-16.4	56.6	0.75 [0.58, 0.97]
6.1.3 ER/PR+							
NSABP B-34	0	0	0	0	-6.46	104.43	0.94 [0.78, 1.14]
6.1.4 ER/PR-							
NSABP B-34	0	0	0	0	-7.22	41.42	0.84 [0.62, 1.14]
6.1.5 Node positive							
NSABP B-34	0	404	0	409	-12.74	51.27	0.78 [0.59, 1.03]
6.1.6 Node negative							
NSABP B-34	0	1252	0	1258	-0.96	95.4	0.99 [0.81, 1.21]



Note. Number of events/participants in each arm not reported for NSABP B-34 subgroups

Figure 38: Overall survival at 5.6 to 7.5 year follow-up



Note. Number of events/participants in each arm not reported for NSABP B-34 subgroups

Figure 39: Treatment-related morbidity: gastrointestinal disorders at 7.5 year follow-up

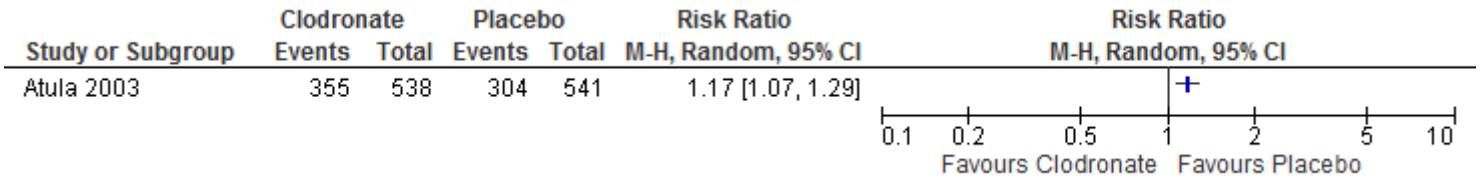


Figure 40: Treatment-related morbidity: diarrhoea at 7.5 year follow-up

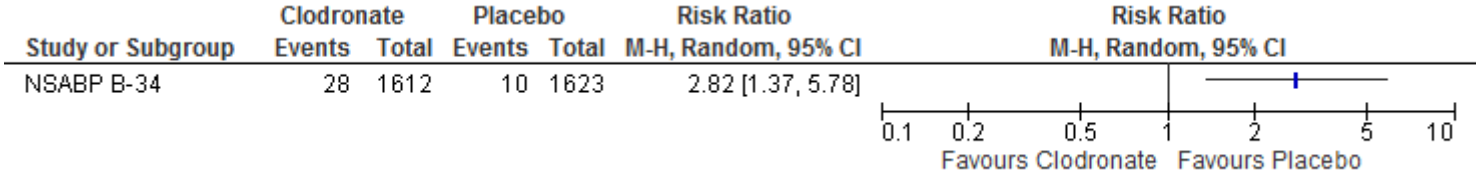


Figure 41: Treatment-related morbidity: hypocalcaemia at 7.5 year follow-up

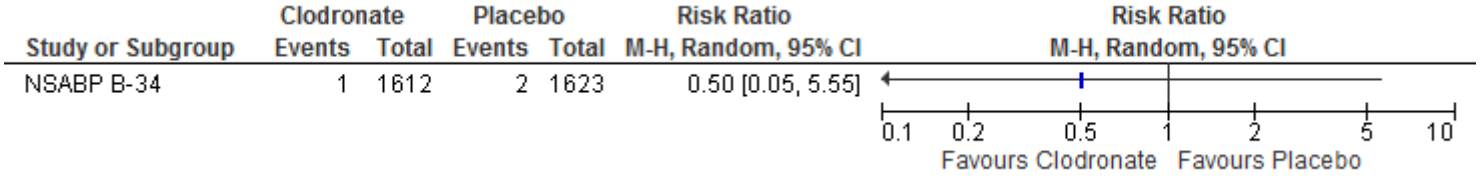


Figure 42: Bone health: fractures at 5.6 year follow-up

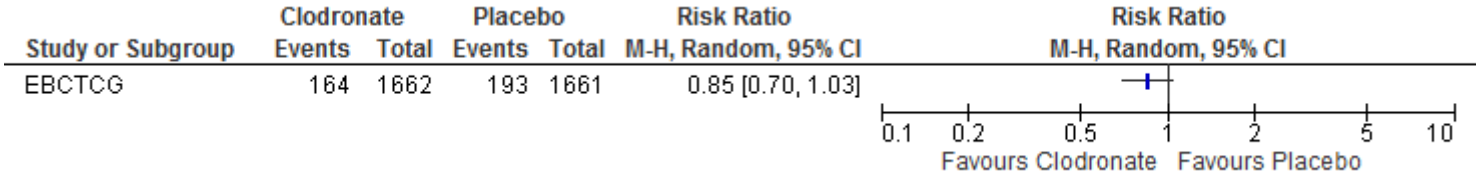


Figure 43: Bone health: % change LS BMD at 2 year follow-up

Study or Subgroup	Clodronate Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
ISRCT83688026	0.06	7.55	419	-1.87	6.87	432	1.93 [0.96, 2.90]

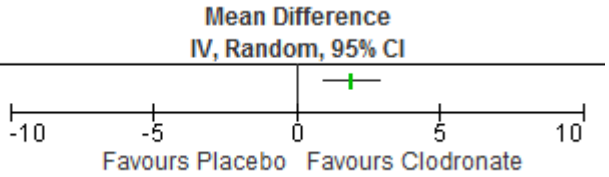
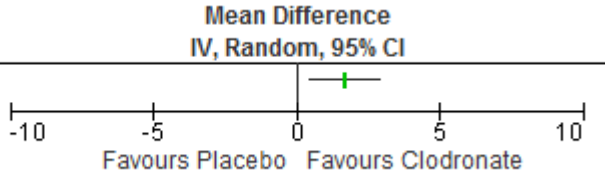


Figure 44: Bone health: % change FN BMD at 5 year follow-up

Study or Subgroup	Clodronate Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
ISRCT83688026	-2.35	9.58	419	-4.05	8.78	432	1.70 [0.46, 2.94]



Comparison 7. Pamidronate versus no treatment

Figure 45: Disease-free survival at 5.6 year follow-up

Study or Subgroup	Pamidronate Events	Total	No treatment control Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
7.4.1 Whole sample							
EBCTCG	236	460	237	493	7.8	88.3	1.09 [0.89, 1.35]
7.4.2 Post-menopausal							
EBCTCG	96	152	108	167	3	35.4	1.09 [0.78, 1.51]

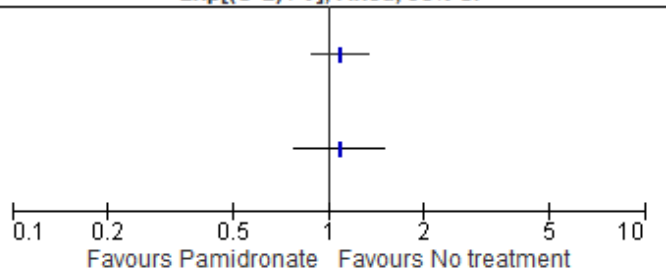


Figure 46: Overall survival at 5.6 year follow-up

Study or Subgroup	Pamidronate Events	Total	No treatment control Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
7.5.1 Whole sample							
EBCTCG	248	460	250	493	3.8	96.8	1.04 [0.85, 1.27]
7.5.2 Post-menopausal							
EBCTCG	108	152	118	167	0.3	40.4	1.01 [0.74, 1.37]

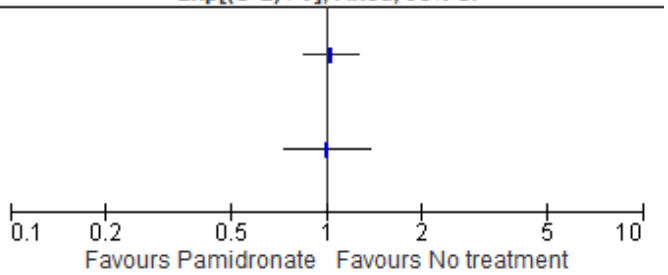


Figure 47: Treatment-related morbidity: nausea/vomiting at 3 year follow-up

Study or Subgroup	Pamidronate Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
DBCG	324	417	337	467	1.08 [1.00, 1.16]

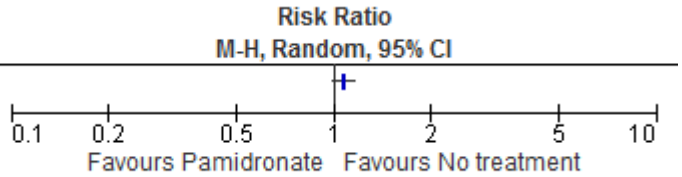


Figure 48: Treatment-related morbidity: abdominal pain at 3 year follow-up

Study or Subgroup	Pamidronate Events	Total	No treatment control Events	Total	Risk Ratio M-H, Random, 95% CI
DBCG	123	417	103	467	1.34 [1.07, 1.68]

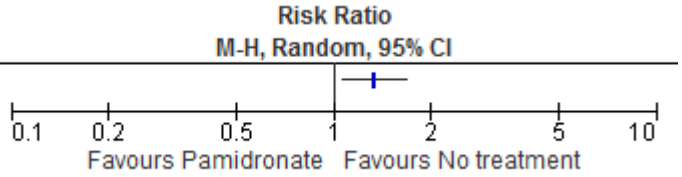
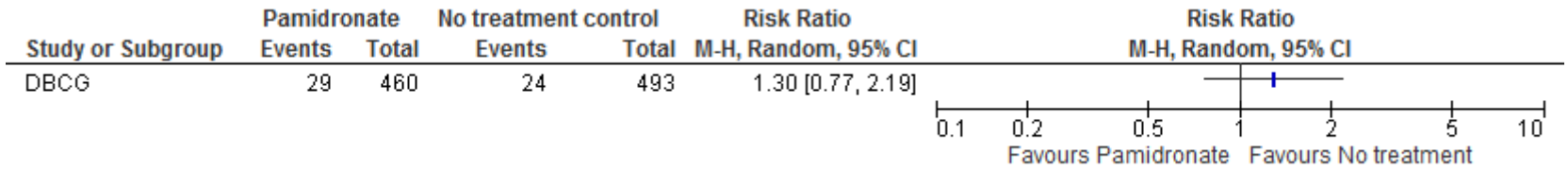


Figure 49: Bone health: fractures at 4 year follow-up



Comparison 8. Sodium clodronate versus no treatment

Figure 50: Bone health: % change LS BMD at 10 year follow-up

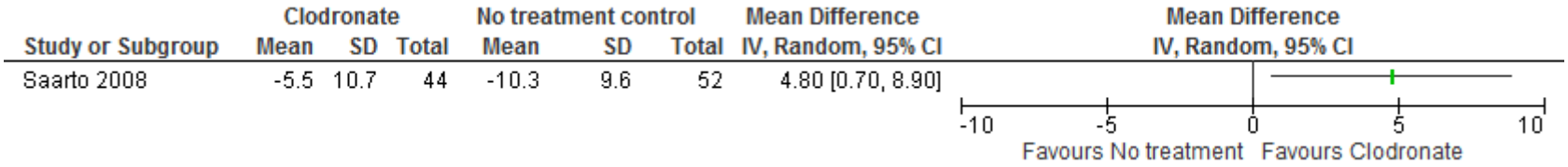
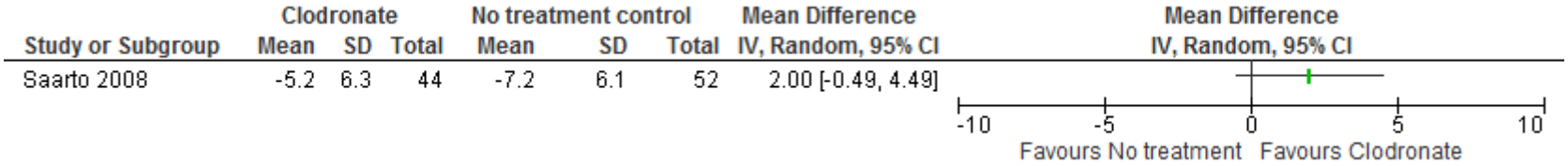


Figure 51: Bone health: % change FN BMD at 10 year follow-up



Comparison 9. Risedronate versus no treatment

Figure 52: Bone health: LS BMD T-score at 2 year follow-up

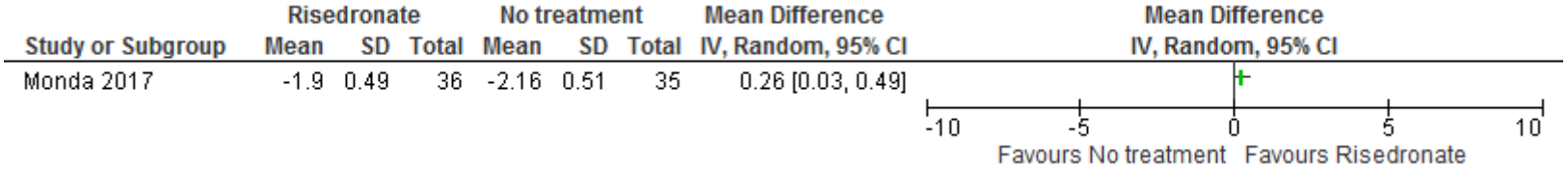


Figure 53: Bone health: FN BMD T-score at 2 year follow-up

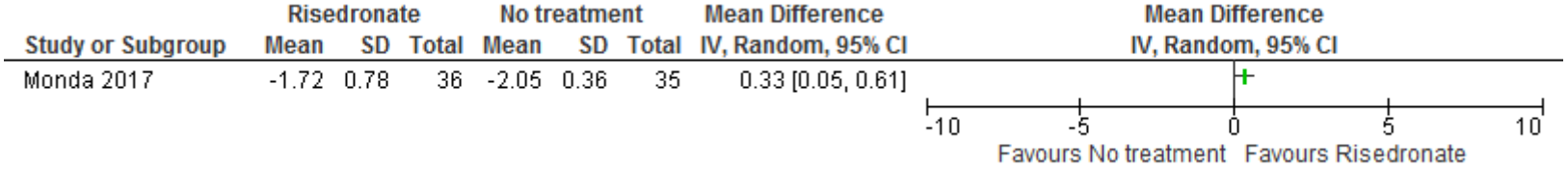


Figure 54: Bone health: fractures at 2 year follow-up

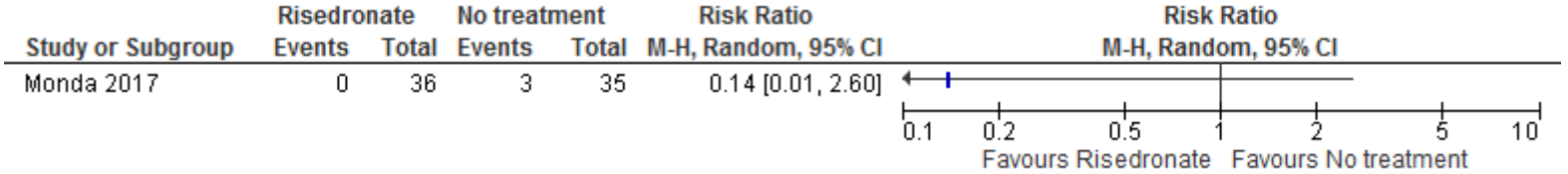


Figure 55: HRQoL: physical component summary of SF-36 (PCS-36) at 2 year follow-up

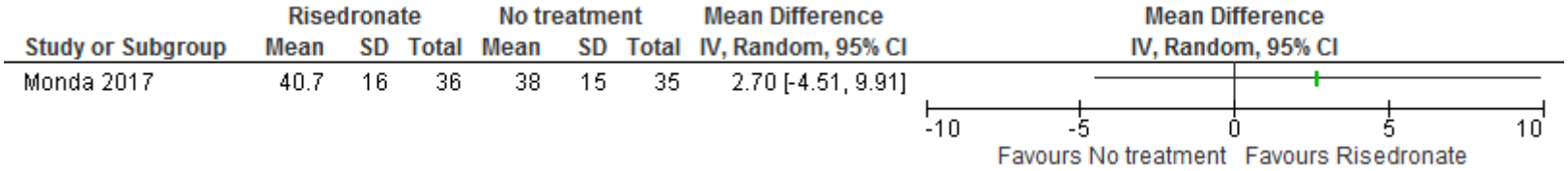
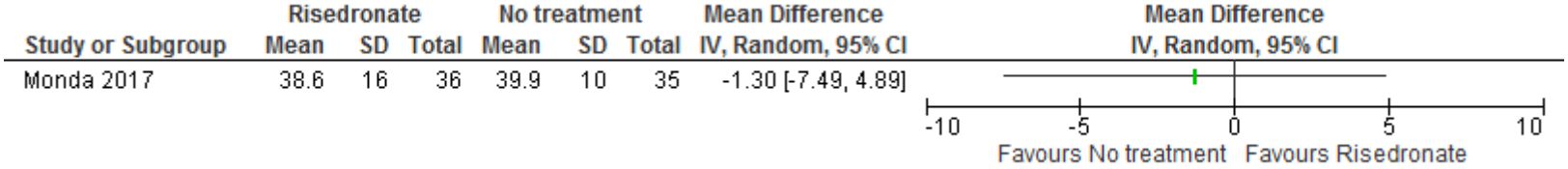


Figure 56: HRQoL: mental component summary of SF-36 (MCS-36) at 2 year follow-up



1

Appendix F – GRADE tables

2 **Table 19: Clinical evidence profile: Comparison 1. Zoledronic acid versus no treatment control**

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
DFS - Whole sample (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	562/2637 (21.3%)	601/2637 (22.8%)	HR 0.95 (0.84 to 1.07)	10 fewer per 1000 (from 33 fewer to 14 more)	HIGH	CRITICAL
DFS - Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	317/1807 (17.5%)	364/1815 (20.0%)	HR 0.84 (0.72 to 0.98)	29 fewer per 1000 (from 4 fewer to 52 fewer)	HIGH	CRITICAL
DFS - Node positive (5.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/275 (0%)	0/275 (0%)	HR 0.67 (0.45 to 0.99)	-	MODERATE	CRITICAL
DFS - Node negative (5.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/602 (0%)	0/609 (0%)	HR 0.66 (0.43 to 1.02)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Whole sample (5.6 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	381/2581 (14.8%)	413/2581 (16%)	HR 0.93 (0.81 to 1.07)	10 fewer per 1000 (from 28	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	No treatment control	Relative (95% CI)	Absolute		
		risk of bias								fewer to 10 more)		
OS - Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	176/830 (21.2%)	195/838 (23.3%)	HR 0.9 (0.73 to 1.11)	21 fewer per 1000 (from 57 fewer to 22 more)	HIGH	CRITICAL
OS - Node positive (5.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/275 (0%)	0/275 (0%)	HR 0.62 (0.34 to 1.14)	-	MODERATE	CRITICAL
OS - Node negative (5.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/602 (0%)	0/609 (0%)	HR 0.7 (0.33 to 1.5)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity: osteonecrosis of the jaw (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	17/1681 (1%)	0/1678 (0%)	RR 34.94 (2.1 to 580.49)	-	MODERATE	CRITICAL
Treatment-related morbidity: myalgia (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	8/153 (5.2%)	3/148 (2%)	RR 2.58 (0.7 to 9.54)	32 more per 1000 (from 6 fewer to 173 more)	LOW	CRITICAL
Treatment-related morbidity: arthralgia (5.2 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	No treatment control	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	145/900 (16.1%)	121/903 (13.4%)	RR 1.2 (0.96 to 1.5)	27 more per 1000 (from 5 fewer to 67 more)	LOW	CRITICAL
Bone health – fractures (1 to 5 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	135/3531 (3.8%)	169/3534 (4.8%)	RR 0.8 (0.64 to 1)	10 fewer per 1000 (from 17 fewer to 0 more)	MODERATE	IMPORTANT
Bone health - LS BMD - LS BMD at follow-up (Better indicated by higher values; 5.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	205	199	-	MD 0.07 higher (0.04 to 0.10 higher)	HIGH	IMPORTANT
Bone health - LS BMD - Absolute change (Better indicated by higher values; 1 year follow-up)												
1	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	Serious[8]	None	29	26	-	MD 0.04 higher (0.01 to 0.07 higher)	LOW	IMPORTANT
Bone health - LS BMD - % change (Better indicated by higher values; 1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	56	56	-	MD 8.6 higher (7.38 to 9.82 higher)	MODERATE	IMPORTANT
Bone health - FN BMD - Absolute change (Better indicated by higher values; 1 year follow-up)												
1	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	Serious[8]	None	30	26	-	MD 0 higher (0.02 lower to 0.02 higher)	LOW	IMPORTANT
Bone health - FN BMD - % change (Better indicated by higher values; 1 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	No treatment control	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	56	56	-	MD 4.5 higher (2.8 to 6.2 higher)	MODERATE	IMPORTANT
Bone health - ≥5% decline in LS BMD (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	2/50 (4%)	10/50 (20%)	RR 0.2 (0.05 to 0.87)	160 fewer per 1000 (from 26 fewer to 190 fewer)	MODERATE	IMPORTANT
Bone health - ≥5% decline in FN BMD (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	4/50 (8%)	12/50 (24%)	RR 0.33 (0.12 to 0.96)	161 fewer per 1000 (from 10 fewer to 211 fewer)	MODERATE	IMPORTANT

BMD, bone mineral density; CI, confidence interval; DFS, disease-free survival; FN, femoral neck; LS, lumbar spine; OS, overall survival
1 Number of events not reported but unlikely to exceed 300 events due to sample size
2 Cannot be determined as number of events not reported
3 events <300
4 <300 events in both arms and 95% CI crosses both thresholds for clinically significant differences based on GRADE default values (0.80 and 1.25)
5 <300 events in both arms and 95% confidence intervals crosses boundary for no effect (1) and clinically important difference based on GRADE default values (1.25)
6 95% confidence interval touches threshold for no effect (1) and crosses boundary for clinically meaningful difference (0.8)
7 Use of calcium and vitamin D was not routinely assessed or controlled for and control arm younger than intervention arm
8 N<400

Table 20: Clinical evidence profile: Comparison 2. Zoledronic acid versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zoledronic acid	Placebo	Relative (95% CI)	Absolute		
DFS (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	1/36 (2.8%)	0/35 (0%)	HR 1.09 (0.31 to 3.85)	-	MODERATE	CRITICAL
Bone health - % change in LS BMD (Better indicated by higher values; 2 year follow-up)												
2	Randomised trials	No serious risk of bias	Very serious[2]	Serious[3]	Serious[4]	None	61	66	-	MD 7.56 higher (3.77 to 11.35 higher)	VERY LOW	IMPORTANT
Bone health - % change in FN BMD (Better indicated by higher values; 2 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	Serious[4]	None	61	68	-	MD 2.57 higher (1.96 to 3.19 higher)	LOW	IMPORTANT

BMD, bone mineral density; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; FN, femoral neck; LS, lumbar spine; MD, mean difference

[1] <300 events

[2] I squared 95%; high rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes. Estimated effect for both studies are in the same direction and exceed threshold for clinically important difference

[3] Some patients in Hershman 2010 received bisphosphonates as neoadjuvant therapy

[4] N<400

1 **Table 21: Clinical evidence profile. Comparison 3: Risedronate versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	Placebo	Relative (95% CI)	Absolute		
DFS (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	2/108 (1.9%)	5/108 (4.6%)	HR 0.41 (0.09 to 1.86)	27 fewer per 1000 (from 42 fewer to 38 more)	MODERATE	CRITICAL
OS (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	2/108 (1.9%)	4/108 (3.7%)	HR 0.48 (0.1 to 2.38)	19 fewer per 1000 (from 33 fewer to 49 more)	MODERATE	CRITICAL
Treatment-related morbidity: gastrointestinal (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	4/55 (7.3%)	13/54 (24.1%)	RR 0.3 (0.11 to 0.87)	169 fewer per 1000 (from 31 fewer to 214 fewer)	MODERATE	CRITICAL
Treatment-related morbidity: arthralgia (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[2]	Very serious[3]	None	0/106 (0%)	3/106 (2.8%)	RR 0.14 (0.01 to 2.73)	24 fewer per 1000 (from 28 fewer to 49 more)	VERY LOW	CRITICAL
Treatment-related morbidity: constipation (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[2]	Very serious[4]	None	53/106 (50%)	61/106 (57.5%)	RR 0.87 (0.68 to 1.12)	75 fewer per 1000 (from 184 fewer to 69 more)	VERY LOW	CRITICAL
Treatment-related morbidity: nausea (1 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	Placebo	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[2]	Very serious[5]	None	5/106 (4.7%)	3/106 (2.8%)	RR 1.67 (0.41 to 6.8)	19 more per 1000 (from 17 fewer to 164 more)	VERY LOW	CRITICAL
Treatment-related morbidity: Abdominal pain (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[2]	Very serious[5]	None	33/106 (31.1%)	30/106 (28.3%)	RR 1.1 (0.73 to 1.67)	28 more per 1000 (from 76 fewer to 190 more)	VERY LOW	CRITICAL
Treatment-related morbidity: diarrhoea (1 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[2]	Very serious[5]	None	30/106 (28.3%)	29/106 (27.4%)	RR 1.03 (0.67 to 1.6)	8 more per 1000 (from 90 fewer to 164 more)	VERY LOW	CRITICAL
Bone health – fractures (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/34 (8.8%)	2/38 (5.3%)	RR 1.68 (0.3 to 9.44)	36 more per 1000 (from 37 fewer to 444 more)	LOW	IMPORTANT
Bone health - % change in LS BMD (Better indicated by higher values; 1 to 2 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	167	170	-	MD 2.43 higher (1.58 to 3.27 higher)	MODERATE	IMPORTANT
Bone health - % change in FN BMD (Better indicated by higher values; 1 to 2 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	119	123	-	MD 1.59 higher (1.26 to	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										1.91 higher)		

BMD, bone mineral density; CI, confidence interval; DFS, disease-free survival; FN, femoral neck; HR, hazard ratio; LS, lumbar spine; OS, overall survival; RR, risk ratio
[1] <300 events
[2] Some patients received bisphosphonates as neoadjuvant treatment
[3] <300 events and 95% confidence interval crosses boundaries for no effect (1) and clinically important differences based on GRADE default values (0.8 and 1.25)
[4] <300 events and 95% confidence interval crosses boundary for no effect (1) and clinically meaningful difference based on GRADE default values (0.8)
[5] <300 events and 95% confidence interval crosses both boundaries for no effect (1) and clinically meaningful differences based on GRADE default values (0.8 and 1.25)
[6] N<400

Table 22: Clinical evidence profile: Comparison 4. Ibandronate versus no treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
DFS - Node positive (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	270/1996 (13.5%)	135/998 (13.5%)	HR 0.95 (0.77 to 1.16)	6 fewer per 1000 (from 29 fewer to 20 more)	HIGH	CRITICAL
DFS - Pre-menopausal (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 1.02 (0.76 to 1.37)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Post-menopausal (3.3 to 5.6 year follow-up)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	117/895 (13.1%)	64/468 (13.7%)	HR 0.89 (0.72 to 1.1)	14 fewer per 1000 (from 36 fewer to 13 more)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Grade 1/2 (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 0.98 (0.7 to 1.37)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Grade 3 (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 0.91 (0.7 to 1.18)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER/PR+ (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 0.9 (0.59 to 1.38)	-	Number of events in subgroup was not	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
											reported - insufficient information to judge imprecision, and therefore overall quality	
DFS - ER/PR- (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 0.94 (0.74 to 1.2)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Whole sample (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	128/2015 (6.4%)	59/1008 (5.9%)	HR 1.03 (0.75 to 1.41)	2 more per 1000 (from 14 fewer to 23 more)	MODERATE	CRITICAL
OS - Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	66/895 (7.4%)	33/468 (7.1%)	HR 0.98 (0.64 to 1.49)	1 fewer per 1000 (from 25 fewer to 33 more)	MODERATE	CRITICAL
Treatment-related morbidity: gastrointestinal issues (3.25 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	113/1832 (6.2%)	34/968 (3.5%)	RR 1.76 (1.21 to 2.56)	27 more per 1000 (from 7 more to 55 more)	MODERATE	CRITICAL
Treatment-related morbidity: renal/urinary issues (3.25 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	No treatment control	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	10/1382 (0.7%)	5/968 (0.5%)	RR 1.4 (0.48 to 4.09)	2 more per 1000 (from 3 fewer to 16 more)	LOW	CRITICAL

CI, confidence interval; DFS, disease-free survival; ER, oestrogen receptor; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; RR, risk ratio

[1] Number of events and participants in each arm not reported so cannot determine imprecision

[2] Number of events and participants in each arm not reported for one study so cannot determine imprecision

[3] <300 events

[4] <300 events and 95% confidence interval crosses both boundaries for no effect (1) and for clinically important differences based on GRADE default values (0.8 and 1.25)

Table 23: Clinical evidence profile: Comparison 5. Ibandronate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	Placebo	Relative (95% CI)	Absolute		
OS (post-menopausal only; 5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	0/25 (0%)	2/24 (8.3%)	HR 0.14 (0.01 to 2.16)	71 fewer per 1000 (from 82 fewer to 88 more)	MODERATE	CRITICAL
Treatment-related morbidity: arthralgia (2 year follow-up)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	6/25 (24%)	5/25 (20%)	RR 1.2 (0.42 to 3.43)	40 more per 1000 (from 116 fewer to 486 more)	VERY LOW	CRITICAL
Treatment-related morbidity: upper GI symptoms (2 year follow-up)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	4/25 (16%)	0/25 (0%)	RR 9 (0.51 to 158.85)	-	VERY LOW	CRITICAL
Bone health – fractures (2 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibandronate	Placebo	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[3]	None	2/25 (8%)	3/25 (12%)	RR 0.67 (0.12 to 3.65)	40 fewer per 1000 (from 106 fewer to 318 more)	VERY LOW	IMPORTANT

CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; OS, overall survival; RR, risk ratio
[1] <300 events
[2] Attrition higher in placebo arm
[3] <300 events and 95% confidence interval crosses both boundaries for no effect (1) and for clinically important differences based on GRADE default values (0.8 and 1.25)
[4] Attrition higher in placebo arm and 2 discontinued study due to decrease in BMD which may minimise difference between groups

Table 24: Clinical evidence profile: Comparison 6. Sodium clodronate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	Placebo	Relative (95% CI)	Absolute		
DFS - Whole sample (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	286/1655 (17.3%)	312/1656 (18.8%)	HR 0.91 (0.78 to 1.07)	15 fewer per 1000 (from 38 fewer to 12 more)	HIGH	CRITICAL
DFS - Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	109/935 (11.7%)	133/898 (14.8%)	HR 0.75 (0.58 to 0.97)	35 fewer per 1000 (from 4 fewer to 59 fewer)	MODERATE	CRITICAL
DFS - ER/PR+ (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.94 (0.78 to 1.14)	-	Number of events in subgroup was not reported - insufficient information to	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
											judge imprecision, and therefore overall quality	
DFS - ER/PR- (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.84 (0.62 to 1.14)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Node positive (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	0/404 (0%)	0/409 (0%)	HR 0.78 (0.59 to 1.03)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Node negative (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	0/1252 (0%)	0/1258 (0%)	HR 0.99 (0.81 to 1.21)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	Placebo	Relative (95% CI)	Absolute		
OS - Whole sample (5.6 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	282/2200 (12.8%)	333/2202 (15.1%)	HR 0.84 (0.72 to 0.99)	23 fewer per 1000 (from 1 fewer to 40 fewer)	HIGH	CRITICAL
OS - Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	135/935 (14.4%)	144/898 (16%)	HR 0.89 (0.7 to 1.13)	16 fewer per 1000 (from 45 fewer to 19 more)	MODERATE	CRITICAL
OS - ER/PR+ (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.9 (0.69 to 1.18)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - ER/PR- (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.72 (0.49 to 1.06)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Node positive (7.5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	Placebo	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	0/404 (0%)	0/409 (0%)	HR 0.72 (0.51 to 1.01)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Node negative (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	0/1252 (0%)	0/1258 (0%)	HR 0.94 (0.7 to 1.26)	-	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity: gastrointestinal disorders (7.5 year follow-up)												
1	Randomised trials	[4]	No serious inconsistency	[4]	No serious imprecision	None	355/538 (66%)	304/541 (56.2%)	RR 1.17 (1.07 to 1.29)	96 more per 1000 (from 39 more to 163 more)	Number of events in subgroup was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity: diarrhoea (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	28/1612 (1.7%)	10/1623 (0.6%)	RR 2.82 (1.37 to 5.78)	11 more per 1000 (from 2	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	Placebo	Relative (95% CI)	Absolute		
										more to 29 more)		
Treatment-related morbidity: hypocalcaemia (7.5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	1/1612 (0.1%)	2/1623 (0.1%)	RR 0.5 (0.05 to 5.55)	1 fewer per 1000 (from 1 fewer to 6 more)	MODERATE	CRITICAL
Bone health – fractures (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	164/1662 (9.9%)	193/1661 (11.6%)	RR 0.85 (0.7 to 1.03)	17 fewer per 1000 (from 35 fewer to 3 more)	MODERATE	IMPORTANT
Bone health - % change LS BMD (Better indicated by higher values; 5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	419	432	-	MD 1.93 higher (0.96 to 2.9 higher)	HIGH	CRITICAL
Bone health - % change FN BMD (Better indicated by higher values; 5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	419	432	-	MD 1.7 higher (0.46 to 2.94 higher)	HIGH	CRITICAL

BMD, bone mineral density; CI, confidence interval; DFS, disease-free survival; ER, oestrogen receptor; FN, femoral neck; HR, hazard ratio; LS, lumbar spine; MD, mean difference; OS, overall survival; PR, progesterone receptor; RR, risk ratio

[1] <300 events

[2] Number of events and participants in each arm not reported so cannot determine imprecision

[3] Number of events in each arm not reported so cannot determine imprecision

[4] Not possible to assess due to study included from previous guideline

[5] <300 events

[6] <300 events; not downgraded based on 95% CI due to very small differences in absolute risk

[7] 95% confidence interval crosses boundary for no effect (1) and clinically important difference based on GRADE default value (0.8)

Table 25: Clinical evidence profile: Comparison 7. Pamidronate versus no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pamidronate	No treatment control	Relative (95% CI)	Absolute		
DFS – Whole sample (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	236/460 (51.3%)	237/490 (48.1%)	HR 1.09 (0.89 to 1.35)	30 more per 1000 (from 39 fewer to 106 more)	MODERATE	CRITICAL
DFS – Postmenopausal (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	96/152 (63.2%)	108/167 (64.7%)	HR 1.09 (0.78 to 1.51)	32 more per 1000 (from 91 fewer to 145 more)	LOW	CRITICAL
OS – Whole sample (5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	248/460 (53.9%)	250/490 (50.7%)	HR 1.04 (0.85 to 1.27)	14 more per 1000 (from 55 fewer to 86 more)	MODERATE	CRITICAL
OS – Post-menopausal (5.6 year follow-up)												
1	Randomised trials	No seriou	No serious inconsistency	No serious indirectness	Very serious[2]	None	108/152 (71.1%)	118/167 (70.7%)	HR 1.01	4 more per	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pamidronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
		s risk of bias							(0.74 to 1.37)	1000 (from 110 fewer to 107 more)		
Treatment-related morbidity: nausea/vomiting (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	324/417 (77.7%)	337/467 (72.2%)	RR 1.08 (1 to 1.16)	58 more per 1000 (from 0 more to 115 more)	HIGH	CRITICAL
Treatment-related morbidity: abdominal pain (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	123/417 (29.5%)	103/467 (22.1%)	RR 1.34 (1.07 to 1.68)	75 more per 1000 (from 15 more to 150 more)	MODERATE	CRITICAL
Bone health – fractures (4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	29/460 (6.3%)	24/493 (4.9%)	RR 1.30 (0.77 to 2.19)	15 more per 1000 (from 11 fewer to	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pamidronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
										58 more)		

1 *CI, confidence interval; RR, risk ratio*
2 *1 <300 events*
3 *2 <300 events and 95% confidence interval crosses boundary for no effect (1) and for clinically meaningful differences based on GRADE default values (0.8 and 1.25)*

4 **Table 26: Clinical evidence profile: Comparison 8. Sodium clodronate versus no treatment**

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sodium clodronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
Bone health - % change LS BMD (Better indicated by higher values; 10 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	44	52	-	MD 4.8 higher (0.7 to 8.9 higher)	LOW	IMPORTANT
Bone health - % change FN BMD (Better indicated by higher values; 10 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	44	52	-	MD 2 higher (0.49 lower to 4.49 higher)	LOW	IMPORTANT

5 *BMD, bone mineral density; CI, confidence interval; FN, femoral neck; LS, lumbar spine; MD, mean difference*
6 *[1] High rates of attrition and higher rates of chemotherapy in the control arm*
7 *[2] N<400*

Table 27: Clinical evidence profile: Comparison 9. Risedronate versus no treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	No treatment control	Relative (95% CI)	Absolute	Quality	Importance
Bone health - LS BD T-score (Better indicated by lower values; 2 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	36	35	-	MD 0.26 higher (0.03 to 0.49 higher)	LOW	IMPORTANT
Bone health - FN BD T-score (Better indicated by lower values; 2 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	36	35	-	MD 0.33 higher (0.05 to 0.61 higher)	LOW	IMPORTANT
Bone health – fractures (2 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/36 (0%)	3/35 (8.6%)	RR 0.14 (0.01 to 2.6)	74 fewer per 1000 (from 85 fewer to 137 more)	VERY LOW	IMPORTANT
HRQoL - physical component summary of SF-36 (PCS-36) (Better indicated by lower values; 2 year follow-up)												
1	Randomised trials	Very serious[5]	No serious inconsistency	No serious indirectness	Very serious[6]	None	36	35	-	MD 2.7 higher (4.51 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risedronate	No treatment control	Relative (95% CI)	Absolute		
										9.91 higher)		
HRQoL - mental component summary of SF-36 (MCS-36) (Better indicated by lower values; 2 year follow-up)												
1	Randomised trials	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	None	36	35	-	MD 1.3 lower (7.49 lower to 4.89 higher)	VERY LOW	IMPORTANT

BMD: bone mineral density; CI: Confidence interval; HR: Hazard ratio; HRQoL: health-related quality of life; LS: lumbar spine; MCS: mental component summary; MD, mean difference; PCS: physical component summary; RR: Risk ratio; SF-36: 36-Item Short Form Survey

[1] High attrition

[3] N <400

[4] <300 events; 95% confidence interval crosses both no effect (1) and minimally important difference (1.25) based on GRADE default value

[5] High attrition and risk of detection bias

[6] N<400; 95% confidence interval crosses both no effect (0) and minimally important difference (0.5 x SD) based on GRADE default values

Appendix G – Economic evidence study selection

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis: The cost-effectiveness of bisphosphonates in the treatment of early and locally advanced breast cancer

Background

In early breast cancer, bisphosphonates are commonly recommended for the prevention or treatment of bone mineral density loss related to aromatase inhibitor therapy or ovarian suppression. However, there is increasingly a view that bisphosphonates could be used to prevent or delay recurrence of disease, potentially making them effective as an adjuvant treatment in early breast cancer. There is uncertainty around the effectiveness of bisphosphonates as an adjuvant treatment however as previous adjuvant bisphosphonate breast cancer trials have provided conflicting results and have not provided evidence of consistent benefit across all subgroups.

The potential benefits of adjuvant treatment with bisphosphonates need to be balanced against the risks of bisphosphonate treatment including renal function impairment, osteonecrosis of the jaw and hypocalcaemia. Furthermore, the cost of bisphosphonates needs to be considered and the cost-effectiveness of treatment with bisphosphonates in this setting is unknown.

Aim

To estimate the cost-effectiveness of bisphosphonates in the treatment of early and locally advanced breast cancer.

Methods

Existing economic evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. Numerous studies were identified which considered the cost-effectiveness of bisphosphonates in treating or preventing bone mineral density loss but no studies were identified that considered the treatment of breast cancer. Therefore, no relevant economic studies were identified which were applicable to this review question.

De novo economic evaluation

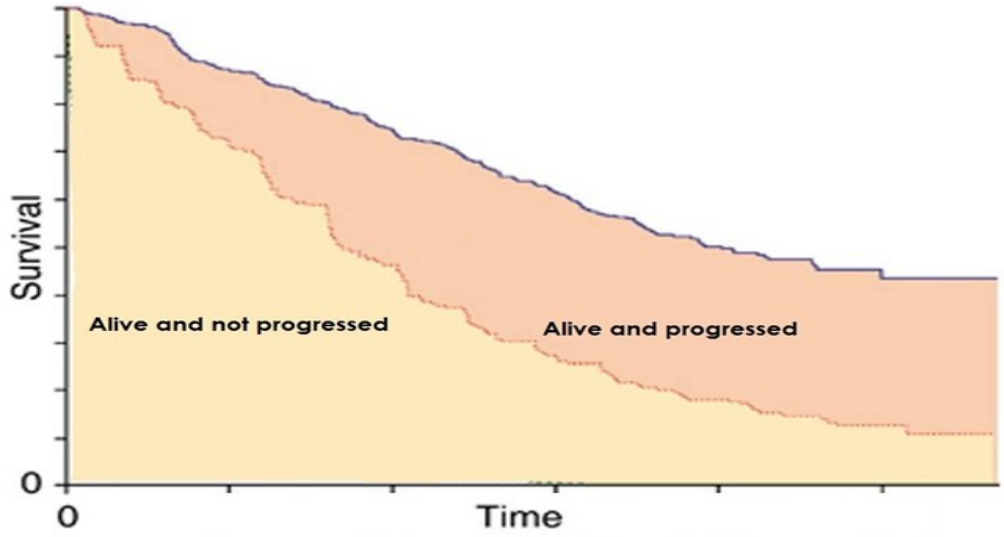
Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (see Developing NICE guidelines: the manual). The model considered a fifty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

Clinical data and model approach

The economic analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis (Figure 57), in which three mutually exclusive health states were derived from the overall survival and progression free survival estimates:

- alive without progressed disease
- alive with progressed disease
- dead.

Figure 57: Illustrative example of partitioned survival analysis



One of the primary aims of the analysis was to identify whether the use of bisphosphonates may be cost-effective in specific subgroups. In particular, the committee were interested in whether the use of bisphosphonates would be cost-effective in women with node positive breast cancer and post-menopausal women with breast cancer. Therefore, these subgroups were given separate consideration in the analysis (in addition to the modelling undertaken for the overall population).

Overall and disease free survival for each of the interventions was estimated using data on absolute and relative risk from the systematic review of the clinical evidence conducted for this topic. In the overall population, baseline absolute values for overall and disease free survival were sourced from the combined evidence for the comparison between zoledronic acid and no treatment (using the values from the no treatment arm). Overall survival was estimated to be 84.0% and disease free survival was estimated to be 77.2% at 5.6 years.

In post-menopausal women, baseline absolute values for overall and disease free survival were sourced from the combined evidence for the comparison between zoledronic acid and no treatment in post-menopausal women (using the values from the no treatment arm). Overall survival was estimated to be 76.7% and disease free survival was estimated to be 73.6% at 5.6 years. Baseline absolute values for overall and disease free survival were not available for people with node positive disease. It was therefore assumed that baseline risk in this group would be equivalent to the baseline risk in post-menopausal women. This assumption is varied in sensitivity analysis where the use of alternative baseline values is explored.

Overall and disease free survival for each of the bisphosphonate treatments was estimated by applying the relative treatment effect (using hazard ratios [HR]) associated with each treatment to the absolute risk estimates. Table 28 to Table 30 show the overall and disease free survival estimates for the overall population, women with node positive breast cancer and post-menopausal women.

Table 28: Overall and disease free survival for the overall population

	Mean		Lower		Upper	
Bisphosphonate	**HR**	**Absolute**	**HR**	**Absolute**	**HR**	**Absolute**
Overall survival						
No treatment	-	84.0%	-	-	-	-
Zoledronic acid	0.93	85.1%	0.81	87.0%	1.07	82.9%
Risedronate	0.48	92.3%	0.10	98.4%	2.38	61.9%
Sodium clodronate	0.84	86.6%	0.72	88.5%	0.99	84.2%
Disease free survival						
No treatment	-	77.2%	-	-	-	-
Zoledronic acid	1.09	75.2%	0.31	92.9%	3.85	12.3%
Risedronate	0.41	90.7%	0.09	97.9%	1.86	57.6%
Sodium clodronate	0.91	79.3%	0.78	82.2%	1.07	75.6%

Table 29: Overall and disease free survival for women with node positive breast cancer

	Mean		Lower		Upper	
Bisphosphonate	**HR**	**Absolute**	**HR**	**Absolute**	**HR**	**Absolute**
Overall survival						
No treatment	-	76.7%	-	-	-	-
Zoledronic acid	0.62	85.6%	0.34	92.1%	1.14	73.5%
Sodium clodronate	0.75	82.5%	0.58	86.5%	0.97	77.4%
Disease free survival						
No treatment	-	73.6%	-	-	-	-
Zoledronic acid	0.67	82.3%	0.45	88.1%	0.99	73.8%
Sodium clodronate	0.78	79.4%	0.59	84.4%	1.03	72.8%

Table 30: Overall and disease free survival for post-menopausal women with breast cancer

	Mean		Lower		Upper	
Bisphosphonate	**HR**	**Absolute**	**HR**	**Absolute**	**HR**	**Absolute**
Overall survival						
No treatment	-	76.7%	-	-	-	-
Zoledronic acid	0.90	79.1%	0.73	83.0%	1.11	74.2%
Ibandronate	0.98	77.2%	0.64	85.1%	1.49	65.3%
Sodium clodronate	0.89	79.3%	0.70	83.7%	1.13	73.7%
Disease free survival						
No treatment	-	73.6%	-	-	-	-
Zoledronic acid	0.88	76.7%	0.73	80.7%	1.07	71.7%
Ibandronate	0.89	76.5%	0.72	81.0%	1.10	70.9%
Sodium clodronate	0.75	79.3%	0.58	84.7%	0.97	74.4%

A simple exponential function was used to estimate overall and disease free survival based on the values at 5.6 years (shown in the tables above). As well as informing data points before 5.6 years, this approach was also used to extrapolate beyond the time period covered

in the studies and up to the modelled time horizon of 50 years. Since it is not known whether the treatment effect with bisphosphonates would endure beyond the period covered in the studies, it was assumed that that there would be no treatment effect after 5.6 years. This follows the conservative approach which has generally been adopted in the analysis whereby, in areas of uncertainty requiring assumptions to be made, we aimed to bias against the intervention and not in favour of it. Alternative treatment effect durations are explored in sensitivity analysis (including a scenario where a lifetime treatment effect duration is assumed).

Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 49 was applied in the model based on the average age reported in Piccart-Gebhart 2005. The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of people that died of disease-specific and other causes.

The possibility of osteonecrosis of the jaw is a major concern when using bisphosphonates as it is a very serious condition with debilitating effects. It has therefore been included in the economic model. In the systematic review of the clinical evidence conducted for this topic, data was only reported on osteonecrosis of the jaw in people treated with zoledronic acid, where it was reported that 1% of people experienced this side effect.

Despite the lack of evidence in the other comparisons, it was thought that there would be a similar level of risk of osteonecrosis when using the other bisphosphonates. However, there is some evidence that the risk of osteonecrosis is lower when using oral bisphosphonates (rather than intravenously). Therefore, it has been assumed that the risk of osteonecrosis is 1% when bisphosphonates are given intravenously and 0.5% when given orally.

The analysis focused on the effect of bisphosphonates on cancer specific outcomes and as such did not consider the possible benefits associated with improvements in bone mineral density (such as a reduction in fractures). The analysis could therefore be considered conservative as the inclusion of such benefits would be likely to improve the cost-effectiveness of bisphosphonates.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Bisphosphonate costs

Bisphosphonate costs were estimated for each of the bisphosphonates considered in the analysis. Zoledronic acid costs were estimated using drug costs from eMit, assuming that 4mg would be given every six months for three years (at a cost of £2.71 for a 4mg dose). Risedronate costs were estimated using drug costs from eMit assuming that 35mg would be given orally every three weeks for three years (at a cost of £0.10 per dose). Ibandronate costs were estimated using drug costs from eMit assuming that 50mg would be given every day for three years (at a cost of £0.28 per dose). Sodium clodronate costs were estimated

using drug costs from eMit assuming that 1600mg would be given every day for three years (at a cost of £3.18 per dose).

Delivery costs for bisphosphonates given intravenously were estimated to be £198.94 based on the cost to 'deliver simple parenteral chemotherapy at first attendance' from NHS Reference Costs 2015/16. Note that there is some uncertainty around the appropriate cost code for the delivery of intravenous bisphosphonates but the use of this code matches previous economic evaluations, including the NICE technology appraisal guidance TA464 on the use of bisphosphonates for osteoporosis (NICE 2017). It was assumed that bisphosphonates given orally would incur the cost of an annual GP visit (£36.00 based on an average consultation lasting 9.22 minutes).

Table 31 details the drug cost, delivery cost and annual cost for each of the bisphosphonate regimens.

Table 31: Bisphosphonate costs

Treatment	Cost	Source
Zoledronic acid		
Deliver Simple Parenteral Chemotherapy at First Attendance	£198.94	NHS Reference costs 2015/16 - Outpatient
Cost per Zoledronic acid 4-mg dose by intravenous infusion	£2.71	eMit
Annual cost of Zoledronic acid	**£403.30**	
Risedronate		
Oral regimen delivery cost - GP visit†	£36.00	PSSRU - Unit costs of health and social care 2016
Cost per Risedronate 35mg oral tablet	£0.10	eMit
Annual cost of once weekly Risedronate	**£4.94**	
Ibandronate		
Oral regimen delivery cost - GP visit†	£36.00	PSSRU - Unit costs of health and social care 2016
Cost per Ibandronate 50mg oral tablet	£0.28	eMit
Annual cost of daily Ibandronate	**£102.20**	
Sodium clodronate		
Oral regimen delivery cost - GP visit†	£36.00	PSSRU - Unit costs of health and social care 2016
Cost per Sodium clodronate 1600mg dose (2x oral tablets)	£3.18	eMit
Annual cost of daily Sodium clodronate	**£1,161.92**	

†*Consultation lasting 9.22 minutes*

Osteonecrosis cost

Cost for the management of osteonecrosis of the jaw has been estimated from an analysis of resource use and cost associated with the management of osteonecrosis of the jaw in the US health care system (Najm 2014). The study was a retrospective review of medical records of 92 people with cancer and included data on medications, imaging and laboratory investigations, procedures and visits. It was estimated that the management of osteonecrosis

cost $1,667 (based on all cancer types). Converting and inflating to UK 2015 prices, this equated to a cost of £1,266.04.

Subsequent treatment costs

Subsequent treatment costs (following disease recurrence or progression) were estimated based on the average treatment that would be most likely to be used (based on the estimation of the guideline committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%).

It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either delayed or at the time of mastectomy). It was further assumed that lymph node clearance would be performed for people with regional recurrence. It was also assumed that radiotherapy would be given in people that were not previously treated with radiotherapy (24% from Cameron 2017) and that everyone would receive adjuvant chemotherapy, trastuzumab and pertuzumab. It was assumed that distant disease would be treated with chemotherapy, trastuzumab and pertuzumab.

Table 32 to Table 35 detail the costs that were applied for each type of recurrence.

Table 32: Subsequent treatment costs for locoregional recurrence

Treatment	Proportion†	Cost	Source
Major breast procedures (in people that originally had mastectomy)			
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	4%	£3,797	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	17%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	59%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 1+ (JA21A)	9%	£4,143	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 0 (JA21B)	10%	£3,834	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,219.70**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient

Treatment	Proportion†	Cost	Source
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	**-**	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	**-**	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	**-**	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	**-**	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	**-**	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	**-**	£1,222.20	BNF
Pertuzumab cost for 420mg vial	**-**	£2,395.00	NICE TA and BNF
Total cost per cycle	**-**	***£3,988.17***	

Treatment	Proportion†	Cost	Source
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Table 33: Subsequent treatment costs for regional recurrences

Treatment	Proportion†	Cost	Source
Major breast procedures with lymph node clearance (for regional recurrences in people that that originally had mastectomy)			
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 5+ (JA38A)	13%	£4,535	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 2-4 (JA38B)	38%	£3,814	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 0-1 (JA38C)	42%	£3,694	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with Lymph Node Clearance (JA39Z)	7%	£5,522	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,971.97**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient

Treatment	Proportion†	Cost	Source
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Table 34: Subsequent treatment costs for contralateral recurrence

Treatment	Proportion†	Cost	Source
Major breast procedures (in people that originally had mastectomy)			

Treatment	Proportion†	Cost	Source
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	5%	£3,797	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	21%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	74%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,036.41**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	51%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	49%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,571.91**	
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	77%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	23%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£6,973.11**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	**-**	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	**-**	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	**-**	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	**-**	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**

Treatment	Proportion†	Cost	Source
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

1 **Table 35: Subsequent treatment costs for distant recurrence**

Treatment	Proportion†	Cost	Source
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF

Treatment	Proportion†	Cost	Source
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Cardiac event monitoring costs

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi gated acquisition (MUGA) scans or cardiac MRI scans may be used.

In the model, a weighted average cost per scan was calculated using weightings estimated by the guideline committee. It was assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that 5 cardiac monitoring scans would be required in the year that receive trastuzumab was given.

Table 36 details the cost of cardiac event monitoring applied in the model.

Table 36: Cardiac event monitoring costs

Treatment	Proportion†	Cost	Source
Simple Echocardiogram, 19 years and over (RD51A)	80%	£72.00	NHS Reference Costs 2015/16 – outpatient
Multi Gated Acquisition (MUGA) Scan (RN22Z)	10%	£204.70	NHS Reference Costs 2015/16 – outpatient
Cardiac Magnetic Resonance Imaging Scan with pre and post contrast (RD10Z)	10%	£329.27	NHS Reference Costs 2015/16 – outpatient
Weighted average cost per scan		**£111.00**	
Average cost for five scans		**£554.99**	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Follow-up costs

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every three to six months in the years one to three, every six to twelve months in years four to five and annually thereafter. The cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

Palliative care costs

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou 2014). A cost of £7,287 for 3 months was applied based on the average resource use of people with cancer in the last three months of life. Table 37 details the palliative care cost applied in the model.

Table 37: Estimated palliative care cost per person in the last three months of life

Type of care	Average cost per cancer person	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per person	**£7,287**	

It should be noted that this cost is generic to all cancers and is not specifically related to breast cancer. However, in the absence of more robust data, it has been assumed that the costs in breast cancer would not differ substantially.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for people with HER2-positive breast cancer and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (TA424, NICE 2017).

Table 38 details the QoL values applied in the analysis. It can be seen that people in the 'disease free' health state would have a QoL value of 0.847 which decreases to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer specific mortality.

A QoL disutility for patients with osteonecrosis of the jaw was sourced from a published economic evaluation of zoledronic acid in people with breast cancer and low oestrogen levels (Lamond 2015). It was assumed that the disutility would apply for one year.

Table 38: Health-related quality of life values

Health state	Value	Source
Event free or remission	0.847	Essers et al. 2010
Recurrence	0.810	Essers et al. 2010
Metastases	0.484	Essers et al. 2010
Disutility – osteonecrosis of the jaw	0.280	Lamond et al. 2015

Results

Base case results

The base case results of the analyses for each of the modelled populations are shown in Table 39 to Table 42. In the overall population, it can be seen that zoledronic acid and sodium clodronate were found to be more effective and more costly than no treatment. Zoledronic acid has an ICER above the NICE threshold of £20,000 per QALY and so was therefore not cost-effective while sodium clodronate has an ICER below the NICE threshold of £20,000 per QALY and was therefore cost-effective. Risedronate was found to be more effective and less costly than no treatment and was therefore dominant**.** Risedronate would

also be preferred if comparing all strategies against each other as it is the most effective and least expensive of all the strategies.

In the node-positive population, zoledronic acid and sodium clodronate were found to be more effective and more costly than no treatment. The ICERs for both treatments were below the NICE threshold of £20,000 per QALY and so both treatments are cost-effective when compared against no treatment. Comparing sodium clodronate and zoledronic acid, it can be seen that zoledronic acid would be preferred as it is less costly and more effective than sodium clodronate.

In the postmenopausal population, sodium clodronate and Ibandronate were found to be more effective and less costly than no treatment and were therefore dominant. Zoledronic acid was found to be more effective and more costly and was cost-effective with an ICER below the NICE threshold of £20,000 per QALY. In order to compare all strategies against each other in this population, a 'dominance rank' approach was adopted. Using this approach, it can be seen that sodium clodronate would be the preferred strategy in cost-effectiveness terms. Zoledronic acid and no treatment were both found to be less effective and more costly than sodium clodronate and were therefore dominated. In comparison to Ibandronate, sodium clodronate was found to be more costly and more effective with an ICER below the NICE threshold of £20,000 per QALY.

While the results of the deterministic analysis are of some interest, it is important to remember when interpreting the results that many of the differences in clinical effectiveness were not statistically significant. This therefore limits the reliability of the base case estimates.

Table 39: Base case results for overall population (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£34,857	-	11.00	-	-
Zoledronic acid	£39,832	*£4,974*	11.10	*0.09*	£53,207
Risedronate	£29,812	*-£5,045*	11.76	*0.76*	Dominant
Sodium clodronate	£39,110	*£4,253*	11.23	*0.23*	£18,837

Table 40: Base case results for people with node-positive breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£18,931	-	9.13	-	-
Zoledronic acid	£20,592	*£1,660*	9.83	*0.71*	£2,355
Sodium clodronate	£22,524	*£3,593*	9.59	*0.46*	£7,816

Table 41: Base case results for postmenopausal women with breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£18,931	-	9.13	-	**-**
Zoledronic acid	£19,180	*£248*	9.31	*0.18*	**£1,395**
Ibandronate	£16,510	*-£2,421*	9.16	*0.03*	**Dominant**
Sodium clodronate	£18,138	*-£793*	9.33	*0.20*	**Dominant**

Table 42: Base case results for postmenopausal women with breast cancer (dominance rank)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Ibandronate	£16,510	-	9.16	-	-
Sodium clodronate	£18,138	*£1,628*	9.33	*0.17*	**£9,863**
Zoledronic acid	£19,180	*£1,041*	9.31	*-0.02*	**Dominated**
No treatment	£28,555	*£10,417*	9.13	*-0.20*	**Dominated**

Deterministic sensitivity results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are shown in the tables below. Table 43 to Table 45 show the cost-effectiveness result for each bisphosphonate in comparison to no treatment in each of the modelled scenarios.

In the analysis for the overall population, it can be seen that zoledronic acid is not cost-effective in comparison to no treatment in the majority of modelled scenarios. However, it is cost-effective (and indeed dominant) in the scenario where the lower HR for disease free survival is used. Risedronate remains cost-effective in most scenarios but notably the conclusion is completely different when using the upper HRs for overall survival and disease free survival. Furthermore, it is not cost-effective when only statistically significant differences are considered. Sodium clodronate is cost-effective in most of the modelled scenarios but is not cost-effective when the upper HRs were used for overall survival and disease free survival or when only statistically significant treatment effects were included.

In the analysis for women with node-positive disease, it can be seen that zoledronic acid remains cost-effective in comparison to no treatment in the majority of modelled scenarios. However, it is notably not cost-effective when only statistically significant differences are considered. Sodium clodronate is cost-effective in most of the modelled scenarios but it was not cost-effective when the upper HR for DFS was applied or when only statistically significant treatment effects were included.

In the analysis for postmenopausal women, it can be seen that zoledronic acid, ibandronate and sodium clodronate remain cost-effective in comparison to no treatment in the majority of modelled scenarios. However, they were not cost-effective when the upper HR was used for DFS or when only statistically significant differences were considered.

Table 43: Deterministic sensitivity analysis results for overall population

Change made	Comparisons against no treatment		
	Zoledronic acid	Risedronate	Sodium clodronate
Base case	**£53,207**	**Dominant**	**£18,837**
Upper HR for OS	Dominated	***£6,532****	***£96,802***
Lower HR for OS	£28,189	£2,239	£16,908
Upper HR for DFS	£1,035,834	***£46,236***	***£37,899***
Lower HR for DFS	***Dominant***	Dominant	£3,482
Statistically significant treatment effects only	Dominated	***Dominated***	***£29,537***
Treatment effect duration of 10 years	£48,058	Dominant	£12,661

Change made	Comparisons against no treatment		
	Zoledronic acid	Risedronate	Sodium clodronate
Treatment effect duration of 20 years	£47,214	Dominant	£9,912
Lifetime treatment effect duration	£49,529	Dominant	£9,160

* ICER result shows a scenario where the bisphosphonate was found to be less effective and less expensive than no treatment. Therefore, interpretation of the ICER result changes with values above £20,000 per QALY indicating cost-effectiveness.

Table 44: Deterministic sensitivity analysis results for women with node-positive breast cancer

Change made	Comparisons against no treatment	
	Zoledronic acid	Sodium clodronate
Base case	**£2,355**	**£7,816**
Upper HR for OS	£12,972	Dominant
Lower HR for OS	£7,910	£10,863
Upper HR for DFS	£16,748	***£24,869***
Lower HR for DFS	Dominant	Dominant
Statistically significant treatment effects only	***£793,678***	***£22,815***
Baseline risk from 'overall population'	Dominant	£5,541
Treatment effect duration of 10 years	£1,642	£4,826
Treatment effect duration of 20 years	£1,283	£3,447
Lifetime treatment effect duration	£1,105	£2,977

Table 45: Deterministic sensitivity analysis results for postmenopausal women with breast cancer

Change made	Comparisons against no treatment		
	Zoledronic acid	Ibandronate	Sodium clodronate
Base case	**£1,395**	**Dominant**	**Dominant**
Upper HR for OS	£16,221	£5,200	£4,734
Lower HR for OS	£10,297	£10,892	£7,373
Upper HR for DFS	***£34,631***	***£122,160***	***£27,7519***
Lower HR for DFS	Dominant	Dominant	Dominant
Statistically significant treatment effects only	***Dominated***	***Dominated***	***£654,577***
Treatment effect duration of 10 years	Dominant	Dominant	Dominant
Treatment effect duration of 20 years	Dominant	Dominant	Dominant
Lifetime treatment effect duration	Dominant	Dominant	Dominant

Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEAC). The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 58 shows the CEAC for bisphosphonates used in the overall population. It can be seen that risedronate is strongly preferred as the optimal strategy with a high probability of being cost-effective which remains fairly constant as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, risedronate has an 76% probability of being cost-effective while zoledronic acid has a 12% probability, sodium clodronate has a 7% probability and no treatment has 5% probability of being cost-effective.

Figure 58: Cost-effectiveness acceptability curves for the overall population

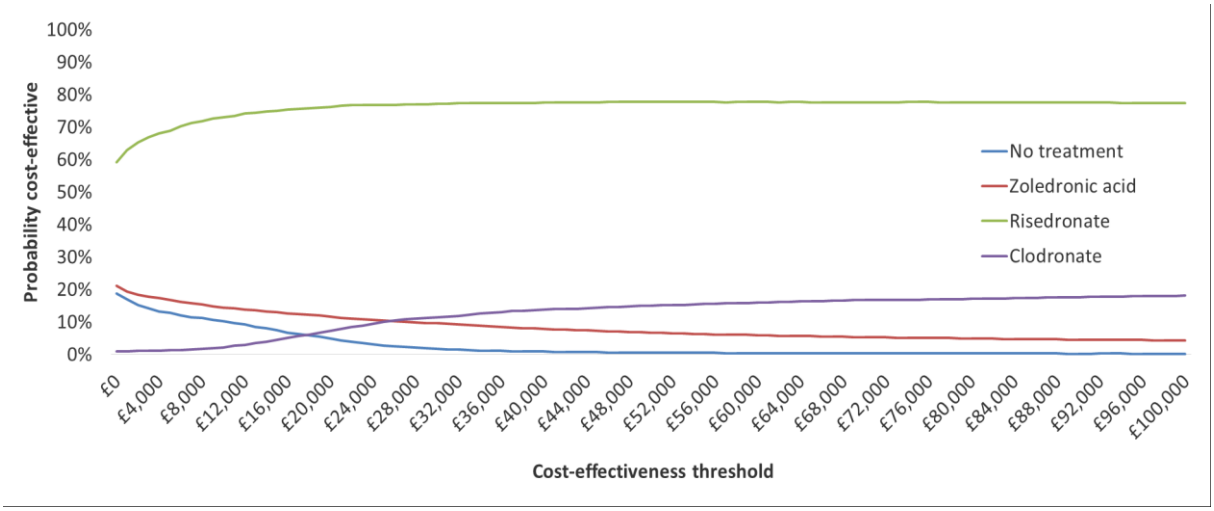


Figure 59 shows the CEAC for bisphosphonates used in women with node-positive breast cancer. It can be seen that no treatment is initially preferred (when the threshold is £0) but is quickly overtaken by zoledronic acid, which remains the preferred strategy as the threshold increases. The probability of sodium clodronate being cost-effective slowly rises as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, zoledronic acid has a 80% probability of being cost-effective while sodium clodronate has a 19% probability and no treatment has 1% probability of being cost-effective.

Figure 59: Cost-effectiveness acceptability curves for women with node-positive breast cancer

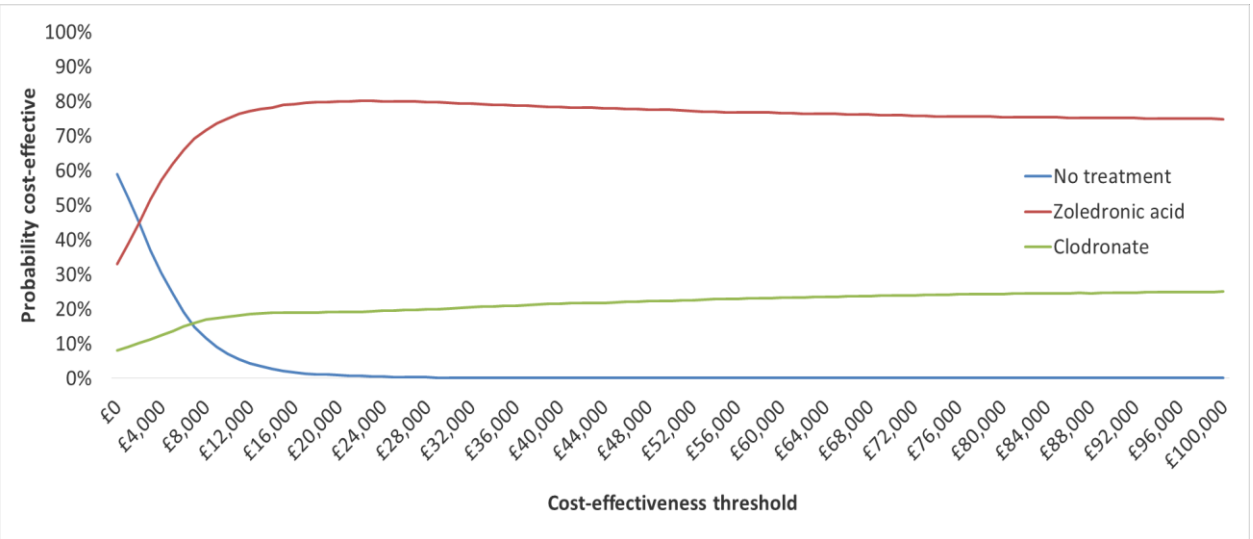
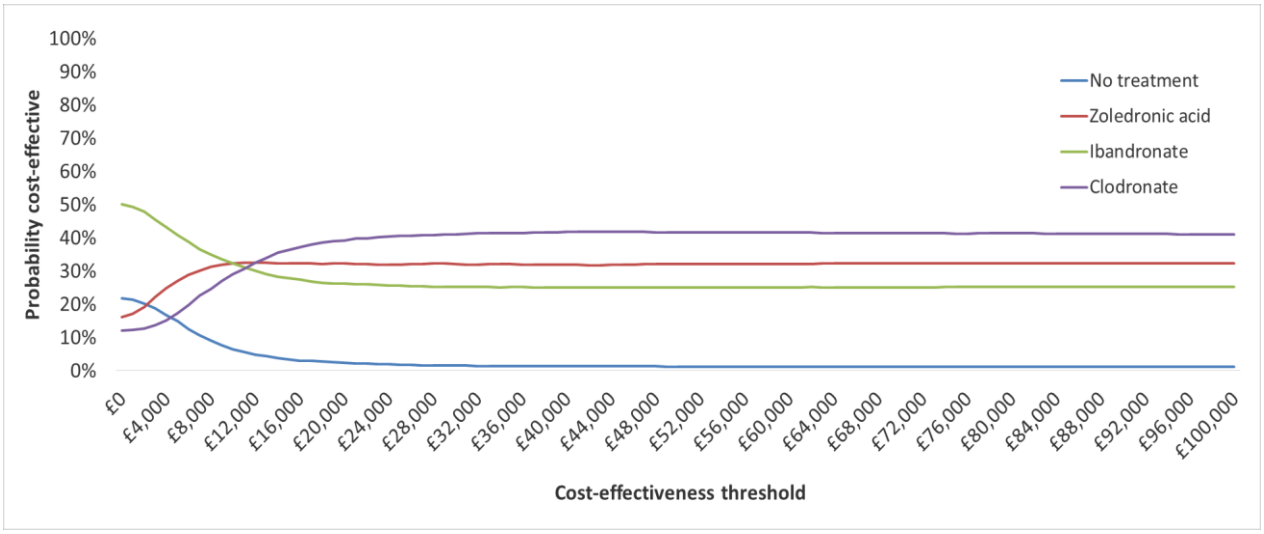


Figure 60 shows the CEAC for bisphosphonates used in postmenopausal women. It can be seen that there is no clearly preferred strategy with the optimal strategy varying as the threshold increases (and the probability of being cost-effective never exceeds 50% for any one strategy). At the NICE threshold of £20,000 per QALY, sodium clodronate has the highest probability of being cost-effective (39%) closely followed by zoledronic acid (32%) and ibandronate (26%) while no treatment had a 12% probability of being cost-effective..

Figure 60: Cost-effectiveness acceptability curves for postmenopausal women with breast cancer



Probabilistic base case results

In addition to the deterministic results, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis. The probabilistic base case results are presented in Table 46 to Table 48.

In the overall population (Table 46), it can be seen that the results do not differ significantly from the deterministic base case results. It is again found that zoledronic acid was more

effective and more costly than no treatment but with an ICER above the NICE threshold of £20,000 per QALY. Sodium clodronate was again found to be more effective and more costly than no treatment with an ICER below the NICE threshold of £20,000 per QALY. Risedronate was again found to be dominant in comparison to no treatment and when comparing all strategies against each other (i.e. it is more effective and less expensive than all other strategies).

In the node-positive population (Table 47), the results were again not found to differ substantially from the base case with both zoledronic acid and sodium clodronate found to be cost-effective in comparison to no treatment. Furthermore, when comparing all treatments against each other, zoledronic acid was again found to be the preferred strategy in cost-effectiveness terms as it was more effective and less costly than sodium clodronate.

In the postmenopausal population (Table 48), the result for zoledronic acid and remains the same as in the deterministic analysis as it was found to be both more effective and more costly than no treatment with the resulting ICER below the NICE threshold of £20,000 per QALY. The result for sodium clodronate changed somewhat with it found to be less costly and more effective than no treatment (i.e. dominant). Ibandronate was also found to be dominant (as it was in the deterministic analysis). The optimal strategy was again found to be sodium clodronate.

Table 46: Base case results for overall population (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£35,012	-	11.01	-	**-**
Zoledronic acid	£47,123	*£12,111*	11.10	*0.09*	**£134,847**
Risedronate	£34,385	*-£628*	11.52	*0.51*	**Dominant**
Sodium clodronate	£39,305	*£4,293*	11.23	*0.22*	**£19,304**

Table 47: Base case results for women with node-positive breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£19,188	-	9.13	-	-
Zoledronic acid	£21,795	*£2,607*	9.78	*0.65*	**£3,991**
Sodium clodronate	£23,256	*£4,068*	9.57	*0.45*	**£9,103**

Table 48: Base case results for postmenopausal women with breast cancer (compared against no treatment)

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
No treatment	£19,425	-	9.14	-	-
Zoledronic acid	£20,206	*£782*	9.31	*0.17*	**£4,587**
Ibandronate	£18,884	*-£540*	9.14	*0.00*	**Dominant**
Sodium clodronate	£20,243	*£818*	9.32	*0.19*	**£4,312**

Conclusion

Conducting a robust economic analysis in this area is very difficult due to a lack of high quality clinical evidence showing clear differences between the approaches. Indeed, if only

statistically significant treatment effects were used in the analysis then no treatment would be the preferred strategy.

Therefore it is difficult to draw any firm conclusion around cost-effectiveness in this area as the clinical evidence upon which it is based is too uncertain. However, one thing that does seem clear from the analysis is that the cost-effectiveness results largely mirror the clinical effectiveness inputs. Therefore if there was evidence that bisphosphonates improved overall and disease free survival then it is likely that their use would be cost-effective.

Appendix K – Excluded studies

Clinical studies

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Abdel-Rahman, O., Denosumab versus zoledronic acid to prevent aromatase inhibitors-associated fractures in postmenopausal early breast cancer; a mixed treatment meta-analysis, Expert Review of Anticancer Therapy, 16, 885-891, 2016	Immediate vs. delayed treatment
Aft, R., Naughton, M., Trinkaus, K., Watson, M., Ylagan, L., Chavez-MacGregor, M., Zhai, J., Kuo, S., Shannon, W., Diemer, K., Herrmann, V., Dietz, J., Ali, A., Ellis, M., Weiss, P., Eberlein, T., Ma, C., Fracasso, P. M., Zoberi, I., Taylor, M., Gillanders, W., Pluard, T., Mortimer, J., Weilbaecher, K., Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: An open label, randomised, phase 2 trial, The Lancet Oncology, 11, 421-428, 2010	Neoadjuvant treatment
Anagha, P. P., Sen, S., The efficacy of bisphosphonates in preventing aromatase inhibitor induced bone loss for postmenopausal women with early breast cancer: a systematic review and meta-analysis, Journal of Oncology Print, 2014, 625060, 2014	Includes comparisons outside scope (immediate vs. delayed)
Anonymous,, Once-weekly risedronate benefits postmenopausal breast-cancer survivors, Nature Clinical Practice Endocrinology and Metabolism, 4, 478, 2008	Review of paper (Greenspan 2008)
Aubailly, M., Combe, B., Gaujoux-Viala, C., Lukas, C., Morel, J., Che, H., Safety of denosumab in postmenopausal osteoporosis and in cancer and bone metastase treatment: A systematic review and meta-analysis, Arthritis and Rheumatology, 68, 419-420, 2016	Abstract only - insufficient information
Bedard, P. L., Body, J. J., Piccart-Gebhart, M. J., Sowing the soil for cure? Results of the ABCSG-12 trial open a new chapter in the evolving adjuvant bisphosphonate story in early breast cancer, Journal of clinical oncology, 27, 4043-6, 2009	Commentary
Brufsky, A. M., Zoledronic acid for cancer therapy-induced and postmenopausal bone loss, Expert Opinion on PharmacotherapyExpert Opin Pharmacother, 9, 1013-1028, 2008	Narrative review
Brufsky, A. M., Bosserman, L. D., Caradonna, R. R., Haley, B. B., Jones, C. M., Moore, H. C. F., Jin, L., Warsi, G. M., Ericson, S. G., Perez, E. A., Zoledronic acid effectively prevents aromatase inhibitor- associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-fast study 36-month follow-up results, Clinical Breast Cancer, 9, 77-85, 2009	Immediate vs. delayed zoledronic acid
Cepa, M., Vaz, C., Management of bone loss in postmenopausal breast cancer patients treated with aromatase inhibitors, Acta Reumatologica Portuguesa, 40, 323-30, 2015	Includes comparisons outside scope (immediate vs. delayed)
Cohen,A., Fleischer,J.B., Johnson,M.K., Brown,I.N., Joe,A.K., Hershman,D.L., McMahon,D.J., Silverberg,S.J., Prevention of bone loss after withdrawal of tamoxifen, Endocrine Practice, 14, 162-167, 2008	Insufficient presentation of results

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Coleman, R., The use of bisphosphonates in cancer treatment, 3-14, 2011	Narrative review
Coleman, R., Cameron, D., Dodwell, D., Bell, R., Wilson, C., Rathbone, E., Keane, M., Gil, M., Burkinshaw, R., Grieve, R., Barrett-Lee, P., Ritchie, D., Liversedge, V., Hinsley, S., Marshall, H., Adjuvant zoledronic acid in patients with early breast cancer: Final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial, The Lancet Oncology, 15, 997-1006, 2014	Same outcomes as Coleman 2011 - 5 year follow-up reported by Coleman 2011 prioritised by the committee
Dranitsaris, G., Hatzimichael, E., Interpreting results from oncology clinical trials: A comparison of denosumab to zoledronic acid for the prevention of skeletal-related events in cancer patients, Supportive Care in Cancer, 20, 1353-1360, 2012	Included studies outside scope due to population
Ethier, J. L., Prince, R. M., Amir, E., Bone Modifier Use as Adjuvant Therapy for Early Breast Cancer, Current Oncology ReportsCurr Oncol Rep, 19, 15, 2017	Contains comparisons outside scope - no new studies identified
Fehm, T., Bisphosphonates: Can they serve as anti cancer agents in the adjuvant setting?, Breast Care, 6, 156-157, 2011	Commentary
Fox, K. R., Adding zoledronic acid to endocrine therapy in the adjuvant treatment of hormone-sensitive breast cancer in premenopausal women: a new care standard or a provocative idea?, Current oncology reports, 12, 1-3, 2010	Review of article (Gnant 2009)
Gagliato, D., Chavez-Macgregor, M., Adjuvant bisphosphonates in breast cancer: Has the time come?, Breast Cancer Management, 2, 327-337, 2013	Narrative review
Gnant, M., Role of bisphosphonates in postmenopausal women with breast cancer, Cancer treatment reviews, 40, 476-484, 2014	Includes comparisons outside scope (e.g., immediate vs. delayed)
Gnant, M., Adjuvant bisphosphonate therapy in postmenopausal breast cancer patients, Breast Care, 5, 298-304, 2010	Narrative review
Gnant, M., Mlineritsch, B., Stoeger, H., Luschin-Ebengreuth, G., Knauer, M., Moik, M., Jakesz, R., Seifert, M., Taucher, S., Bjelic-Radisic, V., Balic, M., Eidtmann, H., Eiermann, W., Steger, G., Kwasny, W., Dubsky, P., Selim, U., Fitzal, F., Hochreiner, G., Wette, V., Sevelda, P., Ploner, F., Bartsch, R., Fesl, C., Greil, R., Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: Final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12, Annals of OncologyAnn Oncol, 26, 313-320, 2015	Same outcomes as Gnant 2011; 5 year follow-up preferred by the commitee
Gnant, M., Mlineritsch, B., Stoeger, H., Luschin-Ebengreuth, G., Poestlberger, S., Dubsky, P. C., Jakesz, R., Singer, C. F., Eidtmann, H., Greil, R., Overall survival with adjuvant zoledronic acid in patients with premenopausal breast cancer with complete endocrine blockade: Long-term results from ABCSG-12, Journal of clinical oncology, 29, 520, 2011	Conference abstract >2 years old
Gnant,M., Mlineritsch,B., Schippinger,W., Luschin-Ebengreuth,G., Postlberger,S., Menzel,C., Jakesz,R., Seifert,M., Hubalek,M., Bjelic-Radisic,V., Samonigg,H., Tausch,C., Eidtmann,H., Steger,G., Kwasny,W.,	Same sample as Gnant 2011 - 5 year follow-up prioritised by the commitee

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Dubsky,P., Fridrik,M., Fitzal,F., Stierer,M., Rucklinger,E., Greil,R., Endocrine therapy plus zoledronic acid in premenopausal breast cancer, New England Journal of Medicine, 360, 679-691, 2009	
Gralow, J., Barlow, W. E., Paterson, A. H. G., Lew, D., Stopeck, A., Hayes, D. F., Hershman, D. L., Schubert, M., Clemons, M. J., Van Poznak, C. H., Dees, E. C., Ingle, J. N., Falkson, C. I., Elias, A. D., Messino, M. J., Margolis, J. H., Dakhil, S. R., Chew, H. K., Livingston, R. B., Hortobagyi, G. N., Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/NRG Oncology study S0307, Journal of Clinical Oncology. Conference, 33, 2015	Abstract only - insufficient information
Greenberg, J., Stemmer, S. M., Bernstein-Molho, R., Pelles-Avraham, S., Stephansky, I., Inbar, M. J., Geffen, D. B., Safra, T., The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: 36-month follow-up, Journal of clinical oncology, 29, e11111, 2011	Abstract >2 years old
Hadji,P., Managing bone health with zoledronic acid: A review of randomized clinical study results, Climacteric, 14, 321-332, 2011	Includes comparisons outside scope (e.g., immediate vs. delayed)
Hadji,P., Kauka,A., Bauer,T., Kalder,M., Albert,U.S., Birkholz,K., Baier,M., Muth,M., Ziller,M., The ProBone study: Influence of zoledronic acid on bone mineral density in premenopausal women with breast cancer and neoadjuvant or adjuvant chemotherapy and/or endocrine treatment, Journal of Cancer Research and Clinical Oncology, 138, 62-, 2012	Abstract >2 years old
He, M., Fan, W., Zhang, X., Adjuvant zoledronic acid therapy for patients with early stage breast cancer: An updated systematic review and meta-analysis, Journal of Hematology and Oncology, 6 (1) (no pagination), 2013	Includes comparisons outside scope (e.g., immediate vs. delayed)
Hershman, D. L., McMahon, D. J., Crew, K. D., Cremers, S., Irani, D., Cucchiara, G., Brafman, L., Shane, E., Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer, Journal of clinical oncology, 26, 4739-4745, 2008	Same outcomes as Hershman 2010 with shorter follow-up; longer follow-up prioritised by the commitee
Huang, W. W., Huang, C., Liu, J., Zheng, H. Y., Lin, L., Zoledronic acid as an adjuvant therapy in patients with breast cancer: a systematic review and meta-analysis, PLoS ONE [Electronic Resource], 7, e40783, 2012	Includes comparisons outside scope (e.g., immediate vs. delayed)
Hue, T. F., Cummings, S. R., Cauley, J. A., Bauer, D. C., Ensrud, K. E., Barrett-Connor, E., Black, D. M., Effect of bisphosphonate use on risk of postmenopausal breast cancer: Results from the randomized clinical trials of alendronate and zoledronic acid [Correction: JAMA Internal Medicine (2014); 174(11): 1875], JAMA Internal Medicine, 174, 1550-1557, 2014	Narrative review
Jungmayr, P., Lowering the recurrence rate after breast cancer: Meta-analyses confirm efficiency of aromatase inhibitors and bisphosphonates, Deutsche Apotheker Zeitung, 155, 1341-1352, 2015	Non-English language
Kadoya, T., Masumoto, N., Shigematsu, H., Emi, A., Kajitani, K., Kobayashi, Y., Funakoshi, M., Kawabuchi, Y., Ohara, M., Matsuura, K., Noma, M., Sasada, T., Okada, M., Prevention of letrozole-induced bone loss using risedronate in postmenopausal women with hormone receptor positive breast cancer: A multicenter randomized	Abstract only - insufficient information

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
clinical trial, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	
Kalder, M, Kyvernitakis, I, Albert, Us, Baier-Ebert, M, Hadji, P, Effects of zoledronic acid versus placebo on bone mineral density and bone texture analysis assessed by the trabecular bone score in premenopausal women with breast cancer treatment-induced bone loss: results of the ProBONE II substudy, Osteoporosis international, 26, 353-60, 2014	Same results as Hadji 2014
Kokufu, I., Kohno, N., Yamamoto, M., Takao, S., Adjuvant pamidronate therapy prevents the development of bone metastases in breast cancer patients with four or more positive nodes, Oncology Letters, 1, 247-252, 2010	Non-randomised
Korde, L. A., Doody, D. R., Malone, K. E., Bisphosphonate use and breast cancer recurrence risk in the QUILT cohort, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Non-randomised
Kourie, H. R., Antoun, J., El Rassy, E., Rassy, M., Sader-Ghorra, C., Kattan, J., Osteonecrosis of the jaw during biyearly treatment with zoledronic acid for aromatase inhibitor associated bone loss in early breast cancer: A literature review, Journal of Bone Oncology, 4, 77-79, 2015	Includes comparisons outside scope (e.g., immediate vs. delayed)
Kuchuk, I., Beaumont, J. L., Clemons, M., Amir, E., Addison, C. L., Cella, D., Effects of de-escalated bisphosphonate therapy on the functional assessment of cancer therapy-bone pain, brief pain inventory and bone biomarkers, Journal of Bone Oncology, 2, 154-157, 2013	Metastatic cancer
Lester, J. E., Dodwell, D., BrownJ.E,, Purohit, O. P., Gutcher, S. A., Ellis, S. P., Thorpe, R., Horsman, J. M., Coleman, R. E., Prevention of anastrozole induced bone loss with monthly oral ibandronate: Final 5 year results from the ARIBON trial, Journal of Bone Oncology, 1, 57-62, 2012	Contains non-random allocation
Livi, L., Meattini, I., Scotti, V., Saieva, C., Desideri, I., Carta, G. A., Russo, M. L., De Luca Cardillo, C., Greto, D., Nori, J., Bernini, M., Casella, D., Orzalesi, L., Sanchez, L. J., Magrini, S. M., Bianchi, S., BONADIUV trial: A single blind, randomized placebo controlled phase II study using oral ibandronate for osteopenic women receiving adjuvant aromatase inhibitors: Final safety analysis, Journal of Clinical Oncology. Conference, 34, 2016	Abstract only - insufficient information
Mathew, A., Brufsky, A., Bisphosphonates in breast cancer, International journal of cancer, 137, 753-764, 2015	Includes comparisons outside scope and studies pre-2008
Mathew, A., Brufsky, A. M., The use of adjuvant bisphosphonates in the treatment of early-stage breast cancer, Clinical Advances in Hematology and Oncology, 12, 749-756, 2014	Narrative review
Mauri, D., Valachis, A., Polyzos, I. P., Polyzos, N. P., Kamposioras, K., Pesce, L. L., Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis, Breast Cancer Research & Treatment, 116, 433-9, 2009	Includes comparisons outside scope and studies pre-2008
Mauri, D., Valachis, A., Polyzos, N. P., Tsali, L., Mavroudis, D., Georgoulias, V., Casazza, G., Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials, JNCCN Journal of the National Comprehensive Cancer Network, 8, 279-286, 2010	Includes comparisons outside scope and studies pre-2008

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Morgan, G., Lipton, A., Antitumor effects and anticancer applications of bisphosphonates, Seminars in oncology, 37 Suppl 2, S30-40, 2010	Narrative review
Perrone, F., Gallo, C., Lastoria, S., Nuzzo, F., Gravina, A., Landi, G., Rossi, E., Pacilio, C., Labonia, V., Di Rella, F., De Laurentiis, M., Piccirillo, M. C., Di Maio, M., Giordano, P., Daniele, G., De Feo, G., Fiore, R., Signoriello, S., Esposito, G., de Matteis, A., Bone effects of adjuvant tamoxifen (T), letrozole (L), or L plus zoledronic acid (Z) in early breast cancer (EBC): The phase III HOBOE study, Journal of clinical oncology, 29, 517, 2011	Abstract >2 years old
Prasad, C., Greenspan, S. L., Vujevich, K. T., Brufsky, A., Lembersky, B. C., van Londen, G. J., Jankowitz, R. C., Puhalla, S. L., Rastogi, P., Perera, S., Risedronate may preserve bone microarchitecture in breast cancer survivors on aromatase inhibitors: A randomized, controlled clinical trial, Bone, 90, 123-126, 2016	Outcome outside scope
Rack, B., Fasching, P. A., Haberle, L., Friedl, T., Rezai, M., Hilfrich, J., Tesch, H., Heinrich, G., Forstbauer, H., Neugebauer, J., Trapp, E., Albrecht, S., Jager, B., Fehm, T., Muller, V., Schneeweiss, A., Friese, K., Lichtenegger, W., Beckmann, M. W., Janni, W., Prevalence of circulating tumor cells (CTCs) after five years of zoledronate treatment in the adjuvant SUCCESS-A study, Cancer Research. Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 75, 2015	2 vs. 5 years of zoledronate
Roberts, K., Rickett, K., Greer, R., Woodward, N., Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: A systematic review and meta-analysis, Critical Reviews in Oncology/Hematology, 111, 66-80, 2017	Comparisons and/or study design outside scope
Rugani, P., Luschin, G., Jakse, N., Kirnbauer, B., Lang, U., Acham, S., Prevalence of bisphosphonate-associated osteonecrosis of the jaw after intravenous zoledronate infusions in patients with early breast cancer, Clinical oral investigations, 18, 401-407, 2014	Results not reported for control group
Safra,T., Bernstein-Molho,R., Greenberg,J., Pelles-Avraham,S., Stephansky,I., Sarid,D., Inbar,M.J., Stemmer,S.M., Geffen,D.B., The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: a prospective, randomized, phase II trial, Oncology, 81, 298-305, 2011	Insufficient presentation of results
Saito, M., Matsuoka, J., Open-label randomized parallel controlled study comparing bone mineral density between alendronate plus alfacalcidol combination and single administration of alfacalcidol in postmenopausal women receiving aromatase inhibitor as adjuvant therapy, Cancer Research. Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 75, 2015	Abstract only - insufficient information
Sestak, I., Singh, S., Cuzick, J., Blake, G. M., Patel, R., Gossiel, F., Coleman, R., Dowsett, M., Forbes, J. F., Howell, A., Eastell, R., Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: An international, double-blind, randomised, placebo-controlled trial, The Lancet Oncology, 15, 1460-1468, 2014	Healthy participants
Shapiro,C.L., Halabi,S., Hars,V., Archer,L., Weckstein,D., Kirshner,J., Sikov,W., Winer,E., Burstein,H.J., Hudis,C., Isaacs,C., Schilsky,R., Paskett,E., Zoledronic acid preserves bone mineral density in premenopausal	Immediate vs. delayed zoledronic acid

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
women who develop ovarian failure due to adjuvant chemotherapy: Final results from CALGB trial 79809, European Journal of Cancer, 47, 683-689, 2011	
Solomayer, E. F., Gebauer, G., Hirnle, P., Janni, W., Luck, H. J., Becker, S., Huober, J., Kramer, B., Wackwitz, B., Wallwiener, D., Fehm, T., Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients, Annals of Oncology, 23, 2271-2277, 2012	Outcome outside scope
Strobl, S., Korkmaz, B., Devyatko, Y., Schuetz, M., Exner, R., Dubsky, P. C., Jakesz, R., Gnant, M., Adjuvant bisphosphonates and breast cancer survival, 1-10, 2016	Narrative review
Su, G., Xiang, Y., He, G., Jiang, C., Li, C., Yan, Z., Zhong, Y., Bisphosphonates May Protect against Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Aromatase Inhibitor Therapy: Results from a Meta-analysis, Archives of Medical Research, 45, 570-579, 2014	Includes comparisons outside scope and studies pre-2008
Swenson, K. K., Nissen, M. J. Mary Jo, Anderson, E., Shapiro, A., Schouboe, J., Leach, J., Effects of exercise vs bisphosphonates on bone mineral density in breast cancer patients receiving chemotherapy, Journal of Supportive Oncology, 7, 101-107, 2009	Comparison outside scope
Theriault, R. L., Bisphosphonates: ready for use as adjuvant therapy of breast cancer?, Current opinion in obstetrics & gynecology, 22, 61-66, 2010	Narrative review
Tolia, M., Zygogianni, A., Kouvaris, J. R., Meristoudis, C., Margari, N., Karakitsos, P., Kokakis, I., Kardamakis, D., Papadimitriou, C., Mystakidou, K., Tsoukalas, N., Kyrgias, G., Armonis, B., Filippiadis, D. K., Kelekis, A. D., Kelekis, N., Kouloulias, V., The key role of Bisphosphonates in the supportive care of cancer patients, Anticancer research, 34, 23-37, 2014	Includes studies outside scope
Valachis, A., Polyzos, N. P., Coleman, R. E., Gnant, M., Eidtmann, H., Brufsky, A. M., Rebecca, A., Tevaarwerk, A. J., Swenson, K., Lind, P., Mauri, D., Adjuvant therapy with zoledronic acid in patients with breast cancer: A systematic review and meta-analysis, Oncologist, 18, 353-361, 2013	Includes comparisons outside scope (e.g., immediate vs. delayed)
Valachis, A., Polyzos, N. P., Georgulias, V., Mavroudis, D., Mauri, D., Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: A meta-analysis, Gynecologic Oncology, 117, 139-145, 2010	Includes comparisons outside scope and studies pre-2008
van Londen,G.J., Perera,S., Vujevich,K.T., Sereika,S.M., Bhattacharya,R., Greenspan,S.L., The effect of risedronate on hip structural geometry in chemotherapy-induced postmenopausal women with or without use of aromatase inhibitors: a 2-year trial, Bone, 46, 655-659, 2010	Insufficient presentation of results
Van Poznak, C., The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials, Breast Diseases, 24, 68-70, 2013	Review of article
Van Poznak, C., Breast-cancer adjuvant therapy with zoledronic acid, Breast Diseases, 23, 262-263, 2012	Review of article
Varun, B., Sivakumar, T., Nair, B. J., Joseph, A. P., Bisphosphonate induced osteonecrosis of jaw in breast cancer patients: A systematic review, Journal of Oral & Maxillofacial Pathology, 16, 210-4, 2012	Included studies are non-randomised

Excluded studies - RQ7.1 What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Wilson, C., Hinsley, S., Marshall, H., Cameron, D., Bell, R., Dodwell, D., Coleman, R. E., Reproductive hormone analyses and effects of adjuvant zoledronic acid in early breast cancer - An AZURE (BIG 01/04) sub-study, Journal of Bone Oncology., 29, 2016	Additional subgroup analysis not of interest
Wong, Matthew Hf, Stockler, Martin R, Pavlakis, Nick, Bisphosphonates and other bone agents for breast cancer, Cochrane Database of Systematic Reviews, 2012	Includes studies outside scope and pre-2008
Yan, T., Yin, W., Zhou, Q., Zhou, L., Jiang, Y., Du, Y., Shao, Z., Lu, J., The efficacy of zoledronic acid in breast cancer adjuvant therapy: a meta-analysis of randomised controlled trials, European journal of cancer, 48, 187-95, 2012	Includes comparisons outside scope (e.g., immediate vs. delayed)
Zhou, W. B., Zhang, P. L., Liu, X. A., Yang, T., He, W., Innegligible musculoskeletal disorders caused by zoledronic acid in adjuvant breast cancer treatment: a meta-analysis, Journal of Experimental & Clinical Cancer Research, 30, 72, 2011	Includes comparisons outside scope (e.g., immediate vs. delayed)
Zhu, J., Zheng, Y., Zhou, Z., Oral adjuvant clodronate therapy could improve overall survival in early breast cancer: Results from an updated systematic review and meta-analysis, European journal of cancer, 49, 2086-2092, 2013	Includes studies pre-2008

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Appendix L – Research recommendations

Which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates?

Why this is important?

Bisphosphonates are widely used in people with advanced malignancies involving bone. Since the publication of the previous NICE guideline (CG80), data have been published exploring the use of bisphosphonates in the prevention of secondary breast cancer, with disease-related outcomes, and information on which subgroups are likely to benefit most from bisphosphonate treatment.

The evidence reviewed for this guideline identified that sodium clodronate leads to improved overall survival in mixed populations and improves disease-free survival in postmenopausal women, and that zoledronic acid improves disease-free survival in postmenopausal women and in node-positive early breast cancer. There is, however, a lack of evidence regarding disease-free survival and overall survival, particularly for specific subgroups, such as premenopausal women on ovarian suppression, those with node-positive or node-negative disease, and those with positive or negative oestrogen or progestogen statuses. Therefore, further research is needed to determine the long-term survival benefits for bisphosphonates and to better define subgroups most likely to benefit.

Table 49: Research recommendation rationale

Research question	Which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates?
Importance to 'patients' or the population	• Improved overall survival and disease-free survival • Improved bone health
Relevance to NICE guidance	It was not possible to make clear recommendations for bisphosphonates in all sub-groups based on the currently available evidence
Relevance to the NHS	Prevention of disease-progression with bisphosphonates is cheaper than treating people with advanced breast cancer, and therefore use of adjuvant bisphosphonates may be a potential cost saving to the NHS
National priorities	Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010) Reduce variation in treatment Evidence based healthcare Prevention of secondary breast cancer
Current evidence base	Lack of evidence on overall survival and disease-free survival for bisphosphonates (excluding zoledronic acid and sodium clodronate), particularly for specific subgroups such as premenopausal women on ovarian suppression, in node positive/negative people, with different oestrogen- and progestogen-receptor status.
Equality	No data on men, as men cannot be postmenopausal

NHS, National Health Service; NICE, National Institute of Health and Care Excellence

Table 50: Research recommendation modified PICO table

Criterion	Explanation
Population	Premenopausal (18 or over) women with invasive early breast cancer (M0) who have undergone surgery, on ovarian suppression for at least 5 years who are recommended chemotherapy or extended adjuvant endocrine therapy
Intervention	Bisphosphonates
Comparator	No bisphosphonates
Outcome	Critical: Overall survival Disease-free survival Treatment-related morbidity (e.g., osteonecrosis of the jaw)
Study design	Randomised controlled trial, multiple sub-group analyses
Timeframe	10 year follow up